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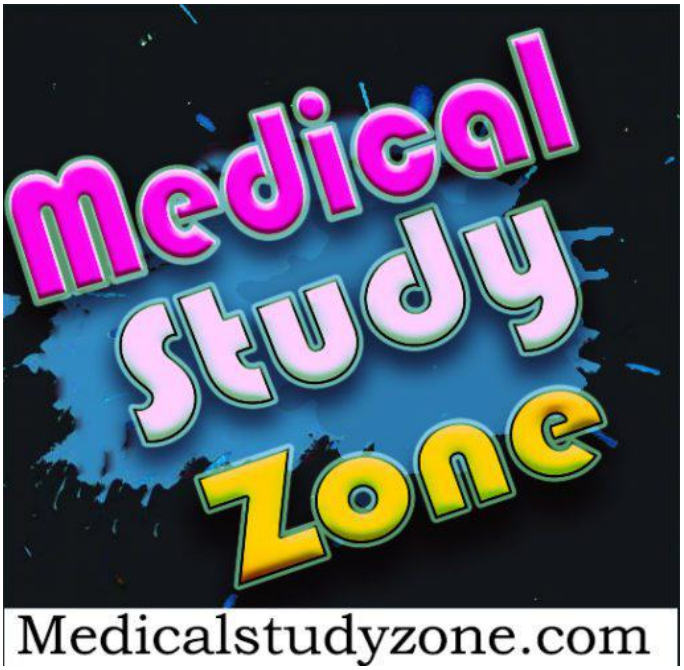


GENERAL PHYSIOLOGY

BODY FLUID COMPARTMENTS

→ Total Body water	→ 0.6 x Body weight	→ 42 L	[70Kg]
→ ICF	→ 0.4 x Body weight	→ 28 L	
→ ECF	→ 0.2 x Body weight	→ 14 L	
Intestitial fluid	→ 0.75 x ECF	→ 11 L	
Plasma	→ 0.25 x ECF	→ 3 L	

→ Blood → 8% of Body weight

Plasma → 5% of Body weight

MEASUREMENT OF BODY FLUIDS

INDICATOR DILUTION METHOD | DYE DILUTION METHOD

→ STEWART - HAMILTON DYE DILUTION METHOD

PRE REQUISITES

1. Dye should be evenly distributed
2. Dye should not leave the compartment

$$V = \frac{I}{C}$$

V = Volume of ECF

I = Initial volume of dye injected

C = concentration of dye

$$V = \frac{I - A}{C}$$

A = Amount of dye that left the compartment

Q 10g mannitol injected, concentration is 50 mg%, Excreted is 10%. ECF volume?

A $V = \frac{10 - 1}{50} = \frac{9}{50} = 18L$

Volume of ECF = 18L

INDICATORS USED

1 Total Body water

→ DUETERIUM [D_2O]

TRITIUM [$3H_2O$]

ANTIPYRINE

AMINOPYRINE

2 ECF VOLUME

→ Non metabolizable saccharides are used

→ INULIN [Best]

SUCROSE

MANNITOL

3 ICF VOLUME → [TBW] − [ECF]

4 PLASMA VOLUME → RADIO LABELLED IODINE

5 RED CELL VOLUME → ^{51}Cr – TAGGING

DISTURBANCES [ĩ respect to ECF]

1 DEHYDATION

2 OVERHYDRATION

DEHYDRATION

1 ISOTONIC DEHYDRATION

→ Water & Na^+ lost in equal proportions

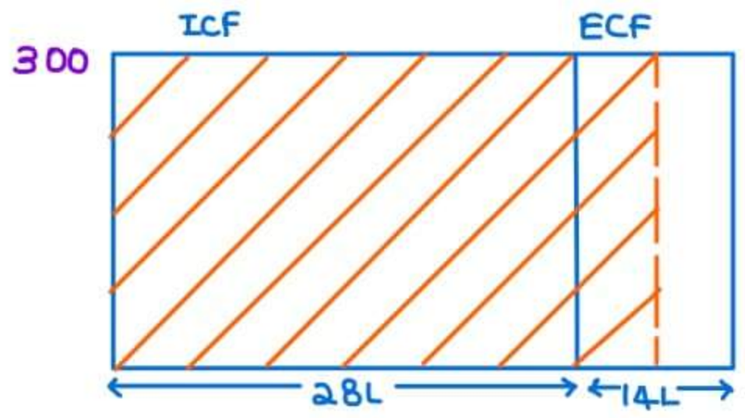
→ No shift of H_2O d/t Isotonicity of ECF

→ CONDITIONS

GI Fluid loss

Burns

Haemorrhage



2 HYPERTONIC DEHYDRATION

→ H_2O lost from ECF

→ ECF becomes hypertonic

→ H_2O moves from ICF to ECF

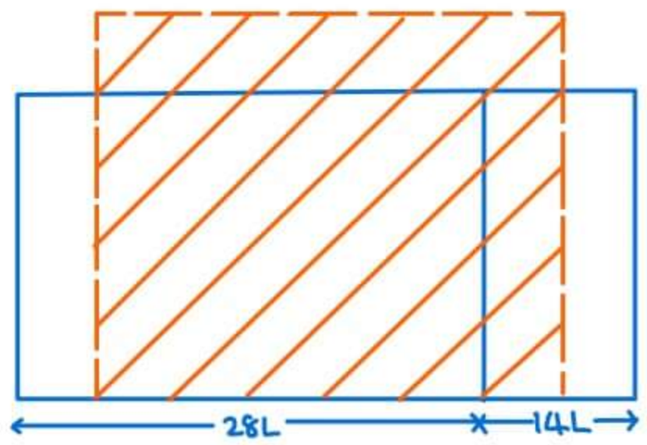
→ ICV volume shrunken secondarily

→ CONDITIONS

DM

DI

Chronic Alcoholism



3 HYPOTONIC DEHYDRATION

→ H_2O & Na^+ lost [Na^+ loss is much higher]

→ ECF becomes hypotonic

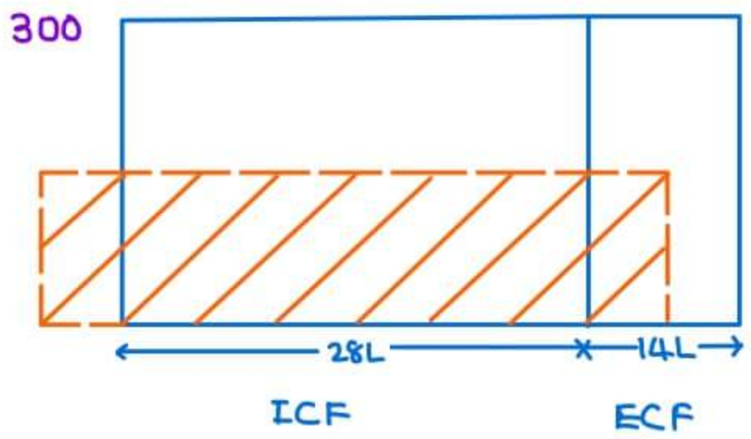
→ ECF H_2O shifts into ICF

→ ICF volume increased secondarily

→ CONDITIONS

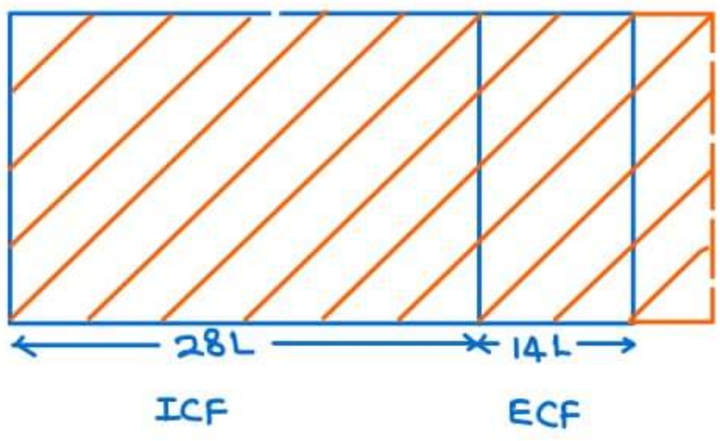
Primary hypoaldosteronism

Primary hypoadreno corticolism



OVER HYDRATION / VOLUME EXPANSION STATES

1 ISOTONIC OVERHYDRATION → administratⁿ of oral | IV isotonic Saline



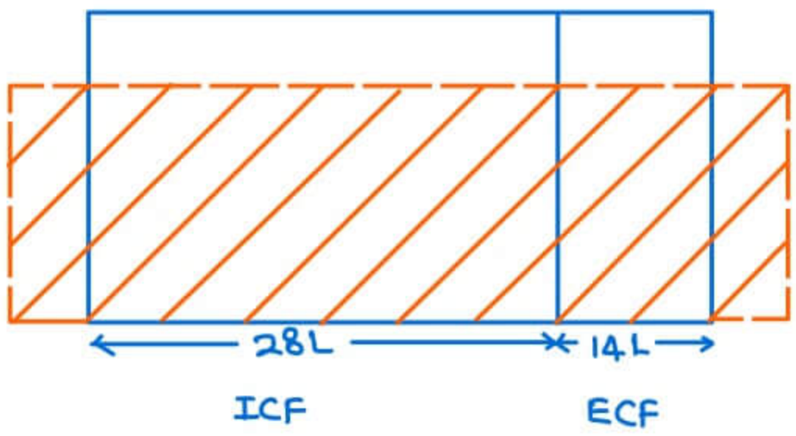
2 HYPERTONIC OVERHYDRATION → administratⁿ of Oral / IV hypertonic saline

3 HYPOTONIC OVER HYDRATION

CONDITION

1 SIADH [Syndrome of Inappropriate ADH Secretion]

→ occurs in surgery & stress



↑ Volume
↓
↑ Atrial filling pressure
↓
Atria → ANP [Natriuretic Peptide]
↓
Natriuresis
Diuresis
[EUVOLEMIC HYPONATREMIA]

→ ANP Synthesized by
BNP Synthesized by
CNP Synthesized by
} HEART

Q A person drunk 1 Ltr of sea water → HYPERTONIC DEHYDRATION OCCURS

→ Sea water osmolarity → 2400 mosm/L
→ max. concentrating ability of Kidney → 1200 mosm/L
→ 2 ltr of urine to be produced, resulting in Hypertonic Dehydratⁿ

If the osmolarity of consumed fluid is < 1200 mosm/L → Hypertonic overhydratⁿ
If the osmolarity of consumed fluid is > 1200 mosm/L → Hypertonic Dehydratⁿ

CONCEPTS IN PHYSIOLOGY

1. ENDOLYMPH

→ ECF which resembles ICF in body
→ has ↑ K^+ concentratⁿ

ICF	ECF
↑ K^+	↓ K^+
↓ Na^+	↑ Na^+

2. IMPERMEANT ANIONS IN ICF

→ Proteins
Phosphates

→ responsible for relative anions in ICF

Na^+ Leaking into the cell
to maintain equilibrium

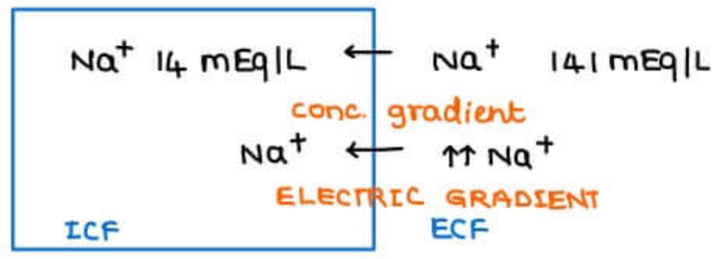
3 DIFFUSION is also occurs d/t electric gradient [along ↑ concentrat^{n} gradient]

Na^+

→ moves into the cell d/t

→ concentrat^{n} gradient

Electric gradient



→ NET MOVEMENT → always diffuse in

K^+

→ moves inside to outside d/t concentrat^{n} gradient

→ ECF K^+ concentrat^{n} → 4 mEq/L

ICF K^+ concentrat^{n} → 145 mEq/L

→ moves outside to inside d/t Electric gradient

→ NET MOVEMENT → depends on predominant gradient

4 MILIEU INTERIEUR [ECF] → Internal Environment OF BODY

5 HOMEOSTASIS → maintaining the constancy / Stability in milieu interieur

MILIEU INTERIEUR, HOMEOSTASIS } coined by CLAUDE BERNARD & WALTER F CANNON

EQUILIBRIUM	STUDY STATE CONDITIONS
Ion Equilibrium [K^+]	Blood Glucose 100mg%
Involves 2 adjacent compartments	Not necessary
Involves 2 equal & opposite forces	Not necessary
ATP not needed	ATP breakdown + nt
Short lived	Long lived

HOMEOSTATIC REGULATORY MECHANISMS

Q Example of feedforward regulat^{n} ?

A BP regulat^{n} by baroreceptor mechanism

B Temp. regulat^{n} by Hypothalamus

C Oxytocin in parturit^{n}

D cephalic phase of Gastric Acid secret^{n}

→ FEED FORWARD REGULATION → No time lag

FEED BACK REGULATION → time lag present

Q most efficient feedback mechanism

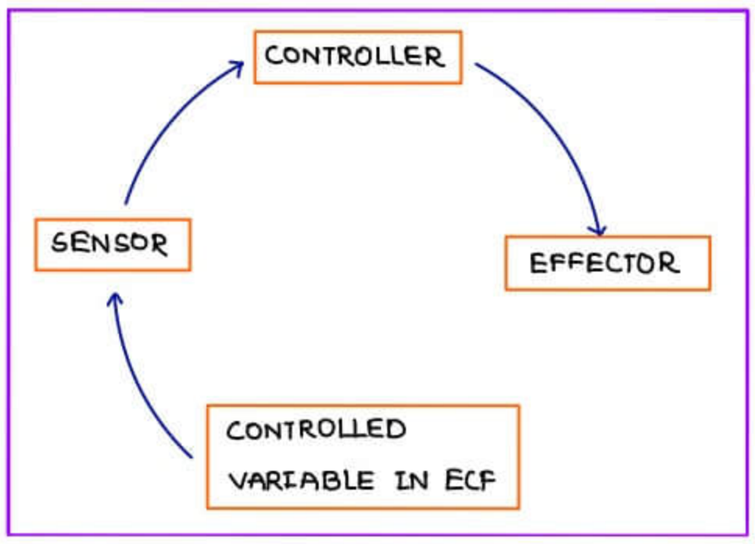
A Baroreflex in BP regulatⁿ

B Temp. regulatⁿ by hypothalamus

C Osmo regulatⁿ by hypothalamus

D Kidney body fluids mechanism in regulatⁿ of BP

SCHEMATIC MODEL



I FEED FORWARD MECHANISMS

→ Controller anticipates changes & takes a desired action

→ no time lag present

→ Ex: 1. cephalic phase of gastric acid secretion
2. ↑ ventilatory drive in exercise

II FEED BACK MECHANISMS

→ Change occur in controlled variable & that change is fedback to controller & then the controller takes action

→ time lag is present

→ TYPES

1. NEGATIVE FEED BACK
2. POSITIVE FEED BACK

1. NEGATIVE FEED BACK

→ Controller does the opposite

→ change is negated or error is minimised

→ Measure of efficiency is GAIN

$$\text{GAIN} = \frac{\text{correction}}{\text{Error}} = \frac{40}{10}$$

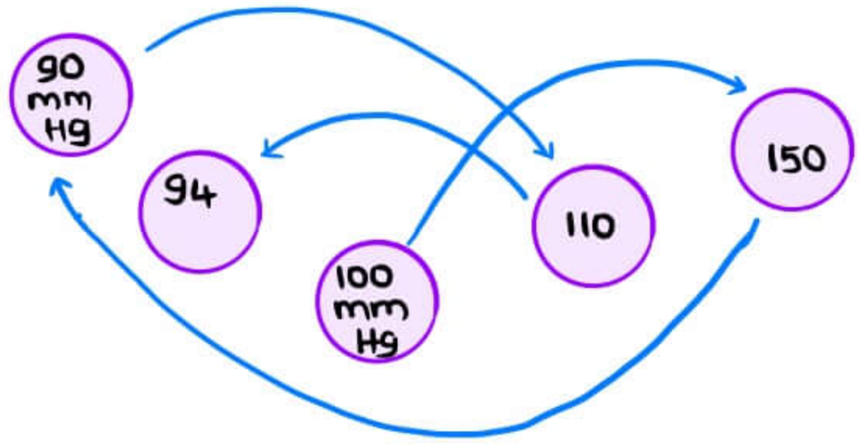
→ Higher the gain, more is the efficiency of system
correction will be large, residual error will be less

→ Ex: a. Kidney Body Fluid mechanism (has infinite gain)
b. Temperature Regulation
c. Baroreceptor mechanism

OSCILLATIONS

→ Ex: Pupillary light reflex

→ TYPES



1. DURING CORRECTION

a. ANS Regulated mechanisms

Ex - pupillary diameter

b. systems ↄ high gain

→ High gain means high correction

System tends to overshoot during correction

→ Ex - BP Regulating Mechanism

2. OSCILLATIONS IN A SET POINT OR GAIN

→ Ex → Muscle spindle in regulation of muscle length during continuous voluntary movement

→ set points are not fixed here

→ such mechanisms are called SERVO MECHANISMS

2. POSITIVE FEED BACK MECHANISM / VISCIOUS CYCLE

→ controller does the same in direction OF error & Error is amplified

→ Ex →

a. circulatory shock (2nd stage)

b. oxytocin in parturition

c. Platelet plug / clot formation

d. Action potential from RMP to threshold

e LH surge leading to ovulation

f Bladder filling → MICTURITION

g. HEAD'S PARADOXICAL REFLEX

→ distentn leads to more distension, occur at birth

h. Vomiting

→ All these positive feed back will end ↄ negative feedback

→ Positive feedback are part of larger scheme of negative feedback process

Ex → a. Oxytocin in partirutn

b. Platelet plug & clot formatn

CELL MEMBRANE & TRANSPORT PROTEINS

CELL MEMBRANE

FLUID MOSAIC MODEL

→ most accepted model [SINGER NICOLSEN MODEL]

→ Lipid Bilayer with Proteins embeded in it

Micro needle injury healed by → HYDROPHOBIC INTERACTIONS [Self Sealing]

Membrane fluidity is determined → Cholesterol

Asymmetry of the membrane dlt → CARBOHYDRATES

COMPOSITION

LIPIDS → occupy 42% surface area

PROTEINS → occupy 50-55% surface area

CARBOHYDRATES → occupy 3% surface area

By weight, Lipids : Proteins → 1:1

CARBOHYDRATES

→ provide asymmetry

→ responsible for immune reactions

LIPIDS

I PHOSPHOLIPIDS

→ maximum concentrat^{n} & main constituent of Lipids

→ at low concentrations → form monolayer
Eg. Surfactant

→ at moderate concentrations → form circular aggregates
Eg. Micelles

→ at high concentrations → form bilayers
Eg. Lipid Bilayer

II CHOLESTEROLS

→ Fluidity Buffer of membrane → responsible for membrane fluidity

PROTEINS

→ Concentration varies from cell to cell

→ Concentration varies from time to time even in the same membrane

PROTEIN CONCENTRATION VARIES BETWEEN DIFFERENT CELLS

Q HIGH PROTEIN LIPID CONCENTRATION

A Presynaptic membrane
B Oligodendrocytes
C Schwann cell membrane
D Hepatocytes

→ Oligodendrocytes & Schwann cell membrane
- Have high lipid content
- forms myelin
- associated ↓ NITROGEN NARCOSIS

HIGH PROTEIN : LIPID CONCENTRATION
1. Inner Mitochondrial Membranes [76% Proteins]
2. Pre Synaptic membranes [70% Proteins]

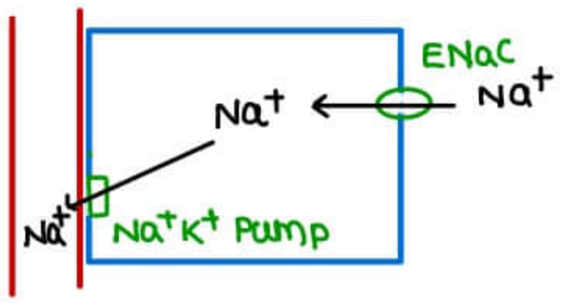
HIGH LIPID : PROTEIN CONCENTRATION
1. Shwann cell membrane [76% Lipids]
2. Oligodendrocytes

PROTEIN CONCENTRATION VARIES FROM TIME TO TIME EVEN IN THE SAME CELL

→ Protein content depends on PROTEIN TURNOVER RATE OF cell
- during removal, it first TAGGED by UBIQUITIN
- degradatⁿ takes place in 26S Proteosome

MECHANISM OF ↑ Na^+ REABSORPTION BY ALDOSTERONE

→ Na^+ Reabsorption Mechanism



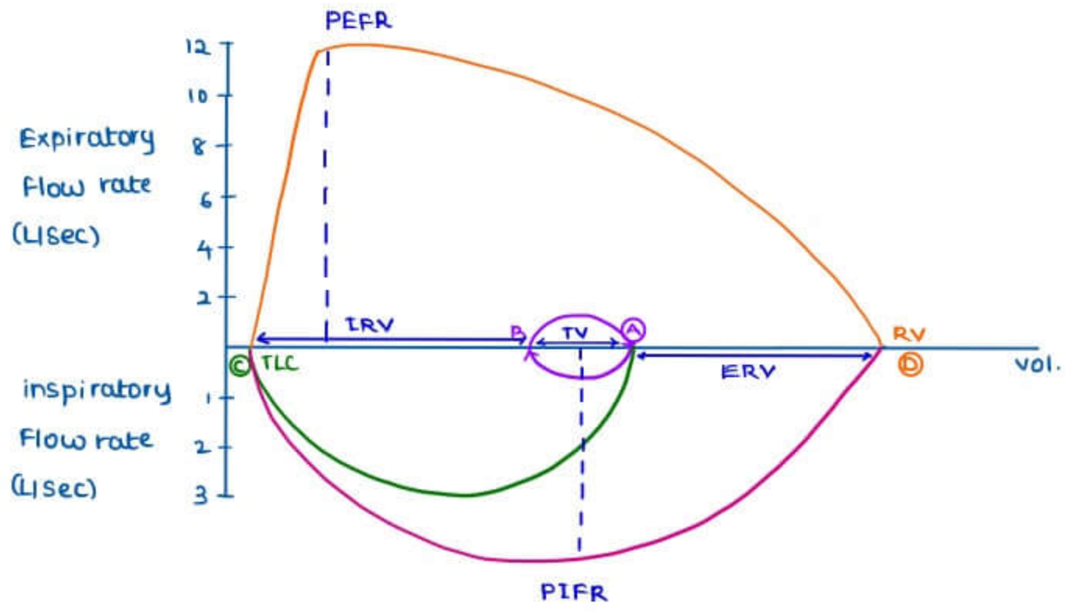
→ ENaC is Tagged by Ubiquitin [NEDD / NEDD-4 like]
→ Aldosterone inhibits NEDD / NEDD-4 like & promotes Na^+ reabsorptⁿ.
→ Aldosterone also ↑ses the no. of Na^+-K^+ pumps on baso-lateral membrane

→ smaller airway obstruction is indicated by MMFR (max. mid expiratory flow rate)

[$FEV_{0.25-0.75}$] → Ⓝ → 3. – 3.25 L/sec

FLOW VOLUME LOOPS

→ NOT A PLOTTED GRAPH [It is obtained loops]



→ Peak Inspiratory Flow Rate (PIFR) → 3L/sec

→ Peak Expiratory Flow rate (PEFR) → 10–12 L/sec

→ FIV_1 : FEV_1 > 1

↳ EXCEPT in Extra thoracic large airway obstruction

CASE 1 → QUITE BREATHING (from a to b)

CASE 2 → Max. FORCEFUL INSPIRATION (from a to c)

CASE 3 → Max. FORCEFUL EXPIRATION (from c to D)

CASE 4 → Max. FORCEFUL INSPIRATION (from D to c)

In Restrictive Lung Disease → Shifts to right

In COPD → Shifts to Left

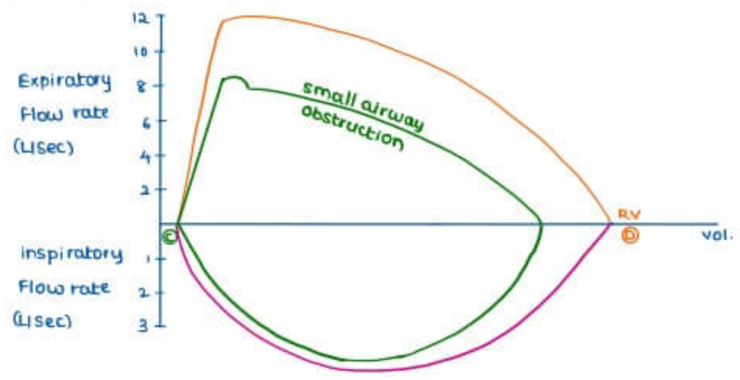
PIFR achieved at → 50% of Lung volume inspired

PEFR achieved at → 20% of Lung volume expired

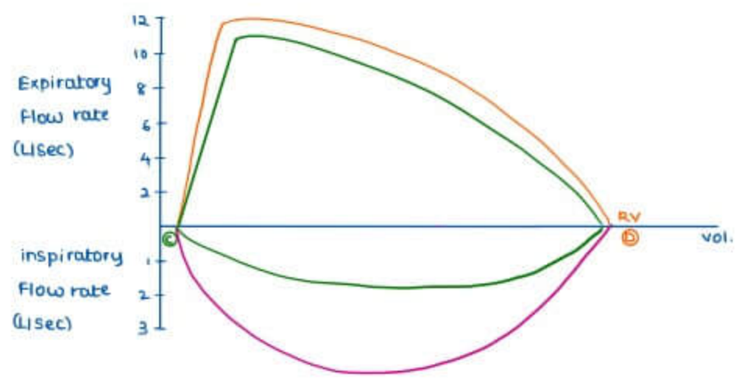
↳ EFFORT DEPENDENT FLOW RATE (more effort, more flow rate) (first 20%)

↳ EFFORT INDEPENDENT FLOW RATE (last 80%)

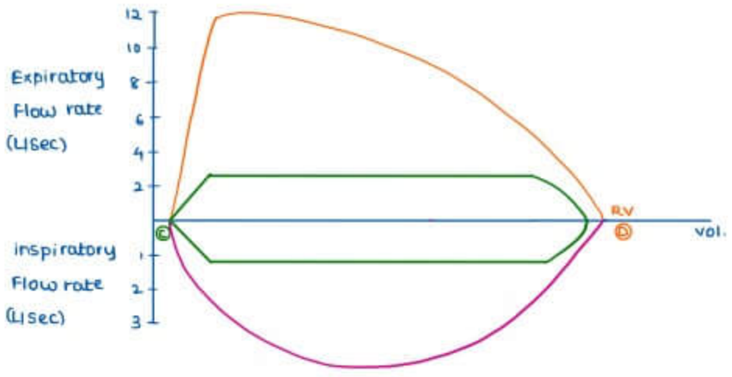
CHANGES



COPD ∵ Small air way obstruction



Extra thoracic large airway Obstruct^{n}
(Tracheal tumor mass)



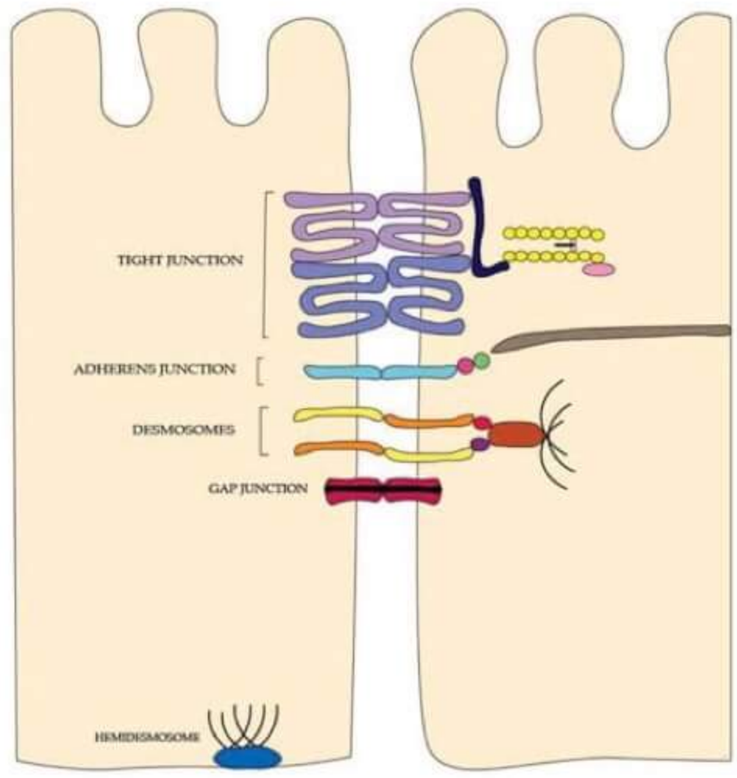
variable obstruction ∵ foreign body

③ TIGHT JUNCTIONS [ZONULA OCCLUDENS]

→ Selectively permeable

→ Found at
- Blood Brain Barrier
- Lining of Gut

→ Proteins involved
- claudins
- occludins
- JAMs [Junctional Adhesive molecules]



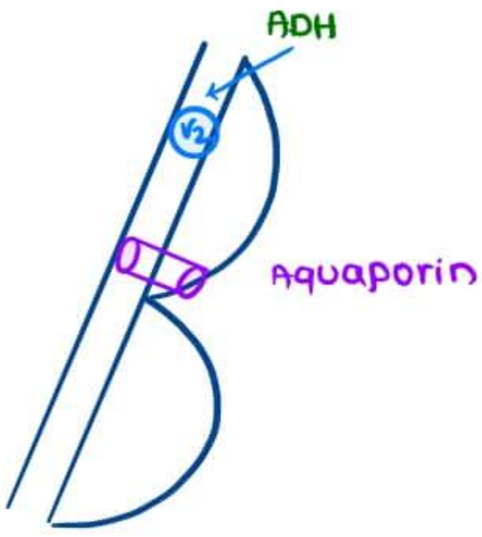
④ ADHERING JUNCTIONS

→ responsible for coherent epithelium formation

→ responsible for identificatⁿ of apical & basolateral sides of a cell

TRANSPORT PROTEINS IN THE MEMBRANE

1 PORES → always open
2 CHANNELS → intermittently open
3 CARRIERS → never open
4 PUMPS [Directly uses ATPs]

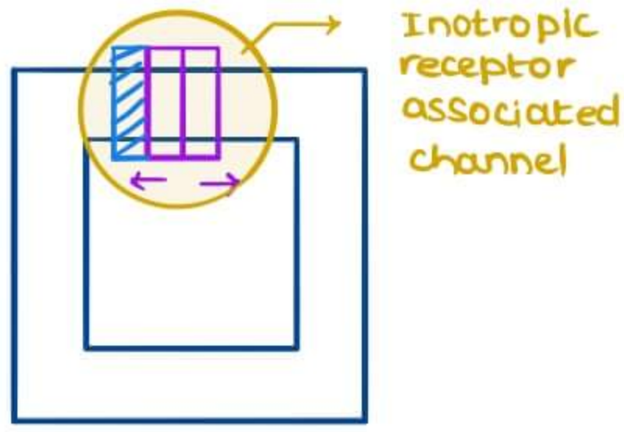


PORES

→ always open

→ Examples → Aquaporins
perforins

→ responsible for H_2O movement



LIGAND GATED ION CHANNEL

CHANNELS

→ carry out simple Diffusion

→ TYPES

LEAKY CHANNELS → Na^+ leaky channel [present on all cells]

GATED CHANNELS

1. VOLTAGE GATED ION CHANNELS → Na^+ channels in nerve membranes
2. LIGAND GATED ION CHANNELS / IONOTROPIC RECEPTOR ASSOCIATED CHANNEL
   - $GABA_A$
   - Nicotinic Acetyl choline Receptor
3. CYCLIC NUCLEOTIDE GATED CHANNEL [cAMP, cGMP] or METABOTROPIC RECEPTOR ASSOCIATED CHANNEL
   → G protein coupled Receptor involved
   → Ex: $GABA_B$, Muscarinic ACh Receptor
   HCN (Hyperpolarizatⁿ activated cyclic nucleotide gated channel)
   → funny Na channel
   → more the hyperpolarizatⁿ, more is activatⁿ of channel

4. TIME GATED CHANNELS

→ Ex : Slow ca^{2+} channels in heart

K^+ channels in nerve membrane

5. MECHANICALLY GATED CHANNELS

→ Ex : Touch Receptors in the skin

NaV 1.8 / TETRODOTOXIN RESISTANT CHANNEL

→ voltage gated channel, involved in pain efferents

6. CHEMICAL GATING CHANNELS

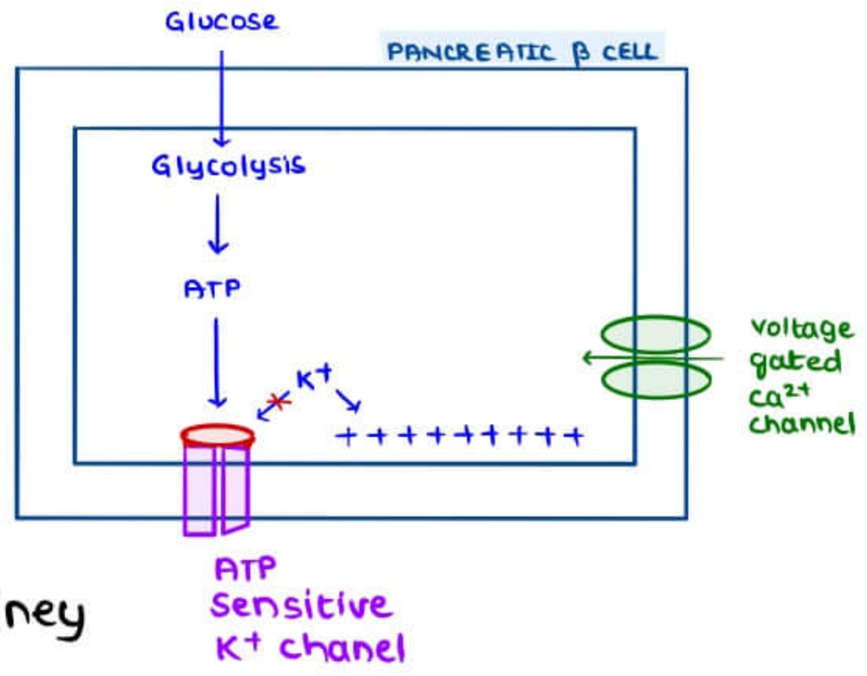
Hypoxia causes vasodilation every where, but vasoconstriction in LUNGS

O_2 SENSITIVE K^+ CHANNELS

→ Found at

carotid Body

Erythropoietin synthesizing cells in kidney



ATP SENSITIVE K^+ CHANNELS

→ Found in PANCREATIC β CELLS

→ Glucose undergoes glycolysis & releases ATP

ATP sensitive K^+ channels causes intracellular K^+ accumulation & causes opening of voltage gated ca^{2+} channels

ca^{2+} enters which results in synthesis of insulin by exocytosis

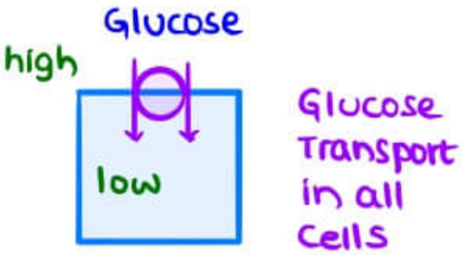
→ study of channels done by PATCH CLAMP TECHNIQUE

POISONS / BLOCKERS OF CHANNELS

1. Na^+ Channel Blockers → Tetrodotoxin
   Saxitoxin
2. K^+ channel BLOCKER → Tetra Ethyl Ammonium
   - component of Mamba Snake venom

CARRIERS

→ involved in facilitated diffusion (uniport)
2° Active transport (symport / antiport)



→ Glucose transports into all cells by facilitated diffusⁿ by GLUT EXCEPT in GIT & KIDNEY (occurs by 2° active transport by SGLT

→ GLUCOSE TRANSPORT IN GIT & KIDNEY

Glucose crosses 2 membranes,

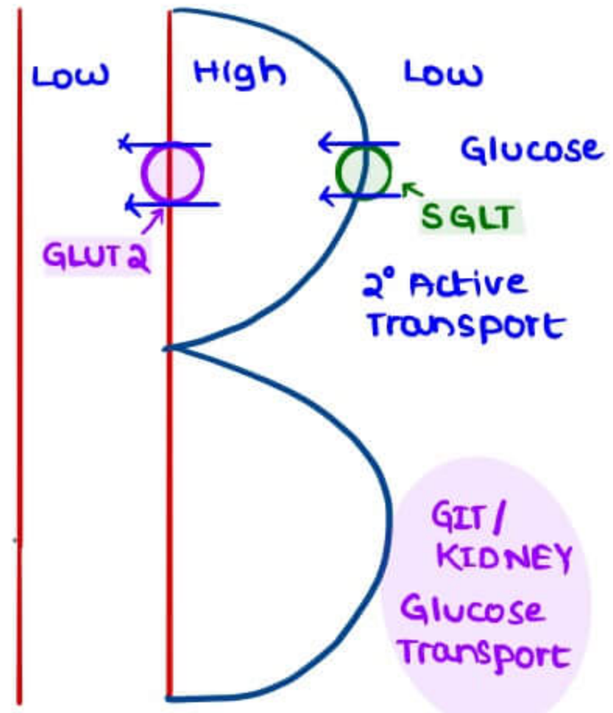
transport occuring for for absorptⁿ or reabsorptⁿ

PUMPS / ATPases

→ carries 1° Active transport

→ they bind & breakdown ATP & utilize ATP directly

→ Ex: $Na^+ - K^+$ Pump in all membranes
SERCA



→ ATP UTILIZING TRANSPORTERS

a. ATPases (pumps)

→ have single domain

→ 3 TYPES

1. P - TYPE [E_1-E_2]
$Na^+ - K^+$ pump

2. V - TYPE
→ present in membranes of vesicles
→ H^+ ATPases

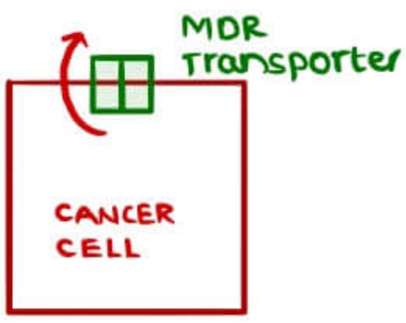
3. F - TYPE
→ $F_o - F_1$ pump
→ Works like a ATP synthase

b. ABC (ATP Binding casette) Transporter

→ have one domain, where ATP will be bound

→ Other part of protein will act as a channel or carrier

→ Ex: MDR transporter (Multidrug Resistance transporter)
→ P - glycoprotein
→ found in cancer cells & XDR (extremely drug resistant)



SUR (Sulfonyl urea transporter)

FTR → Chloride channel

TRANSPORT PROCESSES

2 TYPES

1. ACROSS MEMBRANE
   - → Endocytosis
   - → Exocytosis

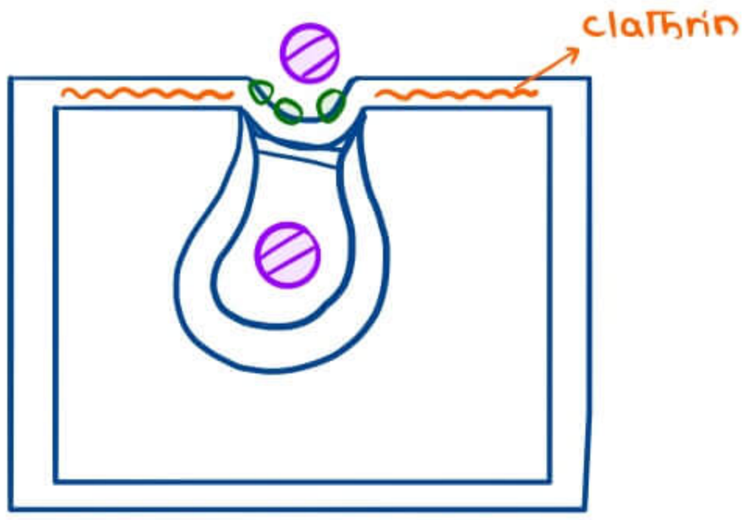
2. THROUGH MEMBRANE
   - → Osmosis
   - → Diffusion
   - → Active transport

ACROSS MEMBRANE

vesicular transport → also called CYTOPEMPSIS

1. ENDOCYTOSIS

→ occur for
- large molecules
- particles
- Foreign substances



clathrin mediated Endocytosis

→ 2 TYPES

a. Phagocytosis (cell eating)
   Ex : Bacteria entry into neutrophil

b. Pinocytosis (cell drinking)
   Ex : Soluble proteins enters the cell

→ MECHANISMS

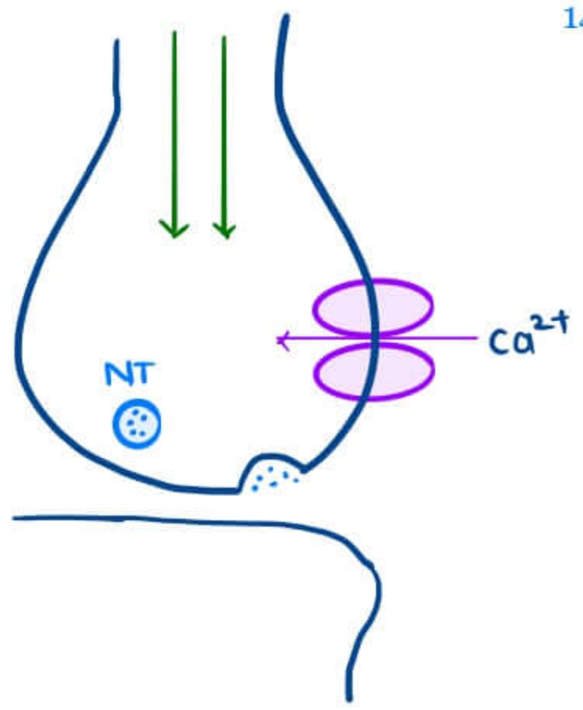
1. CONSTITUTIVE → Vitamin enters the cells
2. RECEPTOR MEDIATED / CLATHRIN MEDIATED ENDOCYTOSIS
   - → In the fig.
     There is a pit i Receptor in the membrane
     CLATHRIN (fibrillar protein) present in the pit
   - → Ex : LDL Entry into steroidogenic cells

3. CAVEOLIN MEDIATED ENDOCYTOSIS (POTOCYTOSIS)
   - → Ex : Folate entry into cells

2. EXOCYTOSIS (CELL VOMITING)

→ Reversed pinocytosis (if liquid)

→ 2 types



a. CONSTITUTIVE EXOCYTOSIS

→ Ex: Mucus secretion

Ig secretion by plasma cell

b. REGULATED EXOCYTOSIS

→ Ex: (i) Neurotransmitter secretion at synapse

(ii) Hormone secretion

All types of EXOCYTOSIS need increased intracytoplasmic ca^{2+} EXCEPT

1. PTH Secretion
2. Renin Secretion by JG CELLS

TRANSPORT THROUGH THE MEMBRANE

1. OSMOSIS

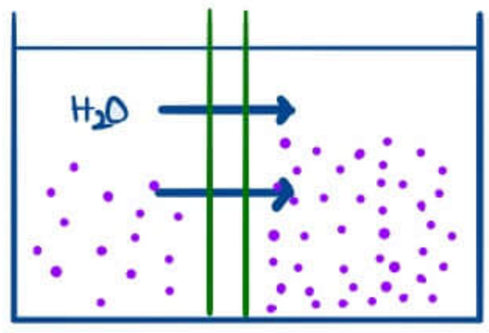
→ H_2O moves from low solute to high Solute concentration

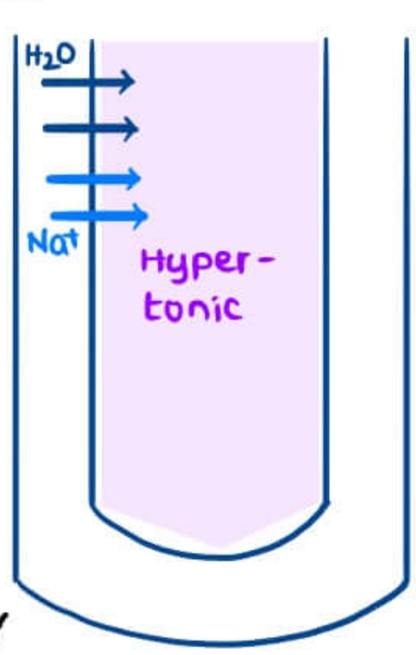
→ Bulk flow or solvent drag protein

→ Water moves in bulk & it drags Na^+ along ī it

→ occurs in

1. CSF absorptⁿ
2. Capillary filtration
3. Descending limb of LH





OSMOSIS

OSMOLARITY → No. of solute / solution in ltr

OSMOLALITY → Mass of Solute / Kg of water

Temperature will influence osmolarity NOT OSMOLALITY

SERUM OSMOLALITY

$$[2.1 \times Na^+] + \left[\frac{\text{Glucose}}{18}\right] + \left[\frac{\text{BUN}}{2.8}\right]$$

→ osmolality includes all solutes

TONICITY → NON PENETRATING SOLUTES ARE CONSIDERED, because

→ they donot cross membrane easily & remains unequal on either side of the membrane & cause movement of H_2O resulting in change in cell size

→ UREA → INEFFECTIVE OSMOLE, NOT CONSIDERED FOR TONICITY

→ Urea permits the membrane very easily & very rapidly it reaches equilibrium. It will not cause movement of water

Q Red cell volume → 100 μ^3, IC tonicity → 300 mosm/L, placed in a solutn c osmolarity of 200 mosm/L, final red cell volume?

A

$$\Pi_i V_i = \Pi_F V_F$$

$300 \times 100 = 200 \times V_F$

$30000 = 200\ V_F$

$V_F = 150\ \mu^3$

Π_i → initial osmolarity
V_i → initial volume
Π_F → final osmolarity
V_F → final volume

Q FICK'S LAW OF DIFFUSION, the rate of simple diffusion is not related to or not proportional to

a. Thickness
b. $C_1 - C_2$
c. Temperature
d. Surface Area

Q Aspirin entry into parietal cell occurs by

a. Simple diffusion
b. facilitated diffusion
c non ionic diffusion
d Translational diffusion

2. DIFFUSION

→ Passive transport (no ATP needed)
→ net effect → down hill transport (High to low)

TYPES

a. SIMPLE DIFFUSION

→ Kinetic energy drives the diffusion
→ Ex: Lipid soluble substances diffusion by Lipid Bilayer
Water soluble substances through channels

b. FACILITATED DIFFUSION → carrier mediated

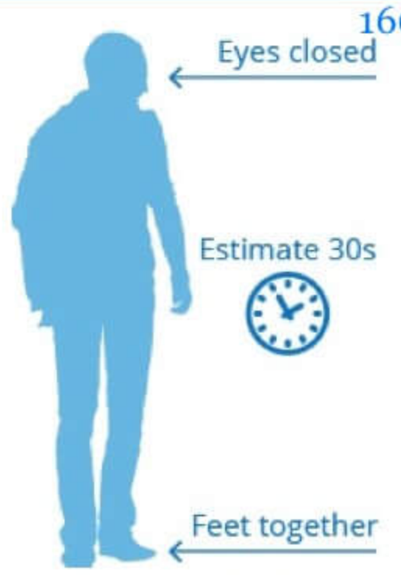
a. SIMPLE DIFFUSION

$$\text{FICK'S LAW (J) (Flux)} = \ominus\ DA \times \frac{\Delta C}{d}$$

D = Diffusion co-efficient
A = surface area
ΔC = concentratn gradient
d = thickness of membrane or diffusion distance

DISORDERS OF CEREBELLUM

→ Ataxia
→ post pointing
→ Loss of muscle tone
→ Intention tremor
→ Romberg Sign ⊕



Romberg test

ATAXIA

1. Sensory ataxia
   → ↑ eyes open → Patient can perform the test
   → ↑ eyes close → Patient can't perform the test

2. Cerebellar ataxia
   → ↑ eyes open/close → Patient can't perform the test

BASAL GANGLIA

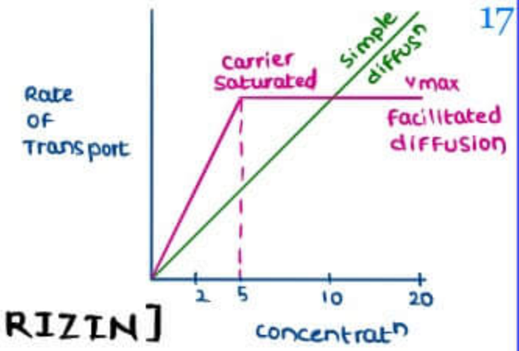
→ subcortical masses of grey mater
   1. caudate nucleus
   2. Putamen
   3. Globus Pallidus
      ↳ GP Externa
      ↳ GP Interna
   4. Substantia nigra
      ↳ Pars compacta
      ↳ Pars reticulata
   5. Subthalamic nucleus / Body of Luy's

→ Functionally
   → caudate nucleus } corpus striatum
   Putamen
   → Globus pallidus → Pallidum

→ Anatomically, on either side of Internal capsule
   → on one side → caudate nucleus
   → on another side → Lentiform nucleus
      ↳ Putamen + Globus Pallidus.

→ In WILSON'S DISEASE, hepato lenticular degeneratn dlt excess copper depositn

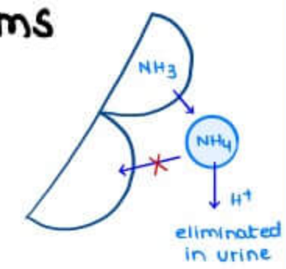
CHARACTERISTICS OF FACILITATED DIFFUSION



1. SATURABILITY [MICHAELIS - MENTON KINETICS]
2. SPECIFICITY
3. INHIBITION
   - → Glucose transport by GLUT inhibited by PHLORETIN [PHLORIZIN]
   - → GLUT [Glucose Transporter] TYPES
     1. GLUT 1 → constitutively expressed, ubiquitous
     2. GLUT 2 → Pancreatic β cell
        → Glucose exit the cell by GLUT 2
     3. GLUT 3 → constitutively expressed, predominant in Brain
     4. GLUT 4 → insulin dependent glucose transporter
        Present in muscle & fat
     5. GLUT 5 → Fructose transporter

NON IONIC DIFFUSION [DIFFUSION TRAPPING]

- → Seen in weak acids & weak bases
- → PRINCIPLE → NON IONIC FORMS ARE MORE DIFFUSIBLE THAN IONIC FORMS
- → EXAMPLES
  1. Aspirin entry into parietal cells
  2. NH_3 buffering in Kidney



3. ACTIVE TRANSPORT

- → Uphill transport (low to high)
- → needs ATP

A. 1° ACTIVE TRANSPORT

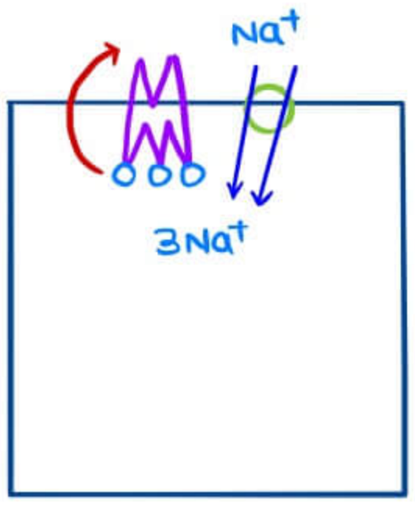
- → carried by pumps
- → ATP used directly
- → Ex: Na^+ K^+ Pump
  SERCA Pump

B. 2° ACTIVE TRANSPORT

- → achieved by carrier
- → ATP used indirectly

1° ACTIVE TRASPORT BY ATP

- → creates & widens the concentratn gradient for Na^+
- → potential energy stored in this concentratn gradient is utilized by carrier to carry 2 substances
  1. Na^+ → high to low
  2. Other substance → low to high



2° ACTIVE TRANSPORT TYPES

A. SYMPORT / CO - TRANSPORT → 2nd substance goes in the same direction

Ex: 1. SGLT

→ For Glucose entry into cells of GIT & KIDNEY

→ 3 types

$SGLT_1$ → carries 2 Na^+, 1 glucose

$SGLT_2$, $SGLT_3$ } carries 1 Na^+, 2 glucose

2. TRANSPORT OF Amino Acids

B. ANTIPORT or COUNTER TRANSPORT OR EXCHANGE → 2nd substance goes opp. to Na^+

Ex: 1. NCX (sodium - calcium Exchanger) → 3 Na^+ : 1 Ca^+
inside outside

2. $Cl^- - HCO_3^-$ Exchanger in Red cell membrane

→ Band 3 protein

→ Anion Exchanger type 1

All the 2° active transports are absolutely dependent on 1° active transport

REPERFUSION INJURY

MECHANISM

Myocardial Ischemia

↓

Na^+ K^+ pump fails

↓

All 2° active transport will fail
(NCX in heart fails)

↓

Ca^{2+} will accumulate in myocardial fibres

↓

REPERFUSION

$Na^+ - K^+$ PUMP

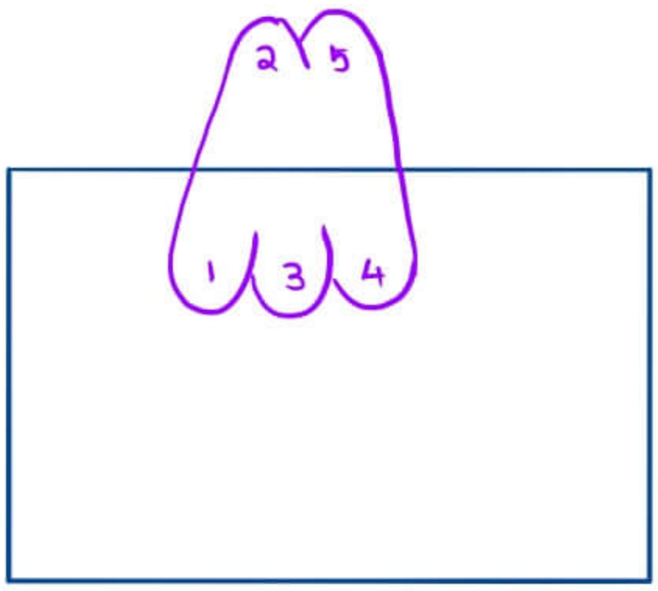
→ 1° active transport

→ has 3 sub units & 5 binding sites

→ discovered by JENS SKOV

→ present in all the membranes & active all the times

→ 3 SUB UNITS → α → catalytic , β & γ → supportive



2 = K^+ binding site

5 = Ouabain binding Site

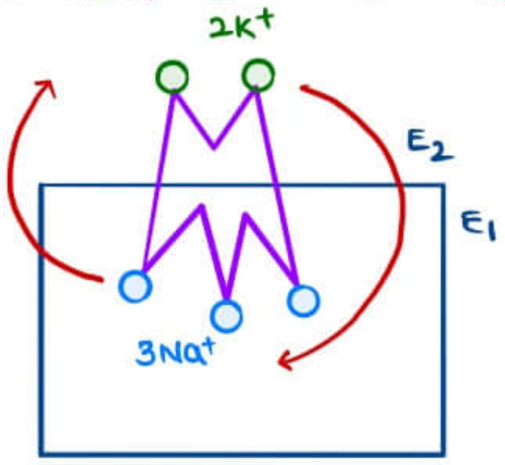
1 = Na^+ binding site

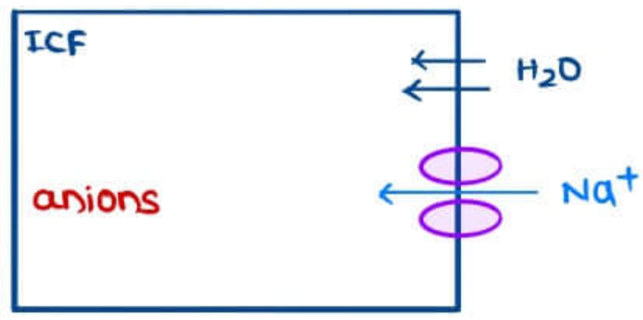
3 = ATP binding site

4 = Phosphorylat^n site

→ Hypokalemia potentiates Digitalis toxicity

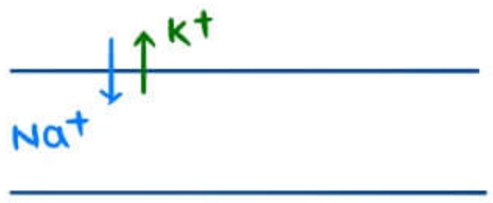
→ ACTIVITY OF $Na^+ - K^+$ PUMP





→ FUNCTIONS

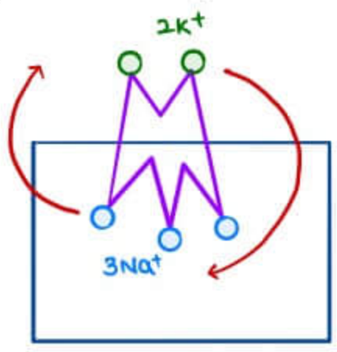
1. Opposes the Donnan Equilibrium d/t excess of impermeant anions
2. Regulates the cell volume
3. Involved in recharging of excitable cells



4. Involved in process of basal metabolic rate or basal energy exchanger

BMR / BEE

→ 40% [for entire body]
70% [for neuron]



5. Electrogenic

→ Contribute to negative charge on membrane

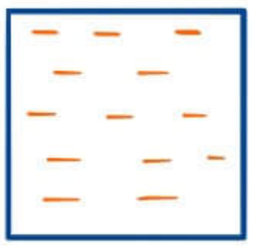
STIMULATOR			INHIBITORS
Aldosterone	→ ↑	$Na^+ K^+$ pump	Digitalis
Thyroid	→ ↑	$Na^+ K^+$ pump	Diuretics
Insulin	→ ↑	pump activity	Dopamine in Kidney
Catecholamines	→ ↑	pump activity	DNP

STRUCTURAL CONFIGURATION OF TRANSPORT PROTEINS

7	GPCR
6	CONNEXON
5	LIGAND GATED CHANNELS / CYS - LOOP RECEPTORS
4	VOLTAGE GATED CHANNELS
3	G - Protein , ENaC , Na^+ / K^+ Pump
2	Integrins

NERVE MUSCLE PHYSIOLOGY

MEMBRANE POTENTIAL

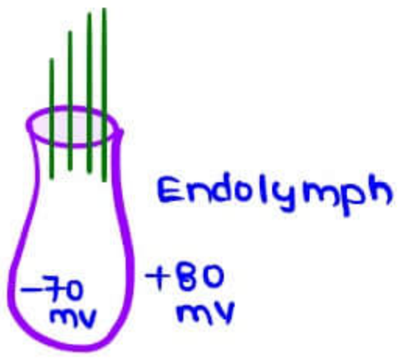


RMP (RESTING MEMBRANE POTENTIAL)

MEMBRANE POTENTIAL

→ dlt excess negative charges which create negative potential

Red cells, Epithelial cells	→	− 8 to − 20 mV
Smooth muscle cells	→	− 35 to − 45 mV
Pacemaker cells − SA Node	→	− 55 to − 65 mV
Nerve	→	− 70 mV
Skeletal Muscle & purkinje fibres	→	− 90 mV



→ All these cells are surrounded by same ECF (potential is '0')

EXCEPT HAIR CELLS IN COCHLEA

→ surrounded by Endolymph (ECF)

but it resembles ICF b'coz it has high K^+ concentration

It's potential taken as + 80 mV → ENDOCOCHLEAR POTENTIAL

Transmembrane voltage difference is 150 mV (highest in body)

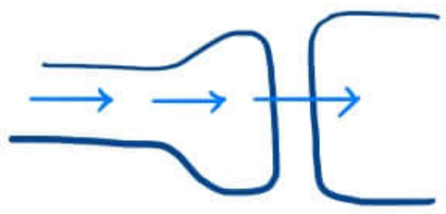
RMP (RESTING MEMBRANE POTENTIAL)

→ applied only for nerve & muscle (excitable tissues)

RMP for nerve → − 70 mV

RMP for muscle → − 90 mV

→ purpose of membrane excitation is for signal transmission from neve to muscle



→ ORIGIN

IN MUSCLE → − 90 mV

EQUILIBRIUM POTENTIAL FOR AN ION

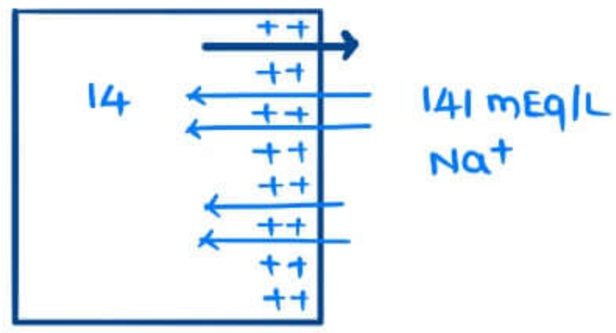
→ As Na^+ move in, concentratⁿ gradient will become narrow

→ it carries lot of positive charges inside, an electrical gradient will be created in opposite direction

→ concentratⁿ gradient & electrical gradient will balance each other & no net movement Na^+ ion occurs

→ NERNST EQUATION → calculates individual equilibrium potential of an ion

$$EMF\,(mV) = \pm\ 61 \times \log \frac{C_1}{C_2}$$

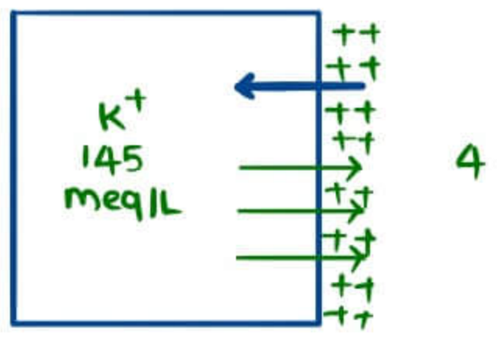


EMF (Na) = $\pm$ 61 x Log $\frac{141}{14}$

= $\pm$ 61 x log 1

= $\pm$ 61 x 1

= + 61 mV



EMF $_{(K^+)}$

→ Electrical gradient & concentratⁿ gradient will be equal
→ no net movement of K^+
→ Concentratⁿ gradient narrows, as ion move from higher to lower concentratⁿ, at the same time electrical gradient is created in opp. directⁿ

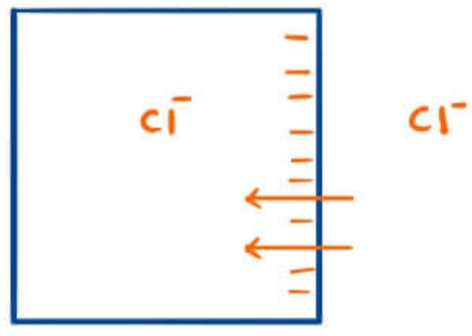
→ EP for K^+ = − 94 mV

IF both Na^+ & K^+ reached equilibrium, & RMP = − 90 mV, it implies
→ K^+ is greater contributor for RMP
→ because membrane is more permeable for K^+ as compared to Na^+

EP for Cl^- = − 89 mV
→ closest to RMP
→ Which implies, When muscle is resting RMP will be − 90mV, Cl^- will be in equilibrium
→ When RMP is equal to EP of an ion, ion movement will not be great Ion remains in equilibrium

GOLDMAN'S CONSTANT FIELD EQUATION (GHK EQUATION)
→ When all 3 ions, Na^+, K^+, Cl^- move and reach equilibrium, charge will be calculated by GHK Equation

→ dependent on
concentratⁿ gradient of 3 ions
membrane permeability
Polarity of charge



→ GOLDMANN'S EQUATION

$$EMF\ (mv) = \pm\ 61 \times \log \left[\frac{(C_{Na_o^+} \times P_{Na^+}) + (C_{K_i^+} \times P_{K^+}) + (C_{Cl_o^-} \times P_{Cl^-})}{(C_{Na_i^+} \times P_{Na^+}) + (C_{K_o^+} \times P_{K^+}) + (C_{Cl_i^-} \times P_{Cl^-})} \right]$$

i → inside
o → outside

→ − 86 mV (majority by K^+ diffusion)
− 4 mV (contributed by $Na^+ - K^+$ pump)
− 90 mV

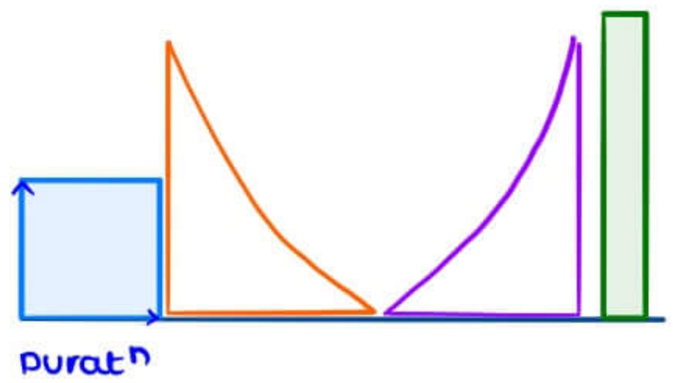
RMP of Nerve	→	− 70 mV
EP for Na^+	→	+ 60 mv
EP for K^+	→	− 90 mv
EP for Ca^{++}	→	+ 129 mv
EP for H^+	→	− 23 mv
EP for HCO_3^-	→	− 25 mv

EXCITATION & ACTION POTENTIAL

ACTION POTENTIAL

MEMBRANE EXCITATION

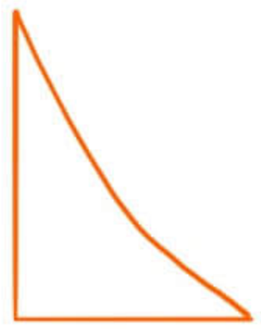
STIMULUS − PROPERTIES



1. INTENSITY
   → Should be rapidly rising
   → Slowly rising stimulus intensity result in membrane ACCOMODATn

2. DURATION
   → Should be OPTImum enough
   → 2 BEST TYPES
      1. RECTANGULAR PULSE
         → Best stimulus
         → Intensity rising rapidly
         → duration is good

      2. EXPONENTIAL PULSE
         → Intensity rises rapidly & then declines
         → duration is good



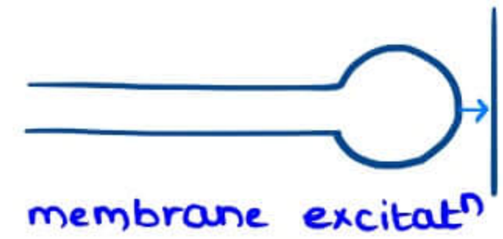
RHEOBASE → minimum strength of stimulus that can excite the tissue

CHRONAXIE → Time taken by tissue to excite, when the stimulus strength is double the Rheobase

→ measure of excitability

→ ↑ing order of chronaxie / ↓ order of excitability

1. Myelinated nerve (least chronaxie, most excitable)
2. Unmyelinated nerve
3. Skeletal muscle
4. Cardiac muscle
5. Smooth muscle

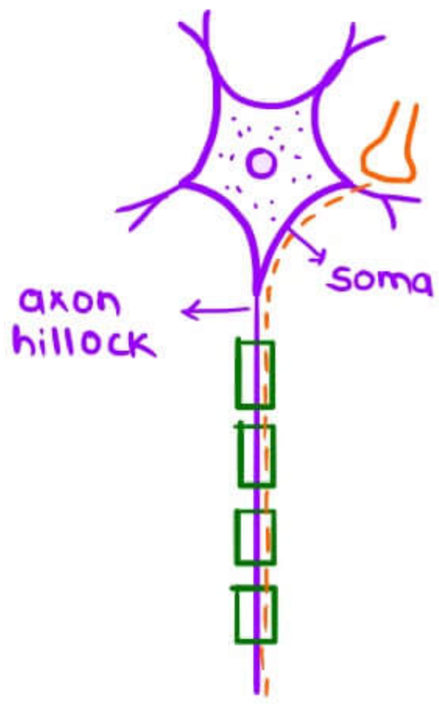


MEMBRANE EXCITATION & IMPULSE TRANSMISSION

MEMBRANE EXCITATION

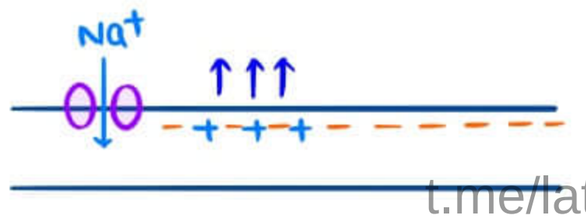
→ occurs in 2 forms

1. Electrotonic conduction
2. Action Potential Propagation



ELECTROTONIC CONDUCTION / GRADED CONDUCTION

→ direct & passive charge spread from point of entry

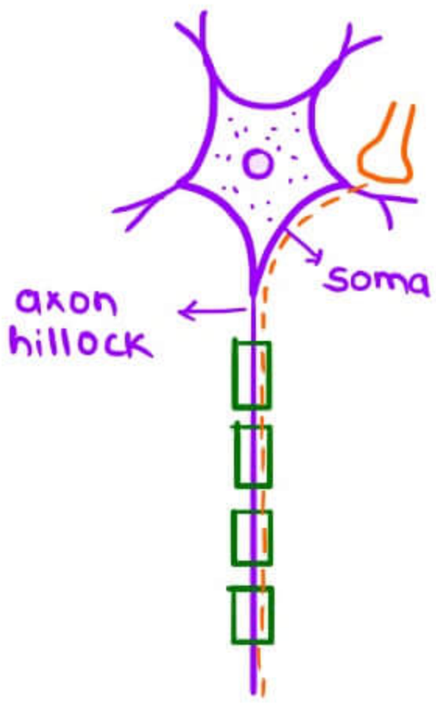


→ charges leak because of membrane capacitance

Strength of signal will become weak

Such transmission is called as DECREMENTAL CONDITION

→ carry impulse only for 10 mm length



From dendrites to axon hillock,
charges travel by electrotonic conductn

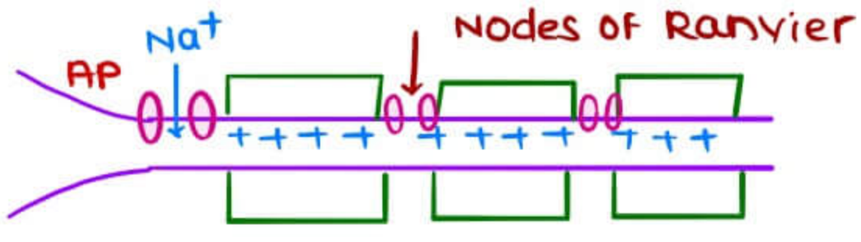
AXON HILLOCK

→ Initiate AP because of enough no. of Na^+ channels & Lower threshold

NODE to NODE

→ Node to node conduction is ELECTROTONIC

→ SALTATORY CONDUCTION → long distance conduction from one node of Ranivier to other



→ Electrotonic conduct^{n} is less decremental

→ as the overlying myelin sheath decreases the capacitance & ↑ the resistance

$$R \propto \frac{1}{C}$$

→ occurs in Retinal cells

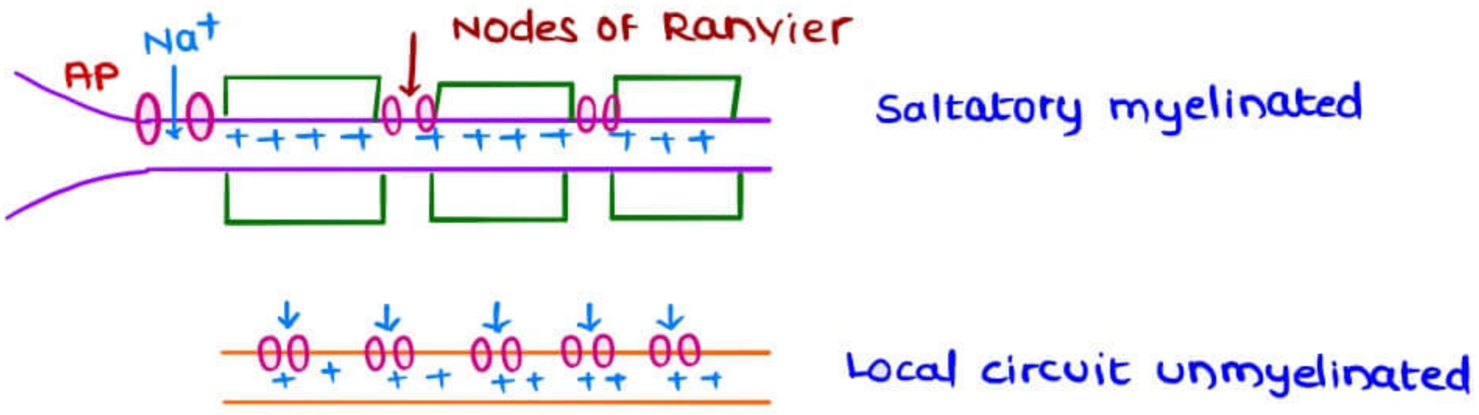
Rods

↓

Bipolar cells

↓

Ganglia



MYELINATED NERVE → Na^{+} channels present at nodes of Raniver
NO Na^{+} channels beneath myelin sheath
→ so, Na^{+} will travel lot of distance → SALTATORY CONDUCTION

UNMYELINATED NERVE → Na^{+} channels are located at regular distance
→ LOCAL CIRCUITE FLOW

SALTATORY CONDUCTION – ADVANTAGES

1. Faster (slower in unmyelinated nerve fibres)
2. Less energy consumed (Which is required for recharging)
   → Recharging occur only at nodes of Ranvier by $Na^{+}K^{+}$ pump (at every point in unmyelinated nerve fibres)

MULTIPLE SCLEROSIS

→ demyelinating disease of neuron
→ After demyelinat^{n}, CONDUCTION BLOCK occurs
   → Na^{+} channels are relocated since there was no myelin sheath
   Leakage of charges results in conduction block

   → Internodal distance → 1 - 3 mm
   Electronic conduction occur only for 10 mm
   MS involves >3 nodes, resulting in conduct^{n} Block

→ Hot bath ↑ conductⁿ Block

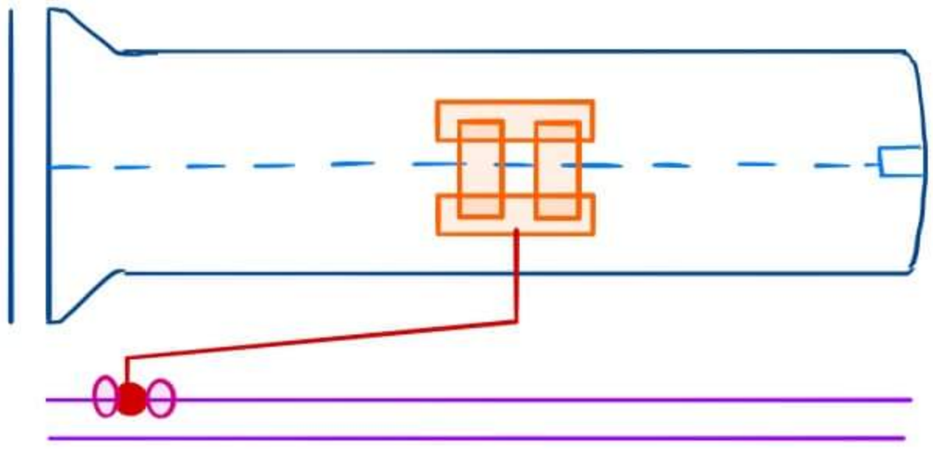
Reason – ↑ in leakage of charges dlt ↑ in membrane capacitance

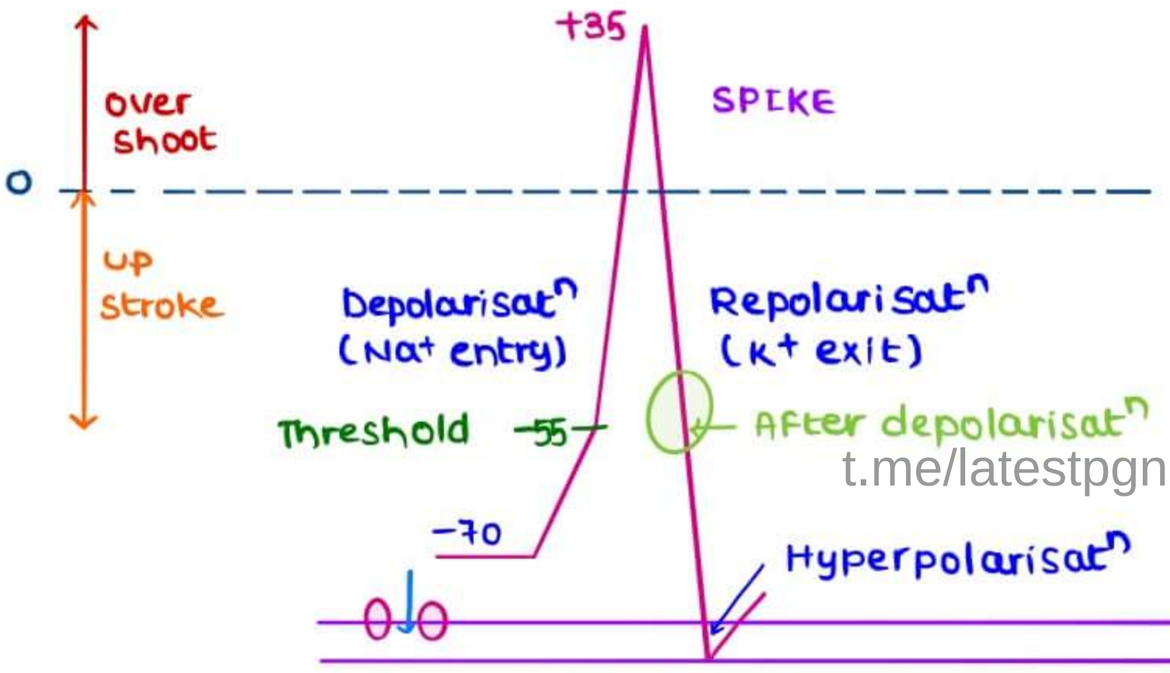
ACTION POTENTIAL

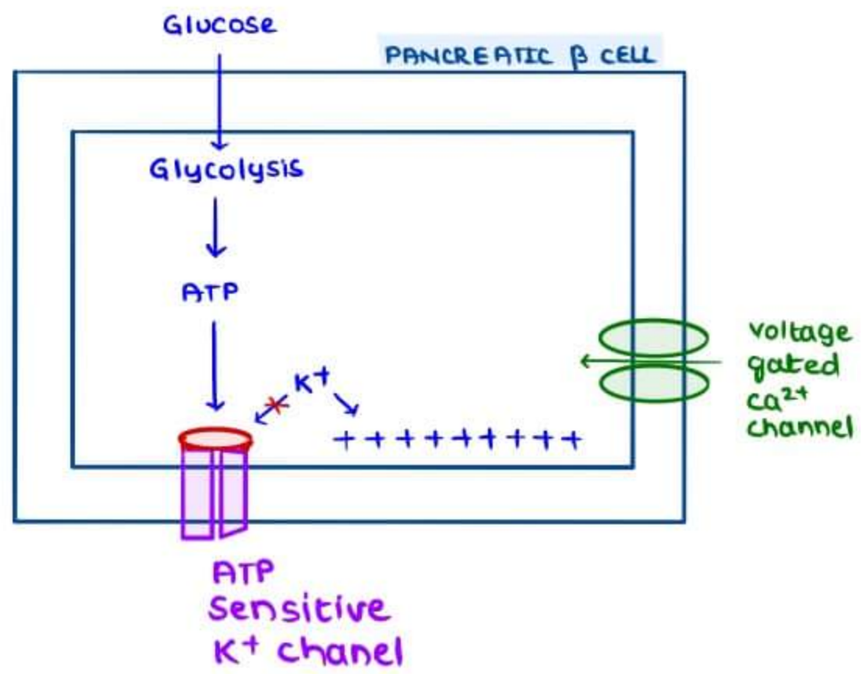
→ self regenerative process
→ self propagated process
→ non decremental conductⁿ
→ obeys all or none law
→ not graded

PHASES OF AP

→ Recorded by cathode ray oscilloscope
→ Depolarisation is dlt Na^+ Entry
Repolarisation is dlt K^+ Exit

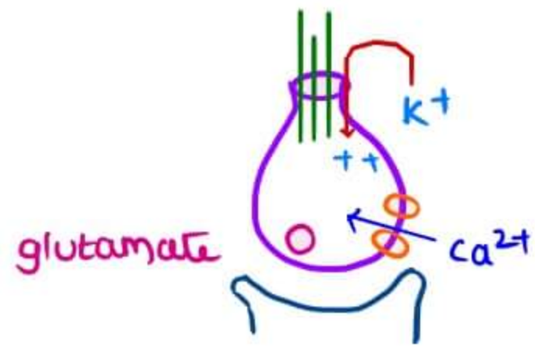






→ OTHER WAYS OF DEPOLARIZATION

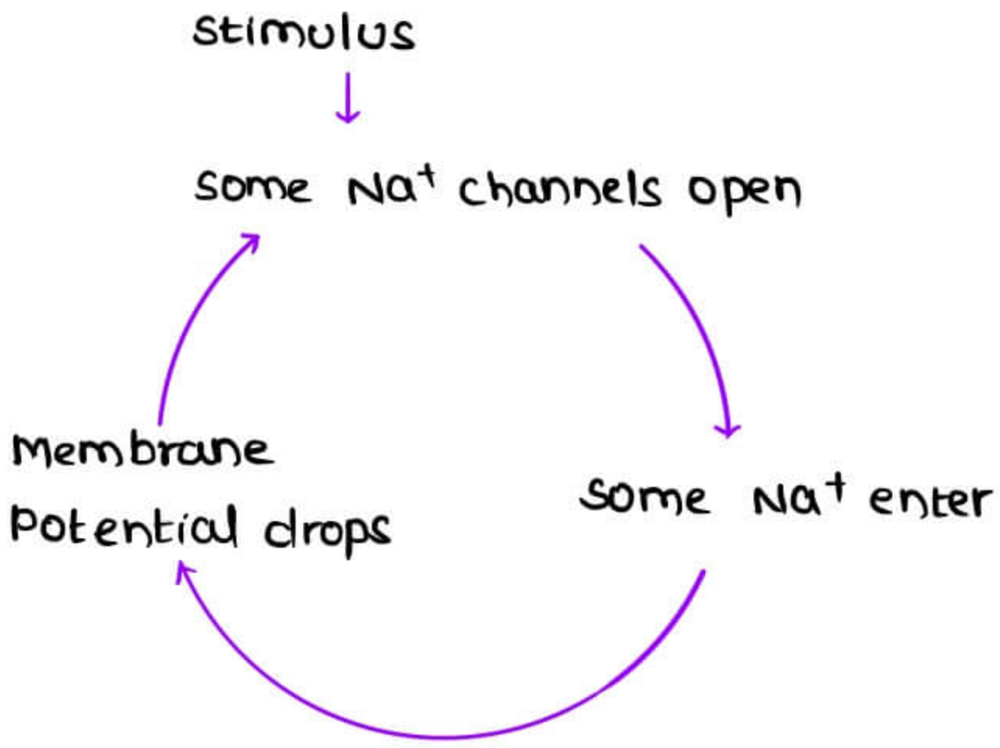
1. Ca^{2+} entry in heart
2. K^+ entry in hair cell
3. Accumulation of K^+ inside the membrane
   Ex: Pancreatic β cells



→ SPIKE → rapid rise & rapid fall of AP
AFTER DEPOLARISATⁿ → Slow down of repolarisation
HYPER POLARISATⁿ → Slow down of repolarisatⁿ & more negative

STAGES

1. DEPOLARISATION
   1. RMP to threshold
      → Positive feedback cycle involving Na^+ channel



2. THRESHOLD

→ Critical no. of Na^+ channels open

→ Massive instantaneous surge of Na^+ followed by closure of Na^+ channels

→ one single push at threshold, & closure of Na^+ channels will reach the potential + 35 mV, closure of Na^+ channels occur just above the threshold

→ IF threshold is reached, ACTION POTENTIAL occurs

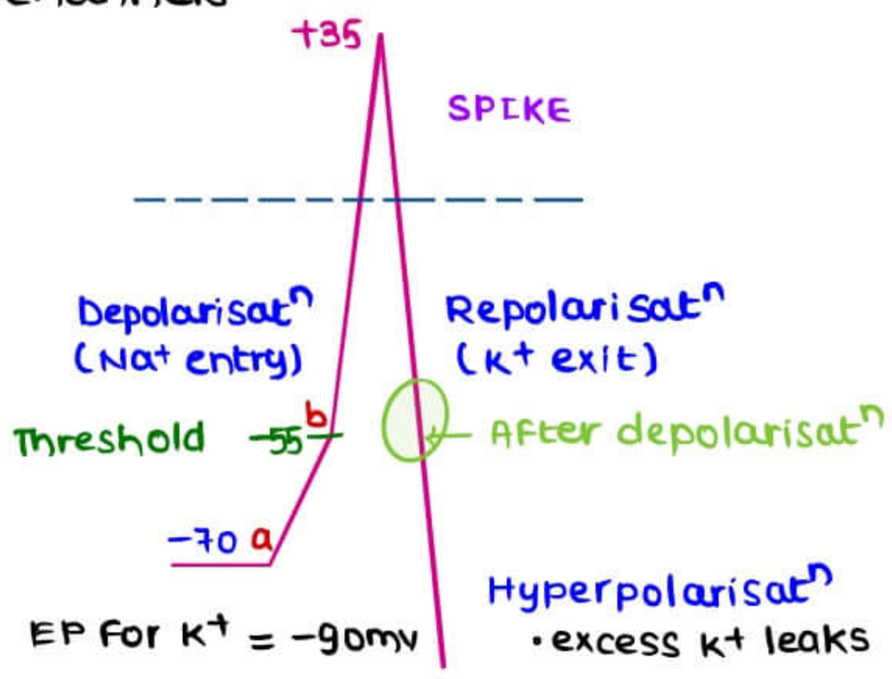
→ IF threshold is reached, & no spike potential occurs, reason is SLOWLY RISING STIMULUS INTENSITY

→ The opening of Na^+ channels slow membrane potential slow, at threshold critical no. of Na^+ channels will not open

→ So, no spike potential

BEHAVIOUR OF K^+ CHANNELS IN REPOLARIZATION

→ K^+ exit starts in Lazy channels



AS EP FOR K^+ (-90 mV) is close to membrane potential (-70 mV), ion will not move much.

→ When membrane excited, Na^+ entry predominates over K^+ exit

→ Depolarisation is due to net influx of positive charges

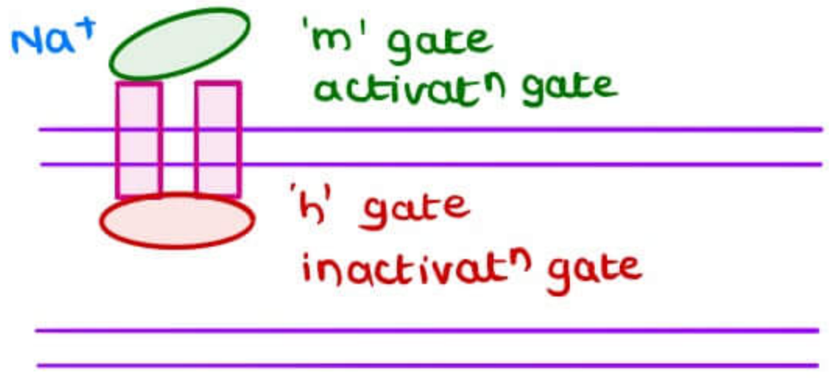
→ most diffusible ion in excited membrane is Na^+

GATING BEHAVIOUR OF Na^+ & K^+ CHANNELS

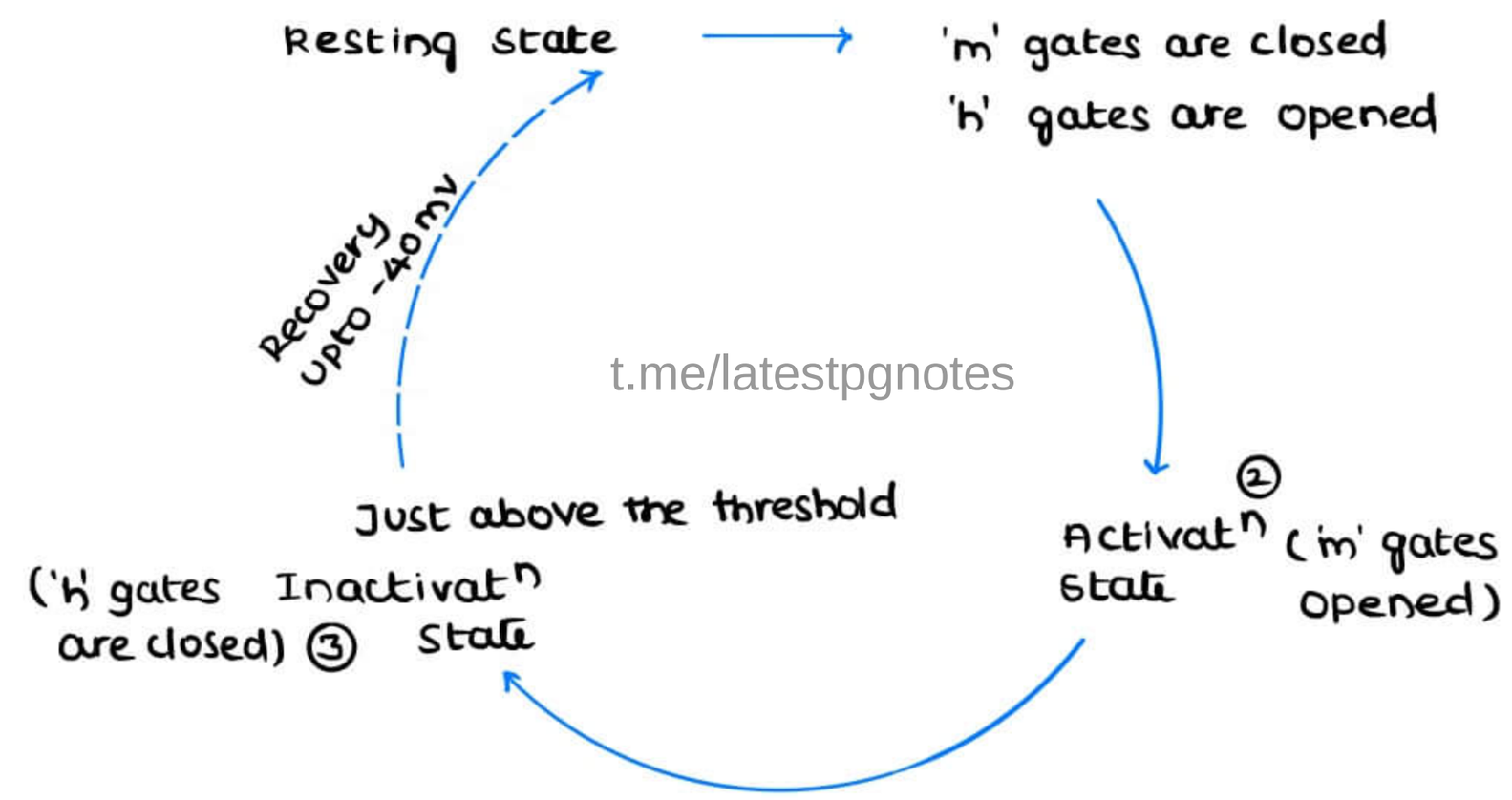
Na^+ CHANNELS

→ 2 gates, 3 possible states
(Refractory period, MOA of LAs)

→ 2 gates
'm' gate (activation gate)
'h' gate (inactivation gate)



→ 3 possible states
① RMP



At +35 mV,
→ K^+ exit gathers momentum, repolarisation takes place
→ then After depolarisatn (slow down of repolarisatn) occurs
→ then Hyper polarisatn occurs dlt delayed closure of K^+, excess K^+ leaks out, membrane will be −90 mV → hyperpolarization

→ Hyperpolarised membrane is difficult to excite
→ If recharging occur at the end of AP, membrane will become more negative, then membrane again go back to −70 mV (original) dlt leaky Na^+ channels & also recharging by Na^+ K^+ pump

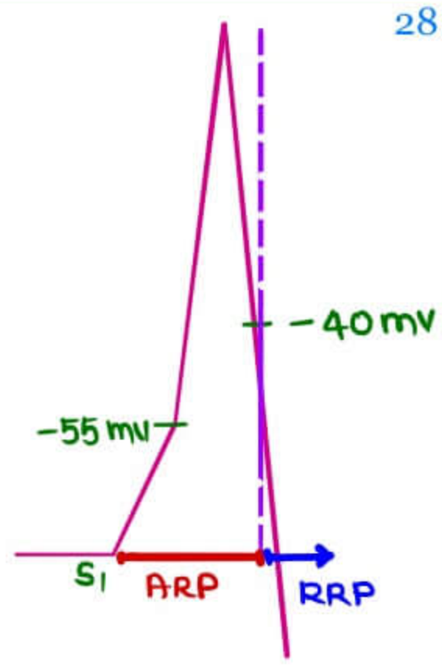
MECHANISM OF ACTION OF LOCAL ANESTHESIA

→ LA has low affinity for resting state, high affinity for inactivated state of Na^+ channels
→ LA bind to & prolong the inactivated state of Na^+ channels

BASIS FOR REFRACTORY PERIOD

ABSOLUTE REFRACTORY PERIOD

→ The time period after stimulus, during which another stimulus can't stimulate for another time



RELATIVE REFRACTORY PERIOD

→ A normal stimulus can't excite tissue, stronger than normal stimulus can generate another action potential

→ SIGNIFICANCE

→ It determines the FREQUENCY OF Stimulation

$S_1 \longrightarrow S_2 \longrightarrow S_3 \longrightarrow$

→ highest frequency time = 60/min

→ Longer the refractory period, frequency of stimulation will not be higher

EFFECTS OF IONS

(Changes in ECF concentration)

1. Na^+

→ Affect action potential

→ Ex:

HYPONATREMIA

→ amplitude of AP will decrease

→ In severe condition, conduction may stop completely

HYPERNATREMIA

→ more conduction → more action potential

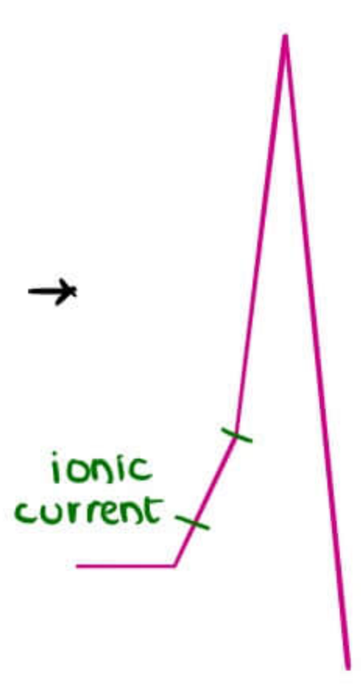
2. K^+

→ RMP will be affected more

→ HYPOKALEMIA → membrane will be hyperpolarised

HYPERKALEMIA → concentration gradient will narrow → membrane will be depolarised

→ less excitable



3 Ca^{2+}

→ Ecf Ca^{2+} is necessary for stability of Na^+ channel gating

→ HYPOCALCEMIA (TETANY)

Na^+ channel gating unstable

↓

i faint stimulus

Na^+ channels open & remain activated

impulse sent to muscle

Sustained contractions → TETANUS

↓

TROUSSEAU'S & CHOVSTEK'S SIGN

↑

Tetanus (↑ sarcoplasmic Ca^{2+}) → ↑ contraction of muscle

NERVE

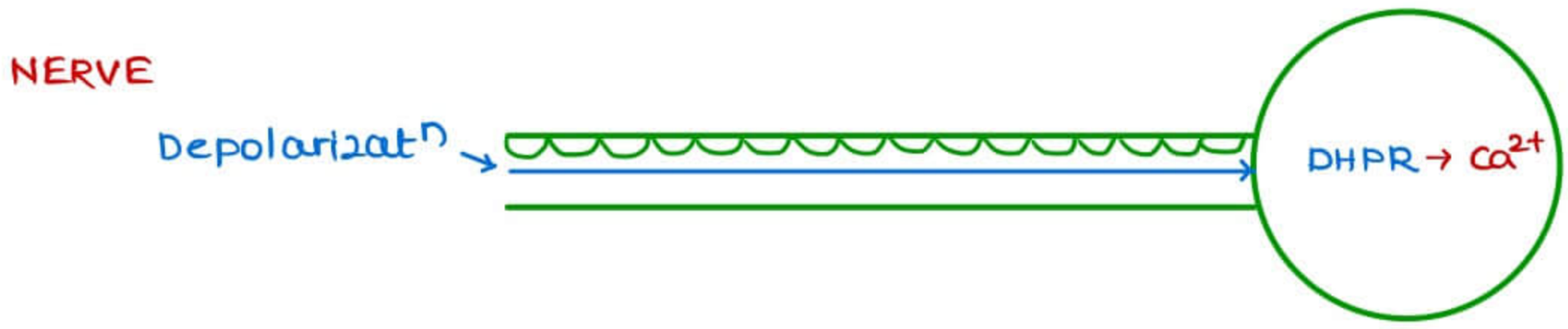
Q choose the correct one

a depolarisatⁿ leads to muscle contractⁿ

b repolarisatⁿ Leads to muscle relaxation

c Action potential Leads to muscle contractⁿ

d Action potential Leads to muscle contractⁿ & relaxation



DEPOLARISATION

→ It is a travelling impulse, resulting in muscle contractⁿ

→ Relaxatⁿ occurs if one more depolarisation does not come in

→ Ca^{2+} pumped back resulting in relaxatⁿ

REPOLARISATION

→ do not travel, occurs by point by point

→ recovery from excitatⁿ

CLASSIFICATION OF NEURON

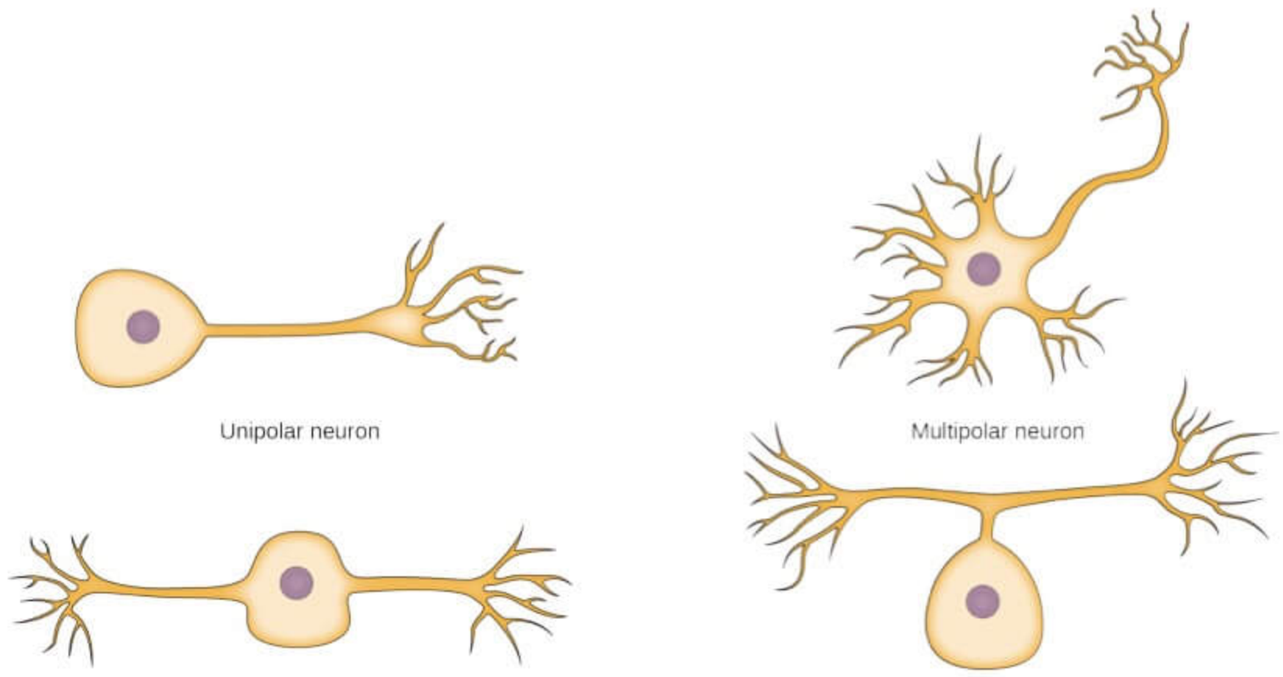
→ Para sympathetic System

→ pre ganglionic nerve is more

→ post ganglionic nerve is less

→ anaxonal neuron

1. MULTI POLAR → Brain & cerebral cortex
2. BIPOLAR → Retina , olfactory neuron
3. PSEUDO UNIPOLAR → Nerve cell in dorsal root ganglion



→ ANAXONAL NEURON → Post ganglionic parasympathetic neuron
→ Ex: Anacrine cell in Retina

→ NO new neurons formed after birth EXCEPT for OLFACTORY NEURONS

CLASSIFICATION OF NERVE FIBRES

6 TYPES	CONDUCTION VELOCITY
Diameter decreases ↓ Aα, Aβ, Aγ, Aδ, B → myelinated C → unmyelinated	1. DIAMETER → Smaller the diameter → more axoplasmic resistance → Lesser is the conduction velocity 2. MYELINATION → conduct^{n} velocity is faster in myelinated nerve fibres

→ In myelinated nerve fibres, conductional velocity is proportional to 6 times the diameter
→ In unmyelinated fibres, conductional velocity $\propto \sqrt{\text{Diameter}}$

→ MYELINATION IS BY
1. In PNS (20:1) → Schwan cells
2. In CNS (1:20) → Oligodendrocytes

NUMERICAL CLASSIFICATION

A_α	→	Ia
A_β	→	Ib
A_γ	→	II
A_δ	→	III
C	→	IV

ERLANGER & GASIER CLASSIFICATION

A_α → proprioception & α - motor neurons
fastest conduction for voluntory movements

A_β → touch & pressure

A_γ → γ motor neuron to muscle spindle
maintains excitability of muscle spindle
EX: JENDRASSIK'S MANEUVER

A_δ → Fast pain & temparature

B → Preganglionic Autonomic nerve fibres

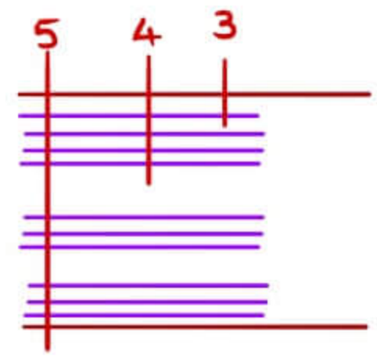
C → Somatic → slow pain
Autonomic → Post ganglionic Sympathetic

→ Opioids acts on type C fibres, relieve slow pain

INJURY TO NERVE FIBRES

	most susceptible
Pressure	A
Hypoxia	B
Local anesthesia	C

SUNDERLAND'S			SEDAN'S
1°	→	mild pressure, hypoxia	NEUROPRAXIA
2°	→	severe & sustained pressure	
3°	→	single axonal transectⁿ	AXONOTMESIS
4°	→	Nerve Fascicles are disrupted	NEUROTMESIS
5°	→	Nerve trunk transection	



WALLERIAN DEGENERATION

→ Repair OF nerve fibres after injury
→ seen after 5 th degree injury When entire nerve trunk damaged
→ changes seen in distal stump or proximal stump near the nodes OF Ranvier

Wiㅌ in 24 - 48 hrs	→	chromatolysis
Upto 3 days	→	distal stump still functional
6 th day	→	Axonal degeneration
10 th day	→	Myelin degeneration
15 th day	→	Repair
		→ Sprouting
		→ schwann cell proliferatⁿ
80 th day	→	Repair completed

NEUROMUSCULAR JUNCTION

→ Ach vesicles will be synthesized in Nerve cell body

→ Ach synthesized locally in nerve terminal

→ NICOTINIC RECEPTOR CHANNEL → non - specific cation channel

→ At - 90 mV, IF membrane excitation allowed or Na^+ & K^+ both to move, then Na^+ entry is much larger, it dominate K^+

→ Net influx of positive chargers → DEPOLARIZATION

I IMPULSE

↓

60 vesicles of Ach

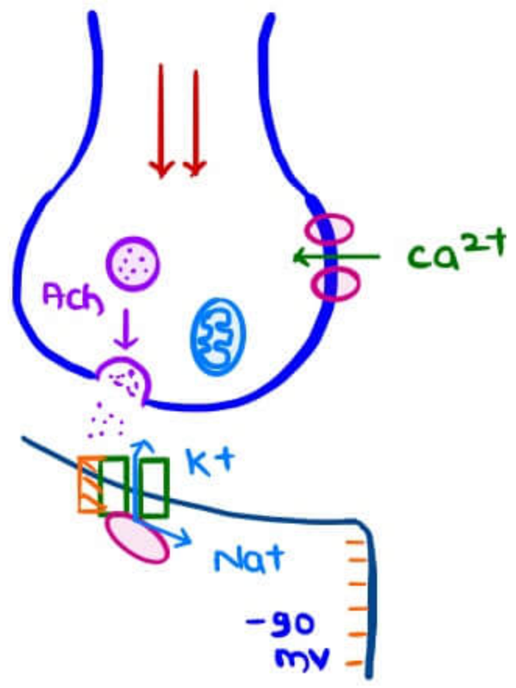
(Each vesicle contain 10,000 molecules)

↓

Localized depolarizat^n of 40 mV

↓

results in END PLATE POTENTIAL (EPP)



EPP (END PLATE POTENTIAL)

→ amplitude is 40 mV,
depolarisation reach threshold → AP → contract^n

→ Graded potential, forerunner of Action potential (AP)

EPSP (EXCITATORY POST SYNAPTIC POTENTIAL)

→ developed in CNS synapses

→ Amplitude is 2, 3, 4 or 5 mV

→ multi EPSP will summate to create Action potential

MEPP (MINIATURE END PLATE POTENTIAL)

→ Even in resting conditions, small pockets of Ach released, creating MEPP

→ amplitude is microvolts

AUTONOMIC DISEASES RELATED TO Nm JUNCTION

→ Ca^{2+} channels → LAMBERT EATON DISEASE

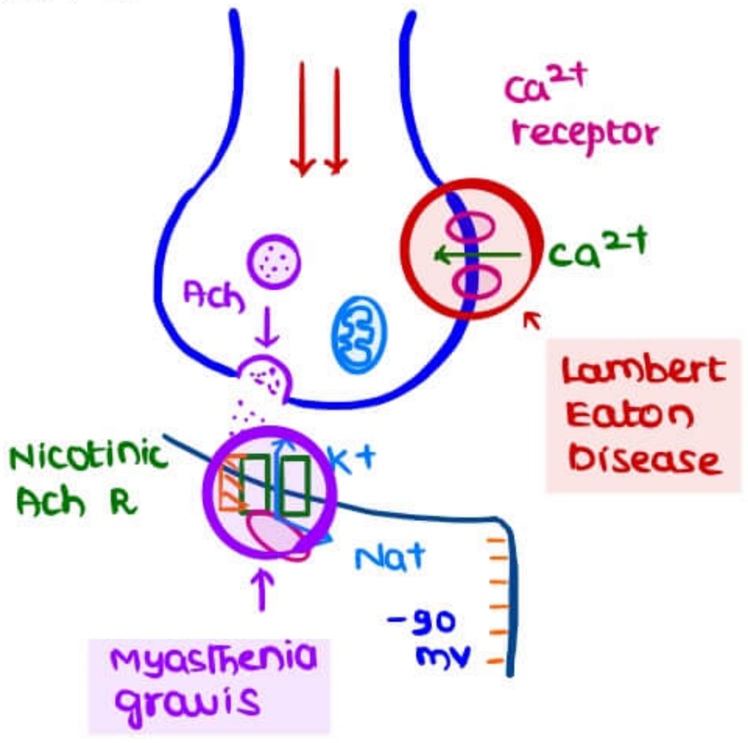
→ Nicotinic Receptor channel → MYASTHENIA GRAVIS

DIFFERENCE,

→ With repeated contractions, ↓ a continuous voluntary activity

→ Strength will worsen in Myasthenia gravis

→ Strength will increase in Lambert Eaton disease (d/t ca^{2+} accumulat^n)



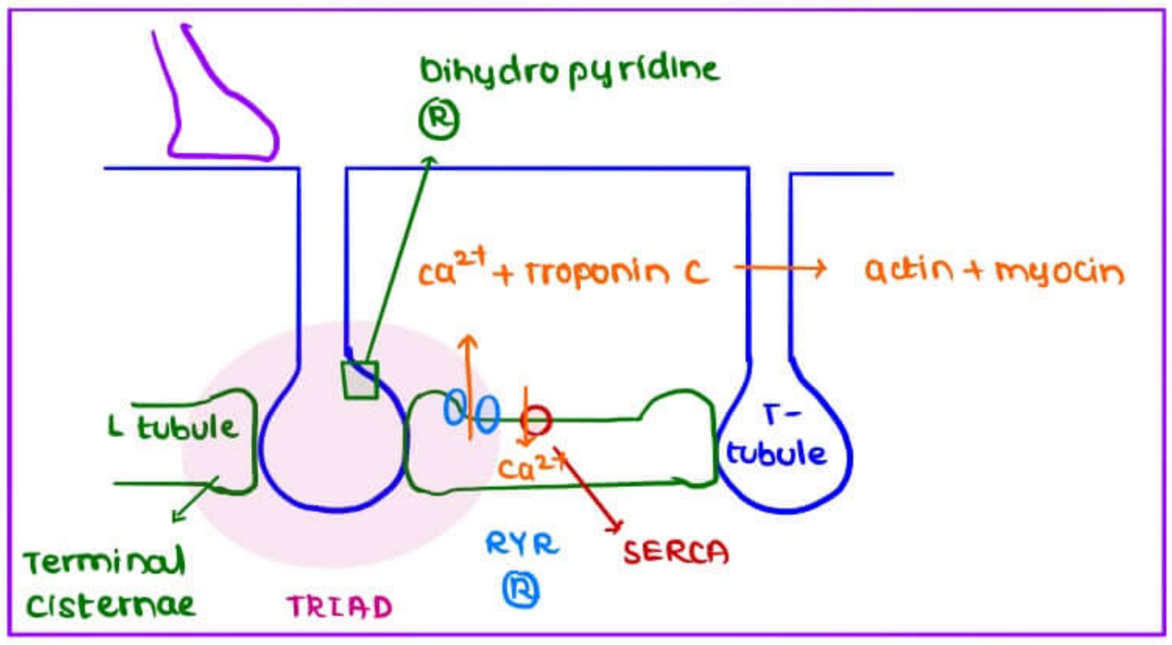
EXCITATION CONTRACTION COUPLING

→ Ca^{2+} said to be coupling agent

→ DHPR (DIHYDROPYRIDINE RECEPTOR)
- → has voltage sensor in muscle tissues
- → L type voltage sensitive Ca^{2+} channel

→ SARCOTUBULAR SYSTEM OF MUSCLE
- → EC coupling occurs in the sarcotubular system of muscle
- → In skeletal muscle → 2 T tubules | sarcomere +nt
- → In cardiac muscle → 1 T tubule | sarcomere +nt
- → coupling occurs in the TRIAD
  - → TRIAD → One end of T tubule & 2 ends of L Tubule on either side
  - → Expanded ends of L tubule are Terminal cisternae

→ RyR [RYANODINE RECEPTOR]
- → When depolarisatn arrives via T-Tubule into muscle, Sensed by DHPR, DHPR interacts & RyR → Ca^{2+} will be released into sarcoplasm.
- → Ca^{2+} combines & Troponin C, resulting in actin & myosin interactn → Muscle contractn
- → During Relaxatn, Ca^{2+} will be pumped out by SERCA pump
- → Genetic defects of RyR result in
  - Malignant hyperthermia
  - central core disease
  - Brody's disease



MALIGNANT HYPERTHERMIA

→ Before Sx, dlt administratn of Sch / halothane / Ether →
Sudden massive release of Ca^{2+} occurs →
results in excessive rhythmic contractn of muscle →
↑ muscle metabolism →
Generation of HEAT in the body →
causing TACHYCARDIA

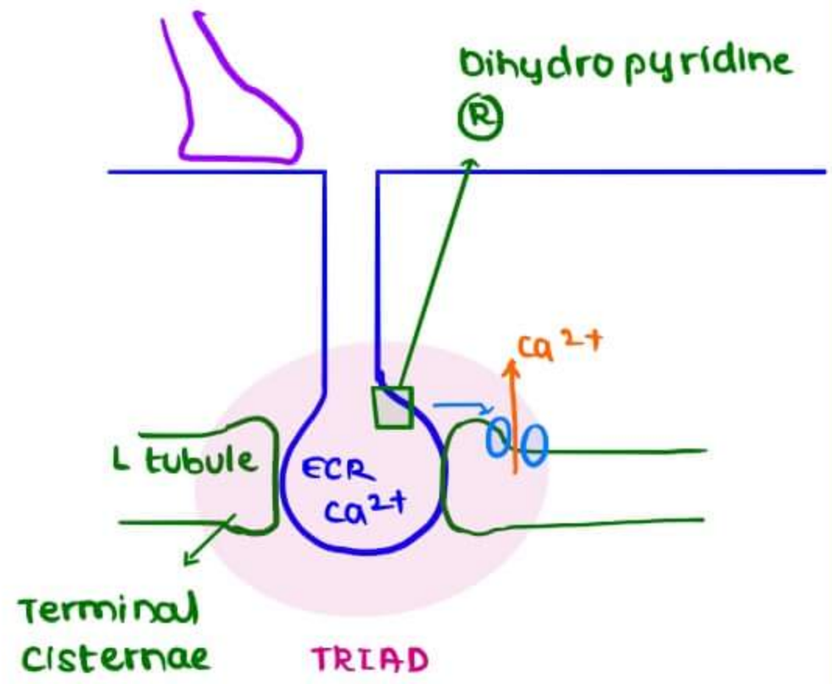
→ Rx by DANTROLENE Na (uncoupler of Excitatn & contractn)

CENTRAL CORE DISEASE

→ Excess Ca^{2+} release, mitochondria Studded ↑ Ca^{2+} & they will disappear
Leaving a cave in the cell

EC COUPLING IN CARDIAC MUSCLE

→ Depolarisatn sensed by DHPR →
DHPR itself Open →
ECF Ca^{2+} enters muscle →
Causes further Ca^{2+} release from RYR
↳ Ca^{2+} induced Ca^{2+} release



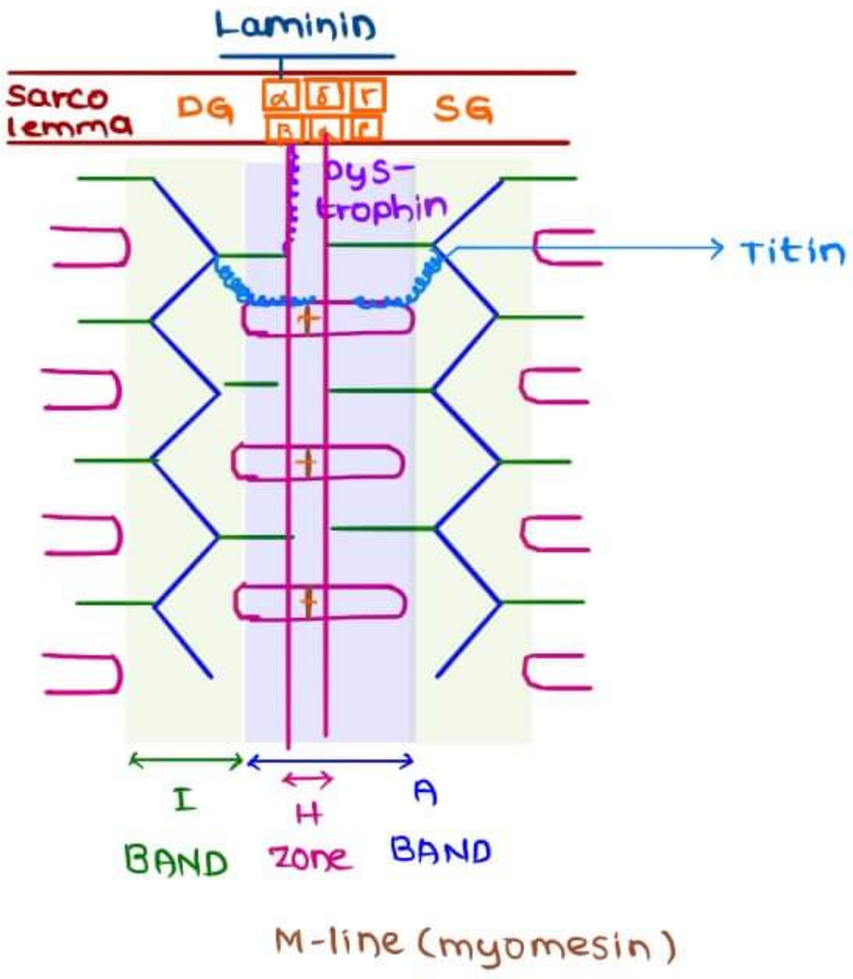
ECF Ca^{2+} influences cardiac contractility

→ Due to difference in the DHPR Receptor structure,
NIFEDIPINE, acts only on cardiac muscle contractility,
won't acts on skeletal muscle contractility

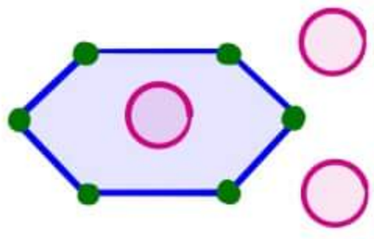
SARCOMERE

→ The distance b|w the @ Z-Lines → SARCOMERE
→ Normal resting length → 2 μ [L_i or L_{rest} = 2 μ]

→ STARLING LAW
→ Greater is the initial length of muscle, stronger is the contract^n
→ ↑ in physiological limits
L_o (Length optimum) → 2.2 μ (produce stronger contract^n)
L_{max} (Length maximum) → 3.7 μ



M-Line + adjacent light areas → PSEUDO H-ZONE



cross sectional view of Z-Line is Hexagonal
Each thick filament will be surrounded by 6 thin filaments
Each thin filament is surrounded by 3 thick filaments
THIN : THICK → 2 : 1

→ TITIN
  → anchored to Z-Lines & it enters thick filament
  → Largest human protein
  → Aids in alignment of thick filament to sarcomere
  → Genetic defects causes LIMB GIRDLE MUSCULAR ATROPHY

→ DYSTROPHIN
  → linked to thin filament & reaches Sarcolemma
  → Dystrophin linked to β dystroglycan in sarcolemma, inturn linked to α dystroglycan, 2 Dystroglycans linked to 4 Sarcoglycans → Total : 6
  → α Dystroglycan linked to LAMININ (ECM PROTEIN)
  → Tension generated by actin - myosin interaction is transported exterior by Dystrophin
  → Defect causes DUCHENNE MUSCULAR DYSTROPPHY

→ I - Band → thin filament on either side of Z Line
→ A - Band → Remaining part
  → contains thin & thick filaments
  → H-ZONE
    → present at the centre of A Band
    → have thick filament
    → In centre of H zone, M-Line is present
    on either side of M-Line, light areas are present

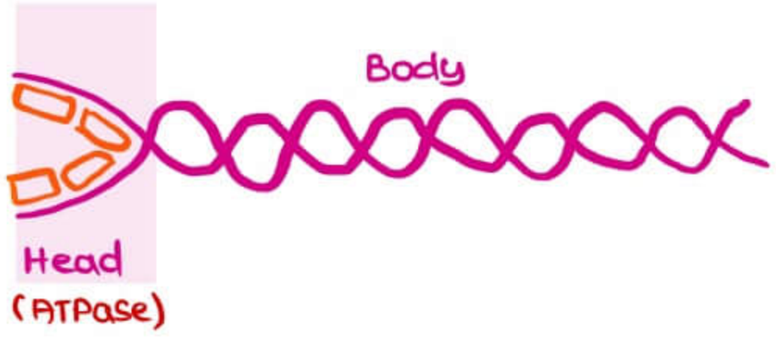
  → PSEUDO H - ZONE
    → Dark M Line & adjoining light areas on either side

DURING MUSCLE CONTRACTION

1. Sarcomere shortened
2. I Band shortened
3. A Band remains unchanged in width
4. H zone disappears
5. M Line becomes prominent
6. At 1.5 μ contractn length → CM Band appears
   At 1.25 μ contractn → CZ Band appears

MOLECULAR BASIS

1. THICK FILAMENT → made up of 500 myosin molecules



2. THIN FILAMENT

∓ Actin → Active site → covered by Troponin - Tropomyosin complex

1 Troponin
- C → affinity for Ca^{2+}
- T → affinity for Tropomyosin
- I → affinity for actin

1 Tropomyocin

MUSCLE CONTRACTION

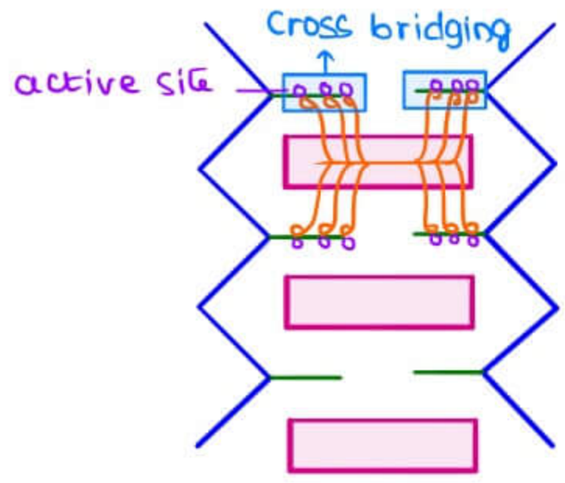
→ is d/t cross bridge cycling

→ Each thin filament active site interacts ε myosin head

DURING CONTRACTION

Tension α No. of active cross bridges

Shortening α spread of cross bridge cycling



ISOMETRIC CONTRACTION

→ only tension developed in muscle

→ no shortening, length remains same

→ no work is done

→ more heat liberated

ISOTONIC CONTRACTION

→ Tension remains same

→ muscle shortening occurs

→ Work is done only during isotonic contraction

ENERGETICS IN MUSCLE

During continuous muscle activity,

1. STORED ATP
   → 1st utilized
   → energise the muscle for 2-3 sec

2. CREATINE PHOSPHATE (PHOSPHAGEN SYSTEM)
   → LOHMANN REACTION

CREATINE PHOSPHATE ⟶ ADP ⟶ ATP ⟶ Utilized

   → Used for immediate synthesis & utilizatⁿ of ATP
   → for only 10 - 12 sec.

3. GLYCOGEN LACTIC ACID SYSTEM

→ next source of energy
→ anaerobic glycolysis for next 1 – 2 min

4. OXIDATIVE PHOSPHORYLATION

→ next source of energy
→ Longest serving energy source of ATP
→ for many hours

TYPES OF MUSCLE FIBRES

RED (Aerobic)	WHITE (Pale)
→ Slow oxidative	→ Fast glycolytic
→ high myoglobin content	→ Low myoglobin content
→ high mitochondria	→ Low mitochondria
→ High vascularity, capillary density	→ Low vascularity, capillary density
→ slow sustained	→ Lesser duration

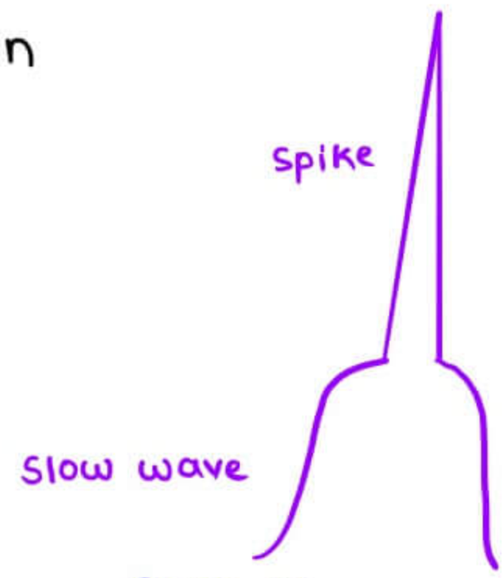
SMOOTH MUSCLE

→ involuntary muscle that lines viscera
→ 2 TYPES

1. SINGLE UNIT → Bunde of fibres work together as single unit
   → Ex: viscera

2. MULTI UNIT → Individual fibres, behave independently as separate units
   → Ex: Iris
   Arrector pili muscles of skin

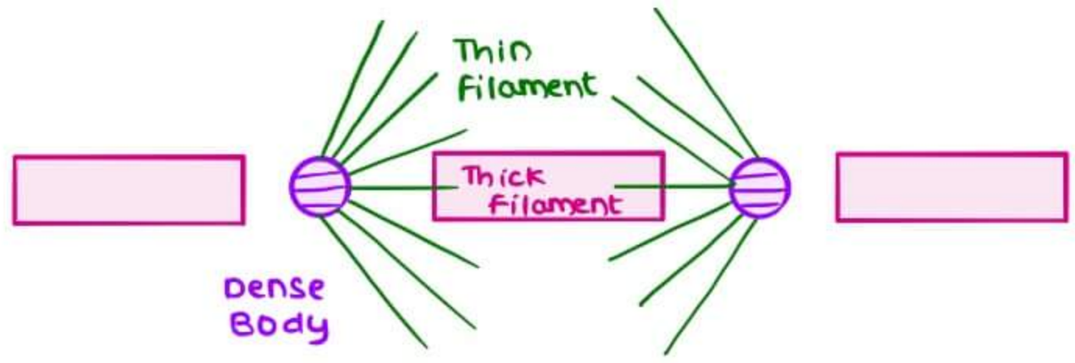
→ RMP
  → – 35 to – 45 mV
  → an oscillatory potential
  → There is electromechanical coupling in addition to pharmacomechanical coupling



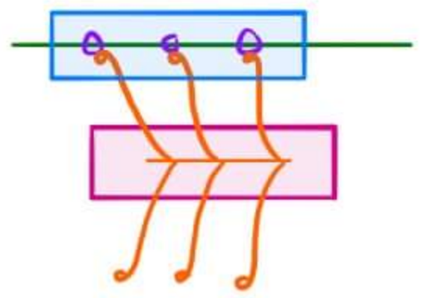
→ TUBULAR SYSTEM is rudimentary
→ CAVEOLAE → membrane depressions
  CAVEOLIN → protein a/w caveolae
→ Insted of 2 lines, DENSE BODIES are present
→ Thin : Thick filaments ratio → 15 : 1

SMOOTH MUSCLE CONTRACTION

Ca^{2+} + CALMODULIN
↓
activatⁿ OF MLCK
↓
Actin, myocin interactⁿ
↓
Contractⁿ



→ Thick filaments regulates the contractⁿ
→ LATCH - BRIDE PHENOMENON shown
  → After a certain time of cross bridge cycling, cross bridges remain latched
  → No further cross bridge cycling &
  → NO further ATP breakdown

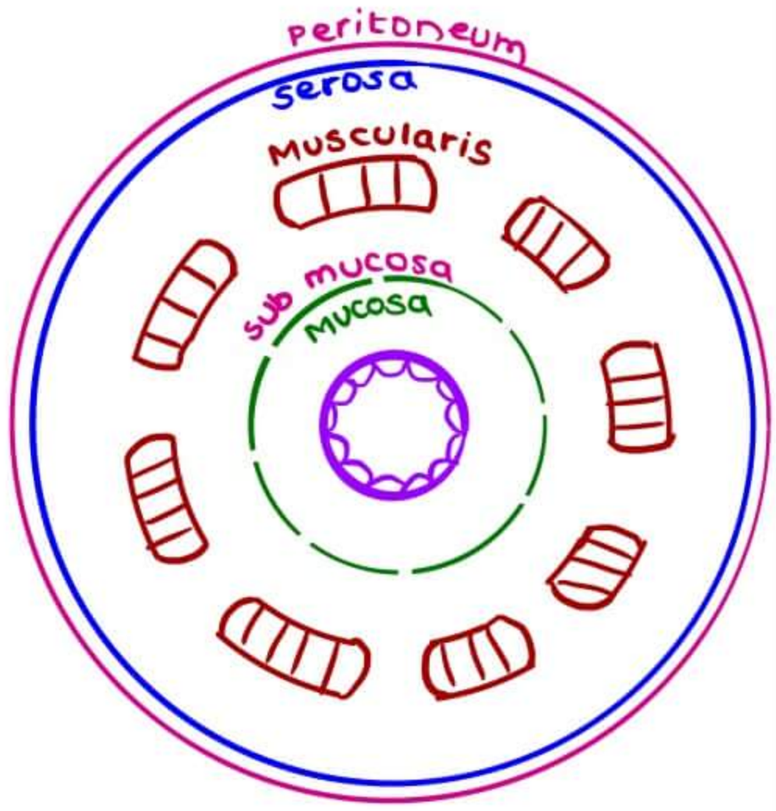


GASTROINTESTINAL TRACT

INTRODUCTION

LAYERS

1. mucosa
2. sub mucosa
3. muscularis mucosae
4. serous layer



INNERVATION

ENTERIC NERVOUS SYSTEM

→ Branch of ANS
→ aka Peripheral / mini brain
→ sub mucous / meissner's plexus (sensory)
→ myenteric plexus / Auerbach's plexus (motor)

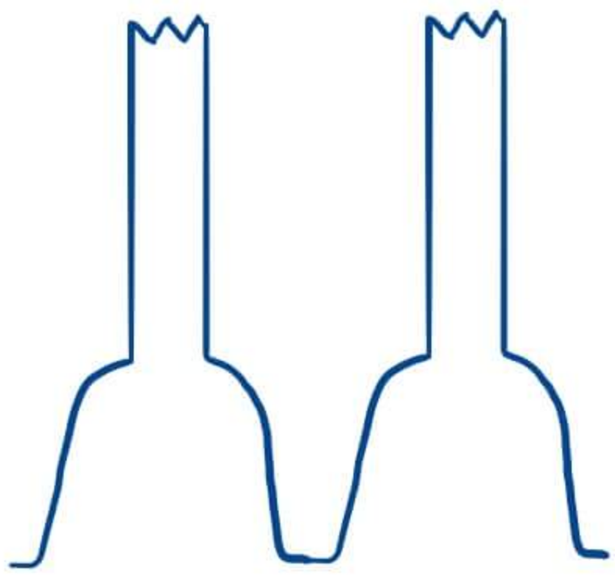
NEUROTRANSMITTERS

EXCITATORY NTs → Ach
substance P

INHIBITORY NTs → VIP (inhibits motility)
NO

ELECTRICAL ACTIVITY

→ Pacemaker Cell → Interstitial cell of CAJAL
→ Electric activity occurs at a frequency
Frequency differs at different parts of GIT



→ BER (Basal Electrical Rhythm)

FREQUENCY

Stomach → 3-4 times/min
Duodenum → 12/min
Jejunum → 9/min
Ileum → 7/min

→ The decrease in the frequency from oral to anal direct^{n} of peristalsis responsible for LAW OF THE GUT EXCEPT colon (antiperistalsis)

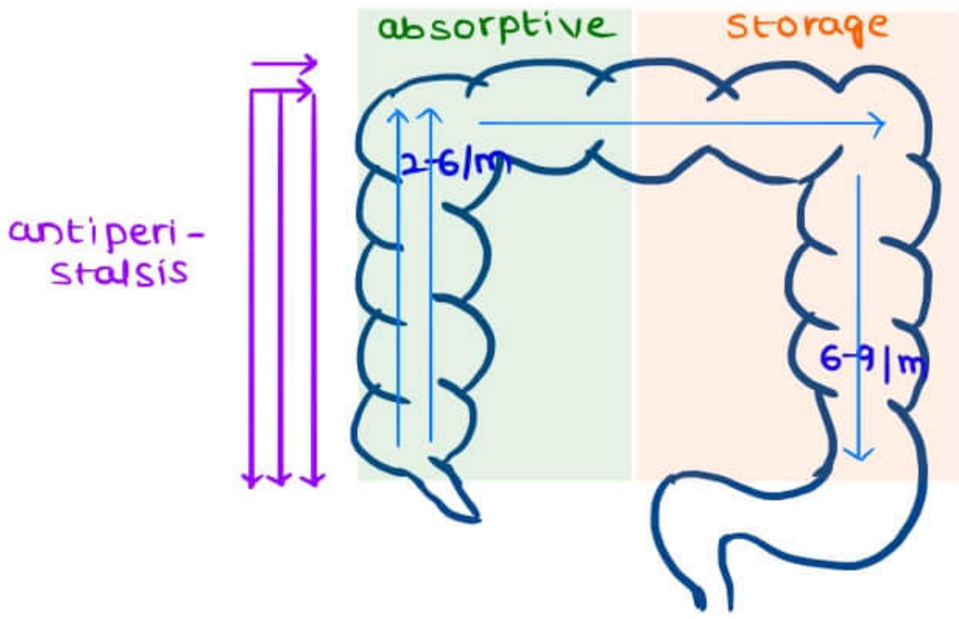
ANTI PERISTALSIS

→ Naturally occurs in colon (from hepatic flexure of colon to caecum)
Frequency at Sigmoid → 6-9/min
at Asc. colon → 2-6/min
→ Significance → to reabsorb water

MAXIMUM ABSORPTION OF WATER TAKES PLACE AT JEJUNUM (6·6 ltr/day)

REFLEXES

Q Defecat^{n} is initiated by which reflex upon rising up from bed in morning
a Gastroileal reflex
b Gastrocolic reflex
c Orthrocolic reflex
d mass peristalsis



TYPES OF REFLEXES

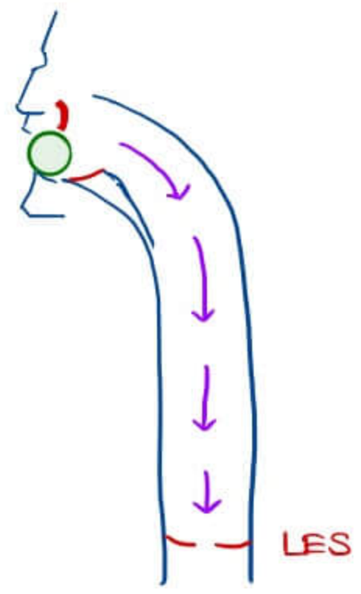
1. LOCAL REFLEXES
→ entirely confined to digestive wall (ENS)
→ Ex: Peristaltic reflex

2. SHORT LOOP REFLEXES
→ ENS ⇌ Spinal cord
→ Ex: orthocolic reflex

3. LONG LOOP REFLEXES
→ ENS → spinal cord → higher centres
→ Ex: Defecation Reflex

MOTILITY IN DIGESTIVE TRACT

1. DEGLUTITION (10-12 sec)
→ 3 PHASES
1. Oral phase → voluntary
2. Pharyngeal } involuntary (reflex phases) } swallowing center in medulla
3. Oesophageal



ORAL PHASE

→ tongue is pressed upward & backward, bolus of food pushed into post. pharynx

Pharyngeal phase

→ sensitive part → tonsillar pillar

→ Food touches tonsillar pillars & swallowing centre in medulla activated cause deglutition apnea & sends srgnals for co-ordinated contractn are seen in pharynx & oesophagus

→ IX & X CN involved

→ EVENTS AFTER UPPER OESOPHAGEAL SPHINCTER RELAXATION

1. soft palate moves upwards so, that posterior nares are closed
2. Epiglottis falls & closes the respiratory passage
3. Palato pharyngeal folds approximate in mid line & leaves a narrow slit for the passage of bolus
4. opening of oesophagus widened & wave of peristalsis sent down wards

OESOPHAGEAL PHASE

→ LOWER / GASTRO OESOPHAGEAL SPHINCTER

→ physiological sphincter / functional sphincter

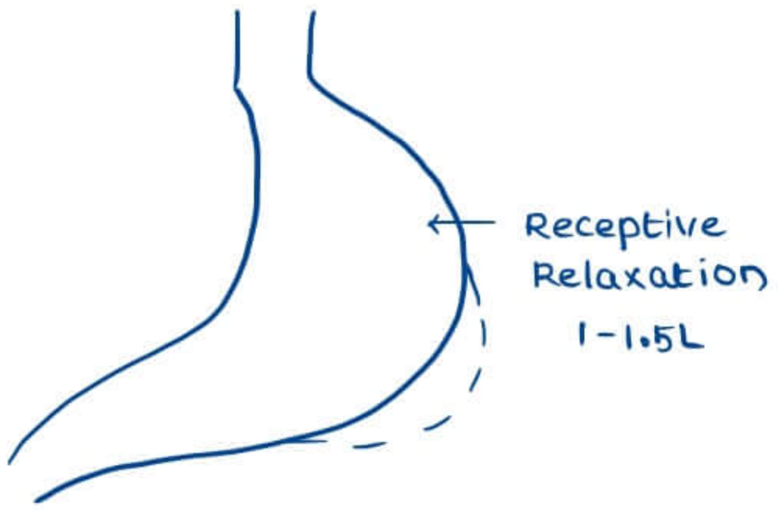
→ no anatomical entity

→ acts as a high pressure sphincter area

→ Food enters the stomach by 1° & 2° peristalsis

MOTOR FUNCTIONS OF THE STOMACH

1. STORAGE
2. MIXING
3. SLOW EMPTYING



1. STORAGE

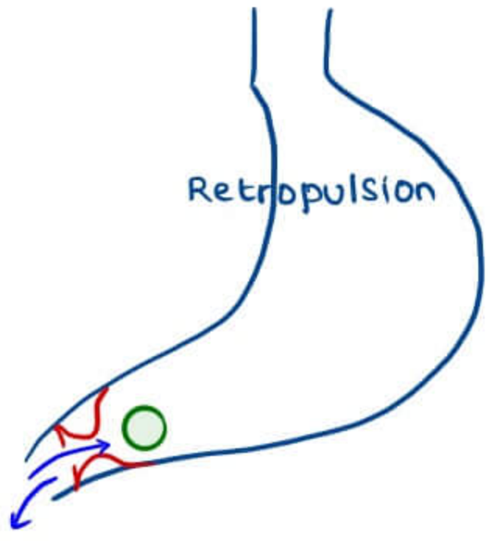
→ RECEPIVE RELAXATION OF STOMACH WALL

→ 1 - 1.5 Ltr Food is accumulated tout rising intra gastric pressure much

→ Pace maker of stomach is located in midportion of Body

2. MIXING → RETROPULSION

→ chyme empties from pyloric sphincter, some of it goes back to stomach & process repeats

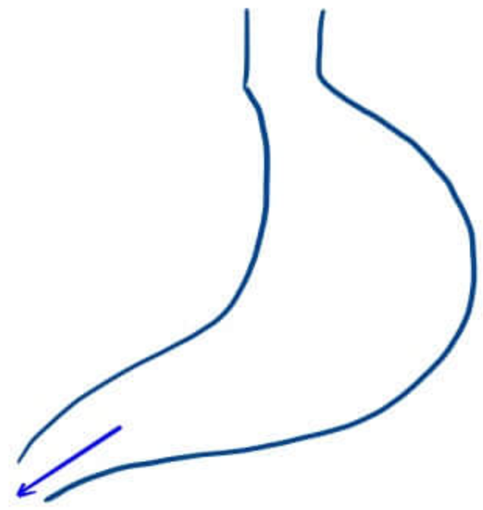


3. SLOW EMPTYING

→ (N) → 4-6 hrs

→ upto 8 hrs for fat foods

FACTORS INFLUENCING EMPTYING



1. WEAK FACTOR (GASTRIC factor)
   - → Gastrin
   - → promotes emptying

2. STRONG (Duodenal factors) → inhibits emptying

a. acidic chyme
↓
secretin (S cells)
↓
constriction of pyloric sphincter

b Irritation of duodenal mucosa
↓
initiation of enterogastric reflex

c Hypertonic contents reaching duodenum (DUMPING syndrome)
→ cause lot of H_2O pulled by osmosis
causes decrease in blood volume & causes DUMPING SYNDROME

HYPERTONIC CONTENTS

↓
OSMORECEPTOR
↓
ENTERO GASTRIC REFLEXES

d FAT Break down products in duodenum
↓
CCK (cholecystokinin) released
↓
↓ Gastric motility
↓
Feeling of fullness

MOTILITY OF SMALL INTESTINE

1. FED
   - → Peristalsis (Propulsion)
   - → Segmentatn (mixing)

2. FASTING → migrating Motor complex (MMC)

MMC (MIGRATING MOTOR COMPLEX)

→ house keeper of Intestine

→ in post absorptive phase, it clears the debris

→ 90 min cycle

3 Phases

1. PHASE I → 70 min
   → quiescent phase, only slow waves

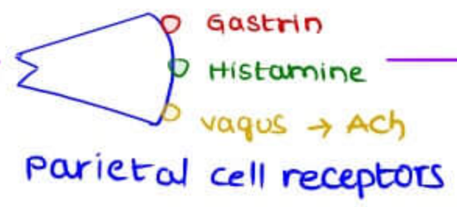
2. PHASE II → 10-15 min
   → Irregular contractions

3. PHASE III → 5-10 min
   → Activity front

→ MOTILIN
   → horomone that strengthens the MMC contraction
   → Erythromycin binds t motilin Receptors

REGULATORY PEPTIDE SECRETIONS IN DIGESTIVE TRACT

CELL SECRETION	FUNCTIONS
Stomach	acts on H_2 receptors on parietal cell
1. ECL CELLS Secretes HISTAMINE	→ ↑ gastric acid secretion → potentiating effect of Ach, gastrin
2. G CELLS Secretes GASTRIN	→ ↑ gastric acid secretion → ↑ motility
3 SOMATOSTATIN [Pro insulin as well as anti insulin] Synthesized by - D-cells in pylorus, duodenum - δ-cells in pancreas - hypothalamic neurons	→ ↓ Gastric Acid secretion → Supresses the insulin & glucagon secretn → secretes GHIH



CELLS IN SMALL INTESTINE	
DUODENUM	
1. S cells Secretes SECRETIN	→ Maintains alkaline pH in duodenum Constricts the pyloric sphincter causes secretion of HCO_3 rich pancreatic juice
2. I CELLS Secrets CCK	→ ↓ gastric motility ↑ intestinal motility causes enzyme rich pancreatic juice to be secreted Bile flow from gall bladder (cholagogue)
3. Mo CELLS Secretes MOTILIN	→ ↑ MMC contraction

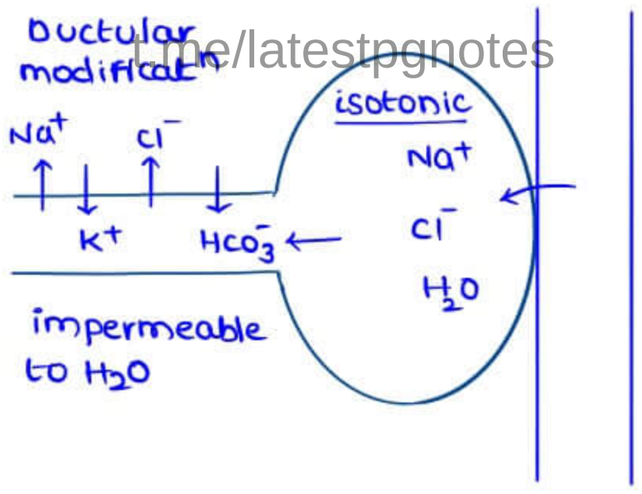
BOMBESIN/
GRP → Gastrin Releasing peptide

PEPTIDE YY (Tyrosine Residues) → Ileal mucosa in response to Fat
prevents Further gastric emptying

INCRETINS
→ released by GI mucosa in response to oral glucose
→ they will go to pancreas & ↑ insulin secretion

GLP1 or
GIP (Glucose dependent insulinotropic peptide

SECRETIONS IN GIT:
SALIVA
→ Secretes highest volume of K^+
→ It neither have endocrine control, only neural control
→ In SIALORRHEA, no ductular modification
pH → 6 - 6.5, hypotonic (N Isotonic)
2 ions → K^+, HCO_3^-
2 enzymes → Ptyalin (α-amylase)
Lingual Lipase (for Lipid digestion)
→ Thiocyanate ions, IgA, Lysozyme



GASTRIC SECRETION

GASTRIC GLANDS
1. MUCUS NECK CELLS → Secretes Mucus
2. PEPTIC or CHIEF CELLS → Secretes Pepsinogen
3. PARIETAL or OXYNTIC CELLS → Secretes HCl & Intrinsic factor of castle

PEPSIN
→ aids in 10-20% of protein digestion
→ needed for further gastric acid secretion & digestion of meat protein (collagen)

RENNIN
→ Secreted in stomach
→ helps in digestion of milk protein

GASTRIC LIPASE
→ a Tributyrase
→ digest tributiric acid / Butter fat

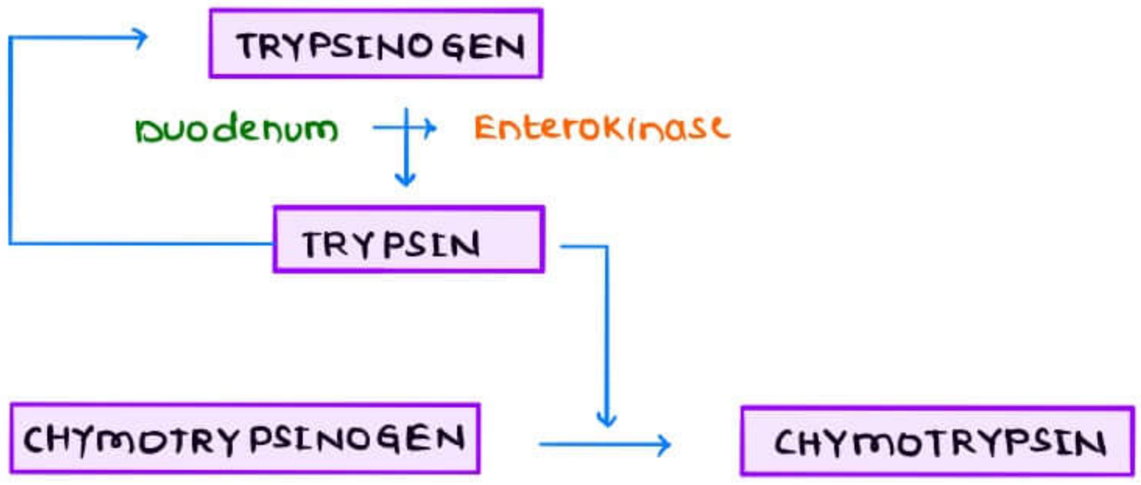
PHASES OF GASTRIC ACID SECRETION

1. CEPHALIC (20%) → mediated by vagus (site & smell of food)
2. GASTRIC PHASE (70%)
   - → partly mechanically → by distensn of stomach wall
   - → partly chemically → by protein breakdown products
   - → mediated by gastrin hormones

3. INTESTINAL PHASE (10%)
   - → mediated partly by gastrin
   - → inhibited by neurotensin

PANCREATIC JUICE

- → pH → 8.0, isotonic
- → HCO_3^- rich (for chyme)
- → Enzyme rich (for nutrients)
- → highest protein content



- → Trypsin, Chymotrypsin are called as ENDOPEPTIDASES
- → Carboxypeptidase, Aminopeptidase are called as EXOPEPTIDASES
- → Lipase, co-Lipase & phospho lipase A & B, Amylase, nuclease
- → DISACCHARIDASES → Di & tripeptidases, Trehalase

BILE

- → Secreted by LIVER
- → Gall Bladder
  - → stores & concentrates bile
  - → acidifies bile
  - → add mucus to bile

DIGESTION & ABSORPTION

FUNCTIONS OF BILE SALTS

1. Digestion of Lipids emulsification
2. Absorption of Lipids
3. micelle formation for fat absorption
   - → ferrying function

   Absorption of nutrients - Stomach

   Stomach - Alcohol absorbed

DUODENUM → Divalent cations Fe^{+2}, Ca^{2+}

JEJUNUM

- → All major nutrients
- → max. H_2O absorption (6.6 L/day) (1.5 L/day from colon)
- → Long chain fatty acids absorbed into lymphatic circulation
  - → appears milky called LACTEALS
  - → Lymphatics in form of chylomicrons

ILEUM

→ Mg^{2+}, Vit B_{12}, Bile salts absorbed from Ileum
→ Enterohepatic cycling occurs 7-8 times a day (of bile)
→ Maternal Antibodies are absorbed from Ileum

GUT or COLONIC MICROFLORA Synthesized & absorb →
Vit B_{12}, folic acid, vit K & short chain fatty acids

BLOOD PHYSIOLOGY

BLOOD COMPOSITION

1. PLASMA (55%.)
2. CELLS (45%.) (RBCs, WBCs, Platelets)

PLASMA PROTEINS

→ Total → 7 - 8 gm%.
Albumin → 4 - 4.5 gm%.
Globulin → 2 - 2.5 gm%.
Fibrinogen → 0.2 - 0.4 gm%.

→ All are synthesized by Liver EXCEPT γ globulin
→ Normal Albumin : Globulin Ratio → 1.7 - 2 : 1
→ Prothrombin Normal level → 0.02 - 0.04 gm%.

→ ALBUMIN → exerts plasma colloid osmotic pressure
→ GLOBULIN
→ α, β, γ
→ α, β → transport proteins → ceruloplasmin Cu^{2+}
Trans ferrin Fe^{2+}
→ γ → Immunoglobulins

RBCs

→ 8μ diameter, biconcave, non - motile, non - nucleated
→ STAGES OF ERYTHROPOIESIS
1. 1st TRIMESTER → mesoderm of yolk sac → MYELOID STAGE
2. 3-6 months of PREGNANCY → Hepatic stage → Liver cells forms RBC
3. 3rd TRIMESTER → Bone marrow → MYELOID STAGE

→ RED BONE MORROW (RBM)
→ At birth, all bones have RBC
→ After fat infiltration, few have RBM
→ Long bones
→ fat bones
→ Sternum
→ ASIS (Ant. Sup. Iliac Spine]

PLEURIPOTENT HAEMATOPOIETIC STEM CELL (24 M)

CFU ERYTHROCYTE	CFU MEGAKARYOCYTE	CFU GRANULOCYTE MONOCYTE
↓	↓	↓
Pro Erythroblast	Platelets	Monocyte
↓		
RBC		

→ In Bone marrow, myeloid : Erythroid ratio → 3:1

→ Precursors are nucleated, matured erythrocytes are non-nucleated

PROERYTHROBLAST } Basophilic

EARLY ERYTHRONORMOBLAST }

INTERMEDIATE ERYTHRDNORMOBLAST → acidophilic, Hb begins to appear

LATE NORMOBLAST

RETICULOCYTE

MATURED RBC

→ Normal Reticulocyte count → 0.2 – 2%.
High in Infants & children & hypoxia

→ Erythropoiesis takes about 7-9 Days

NUTRITIONAL FACTORS

IRON → For heme Synthesis

Vit B_{12}, FOLIC ACID

→ For maturation of DNA

→ Cell division is so rapid → cell size decreases from 24 μ (proerythroblast) (PHSC) to 8 μ (RBC)

→ In vit B_{12} & FA deficiency

→ Cell division do not occur

→ Large & Immature cells, resulting in MEGALOBLASTIC ANEMIA

Other factors → Cu, Zn etc

OTHER FACTORS

1. HYPOXIA

Hypoxia
↓
Interstitial cells of Kidney
Stimulates
↓
ERYTHROPOIESIS (in about 5-6 days)

2. HORMONAL FACTORS

a. ESTROGEN → inhibit Erythropoiesis

b. TESTOSTERONE
→ stimulates Erythropoiesis at } Reason of males having more Hb
1. Kidney
2. Bone marrow
3. Unknown

WBC

I GRANULOCYTES

1. Neutrophils (50 - 70%)
2. Eosinophils (1 - 4 %)
3. Basophils (0 - 1 %)

II AGRANULOCYTES

1. Monocytes (2-8 %)
2. Lymphocytes (20-30%)

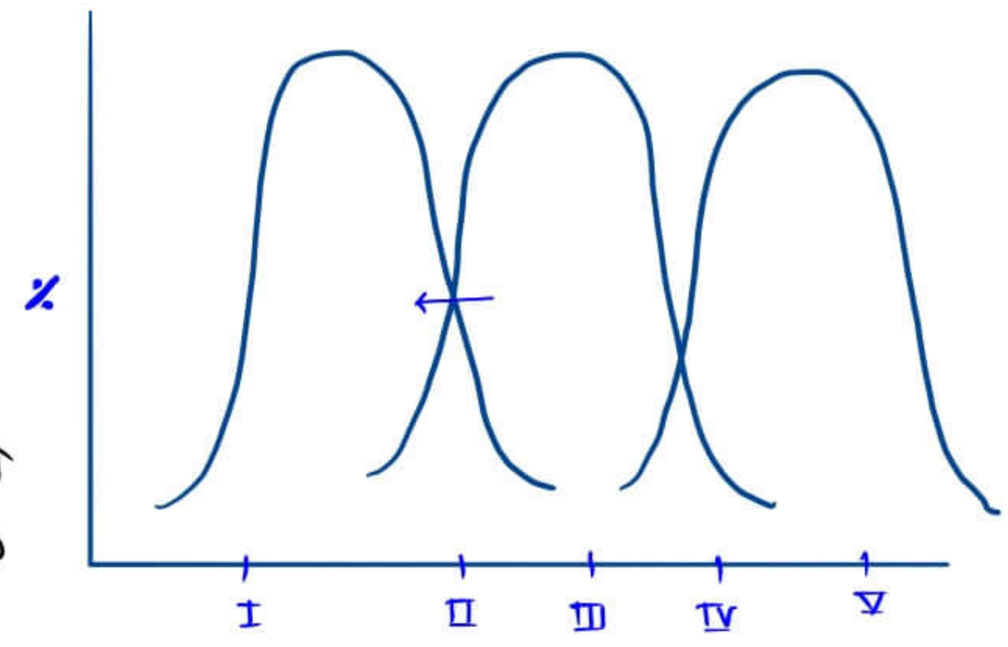
ABSOLUTE COUNTS

→ Total Leucocyte count
→ Differential Leucocyte Count

NEUTROPHILS (50-70%)

ARNETH COUNT

STAGE I (single lobe) → 5% in peripheral circulation
STAGE II (2 lobes) → 15%
STAGE III (3 lobes) → 35 - 45%
STAGE IV (4 lobes) → 10 - 15%
STAGE V (5 lobes) → 5 - 10%



SHIFT TO LEFT → younger neutrophils↑
→ in case of infection

SHIFT TO RIGHT → Older neutrophils in bone marrow↑

LIFE SPAN [SCHILLING'S INDEX]

1. Neutrophils → 4 - 6 hrs
2. Lymphocytes → 300 days
3. Monocytes → Few hrs to few days [converts into macrophages in tissues]
4. RBC → 120 days
5. Stored RBC → 60 days
6. t 1/2 of Stored RBC → 28 - 32 days
7. Neutrophils → 4-8 hrs to few days
8. Platelets → 8 - 12 days
9. t 1/2 of platelets → 4 days
10. t 1/2 of Stored platelets → < 1 day

MONOCYTES

→ 2nd line of defence
→ largest WBC (18 - 20 μ)
→ monocyte count increased in Malaria

LYMPHOCYTES

→ 3rd Line of defence
→ Basis for Immunity
→ T - Lymphocytes → involved in cell mediated Immunity
B - Lymphocytes
→ Involved in Humoral cell Immunity
→ plasma cells → Antibodies Secretion
→ Antibodies in humoral immunity → IgG, IgA, IgM, IgD, IgE
→ IgA → Secretory Ab

→ Small Lymphocytes are more matured

EOSINOPHILS (1-4%)

→ COUNT INCREASES IN
1. Parasitic / worm Infection
→ dlt Major Basic proteins
2. Allergic conditions

BASOPHILS (0-1%)

→ Synthesize & Secrete Heparin & Histamine
→ BASOPHILIA → ↑ Basophilic count
Seen in Allergy

PUNCTATE BASOPHILIA → Seen in Lead poisoning
→ maturation arrested in early stages
→ known as Basophilic Stippling of RBC

PLATELETS | THROMBOCYTES

→ Formed from Megakaryocytes

1 megakaryocytes ⟶ 1000 - 4000

→ N Size → 2-4 μ diameter

→ non motile, non nucleated

→ N count → 1.5 - 3 Lacs | mm^3

CRITICAL PLATELET COUNT

→ < 40,000 | mm^3

→ arrest of bleeding is very difficult

→ OPEN CANALICULI for entry of Ca^{2+} present

→ Granules release ADP & TXA_2

→ Ca^{2+} cause exocytosis of granules

→ more platelets are recruited → Platelet plug formed

→ Ca^{2+} also required for contractile filaments (actin, myosin, Thrombosthenin) → helps in retraction of clot

→ Deficiency leads to THROMBOCYTOPENIA

ITP (Idiopathic Thrombocytic purpura)

→ Platelets stops Bleeding → about 1-3 min (by platelet plug)

CLOT FORMATION

→ occurs in 4-9 min

→ required for

→ Small injuries are addressed by platelet plugs

→ clot formation occurs in larger injuries

→ Platelet plug is temporory

→ clot stabilizes the platelet plug & aids in healing

→ STEPS

1. PROTHROMBIN $\xrightarrow[\downarrow]{\text{prothrombin activator (RLS)}}$ THROMBIN

FIBRINOGEN ⟶ FIBRIN

↓

POLYMERIZATION

→ PROTHROMBIN ACTIVATOR FORMATION BY

→ EXTRINSIC PATHWAY → Tissue injury releases Tissue Thromboplas-

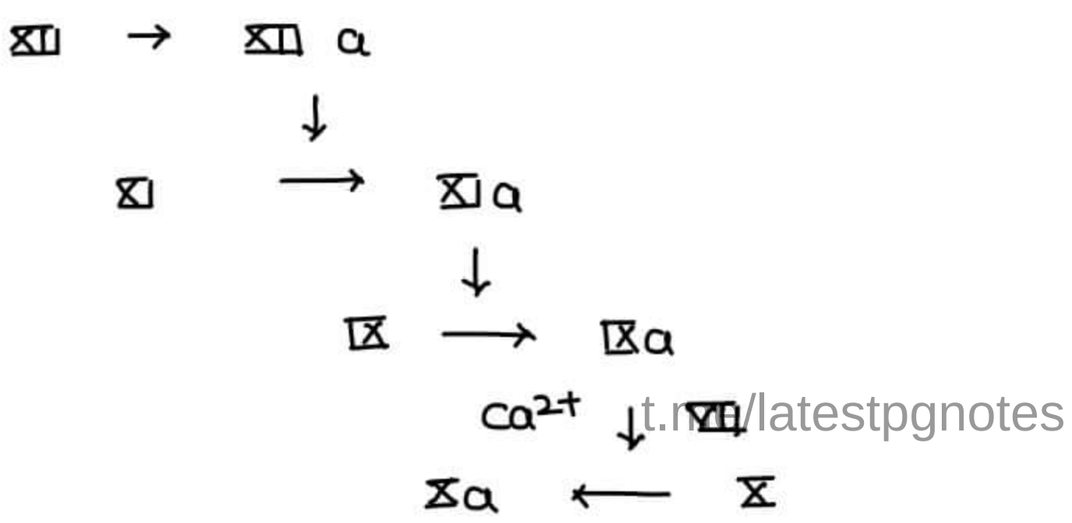
→ INTRINSIC PATHWAY → Trauma to blood itself
Factor XII comes in contact (Subendothelial

CLOTTING FACTORS (ICSH)

I	→	Fibrinogen
II	→	Prothrombin
III	→	Tissue Thromboplastin
IV	→	Ca^{2+}
V	→	Labile factor
VII	→	Stable factor
VIII	→	Anti Haemophilic factor
IX	→	Christmas factor
X	→	Stuwart prower
XI	→	PTA
XII	→	Hagemen factor
XIII	→	Hmwk
XIV	→	Prekallikrein

→ EXCEPT for the 1st 2 steps of Intrinsic pathway, all other steps

ENZYME CASCADE HYPOTHESIS



ANTI COAGULENT MECHANISMS

IN VITRO

- → Dilution of blood > 20 times
- → Heparin
- → Citrates
- → Oxalates
- → EDTA

} used for
- collectⁿ
- Storage

– acts by chelatⁿ Ca^{2+}

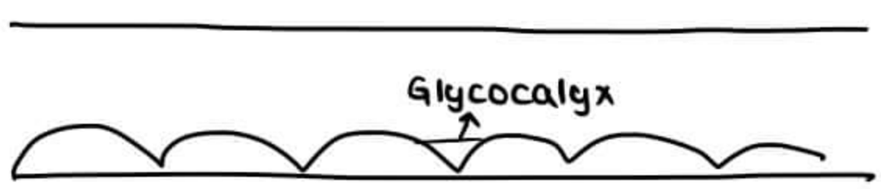
IN VIVO

→ Heparin

HEPARIN → acts via antithrombin III
→ used for Heparinizatʰ in MI etc

IN VIVO

1. Smoothness of Endothelium
2. Glycocalyx layer on Endothelium
3. Thrombomodulin layer Endothelium
4. Heparin
5. Tissue plasminogen activator
   - streptokinase
   - urokinase



→ converts plasminogen → Plasmin

→ Plasmin has trypsin like activity to digest fibrin threads

BLOOD GROUPS

→ divided

20 blood group system so far

- ABO
- Rh
- Kell
- Duffy
- M & N → can be used for paternity dispute

ABO SYSTEM

→ ANTIGENS → A & B

4 Blood Group

A	→	anti B	→ universal receipient
B	→	anti A	→ universal donor
AB	→	NO antibodies	
O	→	anti A, anti B	

→ BOMBAY BLOOD GROUP O 'h'

→

'H' gene	'A' gene	'B' gene
↓	↓	↓
H - Substance (in most)	A Sub - stance	B substance

Significance

→ has anti A, anti B, anti H

→ Only transfused ℞ Bombay blood group only

Rh BLOOD GROUP SYSTEM

→ Based C, c, D, d, E, e

→ 90% of times, Rh = D

→ anti Rh antibody
- → not present in any individual
- → not a naturally occuring antibody
- → 85% Rh positive, 15% Rh negative
- → present only the Rh -ive individuals who exposed to Rh +ve blood

→ Erythroblastosis Fetalis

Mother → Rh -ive
1st Baby → Rh +ive
→ sensitized

Starts forming anti Rh antibodies (48-72 hrs)
anti Rh antibodies Fully developed by 2-4 months

2nd Baby → Rh +ive

↓ antigen & ab reaction occurs

Erythroblastosis fetalis
- → anemia
- → Jaundice

Preventive measure
- → Anti D serum given to mother after delivery of 1st baby

TREATMENT
- → Exchange transfusion for anemia
- → Phototherapy for Jaundice

BLOOD INDICES

1. PCV (Haematocrit) → 38 - 45%
   - → ↓ in anemia
   - ↑ in polycythemia

2. MCV (Mean corpuscular volume)
   - → 78 - 93 μ^3
   - → calculated by $\frac{PCV}{RBC\ count}$
   - → < 78 → microcytic anemia (iron def. Anemia)
   - > 93 → macrocytic / megaloblastic anemia

3. MCH (MEAN CORPUSCULAR Hb) → 28 - 32 pg

→ calculated by

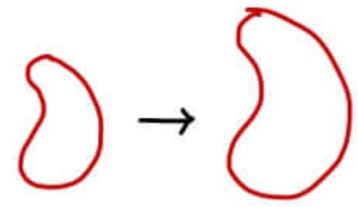
$$\frac{Hb}{\text{Rbc count}}$$

→ ↓ in iron def. anemia

4. MCHC (mean corpuscular Hb concentration) → 32 - 38%

→ percentage of saturation of RBC by Hb

→ MCH → normal
MCHC → reduced
} RBC size increased



- macrocytic | megaloblastic anemia

5. COLOUR INDEX

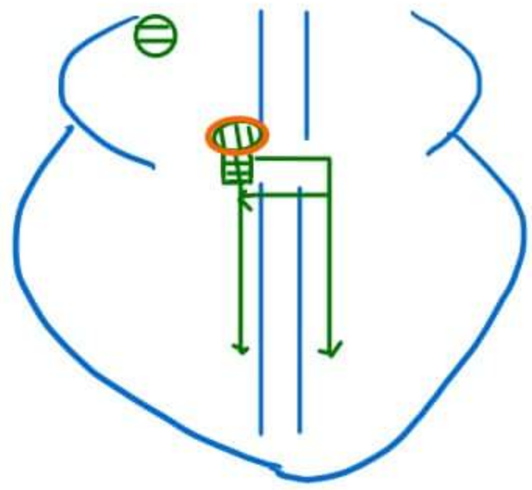
$\frac{Hb\%}{RBC\%}$ → 14.5 mg% → considered 100%.
RBC% → 5 million | mm^3 → considered 100%.

RBC count → 5million | mm^3 → 80%.

→ N value → 0.8 - 1
< 0.8 → hypochromic anemia
0.8 - 1 → normochromic anemia

CONDUCTING SYSTEM OF HEART

INTRODUCTION



Q Choose the correct statement

a Rt atrium excites ahead of lt atrium

b lt atrium excites ahead of Rt atrium

c both atria excites at same time

d depends on size of the atrium

Q Which statement is correct

a Rt ventricular excitation starts first

b Lt ventricular excitation starts first

c Both at the same time

d depends on orientatⁿ

Q Which statement is correct

a Rt ventricle excitatⁿ ends earlier

b Lt ventricle excitatⁿ ends earlier

c Both at the same time

d Some time Rt & some times lt

Q Which ventricular ejection starts first

a Rt

b lt

c both

d Condition of vessel wall

→ Pulmonary valve opens earlier dlt down stream pressures

→ Aortic valves opens later

→ Aortic valve close First

→ Pulmonary valve closes later

Q SA Node is pace maker dlt

a Slow depolarisatⁿ & slow repolarisation

b rapid depolarisatⁿ & rapid repolarisation

c Slow depolarisatⁿ & rapid repolarisatⁿ

d Rapid repolarisation & Slow repolarisatⁿ

INTRODUCTION

1. Heart muscle works like SYNSITIUM
   - → all fibres contracts as a single bundle
   - → dlt numerous GAP JUNCTIONS
     - → rapid passage of ions occurs
   - → made up of 2 syntitia
     - Atria → contracts together
     - ventricles → contracts together

2. Contains INTERCALATED DISCS
   - → provides electro mechanical tethering to fibers

INNERVATION

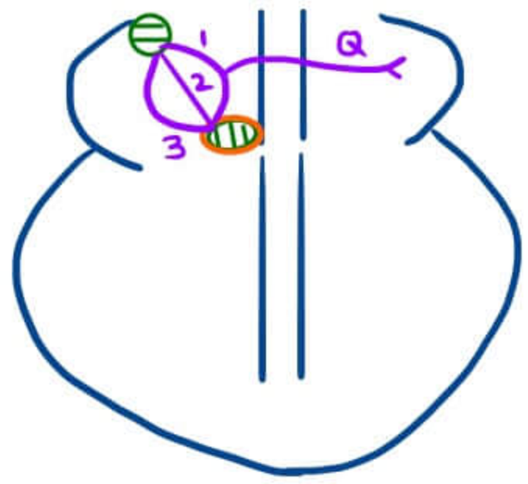
→ Sympathetic fibres (mainly from $T_1 - T_5$)
- → predominantly epicardial distribution
- → mainly control contractility

Vagal Fibres
- → predominantly endocardial distribution
- → mainly controls heart rate
- → Rt vagus innervates SA Node
- → Lt vagus innervates AV Nodes

CONDUCTING SYSTEM OF HEART

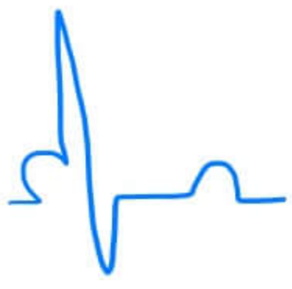
ANATOMICAL PARTS

- → SA NODE
- → AV NODE
- → 3 INTER NODAL TRACTS
  - → connects SA Node to AV Node
  - → 1. Anterior → Bachman's bundle
    2. middle → Wenckebach's bundle
    3. Posterior → Thorel's bundle
    Q. Br. of Anterior bundle → innervates Lt. Atrium



BUNDLE OF KENT

- → aberrent anomalous path that connects atria directly to ventricle bypassing AV Node
- → NO AV Nodal delay
- → shortened PR Interval
  - → appears as δ wave on ECG
  - → seen in wolff parkinson white syndrome



Q Slowest conducting part

a A-N Region

b N Region

c N-H Region

d H Region

A-N Region

→ Junctional fibres at atrium & node
causes great slow down in conduction velocity

N Region (Nodal tissue proper)

→ further slow down

→ max. no. of heart blocks seen here

N-H Region → his bundle arises here

BUNDLE OF HIS

Q Suspected case of RBBB, which interval is prolonged

a PA

b AH

c HV

d None

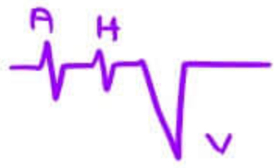
HBE (HIS BUNDLE ELECTROGRAM)

→ INDICATIONS

1. Heart Block → to check whether the block is above (AVNODE) or below (Bundle branches) the His bundle

2. To differentiate blw ventricular & supra ventricular tachycardias

→ A Wave → SA Nodal depolarisation
H Wave → His bundle depolarisatn
V Wave → ventricular depolarisatn



→ AH INTERVAL (55 - 130 ms)

→ HV INTERVAL (35 - 55 ms)

→ IF AH Interval is prolonged → Block is above (AV block)
HV Interval is prolonged → Block is below (Bundle branch block)

→ In ventricular tachycardia, A Wave is absent

→ gives Lt branch &
continues as Rt Branch

→ Impulse enters lt branch first and through IVS goes to Rt. Branch
  → responsible for Q wave deflection

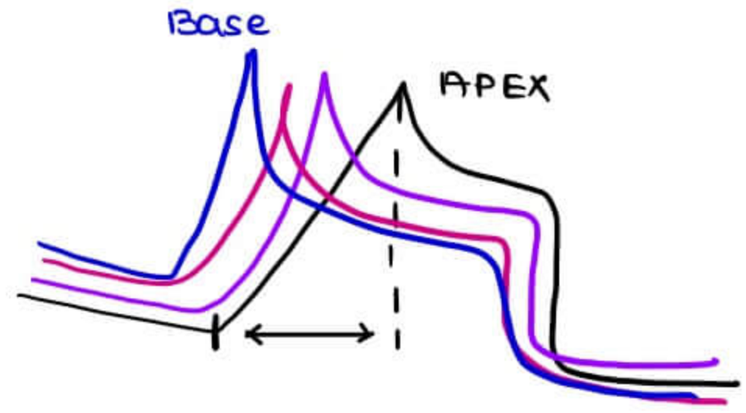
→ Impulse now reaches apex
→ Purkinje fibres are present at apex

→ GATE CELLS OF HEART
  1. AV Nodal cells
  2. Purkinje fibres
    → allows impulses to reach ventricles
    → higher the HR , longer the Refractory period
      → provides a physiological block

→ Impulse spreads from apex to base & from endocardium to epicardium
Last part to get depolarised → Base of left ventricle & its epicardium

LAST PARTS TO DEPOLARISED
1. Epicardium of Base of Left ventricle
2. Pulmonary conus
3. Uppermost part of Interventricular Septum

LAST TO REPOLARISE → Apex endocardium



FUNCTIONAL ASPECTS

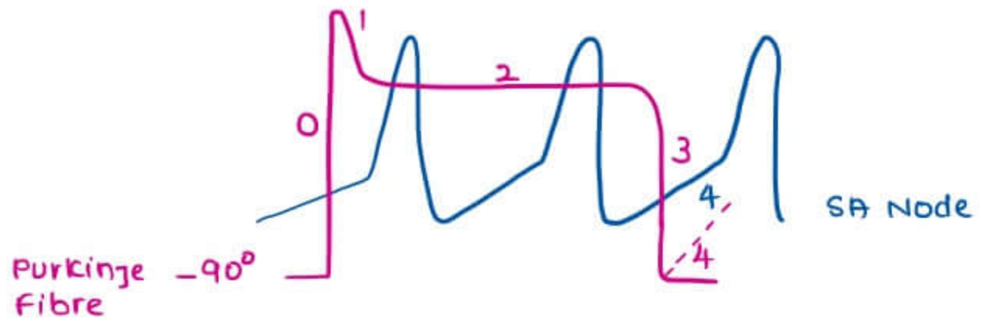
→ RATES OF DEPOLARISATION
  → Fastest depolarising cell is at base

Fibre at apex depolarises first , last to complete the depolarisation
fibre at base repolarises first

ACTION POTENTIAL IN HEART

SLOW RESPONSE TYPE	FAST RESPONSE TYPE
→ SA Node	→ Purkinje fiber
→ AV Node	→ Ventricular fiber
→ Rmp −55 to −65 mV	→ Rmp −90 mV

SLOWLY DEPOLARISING TYPE



→ Amplitude of Purkinje fibre is more than SA Node

→ Natural excitability of purkinje fibre is half that of SA Node

→ Slope of phase 4

→ Flat in purkinje fibre

→ at the end of repolarisation, it can't depolarise by itself

→ Steep in SA node

→ determines automaticity

→ ↑ slope of Phase 4 in purkinje result in enhanced/ abnormal automaticity

→ fast response fibre get converted to slow response fibre & results in Arrythmias

ARRYTHMIAS - PATHOPHYSIOLOGICAL BASIS

1. Enhanced abnormal automaticity
2. Triggered activity (After depolarisation (eary/ Delayed))
3. Re entry & Circus movements

CONDITIONS r/f Enhanced abnormal automaticity

1. Hypoxia
2. Ischemia
3. Tetrodotoxin

ISCHEMIA

MI

↓

Na^+ K^+ Pump fails

↓

K^+ starts accumulating in ECF

↓

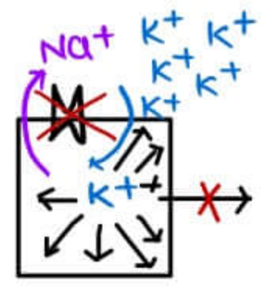
Electric gradient created

↓

I/C K^+ accumulate at inner aspect of membrane

↓

membrane begins to depolarise



RATE OF DEPOLARIZATION determines conductn speed OF 1 impulse

PART	SPEED (m/sec)
SA NODE	0.05 - 0.1
AV NODE	0.05 - 0.1 (slowest)
Bundle OF HIS	1
Purkinje	1.5 - 4 (fastest)

→ AV NODE

Slowest conducting velocity

→ Smallest diameter of fibres

→ least no. of gap junctions

Rate of Repolarisation determines INTRINSIC RHYTHMICITY OF THAT PART

PARTS	RHYTHMICITY / min
SA Node	80 - 100
Av Node	60
Purkinje fibers	15 - 40

→ Fastest repolarising part → SA Node (Pace maker)

→ SA node & AV node has equal AP but SA Nodes recovers earlier → PACEMAKER

→ After cardiac denervatn, HR → increases (80-100/min)

→ SA Node normally under vagal tone

→ after cardiac denervatn, vagal tone is lost

OVER DRIVE SUPPRESSION (STOKE - ADAMS SYNDROME)

→ Pace maker potential of AV node is suppred by SA NODE

→ Recharging after every impulse is done by $Na^+ K^+$ Pump

→ AV node excited by higher frequencies from SA Node →

$Na^+ K^+$ pump activity in AV Node is above the base line →

Hyperactivity OF $Na^+ K^+$ pump

→ results in slight negativity on the inside OF AV Nodal cells

→ AV nodal cells are Slightly hyperpolarised all the time

→ take longer time to reach threshold

BRADY ARRYTHMIAS

→ if SA node impulse frequency is <60 → AV nodal $Na^+ K^+$ pump hyperactivity lost → begins to generate its own impulse, causing Arrythmias

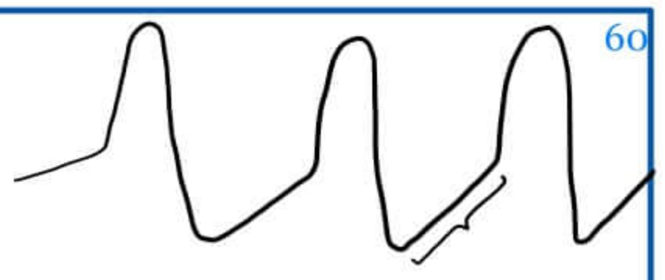
→ If SA node stops, AV node takes some time to overcome overdrive Suppression, to becomes pace maker.

In this time, ventricles will be quiscent

If it is upto 30 sec → causes dizziness

> 1min → causes Syncope

→ STOKES ADAM'S SYNDROME



IONIC BASIS OF AP

SLOW RESPONSE TYPE

Phase 1 — Repolarisation — K^+ exit

Phase 2 — K^+ exit stops
Starts accumulating inside the membrane

Phase 3 — Na^+ Funny current
- → Hyperpolarisation activated cyclic Nucleotide gated (HCN) channels
- → more the hyperpolarisatn, more the activation
- → equally permeable for Na^+ & K^+

Phase 4 — Raching Threshold Through Ca^{2+} T (transient) channels

Phase 5 — Ca^{2+} L (long lasting) channels — Depolarisatn above threshold

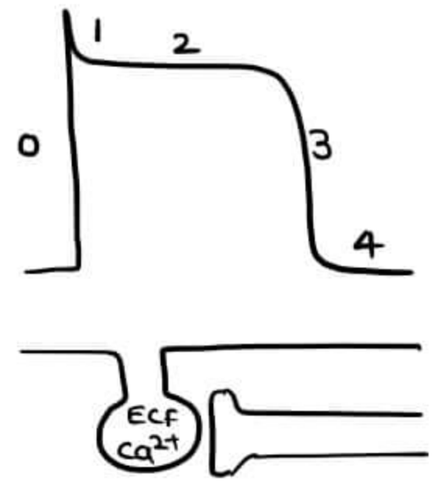
→ Major current caused by which ion for SA node & AV node → Ca^{2+}
for Purkinje fibres → Na^+

PRE POTENTIAL / PACEMAKER POTENTIAL / DIASTOLIC DEPOLARISATION

→ The potential that automatically reaches threshold at the end of every repolarisatn

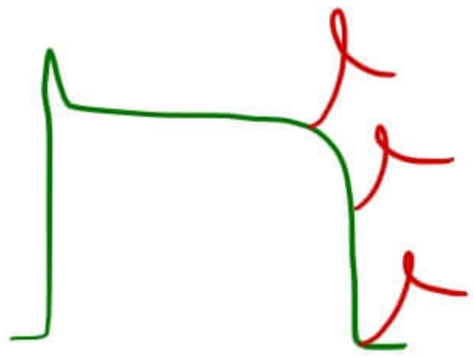
FAST TYPE

0 Rapid upstroke → by Fast Na^+ channels (Tetradotoxin sensitive)
1 Early repolarisatn → by K^+ exit
2 Plateu phase → by slow Ca^{2+} channels
3 Rapid Repolarizatn
4 Resting potential



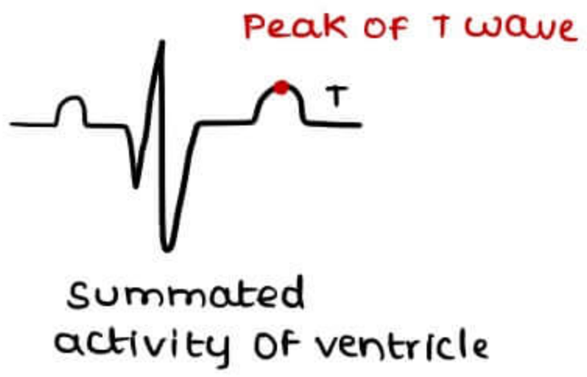
Phase 2
- → by slow Ca^{2+} channels
- → slow inward movement of Ca^{2+} (ECF Ca^{2+})
- → causes electrical & contractile activity (Ca^{2+} Sparks)

AFTER DEPOLARISATIONS



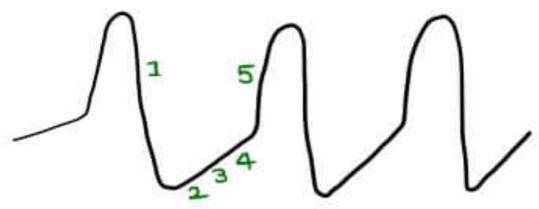
- → misnomer
- → AP are triggered early
- → causes extra systoles
- → Factors responsible are
  1. Digitalis (↑ I/C Ca^{2+})

→ Peak of T wave → VULNERABLE PERIOD IN HEART
→ activity can cause fibrillations



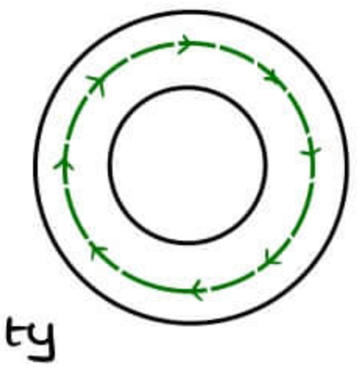
ADVANTAGES OF PLATEAU PHASE

1. Long AP duration (purkinje fibres → 200-300 ms)
2. long repolarizatn
3. long refractory period (can't be tetanized)



REENTRY & CIRCUS MOVEMENT OCCURS

1. Path length increased
   → Ex: Cardiac dilatation
2. Refractory period is shorted
3. Slowed down conduction velocity



→ Enhanced automaticity
→ Triggered activity
→ Re entry (Circus movement)

ECG

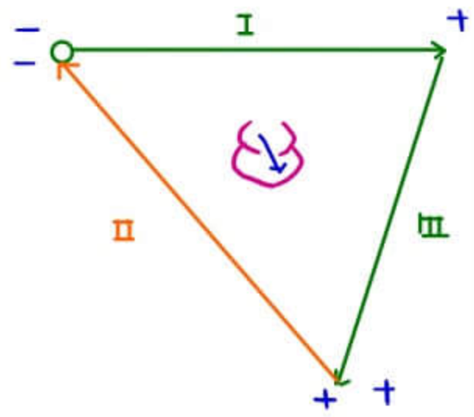
RECORDING OF ECG

→ graphic record of electric activity of heart from body surface
→ Summated activity
→ electric activity carried to the surface through body fluids
→ CARDI JELLY → decreases the resistance offered by the skin
→ NaCl also can be used

LEADS

→ an electrode / pair of electrodes placed on a specific body position
→ EINTHOVEN recorded 1st ECG (1905)
↳ created 3 Bipolar leads by placing 2 electrodes at 2 different points
[Bipolar leads measures potential difference b/w 2 points]

↳ KIRCHHOFF'S LAW → I + II + III = 0



↳ Wave of depolarisatn towards positive electrode gives upward deflectn
↳ wave of depolarisatn towards negative electrode gives down ward deflectn

↳ he reversed polarity of Lead II, to get upward deflections
→ KIRCHHOFF'S LAW
I + III + (−II) = 0
II = I + III → EINTHOVEN EQUATION

↳ EINTHOVEN EQUATION
→ IF potential of 2 leads are known, 3rd lead potential can be calculated
→ Lead II will have high potential (max amplitude)
↳ Long lead II recorded to identify the changes

UNIPOLAR LIMB LEADS

→ positive electrode placed on Rt. arm [VR], Left arm [VL] & Foot [VF] K/a Exploring electrode

→ negative electrode [K/a Indifferent electrode] created by connecting 3 points & passing it through wilson's terminal (5000 Ω)
  ↳ negative electrode record nothing
  ↳ RA − (RA + LA + LL)

→ Amplitude recorded are less

AUGMENTED UNIPOLAR LIMB LEADS

→ positive electrode on one arm
→ negative electrode created by joining the other two → Amplitude of Waves ↑ by 50%.
→ aVR, aVL, aVF

6 LIMB LEADS
- → 3 BIPOLAR
- → 3 AUGMENTED UNIPOLAR

→ LIMB LEADS → record cardiac activity in 2 dimensions [From above downwards]
→ CHEST LEADS → record cardiac activity in antero-posterior direction

CHEST LEADS | PRECORDIAL LEADS

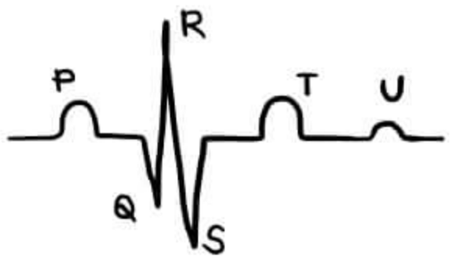
→ electrode placed on anterior wall of heart
→ V_1 to V_6
→ all are unipolar
→ aka Anterior leads

→ V_1 → Right sternal border
  V_2 → Left sternal border
  V_3 → b/w V_2 & V_4
  V_4 → 5th intercostal space, mid sternal line
  V_5 → anterior axillary line
  V_6 → mid axillary line

→ Chest leads → Anterior Leads
  II, III, aVF → Inferior Leads
  V_2 - V_4 → Septal Leads

→ NOTE → In Posterior Wall Infarct, reciprocal changes Seen in anterior leads Long lead II recorded Seperately, to diagnose anomalies, since it has the highest potential

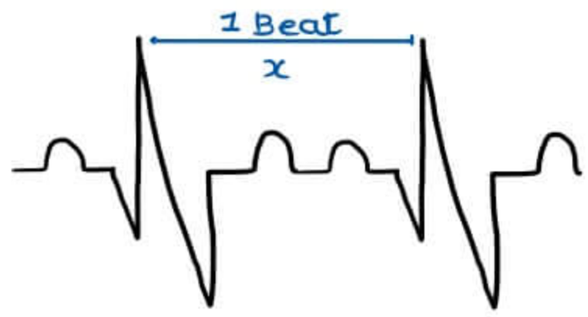
NORMAL ECG



P → atrial depolarisation
QRS → ventricular depolarisation
T → ventricular repolarisation
U → Repolarizatⁿ of Papillary muscles, not always seen

HEART RATE

→ The distance blw two successive 'R' waves → 1 Beat
→ Speed of paper → 25 mm/sec
↳ in 1 min → 1500 mm



→ 1 heart Beat → x

in 1500 mm, no. of heart beats → $\frac{1500}{x}$

→ serves as proof (authentic Way of calculating HR)

ATRIAL DEPOLARIZATION

→ P Wave is the summated potential of both the atria depolarizing
→ BIFID / M SHAPED P WAVE
↳ seen in Mitral stenosis
↳ dlt hypertrophy of Left atrium
↳ this ↑ in mass → ↑ depolarizatⁿ time of LA → BIFID P WAVE

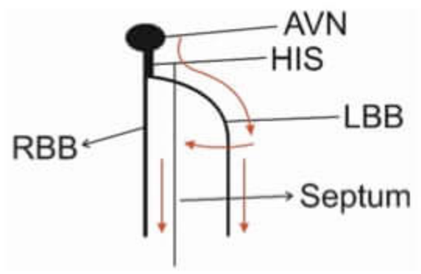
→ SAW TOOTHED P WAVE → seen in ATRIAL FLUTTER

ATRIAL REPOLARIZATION

→ not seen normally
→ merged ī QRS complex
→ can make it visible by changing the Speed of paper
↳ Ⓝ Speed 25 mm/sec

VENTRICULAR DEPOLARIZATION

→ represented by QRS complex
→ Normal → 0.08 - 0.01 sec



→ SAN → AVN → BUNDLE OF HIS —continues down as→ RBB
|—gives Lt. branch→ LBB

→ Impulse enters LBB 1st, via interventricular Septum, enters RBB
This produces downward deflection of Q wave
R & S Wave → ventricular depolarization

VENTRICULAR REPOLARIZATION → represented by T Wave

Q. Ventricular depolarizat^{n} & repolarizat^{n} are electrically opposite events.
Then why are both depicted as positive deflections on ECG ?

A. Firstly, QRS & T Waves → summated potentials of electrical activity of ventricles
Secondly, Direct^{n} of repolarizat^{n} & depolarizat^{n} is in opposite directions, i.e,
↳ depolarizat^{n} → Spreads from apex to base
repolarizat^{n} → Spreads from base to apex

PR INTERVAL

→ Signifies AV nodal delay
→ From the start of P wave to start of R Wave
→ (N) → 0.12 to 0.16 Sec (max. accepted → 0.2 sec)
→ > 0.24 Sec → AV Block

HEART BLOCK

1° → PR interval prolongation [0.24 sec]
→ All P Waves are followed by QRS Complex

2° → Not All P Waves are followed by QRS Complex [aka INCOMPLETE HEART BLOCK]
→ Mobitz Type 1
↳ PR interval goes on increasing in Successive beats
↳ in 1 beat P wave not followed by QRS complex

→ Mobitz Type 2
↳ Atria to Ventricular Ratio → 8:7 (inconsistent)
→ 8th beat not reaching the ventricle

↳ PR Interval is Fixed
↳ but, infrequently, one QRS complex is dropped

→ Mobitz Type 3
↳ Consistent (3:2)
↳ every 3rd beat will not reach ventricle
↳ P wave not followed by QRS complex

3° → NO P Wave is followed by QRS complex

WOLFF PARKINSON WHITE SYNDROME

→ SHORTENING OF PR INTERVAL
→ NO AV NODAL DELAY → dlt accessory connect^{n} from atria to ventricles, bypassing AV Node
→ Delta Wave Seen on ECG

ST SEGMENT

→ ISO ELECTRIC SEGMENT → all the ventricular fibres have completed depolarizat^{n}
→ all the fibres are equipotential at this time

→ J - POINT → End of S Wave ; ISO electric point / reference point

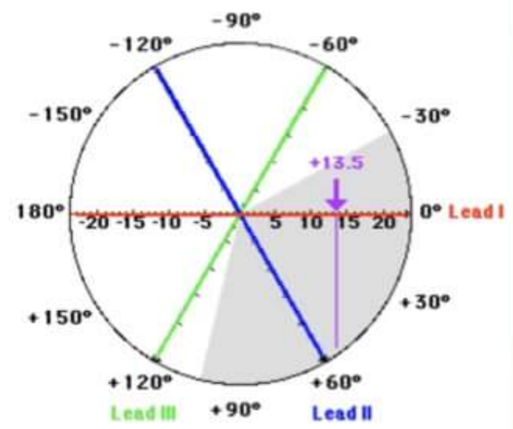
→ PEAK OF T WAVE → vulnerable point of the heart
→ all fibres are in different stages of their electrical activity [Some are repolarized, Some depolarized]
→ at this stage, if an extra systole is initiated, it leads to ventricular fibrillation

QT INTERVAL

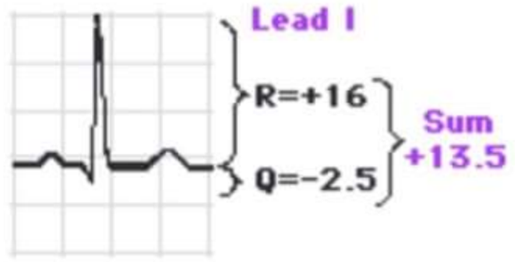
→ Normal → 0.41 - 0.43 sec
→ includes VENTRICULAR DEPOLARIZATⁿ + VENTRICULAR REPOLARIZATION
aka ELECTROMECHANICAL SYSTOLE

HEXAXIAL REFERENCE SYSTEM

→ used to determine
1. CARDIAC AXIS [the 3D Orientation of heart]
2. CHANGES like hypertrophy, bundle branch block etc



→ The Mean QRS vector is plotted on a 360° Plot, Where
↳ Lead I, II, III are plotted according to their vectors
↳ Amplitude of R Waves recorded in any 2 leads & plotted arbitarily on the graph
↳ perpendicular lines from the point of amplitude are drawn so that the perpendicular lines from the 2 leads intersect the line connecting the centre of hexaxial reference system, to the point of intersection of perpendiculars, is the mean QRS vector



→ Normal QRS vector → + 59 degrees
Normal Range → - 30 to + 110 degrees

→ Right axis deviation → clock wise deviatⁿ of mean QRS vector
Left axis deviation → anti - clockwise deviatⁿ of mean QRS vector

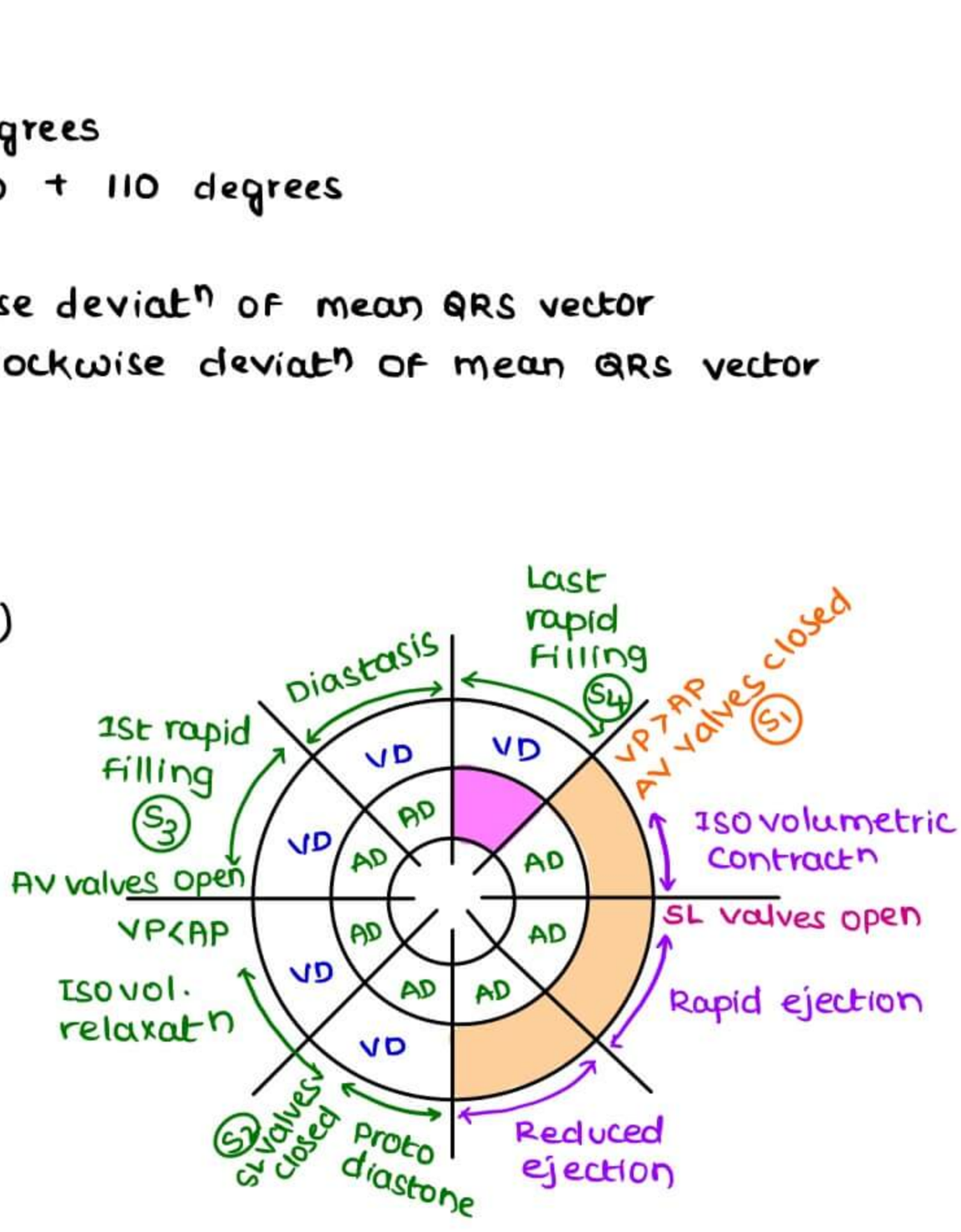
CARDIAC CYCLE

EVENTS (1 Heart Beat)

→ Duration → 0.8 Sec (72/60)

ATRIAL EVENTS (0.8 sec)
1. Systole (0.1 sec)
2. Diastole (0.7 sec)

VENTRICULAR EVENTS (0.8 sec)
Systole (0.3sec)
Diastole (0.5sec)



→ At higher HR, cardiac cycle duration decreases
→ Diastole duration decreases more than Systole

1. MEIOTONIC CONTRACTION

→ Strength of contraction goes on decreasing

→ Ex : Atrial systole

→ 0.05 sec → Dynamic

→ 0.05 sec → Adynamic

→ Ventricular systole starts after atrial systole dlt AV nodal delay

→ AV valves close (ventricular pressure > Atrial pressure)

→ S_1 produced (S_1 - 1st heart sound)

→ ISOVOLUMIC CONTRACTION

→ All valves are closed

→ Aortic pressure > Lt. ventricular pressure

→ In Aortic Regurgitatn, blood enters LV during isovol. contractn

→ ventricular pressure increases than Aortic pressure

→ Semilunar valves open

→ Ejection starts

a. Rapid ejectn

b Reduced ejectn

2. AUXOTONIC CONTRACTION

→ ↑ Strength of contractn

→ Ex : Left ventricular systolic ejection

VENTRICULAR DIASTOLE

→ 75-80% of ventricular filling is passive

→ last 20-25% is active (atria contracts)

a. PROTO DIASTOLE

→ Sudden change in the direction of blood (sudden backflow)

→ Semilunar valves close produces 2nd Heart Sound

b. ISOVOLUMIC RELAXATION

→ all valves closed (LV pressure > LA pressure)

→ In Mitral Regurgitatn, blood moves from LV to LA, even while ventricles are relaxing

→ In Regurgitant conditions, there is no true Isovolumic contractn or relaxation

c. Ventricular pressure decreases than atrial pressure

→ AV valve opens

→ Filling of ventricle starts

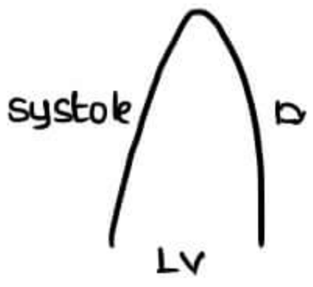
1. Rapid filling → causes S_3 (dlt turbulence)
2. Diastasis
3. Last rapid filling

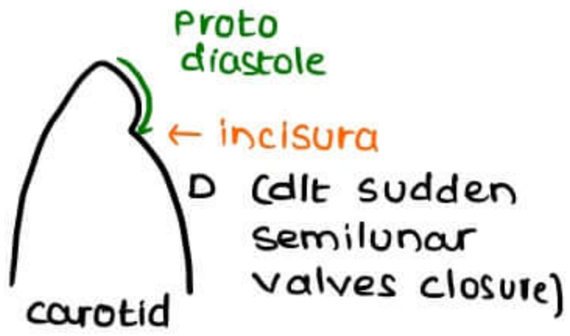
→ dlt atrial systole

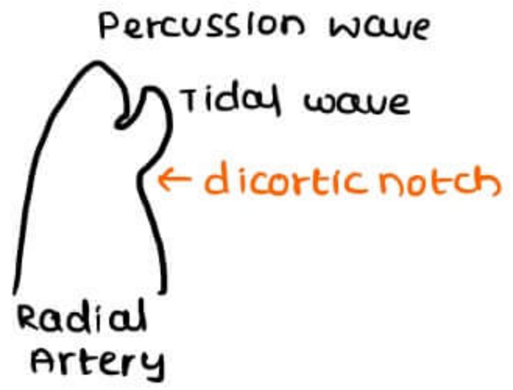
→ causes S_4 (Atrial sound)

PRESSURE - VOLUME CHANGES

ARTERIAL PULSE TRACING







→ recorded by DUDGEON'S SPHYGMOGRAPH

RADIAL PULSE TRACING

→ Percussion wave → true systolic peak

Tidal wave → dlt oscillatⁿ of vessel wall caused by ongoing pulse wave & reflected pulse wave

ATRIAL PRESSURE CHANGES

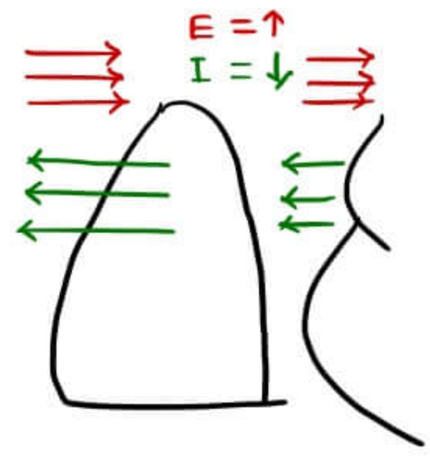
Q CVP changes ī breathing are

a E = +6 I = +2

b E = −6 I = −2

c E = +6 I = −2

d E = −6 I = +2



→ Rt. Atrial pressure ↓ ī inspiratⁿ

Rt. Atrial pressure ↑ ī expiratⁿ

1mm of Hg → 1.3cm of H_2O

JVP (JUGULAR VENOUS PRESSURE)

→ RA pressures are recorded from Internal Jugular veins

→ (N) → 0-5 cm H_2O → 0-2 mm of Hg

(± 5 cm H_2O)

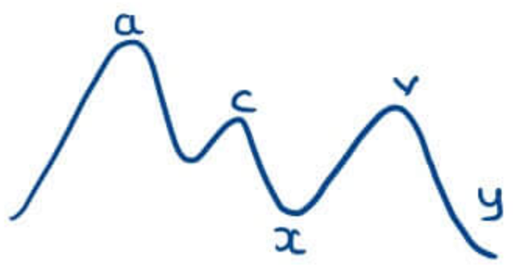
PCWP (PULMONARY CAPILLARY WEDGE PRESSURE)

→ LA pressure is recorded as PCWP

→ not a naturally occuring pressure

→ Normal value → 5mm of Hg or 5-8 cm of H_2O

JVP



a Wave → atrial systole

→ Larger 'a' waves | cannon 'a' waves seen in
- Tricuspid Stenosis
- AV Dissociation

c Wave → isovolumic contractⁿ of rt. ventricle
(ballooning backward of tricuspid valve into Rt. atrium)

x Downslope → ventricular ejection

v Wave → venous blood accumulates in rt. atrium d/t ISOVOLUMIC RELAXATⁿ OF Rt. ventricle

→ V wave is larger in Lt. Atrium

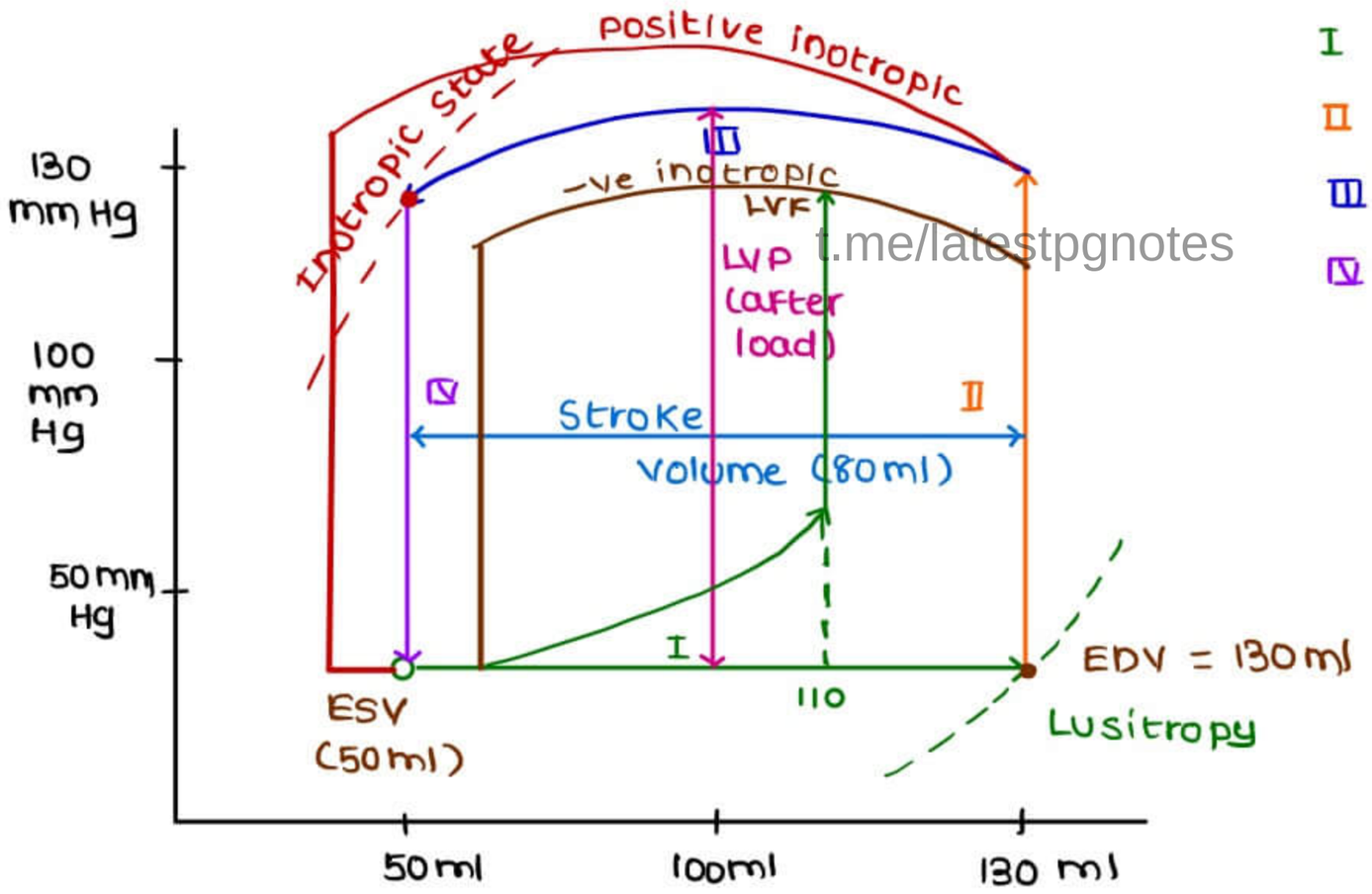
→ receives 1-2% (of bronchial circulatⁿ) more blood

→ also receives some amount of venous admixture of blood

y Downslope → ventricular filling

→ cardiac tamponade, constrictive pericarditis } abnormal y down slope

LEFT VENTRICULAR PRESSURE VOLUME LOOPS



I → Filling

II → Isovolumic contractⁿ

III → Ejection

IV → Isovolumic relaxatⁿ

PRELOAD → Load on muscle before contraction starts
- EDV (End Diastolic volume)
- EDP (End Diastolic pressure)

AFTER LOAD → Load against which ventricle contracts
- Aorta pressure for LV
- Pulmonary artery pressure for RV

Stroke volume → indicated by width of loop

LV Pressure → indicated by height of loop

→ contributed by afterload

COMPARISION BETWEEN RIGHT VENTRICLE & LEFT VENTRICLE

→ Pre load is same

→ After load is 5 - 7 times greater on left ventricle

Aortic pressure → 125 mm of Hg

Pulm. artery pressure → 25 mm of Hg

→ work output by left ventricle is 5-7 times that that by Rt. ventricle

LEFT VENTRICLE

1. ↑ Preload → ↑ Stroke volume → FRANK STARLING LAW

→ more the filling, more the fibre length, more the stroke volume

2. ↑ Afterload → ↓ Stroke volume

IONOTROPIC STATE / CONTRACTILITY STATE

→ Positive inotropism / ↑ myocardial contractility

→ height of loop & width of loop increases

→ DECREASED END SYSTOLIC VOLUME

→ Negative Inotropism / LEFT VENTRICULAR FAILURE

→ height & width of loop decreases

→ INCREASED END SYSTOLIC VOLUME

LUSITROPY / LUSIOTROPY | RELAXABILITY & DIASTOLIC FUNCTION

→ ALTERED LUSITROPY

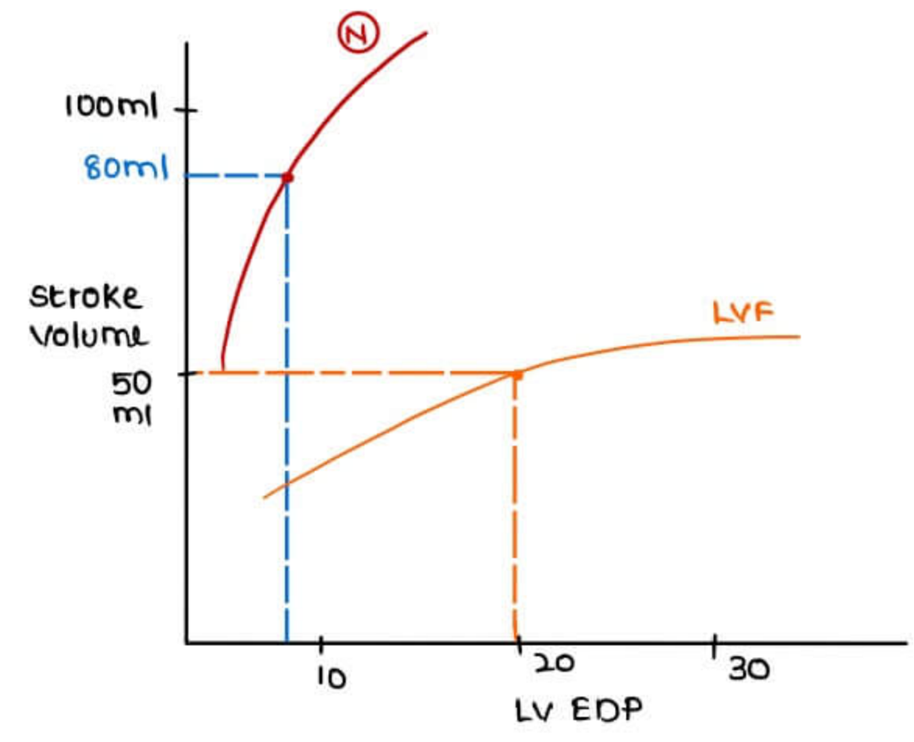
→ Occurs in constrictive pericarditis & cardia tamponade

→ EDV decreases, End diastolic pressure increases

FRANK STARLING CURVE

→ 80 ml of Stroke volume corresponds to 5-10 mm of LVEDP

→ On negative inotropism, stroke volume decreased & LV EDP increased & End systolic volume increases, End systolic pressure also increases



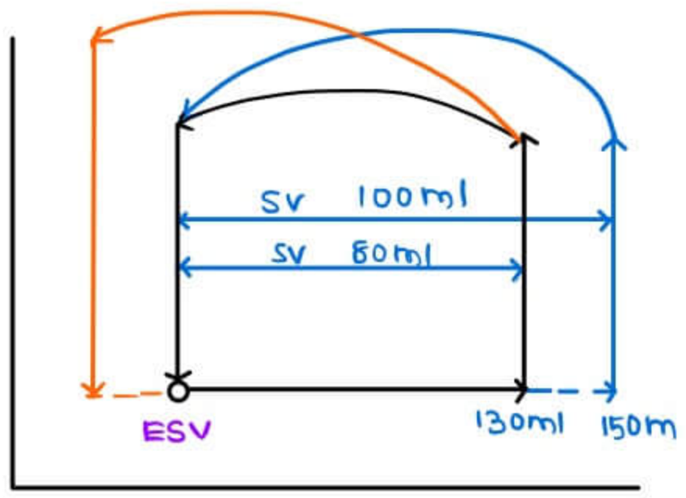
LV PV LOOP

→ ↑ Preload

↑ contractility

↑ contractility

↑ Preload



↑ Preload

→ ↑ Stroke volume

→ ↑ height

→ Normal End Systolic volume

→ characteristic feature of Frank Starlings law

↑ contractility

→ ↑ Stroke volume

→ Normal End diastolic volume

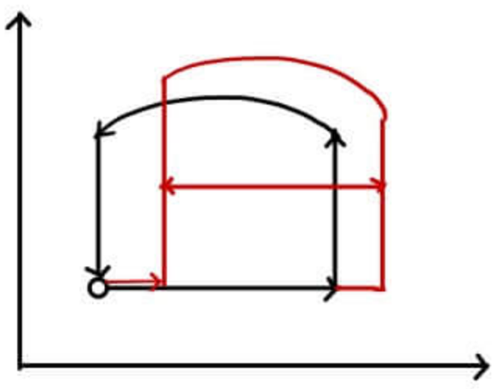
→ ↓ End Systolic volume

↑ AFTERLOAD

→ ↓ Stroke Volume

→ ↑ End Systolic volume

↑ End diastolic volume



1. MITRAL STENOSIS

→ ↓ EDV (Preload)

→ ↓ Stroke volume

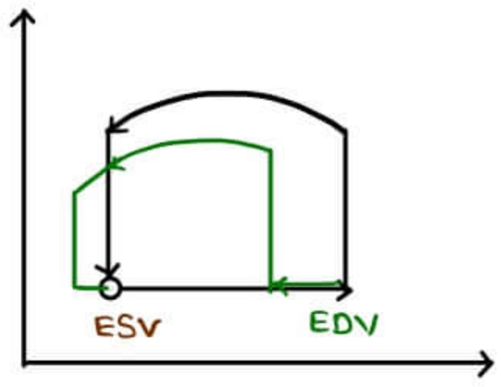
→ ESV constant (normal)

→ compensatory changes

→ ↓ aortic pressure (after load)

↓

↑ Stroke volume



→ LV PV LOOP SHIFTED TO LEFT

2. MITRAL REGURGITATION

→ ESV decreased

→ EDV increased

→ SV increased

→ NO true isovolumic contract^{n}

→ blood goes into LA

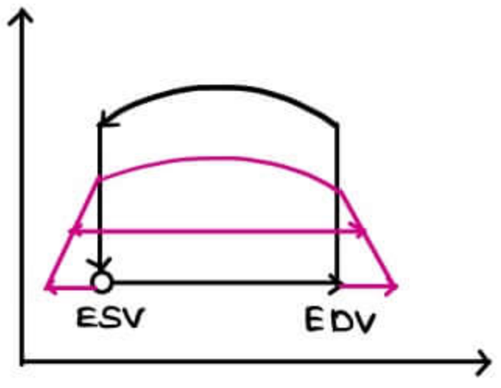
→ NO true isovolumic relaxat^{n}

→ blood goes into LA

→ Height decreases

→ ↑ Preload

→ ↓ After load

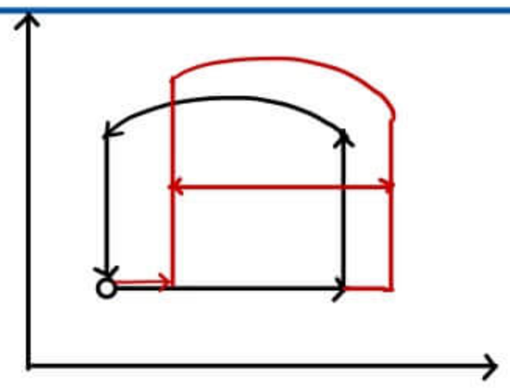


3 AORTIC STENOSIS

→ ↑ After Load

→ ↓ SV

→ ↑ ESV



4. AORTIC REGURGITATIONS

→ ↑ EDV

→ No true isovolumic contract^{n}

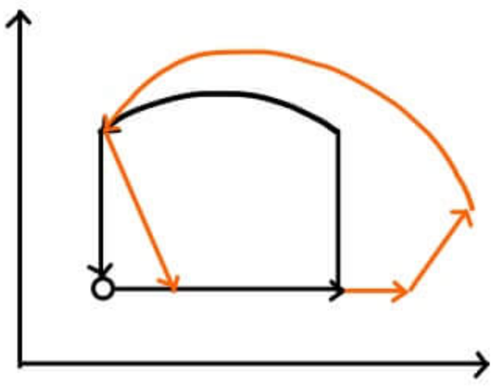
→ blood received into LV

→ No true isovolumic relaxat^{n}

→ blood recieved into LV

→ ↑ Preload

→ ↓ Afterload



CARDIAC OUTPUT

Q HR $_{max}$ on stress test of 40yr old man (220 - age)

a 160 c 200

b 180 d 220

Q Dye Dilution technique. Dye leakes out of capillaries rapidly. How will it affect CO & ECF volume

a Both high c no error in CO & ECF volume

b Both Low d no error in CO & ECF volume

CARDIAC OUTPUT

$$CO = SV \times HR$$

$$= (70\text{-}90) \times 72$$

$$= 5 \text{ ltr/min}$$

CARDIAC INDEX $$\frac{CO}{BSA} = \frac{5L}{1.7\ m^2} = 2.9 - 3 \text{ Ltr/min/m}^2$$

FACTORS DETERMING CARDIAC OUTPUT

STROKE VOLUME

→ depends on Strength of contraction

→ Intrinsic / Heterometric regulation

→ by changing Length

→ SV α EDV

α EDL

α Preload

→ more the filling, more the SV

more the venous return, more the SV

→ determined by frank starling law
→ venodilators reduce the preload
→ Arterial dilators reduce the after load

→ Extrinsic / Homeometric Regulation
→ no change in length
→ positive inotropic effect

→ Factors
↑ sympathetic discharge
↑ circulating catecholamines
Digitalis

→ INDICES

1. EJECTION FRACTION

$$EF = \frac{SV}{EDV} \times 100$$

→ Normal → 60 - 65 %.
→ decreases in LVF

2. LEFT VENTRICULAR SHORTENING FRACTION

$$LVSF = \frac{LVEDL - LVESL}{LVEDL} \times 100$$

LVEDL - LV end diastolic length
LVESL LV end systolic length

→ Normal → 40 %.
→ decreases in LVF

HEART RATE

1. 72 bpm ⟶ 130 BPM
→ ↑ HR → ↑ SV
→ STAIRCASE EFFECT
→ dlt ↑ sarcoplasmic ca^{2+} → contractions becomes stronger
→ reach peaks at 130 bpm


Staircase effect

2 130 bpm → 160 bpm
→ ↑ HR → SV constant
→ even though diastole duration decreased, diastasis disappears to maintain SV (Filling)

3 160 bpm → 180 bpm
→ Filling suffers
→ ↓ SV → ↑ HR

4. > 180 bpm → CO is virtually '0'

→ HR_{max} = 220 - age

BAINBRIDGE REFLEX

→ IV saline

↓

Sudden ↑ HR & CO

EFFECTS

1 LUSIOTROPY

2. CHRONOTROPY → effect on HR
   - catecholamines → ↑ HR
   - vagus → ↓ HR

3. DROMOTROPY → effect on impulse conduction speed

4. INOTROPY → effect on contraction
   - Sympathetics → ↑ contraction
   - vagus → do not ↑ directly

5. BATHMOTROPY → effect on excitability
   - Sympathetics → ↑
   - vagus → ↓

CATECHOLAMINES

→ ↑ HR
- ↓ Systole
- ↓ Diastole

→ ↑ SV

→ During systole

→ ↑ rate of tension development

→ During diastole

→ ↓ duration, yet filling remains uneffected

- ↑ rate of relaxation

→ acts on PHOSPHOLAMBAN (SERCA related protein)

- Keeps check on SERCA
- phosphorylates it → check of SERCA lifted

→ more removal of Ca^{2+} removed from Sarcoplasm

METHODS OF MEASUREMENT

1. DIRECT FICK METHOD

→ based on law of conservat^{n} of mass

$$CO = \frac{O_2 \text{ consumpt}^{n} \text{ (ml/min)}}{A-V\ O_2 \text{ difference}}$$

O_2 consumption by entire body

→ Arterial sample can be collected from any artery

→ venous sample can't be taken from peripheral veins

→ different for different parts of body

→ should be colled from PULMONARY ARTERY

- mixed venous blood
- representative of entire body

RENAL BLOOD FLOW MEASUREMENT

$$RBF = \frac{\text{consumption of 'x' by kidney (ml/min)}}{RA_x - RV_x}$$

RA_x – Renal Artery conc. of x

RV_x – Renal venous conc. of x

→ x = PAH (Para Amino Hippuric Acid)

2. STEWART - HAMILTON DYE DILUTION TECHNIQUE

$$V = \frac{I}{C}$$

I = intial volume of dye

C = concentrat^{n} of dye

→ A known initial volume of dye (I) is injected into vein

↓

Heart

↓ SV dilutes the dye

Artery

- mean concentrat^{n} calculated by serial measurements from continuous samples
- more the stroke volume, more the dissipation of dye

$$F = \frac{I}{Cxt} \times 60$$

I = initial volume of dye

c = mean concentrat^{n} of dye

t = time in seconds at which the dye appeared for the 1st time in artery

→ dye after injecting leaves via capillaries rapidly

→ NO change in CO measurement.

→ We collects the sample from artery before it reaches capillaries

→ NO change in ECF volume measurement

→ from leaking out of capillaries, it reaches interstitial Fluid

→ UNRELIABLE in

1 VSD (ventricular Septal Defect)

2. Regurgitation conditions

3. THERMO DILUTION METHOD

→ cold saline injected into a vein instead of Dye

↓

Heart

↓ Sv dissipates temp.

Artery

CIRCULATION

BLOOD FLOW

→ Largest fraction of blood flow goes to → LIVER

→ Liver → 25 - 27%

→ Kidney → 25%.

→ Blood flow per 100g | min

→ carotid body (Tissue) → 2000 ml | 100gm | min

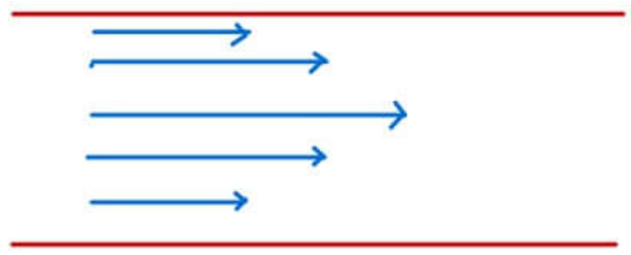
→ Kidney (organ) → 300 - 400 ml | 100gm | min

TYPES

1. LAMINAR / STREAMLINE BLOOD FLOW

→ follows parabolic path

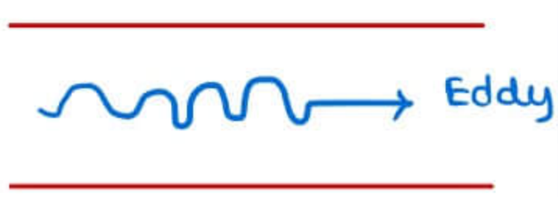
→ silent (stetho)



2. TURBULENT BLOOD FLOW

→ Eddy currents produced

→ sounds heard



REYNOLD'S NUMBER

→ determine the type of Blood Flow

→ Re < 2000 → Laminar

> 3000 → Turbulet

→ depends on

$$Re \propto \frac{VDP}{\eta}$$

V = velocity

D = Diameter

P = density

η = Viscocity

FOURTH POWER LAW

$$Flow \propto (r)^4$$

r = radius

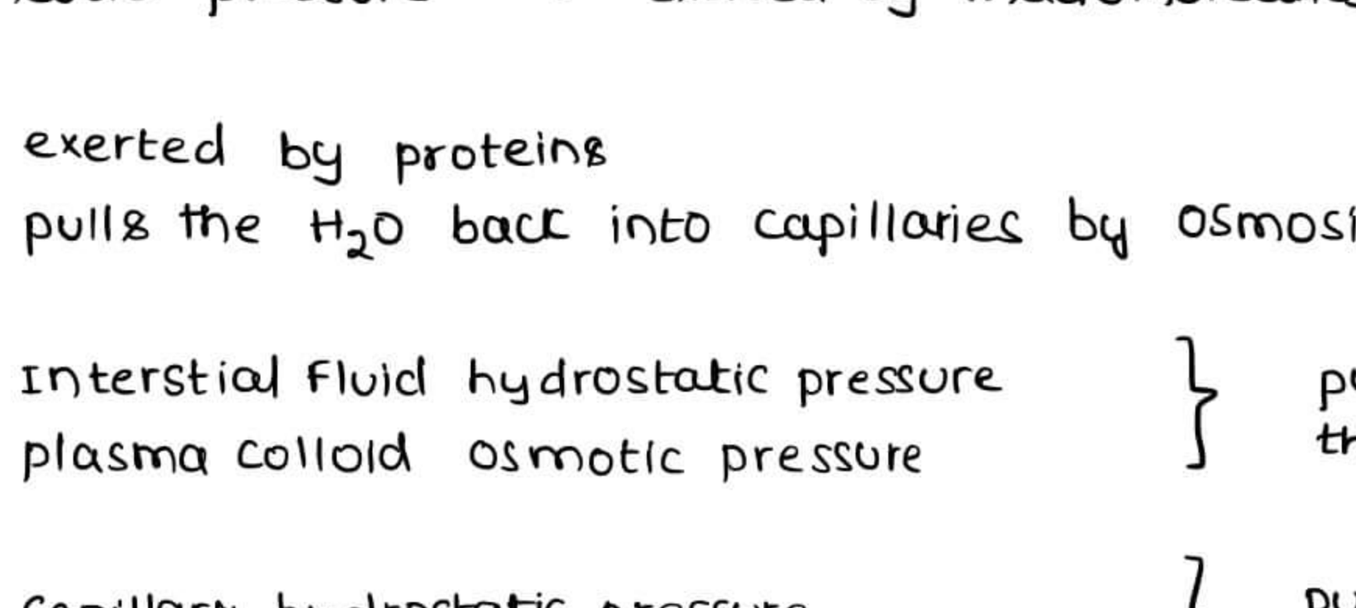
VISCOSITY

- → Unit → Poise (absolute viscocity)
- → Relative viscocity of water, plasma, whole blood → 1 : 3 : 5
- → Plasma → Newtonian fluid
  - → viscocity remains constant
- → whole blood → Non newtonian fluid
  - → viscosity keeps on changing
  - → FAHRAEUS - LINDQVIST EFFET
    - → effect of diameter on viscocity
    - → upto 2mm → ↓ diameter → ↑ viscocity
      <2mm → ↓ diameter → ↓ viscocity (paradoxical)
    - → dlt axial streamlining of RBC

STARLING'S FORCES (STARLING'S EQUILIBRIUM)

1. HYDROSTATIC PRESSURE

- → force exerted by accumulated fluid
- → moves the fluid away into neighbouring compartments
  more the accumulated fluid, more the pressure



2. COLLOID OSMOTIC PRESSURE

osmotic pressure → exerted by all osmotically active molecules
Oncotic pressure → exerted by macromolecules

- → exerted by proteins
- → pulls the H_2O back into capillaries by osmosis

- → Interstial fluid hydrostatic pressure
  plasma colloid osmotic pressure
  } pulls fluid into the capillary

  Capillary hydrostatic pressure
  Interstial fluid colloid osmotic pressure
  } pushes the fluid away from capillary

→ At Arterial end, net force pushes fluid out of capillary
At venous end, net force pulls fluid back into capillary

→ NET SUM OF FORCE ON ARTERIAL END & NET SUM OF FORCE ON VENOUS END ARE NOT EQUAL (NET force on arterial end is little greater)
→ some amount of fluid stays in interstitium forming INTERSTITIAL FLUID

LYMPHATICS

→ accessory routes by which extra interstial fluid drains out of the tissue & finally into venous system
→ Lymph ≅ Interstitial fluids (include proteins)
Digestic tract & Liver lymphatics contains more protein in Lymph & Interstitial mode
protein content in Lymphatics & interstitial fluid of
GIT & Liver → 5%
Other → 2-3%

→ FACTORS INCREASING FORMATION OF LYMPH (can cause EDEMA)
↑ capillary hydrostatic pressure
↓ Plasma colloid osmotic pressure
foot massage (Flow increased)

→ FUNCTIONS OF LYMPH
→ helps in macromolecular absorption
→ LACTEALS (milky appearance)
→ GIT Lymphatics
→ helps in absorptⁿ OF Long chain fatty acids (>18 carbon) in the form of chylomicrons

Q In the recumbent posture, max pressure difference is at
a Saphenous vein to Rt side of heart
b femoral artery to femoral vein
c Rt side of heart to cerebral vessels
d Rt. ventricle to pulmonary vein

FUNCTIONAL TYPES OF BLOOD VESSELS

1. WINDKESSEL VESSELS

→ Aorta, large arteries
→ shows WINDKESSEL EFFECT
→ aorta distends & accumulates the blood during ventricular systole ↑out rising pressure much
→ during Left ventricle diastole, aorta coils back & pushes the blood forward (potential energy → kinetic energy)

2 RESISTANCE VESSELS

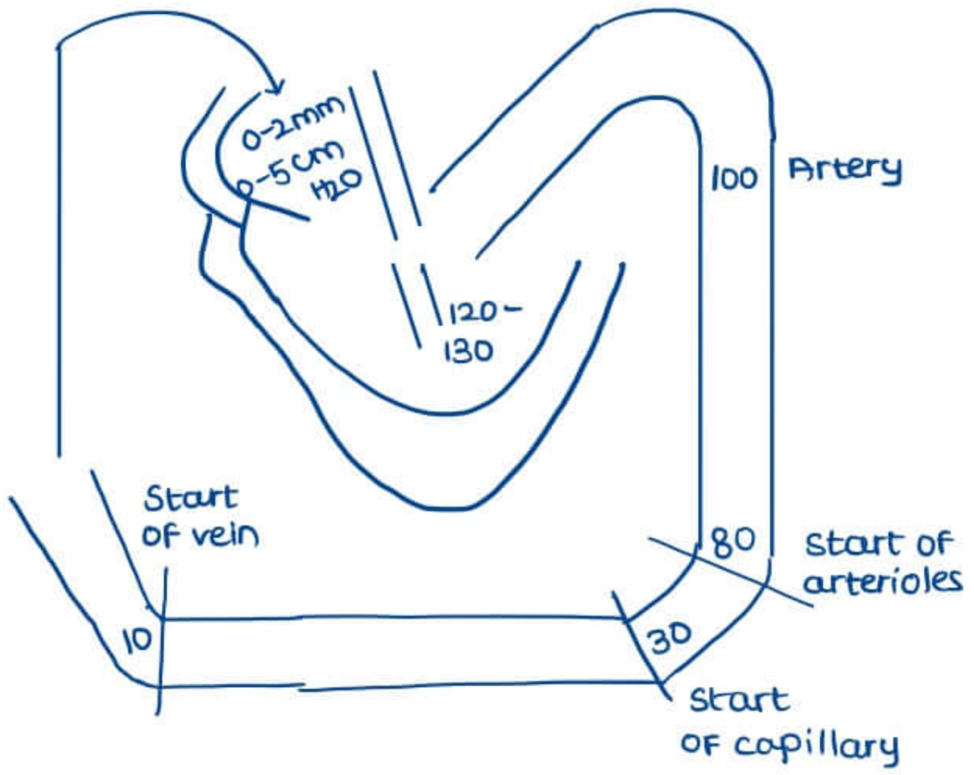
→ Arterioles

→ offer greatest resistance to blood flow

→ has maximum effect on Blood Pressure (pressure head drops maximally)

Greatest drop of pressure occurs at

↳ Arteriolar Segment (Resistance vessels)



Average capillary pressure

↳ 15-20 mm of Hg

Pressure of circulation in a dead person

↳ 6 mm of Hg dlt TISSUE PRESSURE

CRITICAL CLOSING PRESSURE

→ Arterial pressure of 20 mm of Hg

→ pressure below which blood flow stops & vessels close down

3 CAPACITANCE VESSELS

→ veins

→ more than half the volume of blood (54%) is presents in venous compartment

BLOOD VOLUME

Arteries & Arterioles	→	10-15%.
Capillaries		5-8%.
Lungs		15-18%.

4 EXCHANGE VESSELS → capillaries

5. THOROUGHFARE VESSELS → A-V anastomosis / shunt vessels

BLOOD PRESSURE

Q BP → 90 mm Hg, CO → 5.4 ltr/mn, Peripheral Resistance ?

a 1 R c 4 R

b 2 R d 6 R

Q Stroke volume is best indicated by Pulse pressure

Q BP recorded by iv catheter & Sphigmo manom (gives slight higher values) (Regulath)

Q 1st → cuts 9th Nerve → ↑ BP

and → cuts 10th Nerve → no change

DETERMINANTS OF ARTERIAL BLOOD PRESSURE

→ OHM'S LAW

$$Q = \frac{\Delta P}{R} \qquad CO = \frac{BP}{PR} \qquad BP = CO \times TPR$$

PRESSURE IN CIRCULATION - DIMENSIONS

1. $P_1 - P_2$

→ blood flows from high pressure to low pressure

2. Hydrostatic factor

→ Beneath the surface of water, pressure increases

→ at Tricuspid valve level → '0' pressure level | Reference

→ below this level → positive pressure

above this level → negative pressure

3. TRANSMURAL PRESSURE → pressure across the vessel wall

Q CO = 5.4 L/min, BP = 90 mm of Hg, PR ?

→ $PR = \frac{BP}{CO}$

PR units → PRUs / R

$1\,R = \frac{1mm\ of\ Hg}{1ml\ /\ Sec}$

5.4 ltr/min = 90 ml/sec

→ $\frac{90}{90} = 1R$

TYPES OF BP

1. SYSTOLIC BP

→ highest pressure of systole

→ indicates the force of contraction

2 DIASTOLIC BP

→ lowest pressure of diastole

→ indicates peripheral Resistance

→ Greatest peripheral resistance offered by skeletal muscle contract^n (> 50 %)

→ cutaneous circulation contributes to 20-30% of peripheral resistance

CALCULATED PRESSURES

3. PULSE PRESSURE → SBP - DBP

→ indicates Stroke volume

→ DBP + Pulse pressure = SBP

4 MEAN ARTERIAL PRESSURE

→ Average pressure

→ MAP = DBP + ($\frac{1}{3}$rd of Pulse pressure)

→ Ex: SBP = 120 mm of Hg

DBP = 80 mm of Hg

Arithmatic Average → 200/2 = 100 mm of Hg

DBP + PP = SBP

DBP + $\frac{1}{2}$ PP = arithematic mean/average

MAP = DBP + 1/3 rd of PP

= 80 + 1/3 x40

= 80 + 13 = 93 mm of Hg

→ MAP is not the exact arithmatic average dlt longer durat^{n} of Diastole

MEASUREMENT OF BP

→ Riva Rocci cuff measurements are on little higher side dlt the Dissipation of cuff pressure

→ OBESITY → higher pressures are recorded by Riva Rocci cuff

→ ATHEROSCLEROSIS → higher pressures are recorded by the cuff

SMALL CUFF – ERRORS

→ higher pressures are recorded

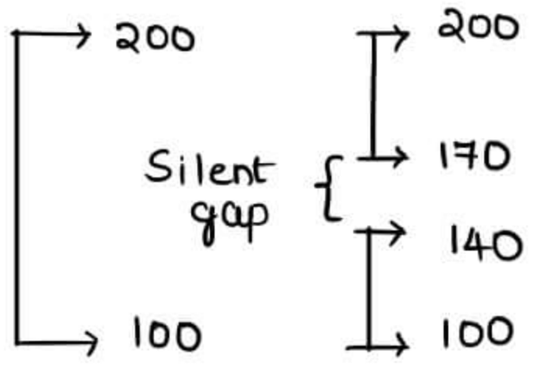
– tends to occlude the Brachial artery incompletely

AUSCULTATORY GAP / SILENT GAP

→ sounds disappears & reappears, silent gap persists in between

→ Reason not known clearly, might be atherosclerotic

→ Low Systolic & normal diastolic BP recorded



KOROTKOFF'S SOUNDS

→ Phase 4 / muffling of sound is more appropriate for taking as Diastolic pressure

→ Phase 1, 2, 3 → TAPPING SOUNDS
- cuff pressure is blw systolic & Diastolic pressure

Phase 4 → MUFFLING SOUND
- cuff pressure reached diastolic pressure
- Sound is dlt turbulent blood flow
- Should be taken for DBP measurement

PHASE 5 → DISAPPEARANCE OF SOUND

- turbulence converted to laminar flow
- majority considered it for DBP measurement as it is easily reproducible (ease of use). compared to muffling

→ Differences blw Phase 4 & phase 5 → 5 mm of Hg

→ Under some high turbulance conditions, Phase 4 & phase 5 difference is around 40 mm of Hg

→ Phase 4 is considered as DBP in such conditions

REGULATION OF BLOOD PRESSURE

1. Chemical
2. Neural / Short term

CHEMICAL REGULATION

VASOCONSTRICTORS (↑BP)

1. Vasopressin
2. Noradrenaline
3. Angiotensin
4. Endothelin (most potent local vaso constrictor)

   ET_{2B} ® → only endothelin Receptor that causes vasodilatⁿ

   → It is for inherent check
5. Urotensin (most potent circulating vasoconstrictors)

Q Angiotensinogen formed by LIVER

→ plasma protein

VASODILATORS

1. HYPOXIA

   → causes VD every where EXCEPT in LUNGS

   → ATP sensitive K^+ channels are present every where → R/F VD

   O_2 sensitive K^+ channel in the membrane of pulmonary vessel → R/F VC

2. CO_2 → Local vasodilator

   → Systemic vasoconstrictor (if it accumulates in medulla)

3. H^+
4. Lactic Acid
5. Histamine
6. Adenosine → coronary vasodilator EXCEPT in afferent arteriole of KIDNEY)
7. Nitric oxide / Endothelium derived Relaxing factor (Strongest VD)

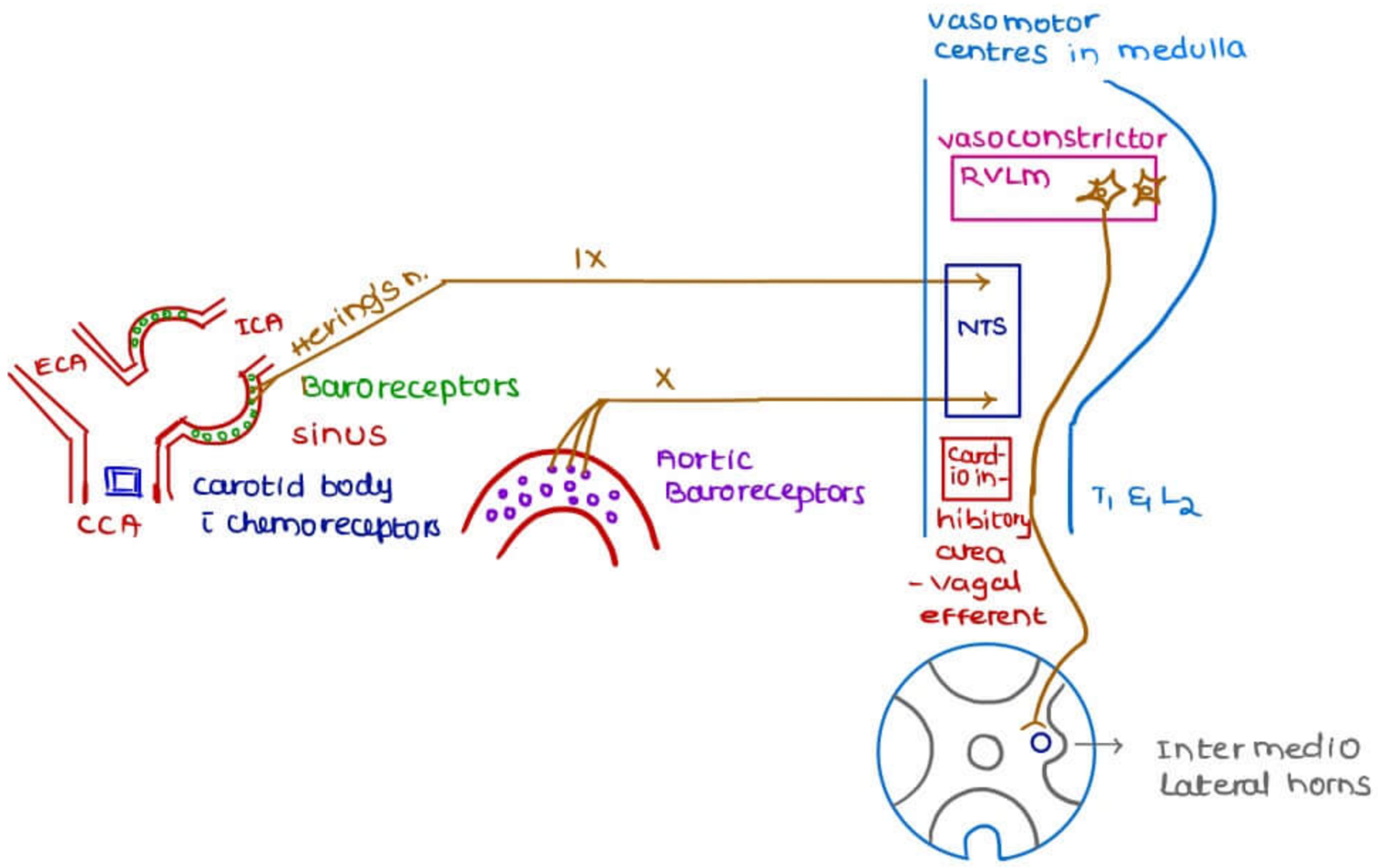
NEURAL / SHORT TERM REGULATION

BARORECEPTOR MECHANISM

→ BR impulse frequency is highest at 180 mm of Hg

→ BR system is most sensitive at 100 mm OF Hg

→ This is the NATURAL SET POINT for BR



RVLM (Rostral ventro lateral medulla) / vasoconstrictor area

4. CARDIO ACCELARATOR AREA → present in medulla behind cardioinhibitory area

BARO RECEPTORS

→ mechano sensitive receptors

→ Strech receptors

→ Spray type endings

→ IX & X th Nerves are called as BUFFER NERVES (Buffer the changes of BP)

→ Operational Range

carotid baroreceptors	→	60 – 180 mm of Hg
Aortic baroreceptors	→	90 – 210 mm of Hg

FREQUENCY MODULATED SIGNALLING

→ At 100 mm of Hg, Steady impulse discharge from baroreceptors & maintains the VASOMOTOR TONE

→ VASOMOTOR TONE / VASO CONSTRICTOR TONE

→ VM centre is continuously tonically active

→ blood vessels are 50% constricted state

→ When BP increases, impulse discharge frequency also increases

→ When BP decreases, impulse discharge frequency also decreases

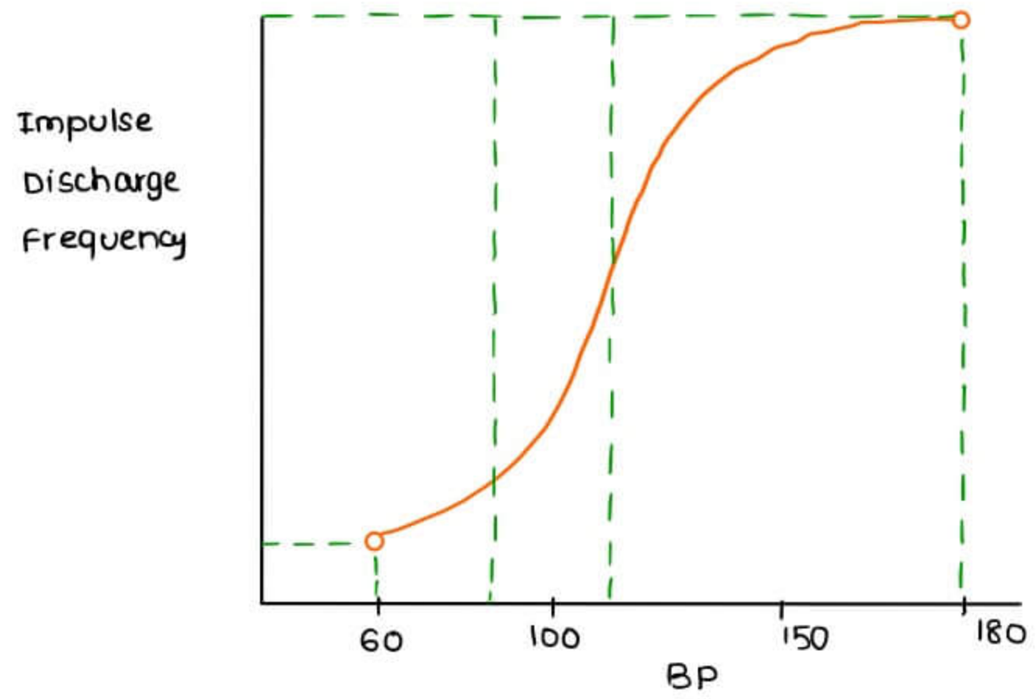
→ Least impulse discharge is at → 60 mm OF Hg

→ Highest impulse discharge is at → 180 mm of Hg

→ Steepest impulse discharge is around → 100 mm of Hg

EFFECT OF CUTTING / SECTIONING OF IX & X Nerves

→ ↓ impulse discharge to VMC,
sensed as a fall in blood pressure, ī in 1 sec BP increased



→ Sleepest around 100 mg of Hg (very sensitive)

BARORECEPTOR RESETTING to New BP → done ī in 48 hrs

2. CHEMORECEPTOR MECHANISM

CAROTID BODY

→ present in common carotid Artery
→ chemosensitive cell → GLOMUS CELL
↳ sensitive to hypoxia
↳ BP from <60 ± 30 mm, causes ↓ Blood Flow (hypoxia)

→ upto 60 mm of Hg → controlled by Baroreceptor mechanism
→ From 60 – 30 mm of Hg → controlled by chemo receptors
→ <30 mm of Hg → controlled by CNS ISCHEMIC RESPONSE

3. CNS ISCHEMIC RESPONSE / LAST DITCH STAND

→ at such Low BP, Blood Flow to VMC is decreased & CO_2 accumulates around VMC & Stimulates vasoconstrictor center & BP rises immediately

→ CUSHING'S REACTION

- ↑ ICT
- (↑ CSF Pressure)
- ICT > Cerebral artery pressure

} CNS ISCHEMIC RESPONSE

INTERMEDIATE TERM REGULATION

1. ADH & Thirst mechanism
2. Capillary fluid mechanism
3. RAAS (intermediate to long term)
4. ANP (Atrial Natriuretic Peptide) mechanism

ANP → Kidney → Natriuresis
Diuresis

LONG TERM REGULATION

KIDNEY BODY FLUID MECHANISM

→ urine out put adjusted on a long term basis

at 100 mm of Hg, Urine output → 1 - 1.5 ltr/day (normal)
at 60 mm of Hg, Urine output → Zero
at 160 mm of Hg, Urine output → 4-6 times the normal

REGIONAL CIRCULATIONS

CAPILLARY CIRCULATION (VASOMOTION) → continuous circulation

CORONARY CIRCULATION

→ At base of Aorta, Rt & lt coronary arteries arises
→ Lt coronary artery gives lt circumflex artery & descends as Lt. anterior descending artery (LAD) | Widow's Artery (commonly involves in MI)
→ Heart receives about 4-5% (225 - 250 ml) of CO
→ AUTOREGULATION OF BLOOD FLOW
  ↳ Adenosine → main autoregulator
    → causes vasodilation
→ A-V O_2 difference → 75% (highest in heart)
→ Heart receives the blood flow during diastole
  ↳ Epicardial vessels receive blood flow during systole
  ↳ Endocardial vessels receive blood flow during diastole
    ↳ endocardial vessels are compressed in systole
    ↳ endocardial vessels open up during diastole
    ↳ At higher heart Rates, sub endocardial infarcts are more common as diastole suffers more

NUTRITION OF HEART

↳ Primary source of energy is free fatty acid (67% of energy)
↳ 30% of energy derived from Glucose

ECONOMY OF MYOCARDIUM

↳ $\frac{\text{Work output}}{O_2 \text{ consumpth}}$

↳ Best economy → ↑ SV & ↓ HR
↳ 2nd Best economy → N SV & N HR
↳ Bad Economy → any SV & ↑ HR (O_2 consumpt^n ↑ proportionately)
↳ worst economy → any CO maintained against ↑ afterload

BLACK OUT

→ Black out Results from → Positive G (Gravity)

Black out
(positive G)
↓
Blood is pooled in LL
↓
↓ venous return to Rt side of heart
↓
↓ Cerebral blood flow

RED OUT

Red out
(negative $^{\circ}G^{2}$)
↓
↑ venous return to Rt. heart
↓
Engorged cerebral Blood vessels

EXERCISE

ISOTONIC / DYNAMIC EXERCISE

→ Shortening occurs
→ tension constant
→ cycling, running, aerobics

ISOMETRIC / STATIC EXERCISE

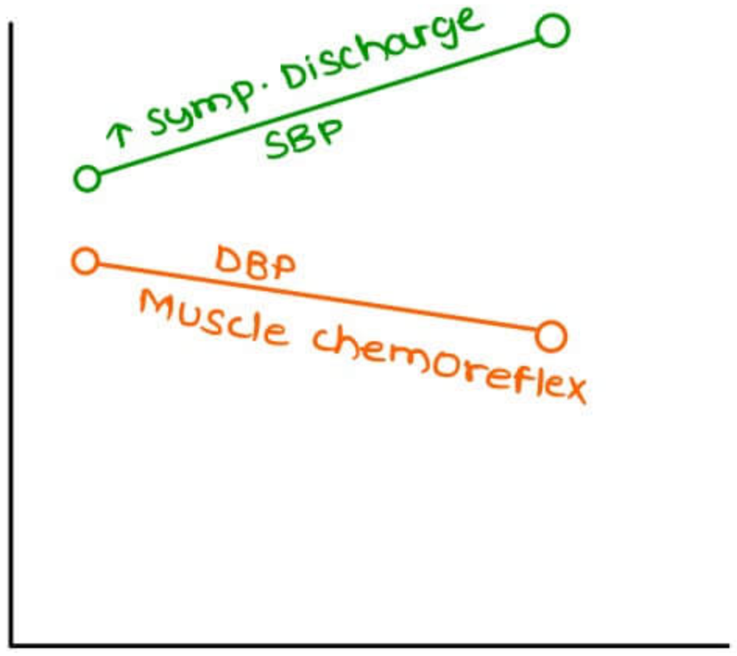
→ length remains same
→ tension develops
→ pulley, weight lifting

ISOTONIC EXERCISE → advised in Hypertensive individuals

→ ↑ HR
→ ↑ SV
→ ↑ CO

} ↑ sympathetic discharge

MUSCLE CHEMOREFLEX
(H⁺, CO_2, Lactic acid)
↓
vasodilatⁿ in skeletal muscles
↓
↓ PR
↓
↓ DBP



ISOMETRIC EXERCISE

→ Contra Indicated in hypertensives

Isometric
↓
Sustained Tension development
↓
Sustained compression of blood vessels in Skeletal muscles
↓
↑ Peripheral Resistance
↓
↑ DBP

→ MEAN ARTERIAL PRESSURE → increases
→ ↑ HR
→ Cardiac out put not increases
↳ as muscle is under Sustained contraction
↳ ↓ SV dlt ↓ venous return

RESPIRATORY SYSTEM PART 1

INTRODUCTION

→ 23 generations of Respiratory Tree
→ Trachea → 0th generation
→ Further divisions → new generations
→ First 7 generations → cartilaginous
→ non compressible

→ Last 16 generations → non cartilaginous
→ compressible
→ Thin layer of Smooth muscles +nt
→ Some Neuro endocrine cells +nt
APUD
KULCHITSKY CELLS

→ First 16 generations CONDUCTING ZONE (DEAD SPACE)
Last 7 generations → RESPIRATORY ZONE

→ CLARA CELL

→ present in middle & Lower generations

→ Synthesizes Surfactant like materials

→ surfactant synthesis begins by 20 weeks of gestation

surfactant begins to appear by 28-32 weeks of gestation

→ Last 6 generations → ACHILLE'S HEEL OF RESPIRATORY SYSTEM

– muco ciliary clearance is weakest

MECHANICS OF BREATHING

→ In normal quiet breathing

inspiratⁿ is Active (work done)

Expiratⁿ is passive

MUSCLES FOR BREATHING

1. DIAPHRAGM (major contribution in males) → Abdomino thoracic breathing
2. EXTERNAL INTERCOSTALS (major Contributⁿ in females → Thoraco abdominal breathing

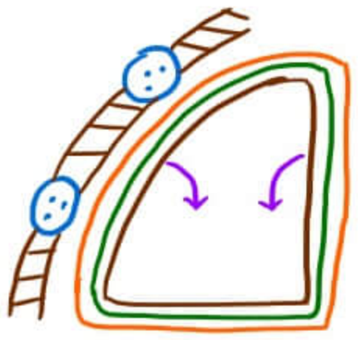
ACCESSORY MUSCLES

1. Ala nasi
2. SCM [Sternocleidomastoid]
3. Scaleni
4. Serratus anterior

Muscles for forceful Expiration

→ Abdominals

Internal Intercostals → depress the rib cage



PRESSURES

1. INTRA PLEURAL / INTRA THORACIC PRESSURE

→ around the lungs, blw the 2 layer of pleura

→ mostly negative except for forceful expiration

→ keeps the lung distended

→ Lung has inward recoil tendency, it counteracts it

→ Primary dlt inward recoiling of Lung

→ during recoil visceral layer is pulled inward

→ which creates piston like action & develop negative pressure

PLEURAL FLUID

→ keeps the pleurae together especially during inspiration

→ during inspiratⁿ, thoracic cage along ↄ parietal pleura pulled outward

Lungs along ↄ visceral pleura pulled inwards during recoil – creating HYDRAULIC TRACTION

→ pleural fluid keeps the pleurae together during inspiration

ROLE OF LYMPHATIC PUMP

→ By draining away excess pleural fluid, it helps to maintain negative pressure blw 2 layer

→ Parietal pleura secretes pleural fluid
→ visceral pleura absorbs it
→ excess is drained by lymphatic pump

→ Greatest negative intra thoracic pressure created at muller's maneuver
→ Greatest positive intra thoracic pressure created at valsalva maneuver

PLEURAL PRESSURES

QUIET BREATHING

→ at start of inspiratn → − 5 cm of H_2O
→ at end of inspiratn → − 7.5 cm of H_2O

2.5 cm of H_2O Pressure change

→ at apex of Lung → − 10 cm of H_2O
→ towards base → − 2 cm of H_2O

} dlt weight of Lung

FORCEFUL BREATHING

A. INSPIRATION

Deep Sigh, Deep yawn → − 30 cm of H_2O

First cry, First breath → − 60 cm of H_2O

Muller's maneuvre → − 100 cm of H_2O
→ Forced inspiratory effort against closed glottis

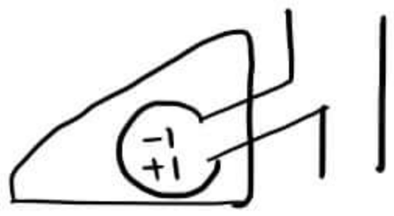
B. EXPIRATION

Dry cough, Sneeze → + 30 to + 50 cm of H_2O

yelling, opera Singing → + 60 to + 80 cm of H_2O

valsalva maneuvre → + 100 to + 150 cm of H_2O
→ Forced Expiratory effort against closed glottis

2 INTRA ALVEOLAR PRESSURE



→ at the start of Inspiration → − 1

at the start of expiration → + 1

3. TRANS PULMONARY PRESSURE

→ alveolar pressure − Intrapleural pressure

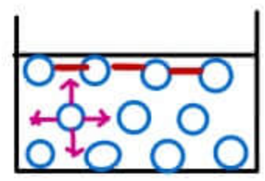
→ responsible for opening of Lungs during inspiratn

4. TRANS MURAL PRESSURE

→ pressure across the airway wall

→ pressure inside the airway − Pressure in interstitium

SURFACE TENSION & SURFACTANT



→ Tension created by surface molecules of a fluid

→ measured by STALAGMOMETER

→ Alveoli lined ī fluid & air → FLUID AIR INTERFACE

→ Surface tensn created

SURFACTANT

→ Surface active material that reduces the surface tension

↓ collapsibility OF the lung

↑ Distensibility OF the lung

PNEUMOCYTES

→ alveolar epithelial cells

→ Type 1 → covers 93% SA OF alveoli

→ helps in gaseous exchange

Type II → covers 5% SA OF alveoli

→ synthesize surfactant

TYPE I & TYPE II exists at Ratio OF 1:1

→ Type II cells are very small & numerous

During development, entire area is covered by Type II cells

at the time OF birth, type 1 replace type II cells

In alveolar injury, Type I degenerates, Type II regenerates

→ PHYLOGENY RECAPITULATES ONTOGENY

TYPE III → cover 2% SA OF alveoli

→ acts as chemoreceptor cells

SURFACTANT

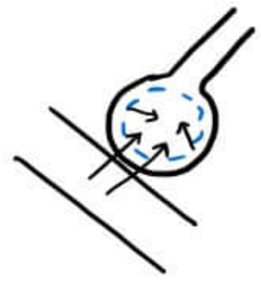
→ precursor stage → Tubular Myelin

→ CONSTITUENTS

1. DPPC (DiPalmitoyl Phosphatidyl choline) (major)
2. Surface apo proteins (Sp A, B, C, D)
   → regulate the surfactant turnover
3. Ca^{2+} ions → helps in faster spread of surfactant

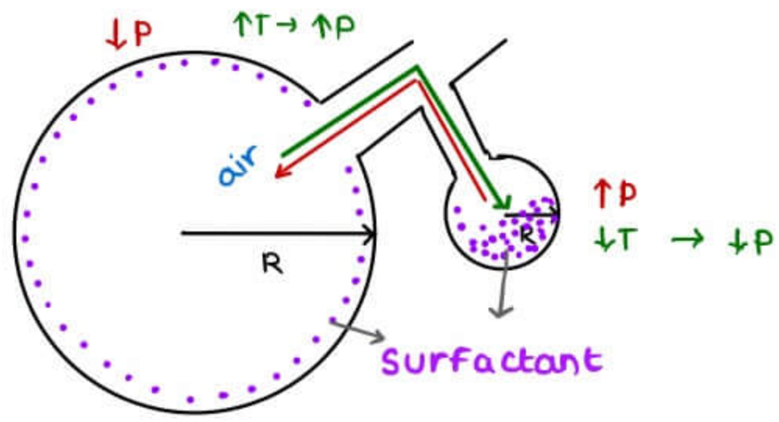
→ FUNCTIONS

1. ↓ Surface tension
2. ↓ Collapsibility
3. ↑ distensibility (compliance)
4. Keeps alveoli dry
5. Stabilizes the alveolar system of interdependence



LAPLACE'S LAW

$$P = \frac{2T}{R}$$



→ Structures not obeying Laplace's law
↳ ureter (not a hallow viscus)

→ IN THE ABSENCE OF SURFACTANT → ALVEOLI COLLAPSE

→ In the presence of surfactant
→ When the alveolus is small, surfactant is concentrated, ST is less & compliance is more
→ Function of alveolar system is established
→ no collapse

COMPLIANCE

Q What is the specific compliance of the lung
a compliance upon body weight
b compliance upon body surface area
c compliance upon FRC
d compliance upon TLC

Q compliance is greatest during which stage of Breathing
a Start of inspiration
b mid inspiration
c End inspiration
d Expiration

COMPLIANCE

→ measure of Stretchability / distensibility of Lung

→ $\frac{\Delta V}{\Delta P}$

→ compliance $\propto \frac{1}{ST}$

→ TYPES

1. STATIC COMPLIANCE
   - → 200ml / cm of H_2O
   - → 200 x 2.5 = 500 ml
   - → Lungs + Thorax = 100 - 110 ml / cm of H_2O

2. SPECIFIC COMPLIANCE
   - → compliance upon FRC (Functional Residual capacity)

3. DYNAMIC COMPLIANCE
   - → changing compliance ($\Delta V / \Delta P$) ī stages of Breathing
   - → a. at the start of Inspiration (near the lower lung volumes)
     - → alveoli are small
     - → ↓ ST
     - → ↑ compliance

   - b. by the end of inspirat^n (at higher lung volumes)
     - → alveoli large
     - → ↑ ST
     - → ↓ compliance

RESTRICTIVE LUNG DISEASES

→ Shallow & rapid breathing near lower lung volumes (most economical way of breathing)

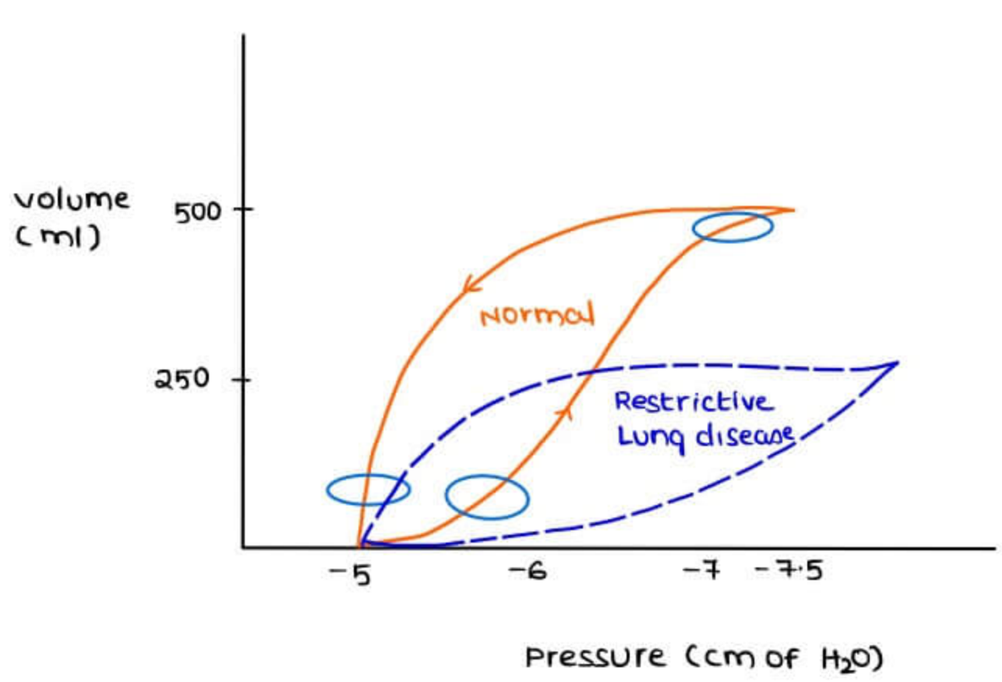
HYSTERESIS

→ system does not follow identical path on application & withdrawal of stimulos

→ STEEP PORTION INDICATES A GOOD COMPLIANCE
   - → For a small pressure change the volume distens^n is good

→ By the end of Inspirat^n, curve becomes FLAT
   - → For ↑ in pressure, no significant change in volume distension

→ Highest compliance is present at end of expiration → STEEPEST CURVE

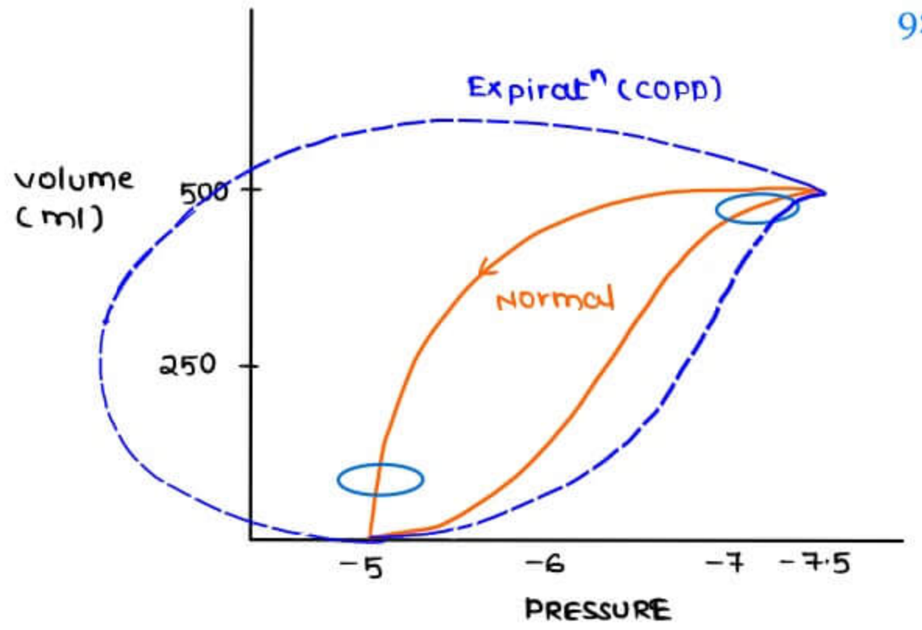


RESTRICTIVE LUNG DISEASE

→ curve comes down

→ Lungs are not distending on increasing pressure

→ Poor compliance



COPD

→ WORK OF BREATHING = $\Delta P \times \Delta V$

→ Area covered under the curve

→ during expirat^{n} more work done (normally no workdone during expirat^{n})

WORK OF BREATHING

IN HEALTHY INDIVIDUALS

1. compliance work (65%)
2. Airway Resistance work (28%) → increases in COPD
3. Tissue Resistance work (7%) → increases in Interstitial Lung disease

IN COPD INDIVIDUALS

→ Breath slow & deep near higher Lung volumes

→ EQUAL PRESSURE POINT (EPP)

→ In normal individuals

→ at maximal forceful expirat^{n},

at the start, intra alveolar pressure is +20 (suppose)

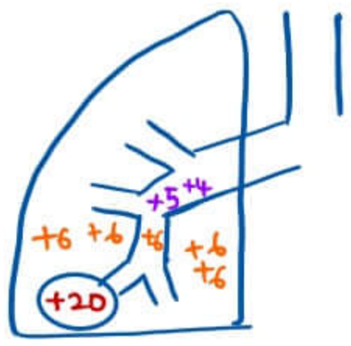
pressure at mouth is "0"

Tissue pressure is +6

The pressure head gradually decreases, and at +6,

↳ The pressure inside the airway is equal to outside pressure

↳ Beyond this point, the pressure inside the airway is less, dynamic compression is possible & respirat^{n} is laborious



→ EPP occurs in 1st 7 generations in normal individuals

→ In COPD, EPP shifts to lower airways (non cartilagenous)

↳ Dynamic compression occurs, remind expirat^{n} is Laborious

↳ overcoming measures

1. SLOW & DEEP INSPIRATION (dlt more negative intrathoracic - pressure created higher Lung volumes attained)
2. EXHALES SLOWLY (to dissipates pressure head slowly
3. PURSING OF LIPS / PINK PUFFERS

↳ Creates artificial resistance at outlet

↳ helps in widening the airways

→ PINK PUFFERS → EMPHYSEMA

→ BLUE BLOATERS → CHRONIC BRONCHITIS

LUNG VOLUMES & CAPACITIES

Q Residual volume to be measured in a patient by Helium Dilution Method.
Initial Helium concentration → 10%.
Final Helium concentration → 6%.
Volume of Spirometer → 2 litres
What is the Residual volume

Q Residual volume to be measured in a patient by nitrogen washout method.
It was found that the volume of N_2 in the residual volume was 800ml.
How much is the RV ?

a. 800 ml
c. 1000 ml
b. 1200 ml
d. 1600 ml

Nitrogen comprises roughly 80% of air in lungs
IF 80% = 800 ml
RV = 1000 ml

Q With each quiet inspiration, how much of the alveolar air get replaced ?

a. half
c. One Seventh
b. One third
d. One tenth

Air in the Lungs at the end of quiet expiration = FRC = 2300 ml
Air inspired with quite inspiration = TV = 500 ml
Out of 500 ml, 150 ml stays in the dead space, 350 ml reaches the alveoli
Thus, amount of air replaced

= 350 | 2300 = 1/7

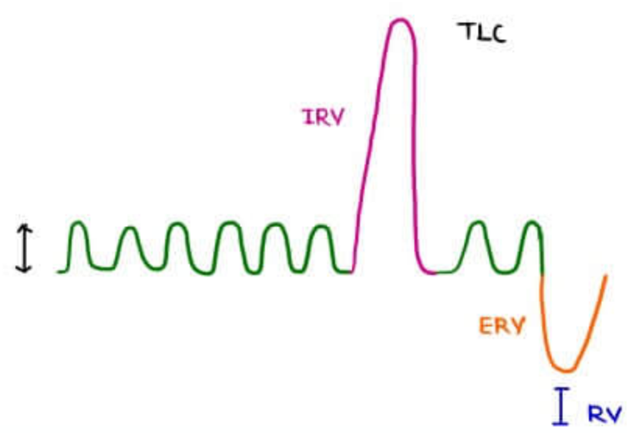
Q Closing volume of Lungs is

a. Residual volume
c. Just above RV
b. 10% below RV
d. approaching FRC

→ measured by HUTCHISON'S SPIROMETER

1. TIDAL VOLUME (TV) (500ml)
→ amount of air that We can inspire or expire ī each quiet breath

2. INSPIRATORY RESERVE VOLUME (IRV) (3000 ml)
→ amount of air that can maximally breath in beyond quiet inspiration



3. EXPIRATORY RESERVE VOLUME (ERV) (1100ml)
   → amount of air, we can forcefully breath out beyond quiet expirath

4. RESIDUAL VOLUME (RV) (1200ml)
   → amount of air that remains in lung after forceful expiration

CAPACITIES

INSPIRATORY CAPACITY (TV + IRV)
→ Total volume of air that can be inspired

FUNCTIONAL RESIDUAL CAPACITY (ERV + RV)
→ amount of air that remains in lung at the end quiet expiration

VITAL CAPACITY (TV + IRV + ERV)
→ amount of air that maximally exhale out after 1st maximal inspiration

TOTAL LUNG CAPACITY (TV + IRV + ERV + RV)

- ↑ maximum inspiration, Lungs are at TLC
- ↑ maximum Expiration, Lungs are at RV
- ↑ quiet expiration, Lungs are at FRC

CLOSING VOLUME

→ That volume just above the RV (starting from TLC) at which airways near the base OF lungs begin to close
→ Base of Lungs closes first
→ ↑ aging, closing volume approaches FRC dlt airway remodeling

SPIROMETRY CAN'T MEASURE Residual volume

RESIDUAL VOLUME MEASURED BY

1. Helium dilution method → $C_1V_1 = C_2V_2$
   C = concentration
   V = Vol. of Spirometer
2. Nitrogen washout method
   → PRINCIPLE → 80% volume comprises N_2

VITAL CAPACITY → ↓ in Restrictive Lung diseases

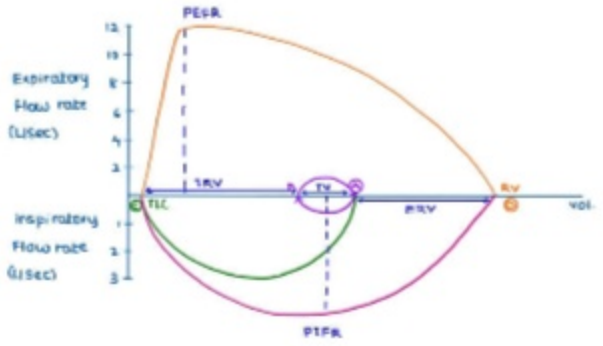
TIMED VITAL CAPACITY [FEV_t]
→ vital capacity fractioned against time
→ FEV_1 = 83%
   FEV_2 = 93%
   FEV_3 = 97%

→ FEV_1 < 70% → indicator of obstruction (COPD)
→ ↓ FEV_t : VC → COPD
   ↑ FEV_t : VC → Restrictive Lung Disease

→ Smaller airway obstruction is indicated by MMFR (max. mid expiratory flow rate)
[$FEV_{0.25-0.75}$] → (N) → 3. – 3.25 L/sec

FLOW VOLUME LOOPS

→ NOT A PLOTTED GRAPH [It is obtained loops]



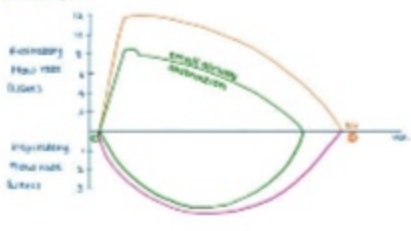
→ Peak Inspiratory Flow Rate (PIFR) → 3L/sec
→ Peak Expiratory Flow rate (PEFR) → 10–12 L/sec
→ FIV_1 : FEV_1 > 1
↳ EXCEPT in Extra thoracic large airway obstruction

CASE 1 → QUITE BREATHING (From a to b)
CASE 2 → Max. FORCEFUL INSPIRATION (from a to c)
CASE 3 → Max. FORCEFUL EXPIRATION (from c to d)
CASE 4 → Max. FORCEFUL INSPIRATION (from d to e)

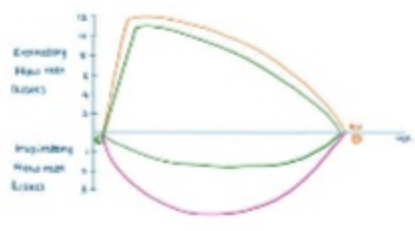
In Restrictive Lung Disease → Shifts to right
In COPD → Shifts to Left

PIFR achieved at → 50% of Lung volume inspired
PEFR achieved at → 20% of Lung volume expired
↳ EFFORT DEPENDENT FLOW RATE (more effort, more flow rate) (first 20%)
↳ EFFORT INDEPENDENT FLOW RATE (last 80%)

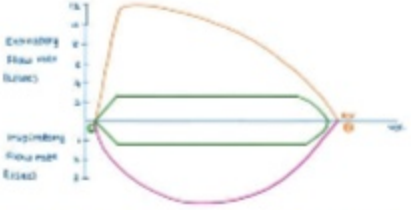
CHANGES



COPD ∵ Small air way obstruction



Extra thoracic large airway Obstruct^{n} (Tracheal tumor mass)



variable obstruction ∵ foreign body

DEAD SPACE [DSV]

→ Normal → 1 ml / pound of body wt
→ 150 ml

1. Anatomical Dead Space
   → 1st 16 generations
   → measured by FOWLER'S METHOD

2. Physiological / total Dead space
   → anatomical dead space + Alveolar dead Space
   → measured by BOHR'S METHOD
   → ↑ deep forceful inspiration ,
      ↳ alveolar dead space decreases
      ↳ anatomical dead space increases

DEFINITIONS

1. RESPIRATORY MINUTE VOLUME (RMV)
   → TV x RR → (500 ml) x (12-14) → 6-8 Ltr/min

2. ALVEOLAR VENTILATION PER MINUTE
   → (TV - DSV) x RR → 350 x (12-14) = 4 - 4.2 Ltr/min

3. MAXIMUM VOLUNTORY VENTILATION / MAX. BREATHING CAPACITY
   → 125 - 170 Ltr/min

4. BREATHING RESERVE (BR)
   → (MVV) - (RMV) → 125 - 8 = 117 Ltr/min

5. DYSPNEIC INDEX

→ $\frac{BR}{MVV} \times 100$ → $\frac{MVV - RMV}{MVV} \times 100$ → 95%

→ < 70% → dypsnea starts → DYSPNEA POINT

PULMONARY CIRCULATION

→ aka Lesser circulation
→ high compliant circulation
   ↳ pulmonary vessels 24% more compliant than their systemic counterpart
   ↳ can accomodate large amount OF BLOOD
      ↳ Lungs are reservoir of blood (15-18% OF total blood)

→ Low resistant circulation

↳ Rt ventricle pressures reflected in pulmonary artery pressures

↓ ↓

25 mm of Hg - Systolic 25 mm of Hg Systolic

0-1 mm of Hg - Diastolic 8 mm of Hg diastolic

↳ Pulm. capillary pressure → 15 mm of Hg

↳ Pulm. Capillary wedge Pressure (PCWP)

→ does not exist normally

→ created → 5 mm of Hg | 5-8 cm of H_2O

→ Hypoxia leads to VASOCONSTRICTION IN LUNGS

→ d/t O_2 sensitive K^+ channel in smooth muscle

→ Beneficial effect → Blood Flow directed towards better Ventilated alveoli

→ Lungs have Dual Blood Supply

PULMONARY CIRCULATION for Gas exchange

BRONCHIAL CIRCULATION

→ for O_2 Supply

→ Bronchial venous blood do not goes to rt. side of heart

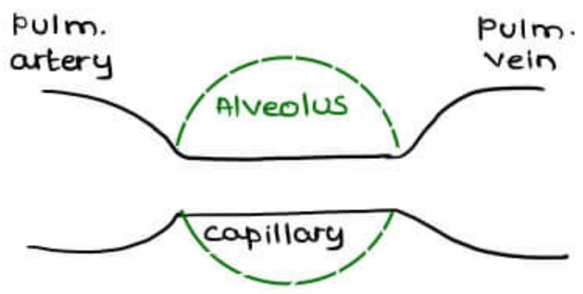
Bronchial veins joins pulmonary vein & goes to lt. side of heart

↳ lt side of heart receives 1-2% of more blood flow

↳ lt side of heart receives venous admixture blood

ZONES OF BLOOD FLOW IN LUNGS (not Fixed)

→ created d/t interplay of Hydrostatic factor & alveolar pressure



→ Alveolar pressure > Vessel pressure

→ compresses vessels → ↓ Blood Flow

→ present at apex of lungs

→ vessel pressure > Alveolar pressure

→ present at base of Lungs

→ can't compress the vessels

ZONE I

→ No blood flow

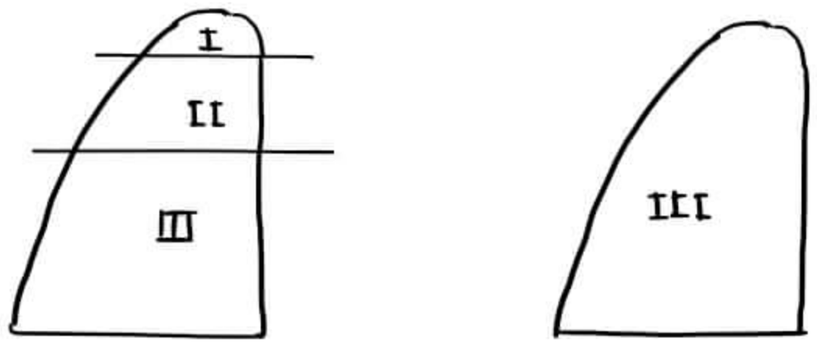
→ $P_{Alv} > P_{art} > P_{vein}$

ZONE II

→ Intermittent blood flow

→ $P_{art,cap} > P_{Alv} > P_{vein}$

→ during systole, blood flows
during diastole, ↓ blood flow



Upright posture

Supine posture

ZONE III

→ Continuous blood flow

→ $P_{art} > P_{vein} > P_{Alveoli}$

→ In IPPV / Assisted ventilation
→ ↑ $P_{Alveoli}$
→ Zone III → ZONE II
Zone II → ZONE I

V/Q RATIO

$$\frac{\text{alveolar ventilat}^{n}}{\text{perfusion}}$$

→ Normal → $\frac{4L/m}{5L/m}$ → 0.8

→ Gravity / Hydrostatic Factor
At Apex,
→ $\frac{\uparrow V}{\downarrow Q}$ → ↑ 3.5

→ contributed to Physiologic dead Space

→ At Base,
→ $\frac{\uparrow V}{\uparrow\uparrow\uparrow Q} = 0.5$

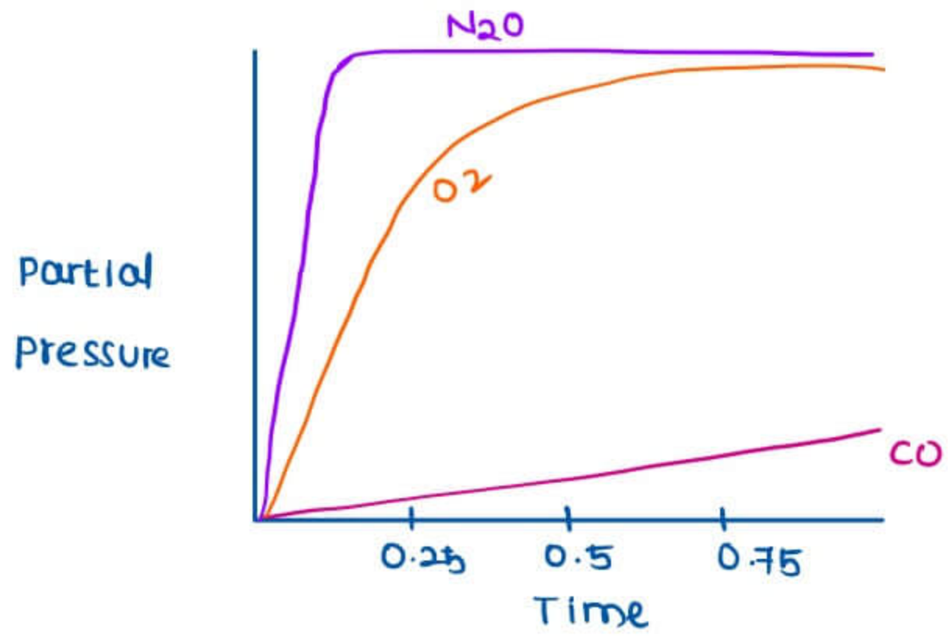
→ aka physiologic Shunt

RESPIRATORY SYSTEM PART 2

DIFFUSING CAPACITY OF RESPIRATORY MEMBRANE (DL_{CO})

→ measured by CO

→



CO → diffusion limited gas

→ rapidly combines ĩ Hb

↳ do not remains free in plasma

↳ do not exerts partial pressure

→ Degradation of heme is the only reactⁿ in the body that releases 'CO'

MEASUREMENT

→ 23 ml/min/mm of Hg is the diffusion capacity of resp. membrane

→ ideal gas to measure it → CO

→ Diffusion limited gas

→ Diffusion limits equilibrium

↳ never reaches equilibrium from alveolus to blood

↑ PCO in alveoli & P_{CO} in blood will be 'ō'

↳ continues to diffuse from alveoli to blood

O_2 / CO_2 → PERFUSION LIMITED GASES

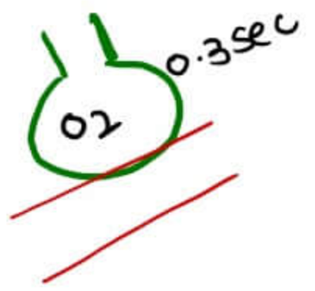
→ O_2 needs only 0.3 sec to reach equilibrium

→ Rate of perfusion to alveoli

↳ an average RBC stays for 0.75 sec in pulmonary blood

↳ in severe intense exercise, perfusion rate to alveoli becomes < 0.3 sec

→ O_2 will not able to reach equilibrium



GAS TRANSPORT

O_2 TRANSPORT

Q a CO poisoning patient was brought to the hospital. He was immediately started on 100% O_2 at 4 Atm pressure. How much will be the total O_2 content of the blood after 30 min.

a. 0.4 ml
b. 8 ml
c. 16 ml
d. None

Q 0.003 ml of O_2 was dissolved in 1 ml of plasma. How much is the PO_2?

a. 1 mm Hg
b. 80 mm Hg
c. 20 mm Hg
d. 100 mm Hg

Q What will be the ambient pressure around the body, at which plasma water starts boiling spontaneously?

a. 47 mm Hg [vapour pressure of H_2O]
b. 300 mm Hg
c. 1200 mm Hg
d. 347 mm Hg

Q. What is the P_{70} of hemoglobin?

a. 5
b. 25
c. 40
d. 70

I FROM ATMOSPHERIC AIR UPTO BLOOD

1. P_{O_2} in the atmospheric air at sea level

LAW of PARTIAL PRESSURE OF GASES

1. In a mixture of gases (>2), not reacting with each other, each gas exerts pressure on other gases → PARTIAL PRESSURE

2. Addition of all partial pressures is the total pressure of the mixture

3. Partial pressure of individual gas corresponds ī it's relative concentratn in the mixture

→

760 mm of Hg

N_2 (80%)

O_2 (20%)

P_{O_2} = 20% of 760 mm of Hg

PO_2 = 154-159 mm of Hg

→ P_{O_2} of atmospheric air at sea level → 154-159 mm of Hg

2. P_{O_2} IN THE DEAD SPACE (Inspired air)

→ humidification occurs

→ addition of water vapour occurs

P_{H_2O} → 47 mm of Hg

Total Pressure → 760 mm Hg → 47mm of Hg [P_{H_2O}] + 713 mm of Hg [N_2 & O_2]

→ P_{O_2} = 20% of 713 = 149 mm of Hg

3. P_{O_2} IN THE ALVEOLI

→ O_2 conc. ↓

→ O_2 replaced by CO_2 gradually

→ P_{CO_2} → 45 mm of Hg

→ 149 − 45 = 104 mm of Hg ≈ P_{O_2} in alveolar air

ALVEOLAR AIR EQUATION

$$P_AO_2 = [fiO_2 (P_B - P_{H_2O})] - \left[\frac{P_ACO_2}{R}\right]$$

20% (760 − 47) − 45

149 − 45 = 104 mm of Hg

R = Respiratory Quotient = $\frac{CO_2 \text{ evolved}}{O_2 \text{ consumptn}}$

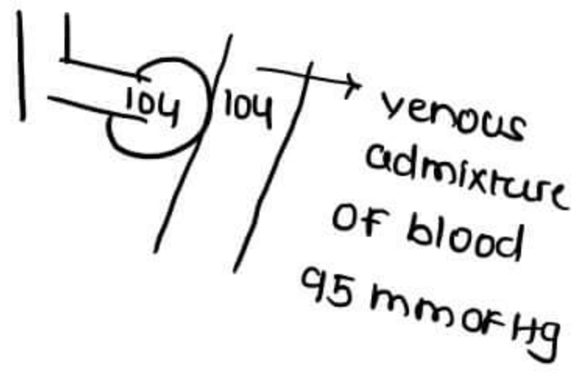
= 0.8 (mixed Diet)

= 1 (carbohydrate rich diet)

= 0.7 (fat rich diet)

4. PO_2 IN THE ARTERIAL BLOOD → 95 mm of Hg

− dlt venous admixture of blood



$AaDO_2$ [Alveolo arterial Difference in P_{O_2}]

→ Alveolar P_{O_2} [104] − arterial P_{O_2} [95] → 9-11 mm of Hg

→ Rt to lt shunt → ↑ $AaDO_2$

Interstitial Lung Disease → ↑ $AaDO_2$

hypoventilation → Normal

II O_2 TRANSPORT IN BLOOD

WITH Hb (97%)

Free / DISSOLVED IN PLASMA (3%)

DISSOLVED IN PLASMA

dissolved O_2 content = (PO_2) x (solubility coefficient for O_2) (0.003 ml / 100 ml / mm Hg)

WITH Hb O_2 CARRYING CAPACITY

→ 1 gm of Hb 100% Saturated carries → 1.39 ml of O_2

1 gm of Hb at 97% Saturath carries → 1.34 ml of O_2

→ Total O_2 content

$$= \underset{\text{Hb}}{[Hb\,(gm\%) \times 1.39 \times \%\ \text{Saturat}^n]} + \underset{\text{Free}}{[PO_2 \times \text{Solubility coefficient}]}$$

$$= [19.6\ ml] + [0.4\ ml]$$

$$= 20\ ml$$

→ Basis for giving hyperbaric O_2 in CO poisoning

↳ to increase the dissolved O_2 content

↳ aim is to increase to 8ml/100ml blood (minimum required for survival)

Q 100% O_2 at 4 atm. dissolved O_2 ?

A 0.4 ml / 100 ml → dissolved O_2 content (breathing atmospheric air at sea level → i.e., 20% O_2 at 1 atm)

→ $0.4 \times 5 = 2$ ml at 1 atm

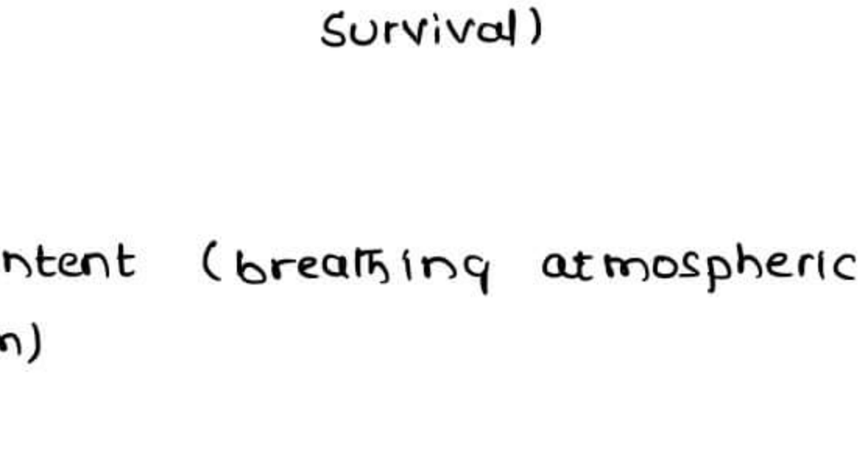
$2 \times 4 = 8$ ml at 1 atm

O_2 UTILIZATION COEFFICIENT

→ 20 ml of O_2 is carried by every 100 ml of arterial blood

→ most of the tissues extract 5 ml of O_2 at normal resting conditions

→ $5/20 \times 100 = 25\%$



↳ O_2 utilization co-efficient → 25%

→ 15 ml goes to venous circulation

↳ A-V O_2 difference = 25%

→ A-V O_2 difference is highest for → Heart (75%)

→ Worst sufferer of ischemia → Heart [dlt poor reserve for O_2]

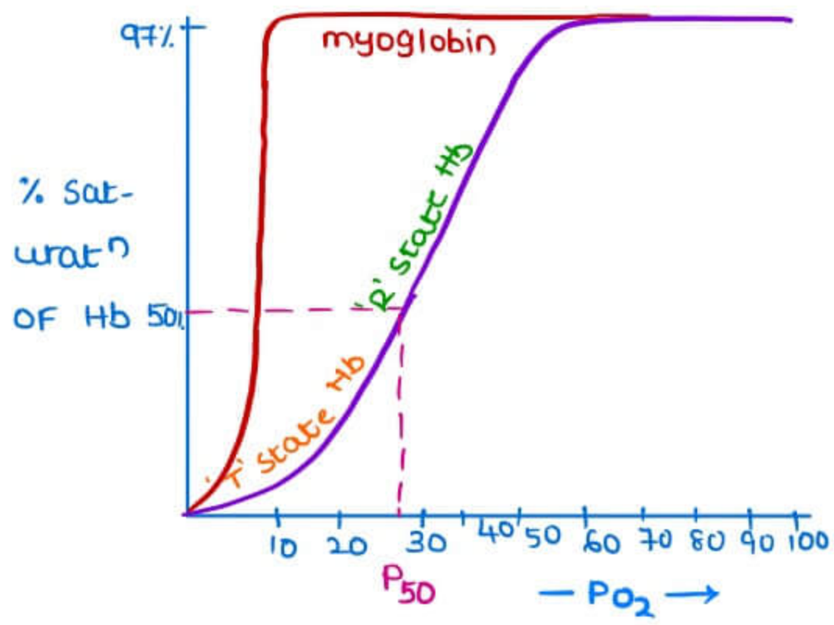
→ Tissue most sensitive to hypoxia → Neuron
dlt poor alternative compensatory mechanism

→ A-V O_2 difference is least for → Kidney (10-12%)

O_2 DISSOCIATION CURVE

→ relation blw P_{O_2} & % saturation of Hb

→ Sigmoid shape



Initial slow rise of curve

→ dlt first O_2 molecules combining ↓ Hb molecules which are in 'T' state (tense state)

Further Rapid rise of curve (Steep Rise)

→ dlt 'R' (Relaxed) state of Hb molecules, the further 2nd, 3rd, 4th O_2 molecules associate rapidly

→ also dlt POSITIVE CO-OPERATIVITY blw O_2 molecules

→ ADVANTAGES

P_{50} → P_{O_2} at which 50% of Hb is saturated

→ 25 - 28 mm Hg

→ P_{50} for myoglobin is 5 mm Hg

↳ Rectangular hyperbola

↳ has high affinity for O_2

DISSOCIATION OF Hb

1. P_{O_2} from 100 - 60

→ Hb still holds it's O_2

→ beneficial during mountain climbing (hypoxic hypoxia)

2. P_{O_2} From 60 - 30

→ small decrease in P_{O_2}, Hb readily gives up it's O_2

→ beneficial during acclimatization & in tissues

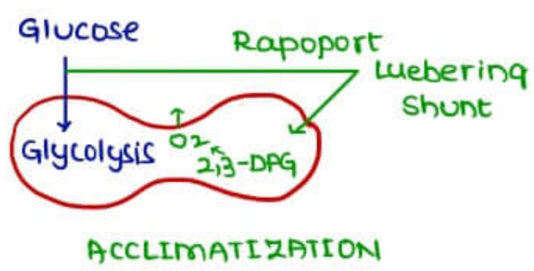
→ SHIFT OF THE CURVE

1. SHIFT TO RIGHTWARD & DOWNWARDS (liberation of 'O_2')

1. ↑ H^+
2. ↑ Temp
3. ↑ $P\,CO_2$

} occurs in tissues

4. ↑ 2,3-DPG → occurs in RBC



BOHR'S EFFECT → shift of O_2-Dissociation curve to right dlt ↑ PCO_2

→ In tissues, the shifting occurs dlt flipping the Hb molecules from 'R' state to 'T' state

→ In RBC, the shift occurs dlt simple displacement

2. SHIFT TO LEFTWARD & UPWARD (holding of 'O_2')

1. ↓ H^+
2. ↓ temp
3. ↓ PCO_2
4. ↓ 2,3 -DPG

} 'T' → 'R' state of Hb

5. CO poisoning
   ↳ binding of CO ī Hb, increases the other Hb molecules affinity for O_2
6. HbF

RESPIRATORY SYSTEM PART 3

CO_2 TRANSPORT

Q MCV in venous blood is

A. more than body average
B. Same
C. Less
D. depends on Hct

→ CHLORIDE SHIFT in venous blood ⟶ H_2O + osmotically active Cl^- drawn into RBC ⟶ ↑ MCV

Q if in the absence of O_2, 2 vol% of CO_2 is liberated from the Lungs, then in the presence of O_2, how much CO_2 will be released ?

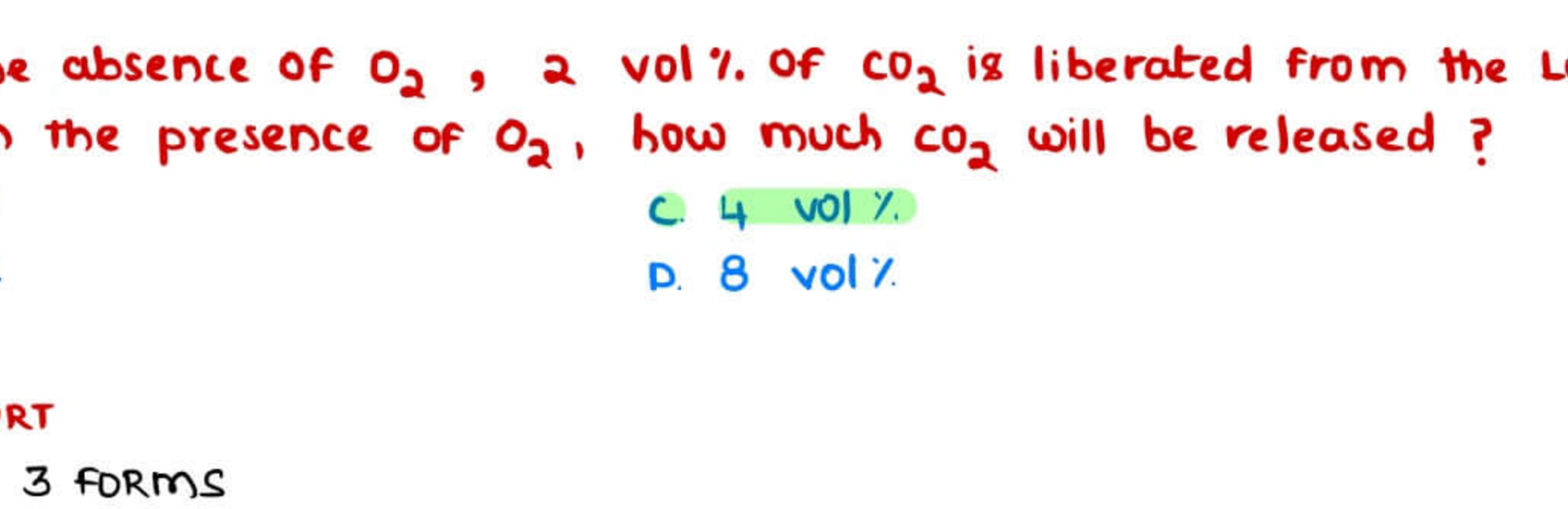
A. 1 vol%
B. 2 vol%
C. 4 vol%
D. 8 vol%

CO_2 TRASPORT

Occurs in 3 FORMS

1. HCO_3^- (70%)
2. carbamino compounds (20-25%)
3. Free / dissolved in plasma (5-7%)

1. HCO_3^-



→ $CO_2 + H_2O \longrightarrow H_2CO_3$

→ It is 5000 times faster in RBC than plasma d/t presence of carbonic anhydrase in RBC

→ $H_2CO_3 \longrightarrow H^+ + HCO_3^-$

→ $Hb + H^+ \longrightarrow HbH^+$

Hb

→ acts as extracellular buffer

→ deoxyhaemoglobin accepts H^+

→ HCO_3^- Leaves the Red cell

Cl^- enters the Red Cell → HAMBURGER | CHLORIDE SHIFT

→ occurs ī the help of Band 3 protein in RBC membrane

→ Band 3

↳ aka AE1 (Anion exchange 1)

↳ transport protein

↳ Band 3 → 3rd Band on electrophoresis

↳ causes Cl^- & HCO_3^- exchange (Cl^- enters, HCO_3^- exits)

→ on the lungs, HCO_3^- enters & Cl^- exits)

→ Cl^- shift causes H_2O to enter the RBC (RBC swells up)

→ MCV in venous blood is → more than the body average

→ BLOOD ENTERS THE LUNGS

→ all reactions reversed when O_2 Combined ī Hb (oxygenated Hb)

→ HALDANE EFFECT / REVERSE BOHR EFFECT

↳ inspired O_2 enters in RBC & combines ī Hb displacing H^+

↳ Cl^- leaves & HCO_3^- enters into RBC through Band 3

↳ CO_2 reformed

↳ DOUBLE THE VOLUME % OF CO_2 IS LIBERATED

In the absence of O_2, 2% volume of CO_2 is liberated

In the presence of O_2, 4% Volume of CO_2 is liberated (HALDANE EFFECT)

REGULATION OF BREATHING

ONDINE'S CURSE

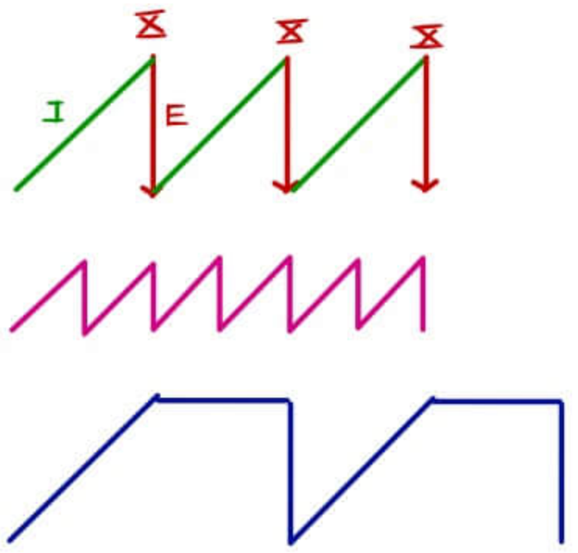
→ Seen in CO_2 narcosis

→ automatic regulatⁿ stops & concious breath continues

NEURAL REGULATION

1. Automatic Regulatⁿ (Brain stem)
2. Voluntary Regulatⁿ (cortex)

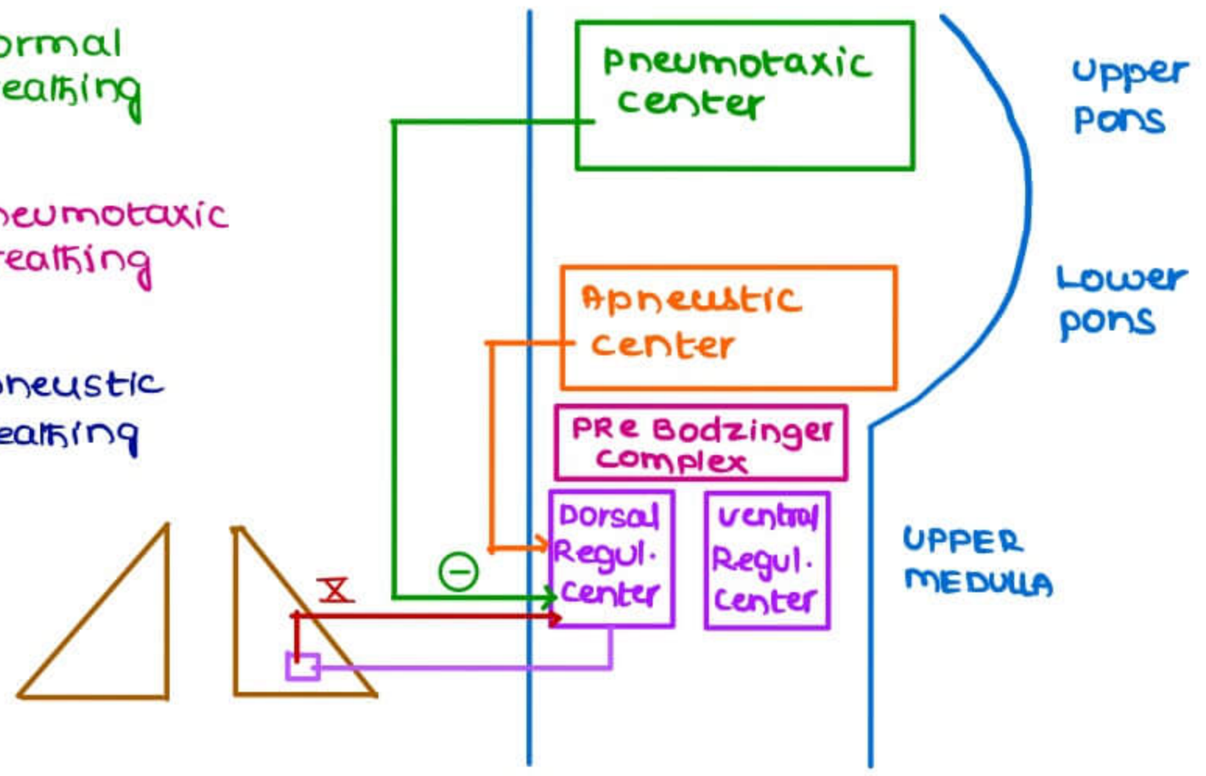
AUTOMATIC REGULATION (BRAIN STEM RESPIRATORY CENTER)



← Normal Breathing

← Pneumotaxic breathing

← Apneustic Breathing



→ INSPIRATORY RAMP SIGNAL for spontaneous inspiration starts from DORSAL REGULATORY GROUP & send to thoracic cage

→ STRECH RECEPTORS IN THORACIC CAGE distorted & Sends feed back signal regarding distenth via vagal fibres to DRG. If feedback signal is strong it abruptly stops Inspiratory Ramp signal, resulting in stoppage of inspiration. Expiration starts as a passive recoil process

PRE BODZINGER COMPLEX

→ present in upper medulla
→ pace maker for Spontaneous breathing
→ Neurons of DRG & VRG synapse here

PNEUMOTAXIC & APONEUSTIC CENTERS

→ controls Rate & Depth of breathing

PNEUMOTAXIC CENTER

→ causes an early switch off to Inspiratory Ramp signal
→ Rapid & shallow breathing occurs

APNEUSTIC CENTER

→ not allow early switch off Inspiratory Ramp signal
→ Slow & deep breathing occurs

VRG

→ In forceful expiration, spill over of impulses from DRG to VRG occurs
→ Neurons of VRG sends signals to forceful expiration (to respiratory muscles)

LESIONS	EFFECTS
VAGOTOMY	Prolonged inspiratn
Transection in Lower border of medulla (above C-3)	Spontaneous breathing stops
Transection in upper border of medulla	Irregular & Jerky Spontaneous breathing
Mid pontine transection	Long inspiratory Spasms Apneustic breathing
Lower pontine transection	Rapid, Shallow Breathing

CHEMICAL REGULATION OF BREATHING

CHEMORECEPTORS

PERIPHERAL RECEPTORS

→ located in Carotid & aortic bodies

→ Glomus Cell

→ chemosensitive cell

→ has O_2 sensitive K^+ channel

→ sense the hypoxia

→ K^+ channel closes, depolarisation occurs

→ sends signals via IX CN from carotid body & X CN from aortic body

→ responds to

1. Arterial hypoxia
2. Fixed Acids (arterial H^+)
   - Lactic acids
   - Keto acids

→ most acid production occur at AEROBIC METABOLISM

→ CO_2 (volatile Acid)

→ all other acids are fixed acids (metabolic Acids)

→ O_2 does not drive the ventilation via peripheral chemoreceptors until PO_2 < 60 mm Hg

CENTRAL CHEMORECEPTORS

→ Situated in 1/5 th mm beneath the upper aspect of medulla

→ part of respiratory center

→ responds to H^+ in CSF or Interstitial fluid of brain

→ H^+ ion reflects the CHANGES IN ARTERIAL CO_2

→ ↑ CO_2 / H^+ → Stimulate ventilatn
↓ CO_2 / H^+ → depress ventilatn

→ When Arterial PO_2 < 60 mm Hg, Hypoxic stimulation of peripheral chemoreceptor is so strong that it overides the effect of CO_2 & H^+ washout acting on central chemoreceptors to depress ventilation

CHANGES DURING ACCLIMATIZATION TO HIGH ALTITUDES (HYPOXIC HYPOXIA)

1. ↑ 2,3 – DPG
2. ↑ Sensitivity of peripheral chemoreceptors
3. ↓ Sensitivity of central chemoreceptors

HYPOXIA

HYPOXIC HYPOXIA

→ occurs at high altitudes, Heart & Lung diseases

ANEMIC HYPOXIA

→ occurs in anemia, CO porsoning

→ Arterial PO_2 is Normal

STAGNANT / HYPOKINETIC / ISCHEMIC HYPOXIA

→ seen in Shock (↓ CO, ↓ BP)

HISTOTOXIC HYPOXIA

→ seen in Cyanide poisoning

J - RECEPTOR

→ by A.S. Paintal

→ Juxta alveolar receptor in pulmonary interstitium

→ accessed from pulmonary vessels

→ Stimulated by

- ↳ pulmonary congestⁿ
- ↳ pulmonary embolism
- ↳ pulmonary edema

→ EFFECTS

- ↳ Apnea
- ↳ Rapid shallow breathing
- ↳ Strong vagal stimulation
  - → Bradycardia
  - → hypotension

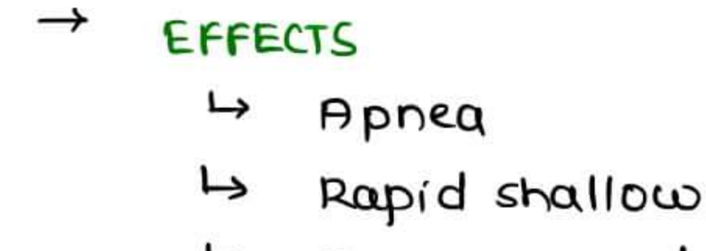
BREATHING

APNEUSTIC BREATHING → long inspiratory spasms

CHEYNE - STOKES BREATHING → apnea followed by hyperapnea

KUSSMAUL BREATHING → increased depth & prolonged inspiration

IRREGULARLY IRREGULAR → seen in meningitis



APNEUSTIC BREATHING

CHEYNE - STOKES BREATHING

KUSSMAUL BREATHING

MOUTH TO MOUTH BREATHING → contains 16% oxygen

Break point in voluntory breath holding is dlt → ↑ arterial PCO_2 (49 mm Hg)

EXERCISE

→ ↑ TV, ↑ RR } ↑ Respiratory Minute volume

→ Stimulation occurs at

1. At the Start of Exercise
   - → Anticipitory Rise
   - → Feed forward mechanism

2. During the course of Exercise
   - → proprioceptive impulses from muscles & joints
   - → Arterial ↑ CO_2 / H^+

3. After the exercise
   - → O_2 Debt
     - ↳ dlt consuming extra O_2
     - ↳ at the start of intense exercise,
       1. stored O_2 utilised (2ltr)
       2. Anaerobic metabolism
     - ↳ Total → 11 L| min
       1. ALACTACID O_2 DEBT (3.5L)
          - ↳ to replenish O_2 stores
       2. LACTACID O_2 DEBT (7.5 L)
          - ↳ to clear lactic Acid

HERING - BREUVER REFLEXES

→ classic negative feedback reflex

→ INFLATION REFLEX
- ↳ protective reflex
- ↳ initiate at TV > 1 ltr

→ DEFLATION REFLEX
- ↳ Ex: Yawning
  - more negative intra thoracic pressure created & opens up terminal alveoli

HEAD'S PARADOXICAL REFLEX

→ 

→ positive feed back occurs at birth

DEEP SEA PHYSIOLOGY

EFFECTS OF HIGH BAROMETRIC PRESSURE

→ seen in divers & mine workers

1. NITROGEN NARCOSIS
2. CAISSON'S DISEASE

→ PV = constant

NITROGEN NARCOSIS

N_2 disolves in body fluids if works at depth for long time

N_2 has high affinity for lipids

dissolves in neuronal membranes of myelin → NITROGEN NARCOSIS

↳ similar to alcoholic intoxication

↳ loss of recent memory

↳ fine motor activity impaired

CAISSONS DISEASE / DECOMPRESSION SICKNESS

→ seen in persons working at depth for long time & comes to the surface suddenly

→ pressure released, N_2 expands suddenly & forms bubbles

→ N_2 BUBBLES

↳ 1st formed in tissues (muscles & tendons) → BENDS

↳ comes to systemic circulation

↳ then comes to pulmonary circulation → CHOKES

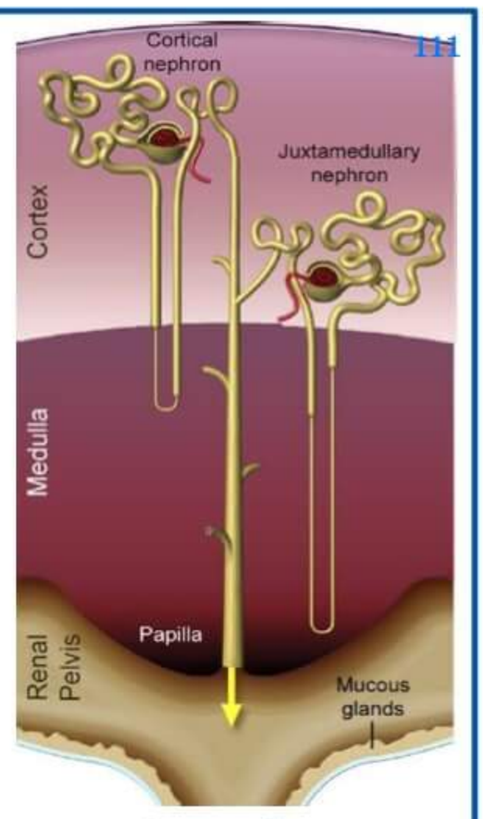
↳ order of elimination

→ systemic & pulmonary circulation & fats (last)

→ prevented by slowly coming to surface

→ Rx by Decompression chambers

EXCRETORY SYSTEM



NEPHRON

1 Cortical Nephrons

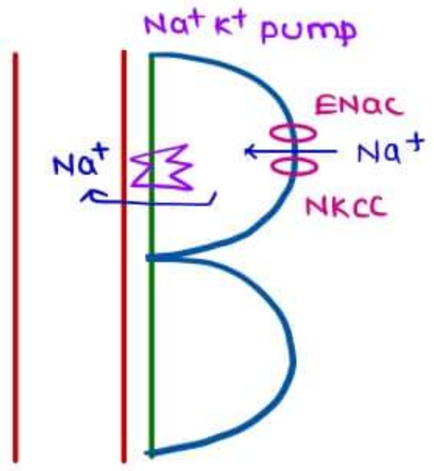
- → 85%
- → have short loops
- → entirely located in cortex
- → forms normotonic urine

2. Juxta Glomerular Nephrons

- → 15%
- → Glomeruli situated in the cortex at the junct^{n} of cortex & medulla
- → have long loops
- → form & concentrated urine

BLOOD FLOW TO THE KIDNEY

- → cortex Receives most of blood flow, because of glomerulus
- → medulla consumes more O_2
  - ↳ O_2 consumption / metabolic rate / ATP load is directely linked to tubular load for Na^+ reabsorpt^{n}
  - ↳ Na^+ REABSORPTION
    - → Na^+ enters the tubular cell through ENaC & NKCC channels on apical membrane
    - → Na^+ reabsorbed via $Na^+ K^+$ pump on basolateral membrane



JUXTA GLOMERULAR APPARATUS

- → Lies close in relation to GLOMERULUS
- → has 3 CELLS
  1. Cell in Wall of afferent arteriole
  2. Cell lining the early DCT
  3. Cell between the above two

- → CELL IN THE WALL OF AFFERENT ARTERIOLE
  - ↳ JG CELL / GRANULAR CELL → Synthesizes Renin (enzyme)

ANGIOTENSINOGEN [Liver] —RENIN→ ANGIOTENSIN I (Decapeptide) —Lungs, ACE→ ANGIOTENSIN II (Octapeptide)

ANGIOTENSIN II FUNCTIONS

1. vasoconstriction
2. Salt & water Retention
3. Aldosterone Secretion (Adrenal gland) → Na^+ Reabsorpt^{n}

CELL LINING THE EARLY PCT

↳ MACULA DENSA CELL

Senses the Na^+ & Cl^- in tubular fluids

↓

TUBULO GLOMERULAR FEED BACK

→ Ligand → ADENOSINE

→ causes vasoconstriction of afferent artioles

MESANGIAL / LACIS / GOORMAGHTIGH / PSEUDO MESENARIAN CELL

→ alter vessel diameter

→ has role in immune complex formation

ERYTHROPOIETIN

→ Type 1 cortical Interstial cell around peritubular capillaries synthesizes it

↳ contains O_2 sensitive K^+ channels

→ 90% produced by kidney

10% produced by Liver

O_2 SENSITIVE K^+ CHANNELS SEEN IN

1. Pulmonary vascular smooth muscle cell
2. Carotid body
3. Type 1 cortical interstitial cell

RENAL CIRCULATION

PECULIAR FEATURES

1. capillaries drain& into arterioles
2. very high blood flow
   ↳ 25% of CO
   ↳ 300 - 400 ml / 100 gm / min
3. Capillary hydrostatic pressure is 3- 4 times the pressure elsewhere
   ↳ 60 mm Hg (Blood accumulates in capillaries)
4. Capillary filtrat^n CO-efficient is highest → 12.5 ml / min / mm Hg
5. A-V O_2 Difference is least (10-12%)
   ↳ renal vein carries more oxygen
6. Metabolic rate is regulated by Blood flow (Na^+ Reabsorpt^n)

CLEARANCE

→ hypothetical volume of plasma that is completely cleared of a substance per unit time

$$C_x = \frac{(U_x)(V)}{P_x}$$

U_x → urinary concentration of x (mg/ml)

V → volume of urine per unit time

P_x → plasma concentration of x (mg%)

→ $(U_x)(V)$ → total excret^{n} rate of the substance per unit time

U_x = 2 mg/ml

V = 100 ml/min

$(U_x)(V)$ = 200 mg/min

GFR

FACTORS

1. Glomerular capillary Hydrostatic pressure (60 mm Hg) → Favours filtrat^{n}
2. Plasma colloid oncotic pressure (32 mm Hg) } Opposes Filtrat^{n} (50 mm Hg) total
3. Bowman's capsule hydrostatic pressure (18 mm Hg) }

NET FILTRATION PRESSURE → I − II

→ 60 − 50 = 10 mm Hg

CAPILLARY FILTRATION COEFFICIENT → 12.5 ml/min/mm Hg

GFR → 12.5 × 10 = 125 ml/min

= 180 Ltr/Day

FILTRATION FRACTION

→ RBF = 25% of CO

= 1250 ml/min

→ Renal plasma flow = 625 − 650 ml/min

→ Filtration fraction = $\frac{GFR}{RPF} = \frac{125}{625} = 1/5 = 20\%$

1. MODERATE CONSTRICTION EFFERENT ARTERIOLES

↑ GFR

↓ RBF

↑ FF

2. SEVERE, SUSTAINED CONSTRICTION OF EFFERENT ARTERIOLES

↓ GFR

↓ RPF

↔ FF (No change)

3. NEPHROLITHIASIS

↓ GFR

↔ RPF (No change)

↓ FF

MEASUREMENT OF GFR

→ Best substance → Inulin (has to be injected)

→ mc substance → creatinine (endogenous, need not be injected)

SUBSTACES USED & CRITERIA

1. Should be freely filtered
2. neither reabsorbed nor excreted

CREATININE CLEARANCE

→ gives 5-10% over estimate of GFR

→ $\frac{U_{Cr} \times V}{P_{Cr}}$ > GFR

1. NUMERATOR → 20% over estimate
   ↳ dlt tubular secretion
2. DENOMINATOR → 10% False over estimate

→ PLASMA CREATININE
   ↳ False over estimate
   ↳ dlt JAFFE REACTION
      → In calorimetric method measurement, some non specific chromogens in plasma are added

→ COCKROFT & GAULT FORMULA

$$C_{Cr} = \frac{(140 - Age) \times Body\ Wt}{72 \times P_{Cr}}$$

↳ unreliabe in
   1. extreme obesity
   2. advanced pregnancy

MEASUREMENT OF RENAL BLOOD FLOW (RBF)

DIRECT FICK METHOD

→ based on FICK'S EQUATION

$$CO = \frac{O_2\ consumption\ (ml/min)}{A\text{-}V\ O_2\ difference\ (ml)}$$

$$RBF = \frac{consumption\ of\ x\ by\ Kidney\ (ml/min)}{RA_x - RV_x}$$

CRITERIA FOR SUBSTANCE

1. Numerator
   - → consumed by kidney, but not by metabolism, but into urinary excretion

2. Denominator
   - → RA_x
     - ↳ not handled by any other organ except kidney
     - ↳ $RA_x = P_x$
   - → RV_x
     - ↳ RV_x = zero
     - ↳ Completely removed by the Kidney in a single pass

$$RBF = \frac{(U_x)(V)}{P_x - 0}$$

→ Best substance → PAH (Para Amino Hippuric Acid)

PAH clearance = RBF

$$\frac{U_{PAH} \times V}{P_{PAH}} = RBF$$

PAH CLEARANCE

→ Occurs
1. 20% by Filtratⁿ
2. 80% by tubular secretion
   - ↳ carrier protein is needed

→ if double dose given for RBF measurement → NO change in the Value
- ↳ ↑ P_{PAH}
- ↳ ↑ $(U_{PAH})(V)$ as carrier excretes accordingly
- ↳ No change in RBF value

→ if thrice recommend dose given, then Low RBF values are recorded
- ↳ ↑ P_{PAH}
- ↳ carrier get saturated
  - → $(U_{PAH})(V)$ do not increase as much
- ↳ ↓ RBF value

RBF & RPF

$$RBF = RPF \times \frac{1}{1 - Hematocrit}$$

Q U_x, P_x, GFR, V values given

A	B
$[P_x \times GFR]$	$[U_x \times V]$
Total filtered amount of 'x' Per unit time	Total excreted amount of 'x' per unit time

→ If A > B → Reabsorbed
→ If A < B → Secreted

EVENTS IN URINE FORMATION

URINE FORMATION → Glomerular Ultrafiltrat^n − Tubular Reabsorpt^n + Tubular Secretion

→ Substances that are filtered, reabsorbed & secreted are → K^+, Urea

TUBULAR FUNCTIONS

1. GLOMERULUS → Isotonic Ultra filtrat^n
2. PCT Reabsorbs
   - → 67% Na^+
   - → 67% H_2O
   - → 100% Glucose
   - → 100% Amino Acids
   - → > 90% HCO_3^-
   - → 70-75% K^+, Ca^{2+}, Cl^-

   → Isotonic

H_2O REABSORPTION

↳ PCT → 67% → OBLIGATORY H_2O REABSORPTION
↳ irrespective of body osmolarity

↳ LH, DCT } 10-15%

↳ Collecting Duct (ADH) → 10-12% → FACULTATIVE REABSORPTION
↳ under the influence of osmolarity

↳ under ADH influence, greatest fraction of H_2O is reabsorbed from → PCT (not collecting duct)

↳ in the absence of ADH, 88% of water is reabsorbed
in the presence of ADH, 99% of water is reabsorbed

3. LOOP OF HENLE

→ Descending Limb
↳ some H_2O into interstitium
↳ Na^+ (Bulk flow/ solvent drag)

→ Thick Ascending Limb
↳ NKCC Transporter ($Na^+ K^+ 2Cl^-$ co transporter)
↳ loop diuretics acts on it
↳ impermeable to H_2O
↳ fluid reaching at early DCT → hypotonic
↳ DILUTING SEGMENT → Thick Ascending Limb

4. DCT

→ contains NCC transporter
↳ Thiazides acts on it
→ 10% of Na^+ & Cl^- removed
→ removes some H_2O

5 COLLECTING DUCT

→ absorbs 10 – 12% of H_2O under ADH
→ CONCENTRATING SEGMENT
→ 'P' CELL (PRINCIPLE CELL)
↳ reabsorbs Na^+
↳ secretes K^+

→ 'I' (INTERCALATED) CELL
↳ reabsorb K^+
↳ Secretes HCO_3^-
↳ Buffering cell of kidney

TUBULAR / TRANSPORT MAXIMUM (T_{max})

→ maximum rate, upto which a substance can transported across tubule
→ Glucose T_{max} → 320 mg/ min (373 in males, 303 in females)
→ only substance ī out transport maximum → Na^+ reabsorptn
→ K^+ secretion in distal nephron has no transport maximum

SPLAY

- → Glucose T_{max} → 320 mg/min
- → RENAL THRESHOLD For Glucose = 180 mg%.
- → dlt heterogenity among nephrons
  - → some nephrons have
    - Large glomerulus → more Glucose filtered
    - Short loops → less no. of carrier protein
      - → less amount of Glucose reabsorbed

CONCENTRATION OF URINE

- → function of Juxta medullary nephrons (15%)
- → minimum amount of urine lost
- → achieved by
  1. Hyperosmolarity in medullary interstitium
  2. Role of ADH

HYPEROSMOLARITY IN MEDULLARY INTERSTITIUM

- → achieved by
  1. counter current multiplier
  2. Counter current exchanger

- → COUNTER CURRENT MULTIPLIER

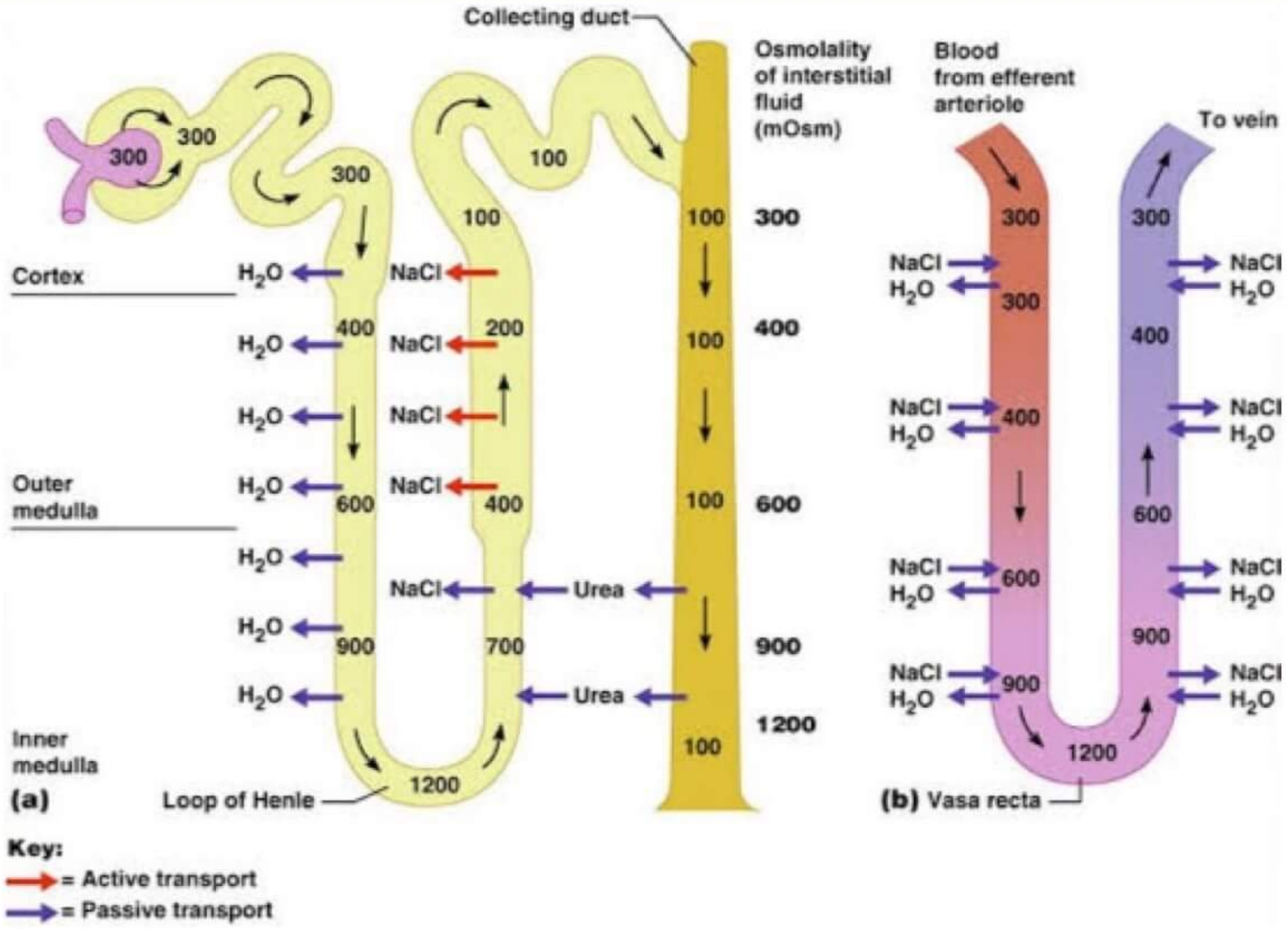
  - ↳ counter current flow helps to hold solutes temporarily in medullary interstitium

  - ↳ MULTIPLIER MECHANISM
    - → Starts at thick ascending Limb of LH
      - ↳ NKCC cotransporter removes $Na^+, K^+, 2Cl^-$ into interstitium
      - ↳ impermeable to H_2O
      - ↳ tubular fluid is hypotonic & Interstitium is hypertonic
        - → horizontal osmotic gradient → 1:2
        - → vertical osmotic gradient → 1:4
          - ↳ max. osmolarity achieved at tip of LH (1200 mos/L)
          - ↳ max. concentratⁿ of urine → 1200 mosm/L
          - ↳ urea contributes to 40% of hyperosmolarity

      - ↳ H_2O moves from descending Limb

UREA

- → urea transported via UT_1, UT_2
- → urea transport is under the influence of ADH
- → contributes to 40% of interstitial osmolarity
- → Recycled & excreted in a concentrated manner



COUNTERCURRENT EXCHANGE

→ VASA RECTA (Blood vessels)

↳ Responsible for counter current Exchange

↳ do not actively contribute to hyperosmolarity

↳ Blood flow is sluggish

↳ Blood collects Na^+, K^+, Cl^- & gives out as it moves down in descending limb

↳ hyper osmolarity maintained at tip

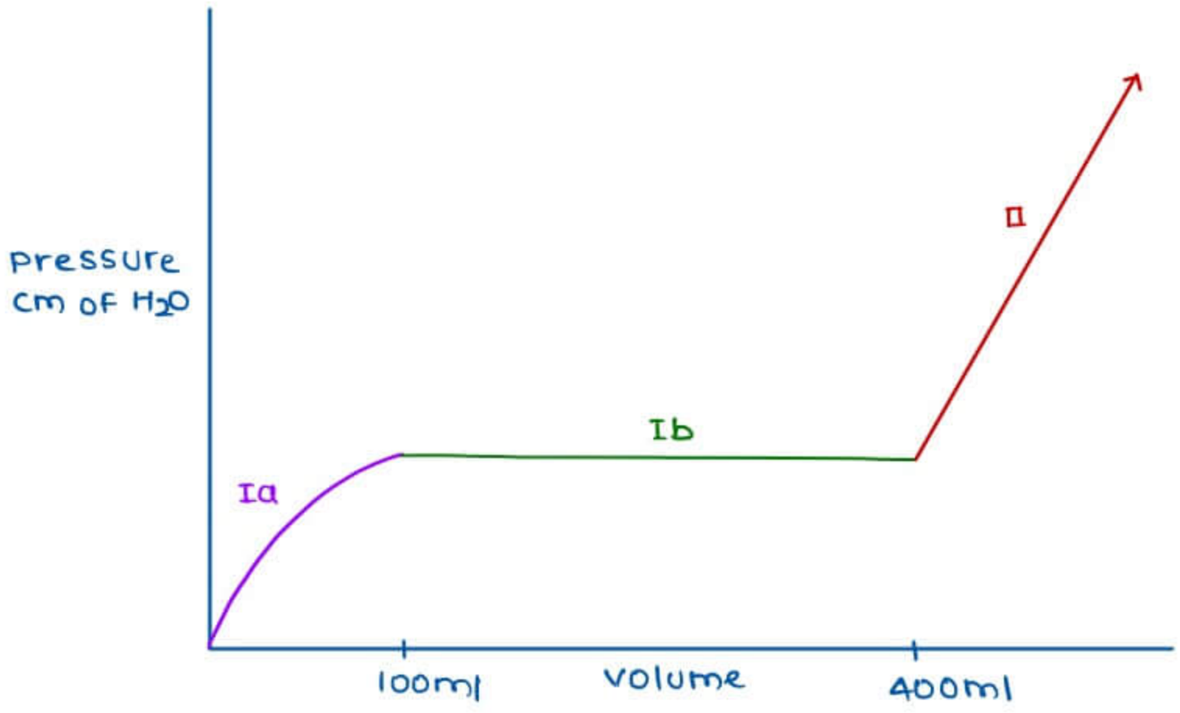
↳ Blood gives Na^+, K^+, Cl^- & collects H_2O While in moves up In ascending Limb & becomes hypotonic

1. maximum concentrated urine → 1200 mosm/L (4 times the normal)
2. most hypotonic urine → 50 mosm/L
3. At least Avg. 600 mOsm of solutes to be excreted by healthy individual daily
4. OBLIGATORY URINE OUTPUT (0.5 L/day)
   → minimum urine output required to excrete at least 600 mosm/day of solutes if urine is concentrated maximally
5. oliguria → < 400 ml/day
   anuria → < 100 ml/day
6. max. urine output & most hypotonic urine → 18 Ltr/Day

BLADDER

1. 50 ml → Residual volume
2. 150 ml → First reflex
3. 250 ml → First desire
4. > 400ml → urgency
5. > 600 ml → painful urgency
6. 800-900ml → physiological capacity
7. 1000 ml → Anatomical capacity

CYSTOMETROGRAM

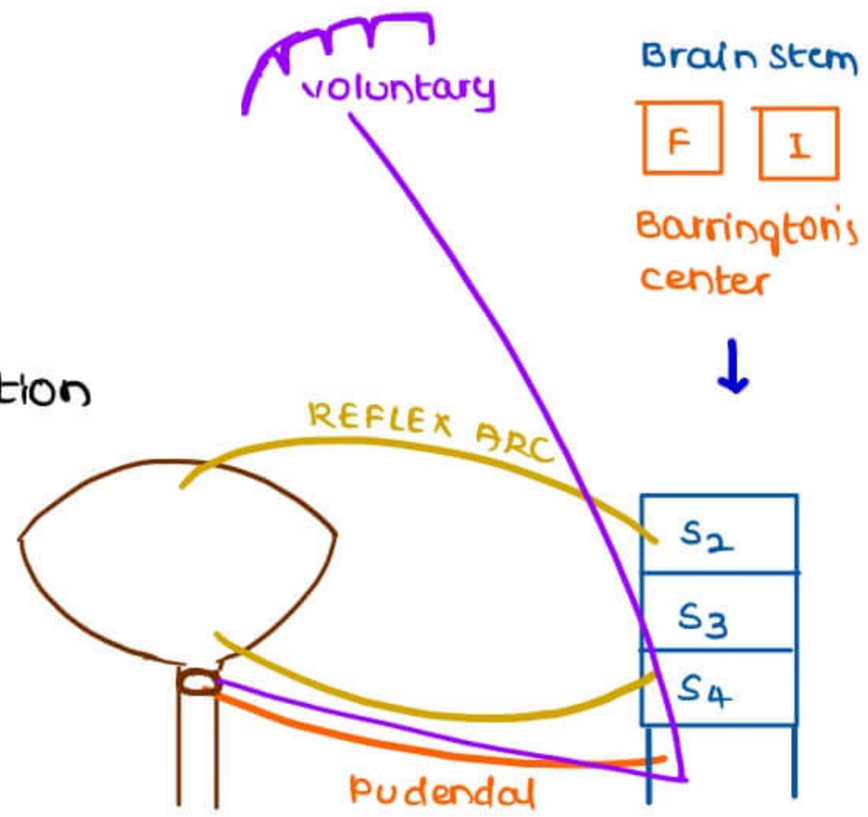


Laplace's LAW

$$P = \frac{2T}{R}$$

INNERVATION

MICTURITION



- → mainly under Parasympathetic control (S-2,3,4)
- → forms REFLEX ARC
- → Sympathetic innervation carries pain sensation
- → PUDENDAL NERVE
  - → somatic nerve
  - → controls external urethral sphincter
- → BRAIN STEM
  - → BARRINGTON'S MICTURITION CENTER
    - ↳ for facilitatn or inhibitn of reflex arc
    - ↳ micturitn reflexes → Barrington's reflexes
- → CEREBRAL CORTEX
  - → Paracentral lobule of frontal lobe has cortical voluntary centre for micturition
  - → predominanty inhibitory to external urethral sphincter

LESIONS

→ If afferents from bladder are cut → Atonic bladder

Transect^{n} above S_2, Reflex arc intact → Autonomous bladder

higher up transect^{n} in Spinal cord → overflow incontinence

Lesion b/w voluntary centre & Brain stem → urge incontinence (or)
spastic neurogenic bladder (or)
uninhibited bladder &
mid stream holding lost

ACID BASE BALANCE

BUFFER SYSTEMS

1. CHEMICAL (⊥ in few sec) → 1st to be activated
2. RESPIRATORY (3-12 min)
3. KIDNEY (> 30 min) → Last to be activated

CHEMICAL BUFFERS

1. HCO_3^-
2. Phosphate
3. Proteins

HCO_3^-

→ PKa → 6.1

→ most important & plentiful buffer in ECF

Phosphate

→ pKa → 6.8

→ intracellular buffering

→ Renal tubular Fluids

Proteins

→ > 70% of ICC buffering is by ICC proteins

→ pKa → 7.1 - 7.2

RESPIRATORY BUFFERS

→ physiological buffers

→ metabolic acidosis & alkalosis corrected

→ If Respiratory rate is doubled → pH increases by 0.45

→ If RR is halved, PH decreases by 0.23

→ stronger buffer in acidic pH

KIDNEY

1. PHOSPHATE AMMONIA
2. REABSORPTION OF FILTERED HCO_3^-
3. GENERATION OF NEW HCO_3^-

REABSORPTION OF FILTERED HCO_3^-

→ HCO_3^- → 24 mEq/L

GFR → 180 L/Day

P_x x GFR → 4320 mEq/Day

↳ for the reabsorption, 4320 meq H^+ + 80 m.eq secreted at PCT

↳ 80 meq → NET ACID OUTPUT

↳ H^+ secreted in PCT is along the concentratⁿ gradient

↳ H^+ secreted in collecting duct is against the conc. gradient (1:1000)

↳ pH of urine becomes 4.5 (Limiting pH)
maximally acidic urine pH is 4.5

TITRATABLE ACIDITY

→ acidity buffered in the urine by phosphate

→ NH_3 → buffer for chronic respiratory acidosis

→ pKa of NH_3 → 9

→ collect the urine sample,
titrate it ī NaOH to bring it's pH to 7.4

↳ this will provide the informatⁿ about phosphate buffer only

ANION GAP

→ LAW OF ELECTRO NEUTRALITY → no. of cations = no. of Anions

→ $(Na^+) + (K^+) + (\text{unmeasured cations}) = (Cl^-) + (HCO_3^-) + (\text{unmeasured anions})$

→ cations can be measured
Some of anions can't be measured, creating ANION GAP

→ It's a virtual gap

→ Measured by

$$[Na^+] - [(Cl^- + HCO_3^-)]$$

$$141 - (105 + 24)$$
$$141 - 129$$
$$= 12 \text{ mEq/L} \pm 4 \text{ (for } K^+)$$

→ Normal anion gap = 8-16 mEq/L

→ Anion gap increased in some acidosis condition not in all

→ In some metabolic acidosis conditions anion gap is normal

Ex: GI fluid loss
The conditions where the anion of acid is Cl^-

PEPTIDE / PROTEIN HORMONES	STEROID HORMONES
→ not bounded to plasma proteins have short $t_{1/2}$	→ Bound to plasma proteins have longer $t_{1/2}$
→ EXCEPTION IGF (Insulin Like growth factors/ Somatomedins)	

FACTS ABOUT INSULIN LIKE GROWTH FACTORS [IGF]

→ 6 types of INSULIN LIKE GF BINDING PROTEINS [IGFBPs] present in plasma
  ↳ IGFs have longer $t_{1/2}$

→ GH has very short $t_{1/2}$ [1-2 min]. But in that $t_{1/2}$, it reaches Liver & causes IGFs secretion & IGFs exert effect on GH

SYNTHESIS OF PROTEIN HORMONES

PEPTIDES ARE SYNTHESIZED IN PRECURSOR FORM

1. Insulin + C-peptide produced as a single copy

PRE-PRO INSULIN
↓ cleaved
PRO-INSULIN
↓ ↓
INSULIN C-PEPTIDE

2. TRH produced as multiple copies [6 copies are formed of TRH]
3. POMC (Pro Opio Melano Cortine) produces multiple hormones

POMC
↓ First proteolytic cleavage
CORTICOTROPIN β LPH
↓ further cleavage ↓ further cleavage
MSH CLIP ENDORPHIN
[corticotropin like intermediate lobe peptide]

PEPTIDE / PROTEINS	STEROIDS
PERIPHERAL CONVERSION	PERIPHERAL CONVERSION
NO further modifications Once final hormone formed, it acts On the target cells	further modifications occurs before final hormone going to act on target cells
	TESTOSTERONE [Active] —(5α-reductase)→ 5 DHT [Active]
MECHANISM OF ACTION	MECHANISM OF ACTION
Not lipid soluble [can't enter easily] act via cell membrane receptors	Lipid soluble [enter the cell easily] act via intracellular receptors [cytoplasmic or nuclear receptors]
	Eg. Estrogen acts via nuclear ®

RECENT EVIDENCE

→ Intra cytoplasmic receptors of steroids are just Primary receptors

STEROIDS ENTER THE CELL EASILY [Lipid Soluble]

↓ crossing the lipid Bilayer

Binds ī its receptors

↓

formatⁿ of Hormone receptor complex

↓

H-R complex enter the nucleus

↓

So, anyways steroid hormone enters the nucleus

DERIVATIVES OF SINGLE AMINO ACIDS

→ Thyroid hormones
catecholamines

→ Thyroid hormone also has intra nuclear receptors
catecholamine has cell membrane receptors

RECEPTORS

CELL MEMBRANE RECEPTOR

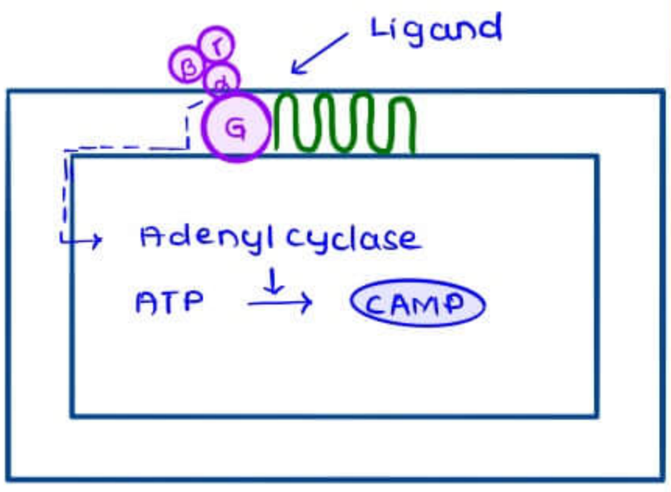
TYPES

1. GPCR
2. CATALYTIC RECEPTORS

1. GPCR (G - Protein Coupled Receptor)

→ aka HETERO TRIMERIC G - PROTEIN [has 3 sub units ; α, β, γ]

→ has 7 transmembrane segments
aka GTP binding protein
aka Serpentile receptor



→ Ligand + Receptor → α sub unit dissociated
it move along the membrane & activates
EFFECTOR PROTEIN [adenyl cyclase | guanyl cyclase]

→ A. ADENYL CYCLASE → converts ATP → cyclic AMP [cAMP]
↳ c AMP → activates Protein Kinases → Hormonal action ⊕

→ B. GUANYL CYCLASE → converts GTP → cyclic GMP [cGMP]
↳ c GMP → activates Protein Kinases → Hormonal action ⊕

cAMP acts as second messenger for
1. ACTH
2. FSH
3. LH
4. TSH
5. PTH
6. GLUCAGON
7. CATECHOLAMINES

cGMP acts as second messenger for
1. ANP
2. NO

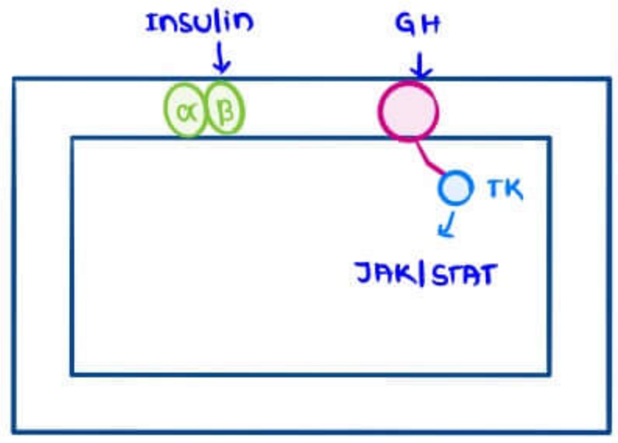
2. CATALYTIC RECEPTORS

a. RECEPTOR TYROSINE KINASE

→ Receptor for Insulin
→ has 2 sub units α, β
→ insulin binds ī α sub unit, auto phosphorylatⁿ occurs
→ β sub unit has the tyrosine kinase activity

b. TYROSINE KINASE ASSOCIATED RECEPTOR

→ Receptor for GH
→ do not have tyrosine kinase activity by itself
→ tail of Receptor alw tyrosine kinase enzyme
→ tyrosine kinase activates JAK/STAT MACHINERY



Shortest $t_{1/2}$	→	Catecholamines (few sec)
Longest $t_{1/2}$	→	Steroid Hormones – Vit. D_2 (15 Days) THYROXINE (7-8 days)

Shortest hormone	→	TRH (Tripeptide)
Longest hormone	→	HCG (250 AA)

Shortest latency for actⁿ	→	Oxytocin (few sec)
Longest latency for actⁿ	→	Thyroxine (48-72 hrs)

LATENCY OF THYROID HORMONES can be known from Shift From Shivering Thermogenesis to Non Shivering Thermogenesis (48-72 hrs)

PITUITARY GLAND

ADENO HYPOPHYSIS Secretes

1. GH
2. Prolactin
3. FSH
4. LH
5. ACTH
6. TSH

NEUROHYPOPHYSIS Secretes

1. ADH
2. OXYTOCIN

INTERMEDIATE LOBE

↳ has Basophils which synthesize POMC (Proopiomelanocortin)
↳ ACTH → MSH, CLIP
↳ β-LPH
↓
Endorphin

→ ACTH & MSH are homologus (shares 1st 13 AA)
↳ ACTH Actⁿ ≅ MSH Action

ADH & OXYTOCIN

→ synthesized in supra optic, para ventricular nuclei of hypothalamus
→ bound to NEUROPHYSINS, carried to post. pituitary
→ cleaved from Neurophysins & free hormones released

HERRING BODIES → ACTH & Oxytocins are released

OXYTOCIN

1. MILK Ejection Reflex
2. Contractn of uterus during parturitn

ANT. PITUITARY HORMONES

→ under the hypothalamic pituitary control
  ↳ GHRH, GHIH
  ↳ under Excitatory (predominant) & inhibitory control
  ↳ Except PROLACTIN
    → predominantly under inhibitory controls
    → TRH → thought to be prolactin Releasing factors

CELLS IN ANTERIOR PITUITARY

1. CHROMOPHIL CELLS (50%)
   a. ACIDOPHILS (80%) → GH & Prolactin
      ↳ SOMATOTROPES (50%) → GH
      ↳ LACTOTROPES (10-20%) → Prolactin

   b. BASOPHILS (20%) → FSH, LH, ACTH, TSH
      ↳ GONADOTROPES
      ↳ CORTICOTROPES } 10 - 20%
      ↳ THYROTROPES

ADH / VASOPRESSIN

→ primarily regulates the OSMOLARITY (not the volume)
→ Nerve cells in hypothalamus sense, osmolarity OF plasma if it is HYPERTONIC

Shrinking of Nerve cell Bodies
↓
osmoreceptors activated
↓
ADH Secretion
↳ V_1 → vasoconstrictn
↳ V_2 → predominant on collecting ducts
→ aqua porins formed, H_2O reabsorbed
→ concentrates Urine & normalises plasma osmolarity

→ HYPOSECRETION → DIABETES INSIPIDUS
  ↳ CENTRAL DI → ADH synthesis & release affected
  ↳ NEPHROGENIC DI → Actⁿ on kidney affected dlt lack of receptors
  ↳ Diuresis occurs

→ HYPERSECRETION → SIADH (Syndrome Of Inappropriate ADH)
  ↳ plasma Osmolarity is normal, still ADH secreted
  ↳ occurs in stressful conditions (Sx, stress)
  ↳ hypotonic plasma
  ↳ plasma volume increases

GROWTH HORMONE
→ contains 191 AA
→ Diabetogenic / Anti insulin Hormones
→ ACTIONS

METABOLIC
carbohydrate metabolism
  ↳ ↓ peripheral utilisatⁿ
  ↳ hyperglycemia
  ↳ PITUITARY DIABETES

NON METABOLIC (ACTION on Growth)
→ SOMATOMEDINS / IGFs
  ↑ osteoblastic activity
  ↑ depositⁿ of new bone
  ↑ Protein deposition
  ↑ SOFT tissue mass

DIABETES MELITUS

PITUITARY DIABETES
→ Weakly Sensitive to Insulin

ADRENAL DIABETES
→ moderately sensitive to insulin

PANCREATIC DIABETES
→ Strongly Sensitive to insulin

PROTEIN METABOLISM
  ↑ Protein synthesis
  ↓ Protein degradation

FAT METABOLISM
  ↑ breakdown of TG
  ↑ FFA levels

STIMULATORS

→ GHRH
→ Exercise
→ hypoglycemia
→ sleep (largest pulse)
→ Arginine

INHIBITORS

→ FFA
→ GHIH / somatostatin

DISORDERS

HYPERSECRETION

→ Before puberty → GIGANTISM
→ After puberty → ACROMEGALY
↳ ↑ thickness of bone (membranous bones)
↳ Prognathism
↳ organomegaly
↳ macroglosia

HYPOSECRETION

→ Before puberty → DWARFISM
↳ pituitary Dwarf

→ After puberty → ACROMICRIA

LEVI LORAEN DWARFISM

→ Seen in African pigmes
→ GH is normal
→ deficiency of somatomedin C

LARON'S DWARFISM

→ GH is normal / increased
→ Receptor insensitivity

THYROID HORMONE

→ Regulates BMR

THYROID HORMONE SYNTHESIS (T_3, T_4)

→ Iodides enter thyroid gland through Na^+I symporter

TYROSINE + Iodine → MIT
MIT + I → DIT
DIT + DIT → T_4
DIT + MIT → T_3

→ Enzyme involved → Peroxidase

→ 90% → T_4

9% → T_3

1% → Reverse T_3

→ In cells,

$$T_4 \xrightarrow[\text{↳ I}]{\text{Deiodinase}} T_3 \text{ (responsible for Actions)}$$

→ T_3 is 4 times potent than T_4

T_3 $t_{1/2}$ → 1 day

T_4 $t_{1/2}$ → 7-8 day

Daily turnover

T_3 → 70%

T_4 → 10%

T_4 → extensively plasma protein bound

→ T_4 provides a more stable Extra Thyroid pool

ACTIONS

1. Regulates BMR
   - ↳ ↑ carbohydrate metabolism → ↑ Glucose
   - ↳ ↑ fat metabolism
   - ↳ ↑ Protein metabolism → Slightly more catabolic

2. CVS
   - ↳ stimulatory
   - ↳ ↑ SV
   - ↳ ↑ HR
   - ↳ ↑ CO
   - ↳ ↑ BP

3 RS
   - ↳ stimulatory
   - ↳ ↑ TV
   - ↳ ↑ RR
   - ↳ ↑ RMV

4 GIT → ↑ motility

5. CNS & NMJ → ↑ synaptic excitability

6. Reproductive System

   Hyperthyroidism → oligomenorrhea , Amenorrhea

   Hypothyroidism → Polymenorrhea , menorrhagia

DISORDERS

HYPO SECRETION

a. In pregnancy, In Infancy } CRETINISM

CRETINISM

- ↳ short statured
- ↳ mentally retardatⁿ (hall mark) (not seen in Dwarfism)
- ↳ milestones delayed
- ↳ sexual immaturity

b. Adults → MYXEDEMA
   - ↳ non pitting edema
     - → dlt mucopolysaccharides (GAGs) accumulatⁿ in tissues
       - ↳ absorbs water
   - ↳ Pretibial myxedema

GOITRE → Enlargement of Thyroid gland for any reason

HYPER SECRETION

THYROTOXICOSIS (Hyperthyroidism ī toxic manifestations)

→ Toxic manifestations
- ↳ Tachycardia (ī sleeping HR > 90)
- ↳ Tremors

→ GRAVE'S DISEASE
- ↳ Autoimmune disease
- ↳ LATS (Long Acting Thyroid Stimulator) / TSI (Thyroid stimulating Immunoglobulin)
- ↳ Exophthalmos
  - → dlt depositⁿ of fat & fluid in retrobulbar space
    degeneratⁿ of EOM (extra ocular muscles)

ADRENAL GLAND

CORTEX

1. Zona Glomerulosa → Mineralocorticoids (Aldosterone)
2. Zona Fasciculata → Glucocorticoids
3. Zona Reticularis → Sex steroids

MEDULLA

→ Adrenaline (Epinephrine)

GLUCO CORTICOIDS

Metabolic actions

↳ ↑ Gluconeogenesis → ↑ Blood glucose (Adrenal diabetes)

Non metabolic actions

↳ Anti inflammatory action
↳ immuno suppressives
↳ Anti allergic
↳ Anti stress

HYPOSECRETION

ADDISON'S DISEASE

↳ weak & frail patient ∴ low glucose, low BP
↳ ↑ ACTH → pigmentation

HYPERSECRETION

CUSHING DISEASE

→ dlt fat breakdown & centripetal redistribution of fat
  ↳ moon face
  ↳ Buffalo hump
  ↳ protuberant belly

→ Thin limbs
→ striations

CALCIUM HOMEOSTASIS

CALCIUM

→ 45% → free calcium → Diffusible calcium
  45% → bound to albumin } Non Diffusible calcium
  10% → bound to others }

→ 2% → EXCHANGABLE Ca^{2+}
  ↳ available in young bone

→ 9-11 mg% → Normal serum calcium

$[Ca^{2+}][Ea^{2+}][PO_4^-]$ → 10 x 4 = 40
  ↳ held constant always normally

HORMONES	SITES / Organ system	CELLS
PTH	Intestine	Osteoblasts
calcitonin	Bones	Osteoclasts
Vit D	Kidney	Osteocytes

CALCIUM HOMEOSTASIS

1 PTH

→ ↓ Serum ca^{2+} → ↑ PTH

→ Anticipatory release

→ osteoblast

↳ has PTH (R)

↳ ↑ osteoclastic activity → ↑ Bone resorption

→ ↑ ca^{2+} reabsorptn from Kidney

↑ phosphate excretion

→ potentiate the action of Vit D

↳ ↑ ca^{2+} absorption from intestine

→ DEFECT

TETANY (Hypocalcemia)

↳ 1st manifestatn occurs at < 7 mg%.

< 6 mg%. → death can occur

↳ Trousseau's sign → Carpopedal spasm

↳ Chvostek's sign → Facial muscle spasm

2. CALCITONIN

→ Synthesized by Para follicular 'c' cells of Thyroid gland

→ ↓ ca^{2+}

↓

deposits on bone

3. VITAMIN D

→ ↑ ca^{2+} absorption from intestine

↓

Deposits on Bone

→ Deficiency → children → Rickets

→ Adults → Osteomalacia

ENDOCRINE PANCREAS

→ 98% → exocrine

2% → endocrine

↳ by Islets of Langerhans at tail portion

α CELL (10%)	Outer rim	Glucagon
β CELL (75-80%)	Center of Islet	Insulin
δ CELL (5%)	Disperse	Somatostatin
F CELL		Pancreatic Polypeptide

INSULIN

→ Anabolic Hormone

→ STRUCTURE

→ IGF family

Preproinsulin

↓

Proinsulin (retains ~ 8% Biological activity of insulin

↓

Insulin + 'C' peptide [equimolar concentration]

→ $t_{1/2}$ → 5-8 m

→ primary stimulus → Plasma Glucose

→ sulfonyl urea → acts on SUR (ATP sensitive K^+ channel)

INSULIN RECEPTOR

→ has α, β sub units

→ Receptor Tyrosine Kinase (catalytic receptor)

↳ termination is by auto phosphorylation (internalised & degraded)

METABOLIC ACTION

1. CARBOHYDRATES

→ ↑ peripheral uptake & utilization

↳ done via GLUT-4 at skeletal muscle & fat cell

→ upregulates Glycogen synthase, & cause Glycogen synthesis

→ ↓ Glycogenolysis

2. FATS

→ ↑ uptake & lipogenesis promoted by ↑ expression of lipoprotein lipase

3 Skeletal muscle → ↑ Protein synthesis & ↓ Protein degradatn

TYPE I DM → Absolute lack of Insulin

TYPE II DM → Relative lack of Insulin (peripheral Insulin Resistance)

TYPE I DM → Juvenile Onset

TYPE II DM → adult onset

LADA → Late Adulthood onset Diabetes of Autoimmune origin

→ has Anti-GAD Antibodies

GLUCAGON

→ Secretin Gene family
→ sereted by α cells
→ ↑ Blood glucose (Diabetogenic)
  ↳ glycogenolytic
  ↳ gluconeogenic
  ↳ stimulates lipolysis
  ↳ ketogenic

→ Molar Insulin : Glucagon
  ↳ on Fed State → 30
  ↳ after an overnight Fast → 2
  prolonged fasting → 0.5

SOMATOSTATIN

→ secreted by
  ↳ δ cells of pancreas → inhibit both insulin & Glucagon
  ↳ Stomach (D cells) → ↓ gastric acid
  ↳ hypothalamic neurons → GHIH

→ inhibits Gastrin secretion
  TSH secretion
  VIP secretion

FEMALE REPRODUCTIVE SYSTEM

→ Primary aim → Survival of species
  ↳ indirect way of homeostasis

PUBERTY

→ pulsatile GnRH secretions causes puberty

GIRLS

Sequence

1. Thelarche
2. Pubarche
3. Menarche

→ Adrenarche

FEMALE REPRODUCTIVE SYSTEM

→ inherently cyclic function

OVARIES

OVARIN SEX STEROIDS & FUNCTIONS

1. Secreted locally, nourishes the ovum
2. circulating & acts on different organs

→ Fundamental reproductive unit → Single ovarian follicle

OOGENESIS

→ Upto 5 th month of IUL, mitosis occurs

→ After 5 th month of IUL, meiosis begins, mitosis stops
  ↳ no. of ova not increase (7M at 5-6 m of IUL)

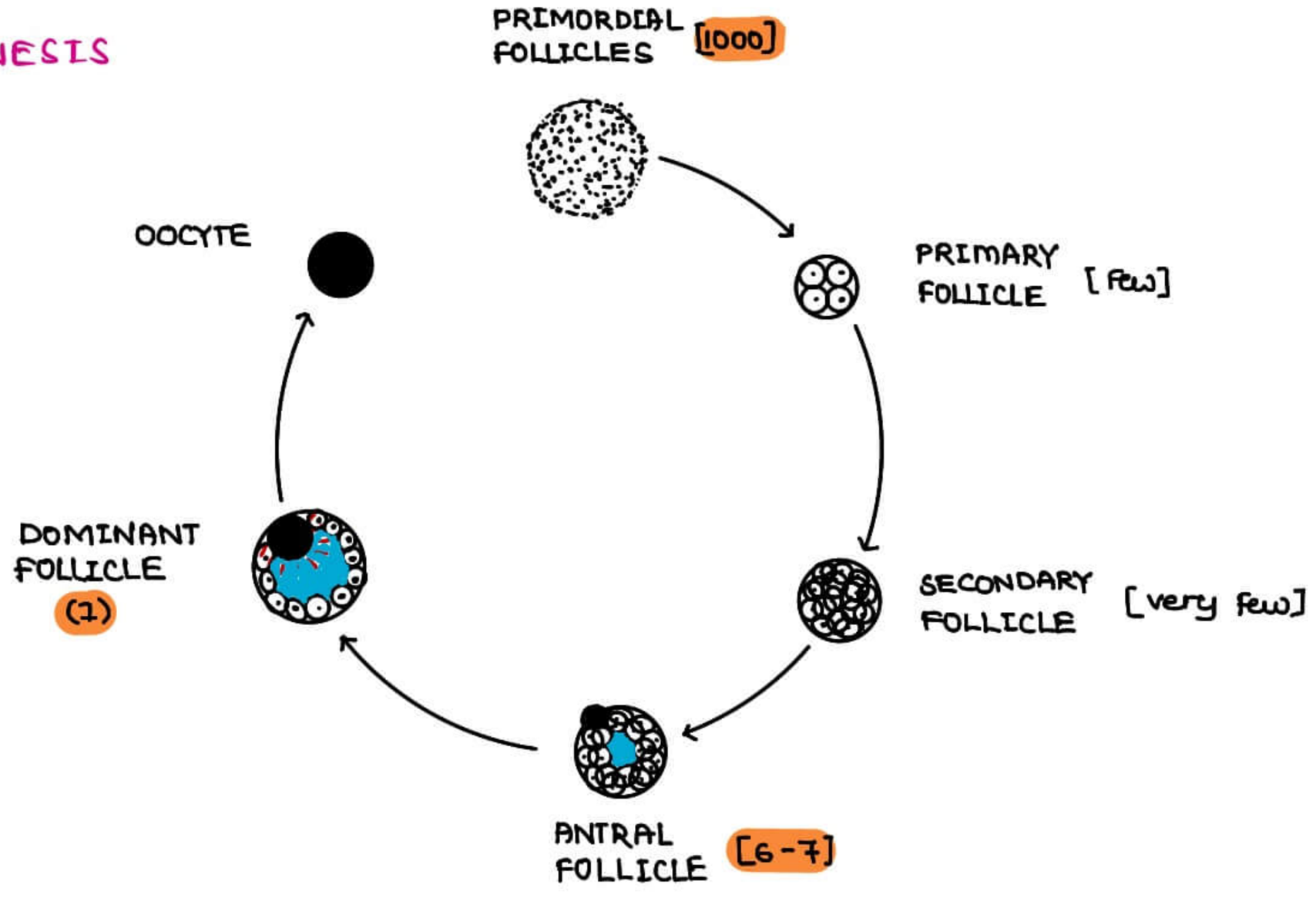
→ 7 Million (max) → at 5-6 months of IUL
  2 Million → at birth
    ↳ 50% are atretic
    ↳ 50% enter 1st meiotic division, arrested in Prophase stage

↳ APOPTOSIS
  → oocyte atrision occurs by apoptosis
  → stimulated by
    ↳ TGF β
    ↳ FAS Ligand
  → inhibited / opposed by [survival factors]
    ↳ FGF
    ↳ LIF (Leucocyte Inhibitory factor)
    ↳ Kit ligand

→ just before the ovulatn, 1st meiotic division completed & 1st polar body formed

→ secondary oocyte, immediately enters the second meiotic division Arrested in metaphase stage
  ↳ 2nd meiotic division will be completed immediately after fertilizatn of ovum

FOLLICULOGENESIS



PRIMOIDAL FOLLICLE

→ Oocyte ī surrounding granulosa cells

SECONDARY FOLLICLES

→ Granulosa cells forms multilayered epithelium

→ Granulosa cells secrete paracrine factors

↳ stromal cells differentiated into epitheloid cells → THECA CELLS

→ Now, it forms MATURE FOLLICLE

MENSTRUAL CYCLE

→ At the start of each cycle

↳ 5-6 follicles enlarge

↳ cavity is formed around the ovum → ANTRUM

→ Filled ī Antral / follicular fluid

→ contains GAGs, electrolytes, FSH, LH, IGF1, IGF2, TGF β etc

→ At 5-6 Day, 1 follicle becomes dominant

↳ High mitotic index of the granulosa cells surrounding the ovum is the characteristic feature of dominant follicle & ability to secrete Estrogens

ESTROGEN

↳ all the circulating estrogen comes from theca interna cells
Local estrogen comes from Granulosa cells.

→ At 14th day, ovum ī surrounding cumulus oophorus extruded from follicle

→ Remaining part, converted into corpus luteum

↳ On the 1st day, it converted into corpus Haemorrhagicum

↳ MITTELSCHMER2 → minor bleeding into peritoneum & pain

↳ granulosa & Theca cells line the corpus luteum, called granulosa lutein cells, theca lutein cells

↳ growth of CL requires VEGF

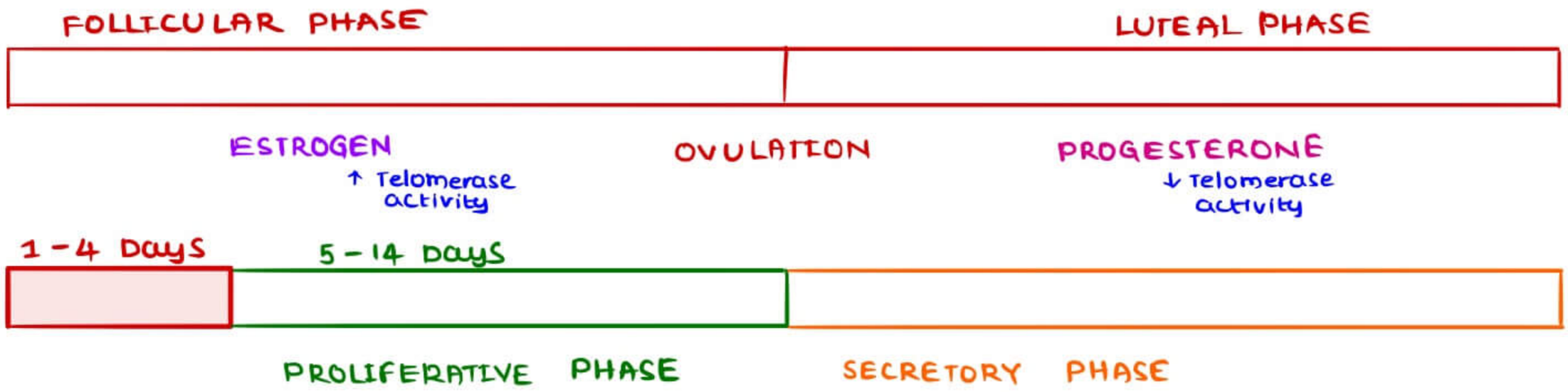
↳ dominated by progesterone

↳ if pregnancy occurs, corpus luteum persists

↳ if pregnancy do not occurs, CL regressed by Luteolysis
4 days prior to next cycle

↳ replaced ī scar tissue & converted into corpus albicans

UTERINE CYCLE



ENDOMETRIUM

→ Inner 2/3rd of endometrium wall → STRATUM FUNCTIONALE
  ↳ supplied by long, coiled arteries
  ↳ it's going to be shed

→ outer 1/3rd called → STRATUM BASALE
  ↳ supplied by basilar arteries

MENSTRUATION

→ 1st patches of endometrium occurs
→ later they coalise to form large patch & bleeding occurs
→ vasospasm occurs dlt $PGF_{2\alpha}$

CYCLE LENGTH

→ varies dlt follicular phase
→ Luteal phase / secretory phase is constant (14 days)

NORMAL MENSTRUATION

MENSTRUAL BLOOD

→ predominantly arterial
→ 25% → venous
→ contains tissue debris, PGs, fibrinolysin
→ average loss → 30 ml

CYCLICAL CHANGES IN CERVIX

→ Before ovulatn (estrogen) → Cx mucus thinner & more alkaline
→ After ovulatn (progesterone) → Cx mucus thick, cellular, tenacious
→ SPINNBARKEIT (Elasticity)
  ↳ can be stretched into long thin thread
  ↳ dries in a arborising / fern like pattern

VAGINAL CYCLE

→ under Estrogen, vaginal epithelium cornified
→ under progesterone, vaginal epithelium proliferated, mucus becomes thick,

CYCLICAL CHANGES IN BREAST

→ estrogen → proliferation of mammary ducts
→ progesterone → growth of lobules, alveoli

OVARIAN STEROIDOGENESIS

→ Before ovulatⁿ, LSH & FH acts on cells of developing follicles
→ Theca cells
  ↳ have the receptors for LH
  ↳ can take up cholesterol & produce testosterone under LH
  ↳ but do not have aromatase enzyme, essential for the conversⁿ of testosterone into estrogen

→ Granulosa cells
  ↳ have receptors for both LH & FSH
  ↳ contains aromatase & converts testosterone into estrogen under FSH

→ AFTER OVULATION, LUTENIZATION OF FOLLICLE occurs
  ↳ Theca lutein cells } occurs under LH
  ↳ granulosa lutein cells }

→ maintainance of CL is under LH
→ predominant hormone secreted by CL is progesterone

HORMONAL PATTERNS

→ towards the end of Luteal phase,
  ↳ the FSH & LH levels decreases significantly (Lowest level)
    → LH : FSH Ratio → 1

→ 1 or 2 days before the onset of menses, FSH levels begin to rise
→ in 2nd half of follicular phase (8-14 D), FSH ratio decreases modestly & LH ratio begins to increase
  ↳ LH : FSH → 2

→ just before ovulatⁿ, mid cycle LH surge occurs
  ↳ LH : FSH → 5

MID CYCLE LH SURGE

→ estrogen creats a positive feedback ↑ LH
→ just before ovulatⁿ, estrogen creates a positive feed back to LH
→ for that to happen, 200 pg/ml critical plasma estradiol is required & should be sustained for 2 days

LH SURGE

→ Stimulation of progesterone → ↑ Progesterone → ↑ proteolytic enzyme activity

→ Distensibility of follicle increases
Follicular fluid content increases → wall becomes tensed

→ Induces Prostaglandin Endoperoxidase synthase
↳ present in granulosa cells
↳ ↑ synthesis of PG, TXA, LT → PSEUDO INFLAMMOTORY RESPONSE
→ follicular rupture

→ Stimulation of Plasminogen activator by FSH
↳ generates plasmin → catalyses the breakdown of Follicular wall

→ In case of pregnancy, CL is maintained by placental HCG
→ Luteolysis occurs by apoptosis
↳ oxytocin plays a role in Luteolysis

MALE REPRODUCTIVE SYSTEM

TESTIS

SEMINIFEROUS TUBULES

→ FLUID COMPOSITN
↳ less glucose & proteins
↳ rich in androgens, estrogens, K^+, inositol, glutamic acid, aspartic acid

→ SPERMATOGENESIS
↳ occurs here
↳ Phase I
→ Stem cell renewal & production of spermatogonia

Primitive germ cells
↓ mitosis
Primary spermatocytes

↳ PHASE II

Primary spermatocytes
↓ meiosis

Secondary spermatocyte
↓
spermatids

↳ PHASE III

Spermatids
↓ spermiogenesis
Spermatozoa

→ mitosis & meiosis require cyclins & cyclin dependent kinases
→ 1 Spermatogonium → 64 Spermatozoa
→ Spermatogenesis completes in 74 days
→ Sperm production Rate
↳ most reliable expression of Sperm production

SPERMATOGENESIS VS OOGENESIS

→ In female, the mitotic proliferation of oogonia occurs entirely before birth, in male, the mitotic proliferation of spermatogonia occurs only after puberty

→ Meiotic division of
↳ 1° oocyte → single ovum
↳ 1° Spermatocyte → 4 Spermatozoa

→ In female, 2nd meiotic division completed after fertilizatn immediately & there is no further development
In male, Spermatids undergo further differentiation to produce mature spermatozoa

SPERM

→ Intricate motile cell
→ rich in DNA
→ ACROSOME
→ cap ☂ hyaluronidase enzyme
↳ essential for dilutn of Hyaluronic acid for penetrating Cx mucus

→ also contain Germinal ACE
↳ This factor was related to fertility

SPERMATOGENESIS REGULATED BY

→ LEYDIG CELLS → produce testosterone → for sperm maturation
→ SERTOLI CELLS → nurture spermatozoa
→ LH / INTERSTITIAL CELL STIMULATING HORMONE
↳ acts on Interstial cells of Leydig to form testosterone
→ FSH → for Spermato genesis

PROGRESSIVE MOTILITY

→ mature Sperm aquires motility in epididymus after 48hrs

→ protein involved is CATSPER

SERTOLI CELL FUNCTIONS

→ Forms Blood Testis barrier

→ Secretes inhibin (inhibits FSH)

→ Testosterone exerts negative feedback on pituitary gonadotropin LH as well as hypothalamic GnRH

→ nurture Spermatozoa

→ Synthesize mullerian Inhibiting Substance

THE NERVOUS SYSTEM

INTRODUCTION TO CNS

NERVOUS SYSTEM

1. CNS
2. PNS
3. ANS

ANS

→ controls involuntary functions

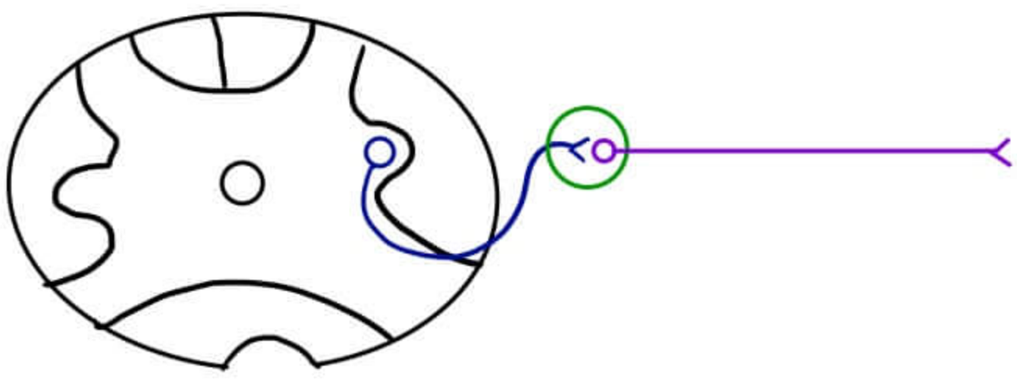
→ INCLUDES

1. Sympathetic Nervous System
2. Parasympathetic Nervous System
   → controls day to day functions of the body
   → Resting HR
   Secretions & movements GIT

SYMPATHETIC NERVOUS SYSTEM

→ Thoraco lumbar outflow

→ Preganglionic fibres are short
Post ganglionic fibres are long



PARA SYMPATHETIC SYSTEM

→ Craniosacral outflow

→ CN 3, 7, 9, 10

→ pre ganglionic fibres are long

→ post ganglionic fibres are short (Canaxonal type)

→ Ganglion is located just outside | wall of organ

Preganglionic nerves are cholinergic
↳ ganglionic transmission is cholinergic

Post ganglionic nerves
Parasympathetic → Cholinergic
sympathetic → adrenergic (NA)

RECEPTORS

PARA SYMPATHETIC SYSTEM

Nicotinic

→ N_1, N_2

→ Found at ganglia, NMJ, CNS neurons

Muscarinic

→ M_1, M_2, M_3, M_4, M_5

→ M_3, M_4, M_5 mediate excitatory effects

→ M_2 found in heart
inhibitory on cholinergic actions

SYMPATHETIC SYSTEM

α RECEPTORS

→ α_1, α_2
→ mainly mediates excitatory effects of adrenaline
→ α_2 → presynaptic autoreceptors
→ modulates the further release of NA

β RECEPTORS

→ β_1, β_2, β_3
→ β_2 → mainly inhibitory on Adrenaline & NA
→ present on skeletal muscles & bronchi
↳ Bronchodilaton
↳ vasodilation

→ β_1 → present in heart
→ mediate excitatory actions

CNS

INTRODUCTION

CELLS

1 Neurons
2. Glia → 4-10 times the no. of neurons

Neurons

→ majority in CNS → multipolar
→ no neurons formed after birth EXCEPT for OLFACTORY NEURONS
→ new synapses can be formed after birth

GLIA

→ Supporting cells
→ only cells formed outside the CNS & migrates to CNS → microglia
→ TYPES

1. MACROGLIA

a. Astrocytes

→ involved in formation of BBB (Blood Brain Barrier)
↳ reinforce BBB
→ involved in NT reuptake & redistributh
→ involved H^+ & K^+ homeostasis

b oligodendrocytes

→ involved in myelinath of CNS
↳ 1:20 → 1 cell myelinates 20 axons
↳ after the injury, repair is not possible as no intact neurilemma present & no definitive path to regrow

2. MICROGLIA

→ Scavengers of CNS → Phagocytic cells
→ derived from macrocyte monocyte lineage

→ CEREBELLUM → has highest no. of neuron
→ greatest density of serotinergic neurons found in NUCLEUS RAPHE MAGNUS (part of descending analgesia System)
→ max density of nor adrenergic neurons found in Locus Coeruleus (part of descending analgesia System)
→ max. density of dopaminergic neurons found in
↳ Nucleus accumbens (D3) (involved in reward & addictive behavior)
→ Orexigenic neurons found only in hypothalamus

NEUROTRANSMITTER

EXCITATORY NTs

→ Glutamate
→ Aspartate
} opens Na^+/Ca^{2+} channels in post synaptic membrane

INHIBITORY NTs

→ Glycine (commonest in Spinal cord) (STRYCHNINE – antagonist)
→ GABA (commonest in Brain)

→ opens K^+ / Cl^- channels in post synaptic membrane

Low Molecular weight NT	High molecular weight NTs] Neuropeptides
→ Glutamate	→ NP Y
→ GABA	→ Orexins (hunger)
→ Ach	→ Opioid
→ NA	→ CART (Coccaine & Amphetamine regulated transcript) (role in Satiety)
→ Dopamine	
→ synthesized locally in the terminal	→ synthesized in nerve cell body & transported to terminal

GLUTAMATE

→ RECEPTORS
1. Kinate
2 AMPA
3 NMDA (N-methyl-D-Aspartate)
→ involved in long term potentiation in hippocampus
Ketamine & dissociative anesthesia

→ voltage + 2 ligand gated channel

→ Glycine action is needed to remove the block

→ PENUMBRA

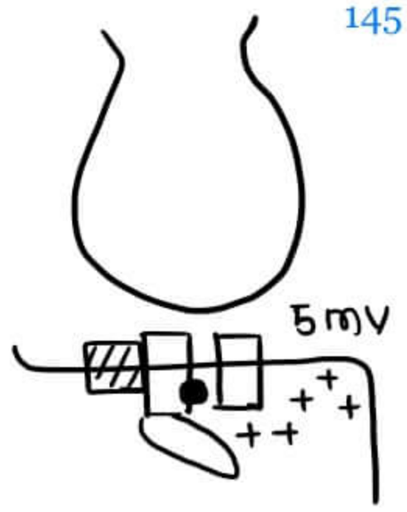
→ Lighter shadow at periphery

→ dark dense core at centre

→ Excito toxicity to brain

↳ extension of damage beyond the original

↳ dlt cerebral Ischemia



CEREBRAL ISCHEMIA

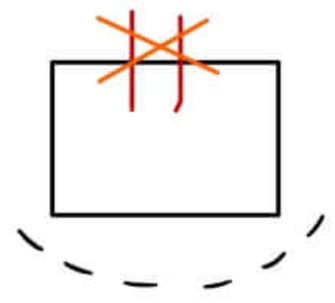
→ failure of $Na^+ - K^+$ pump

→ 2° active transports are failed

→ Glutamate reuptake is Na^+ dependent symport

→ Glutamate accumulates in near by synapes

→ Glutamate causes excessive excitatn of other neurons causing Ca^{++} influx, leading to damage



GABA

STIFF MAN SYNDROME (SMS)

→ Glutamate

↓ Glutamate Decarboxylase

GABA

→ auto immune disease Anti GAD antibodies developed → GABA Deficiency

→ Excess facilitatn of strech reflexes, results in Hypertonia

→ LADA (Late Adulthood Diabetes of Autoimmune origin)

↳ has anti - GAD antibodies

SYNAPSE

→ Junctional region b/w the 2 neurons

→ commonest type of synapse in brain → Axodendritic SYnapse

→ TYPES

Electrical Synapse

Chemical Synapse

ELECTRICAL SYNAPSE

→ direct transfer of charges from one cell to other by gap junctions

→ faster transmission

→ Bidirectional

→ Plasticity rarely seen

→ Ex: Heart

Retina

↳ Rod

↳ Bipolar cell ↓ Electrotonic

↳ ganglion cells ↓

Inferior olive

↳ olivo cerebellar tract

→ Signals collected from various sources collected by olive

→ Faster transmission occurs (for voluntary movements)

CHEMICAL SYNAPSE

1. AXODENDRITIC SYNAPSE

→ commonest type of synapse in brain (>95%)

→ Excitatory / facilitatory

2. AXOSOMATIC SYNAPSE (2-3%)

→ Inhibitory synapse

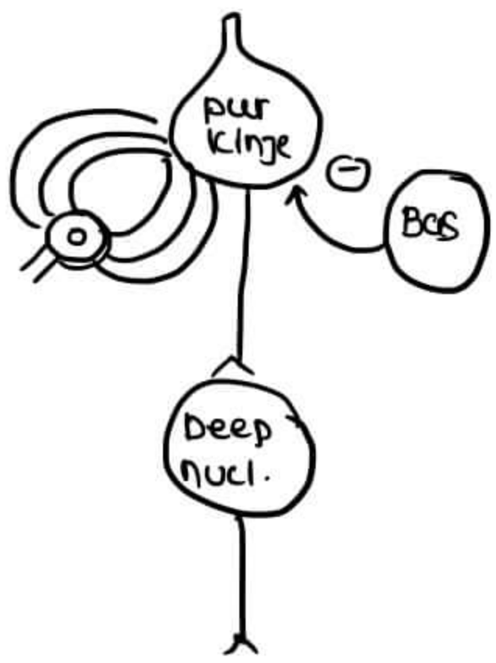
→ Ex :

Basket cell on Purkinje cells on cerebellum

↳ deep nuclear cell output is inhibited by purkinje cells

↳ Basket cell inhibit the purkinje cell

↳ Net effect → deep nuclei cells can Send output to muscles



Candelabrum cell

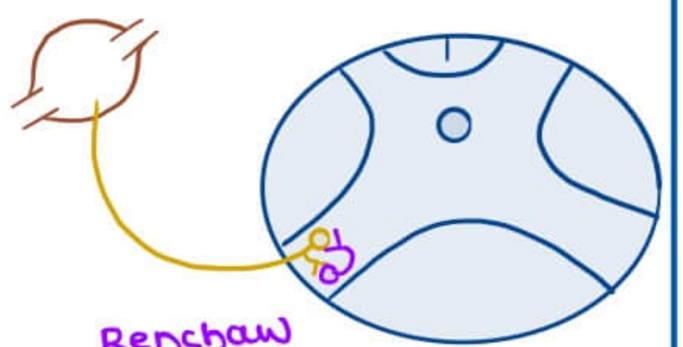
↳ found in cerebellum

Renshaw cell on the anterior motor neuron

↳ renshaw cell inhibitⁿ is recurrent type

↳ short inhibitory interneuron

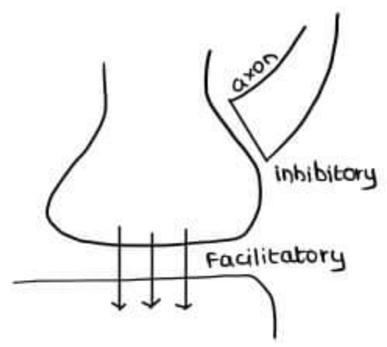
↳ collateral excites renshaw cell which inturn inhibits the same neuron



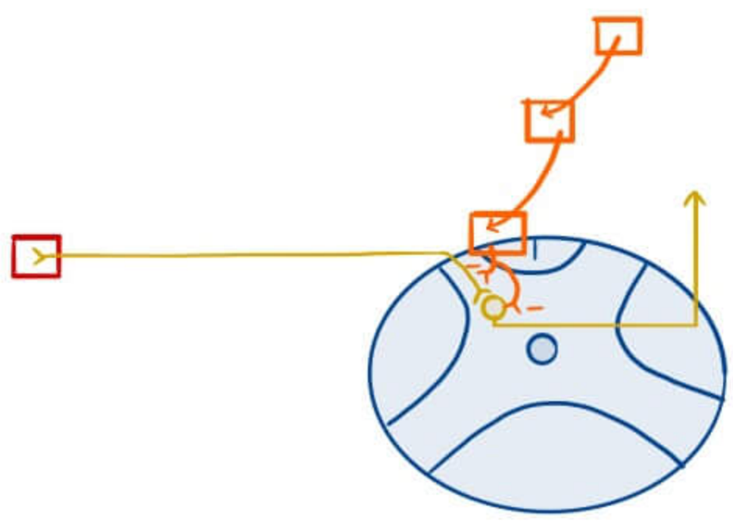
3. AXOAXONAL SYNAPSE

→ Pre synaptic inhibition

→ Seen in Descending analgesia System

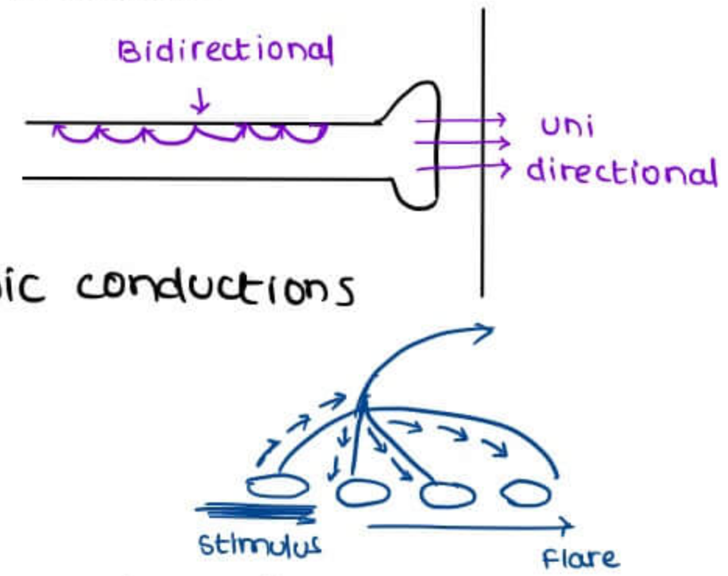


4. DENDRODENDRITIC SYNAPSE → found in hippocampus



PROPERTIES

1. One way conduction (from presynaptic neuron to post synaptic neuron)
   a. Bidirectional
   b. Unidirectional → synapse always conducts unidirectionally
   c. Orthograde / anterograde → can't excite previous area (Ref. period)
      → onward straight conduction
   d. Retrograde / Antedromic
      → seen in Triple response of cutaneous neurons
      → When skin area Stroked firmly,
         Red Reaction
         Wheal (edema)
         Flare (spread) → dlt antedromic conductions



2. DELAY of 0.5 m.sec per synapse occurs
3. FATIGUE
   → repeated stimulation (low frequency) for Long durat^{n}, transmission stops for some time
   → dlt temporary exhaustion of NTs

4. POST TETANIC POTENTIATION
   → basis for short term memory
   → tetanic (high frequency, short) stimulation

↓

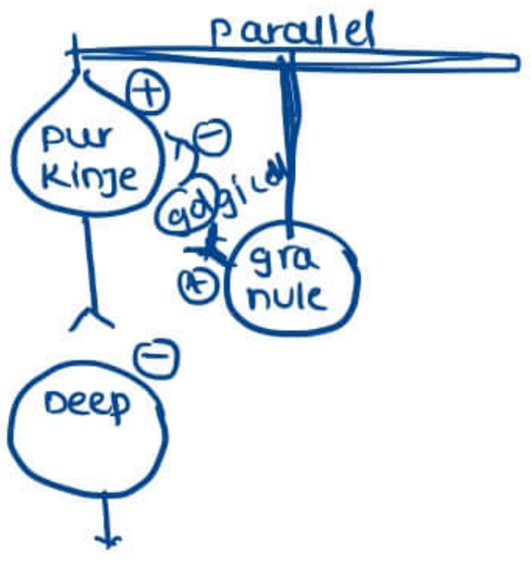
Transmission enhanced for some time
dlt accumulat^{n} of Ca^{2+} in pre synaptic terminal

PRE SYNAPTIC FACILITATION
→ another basis for short term memory

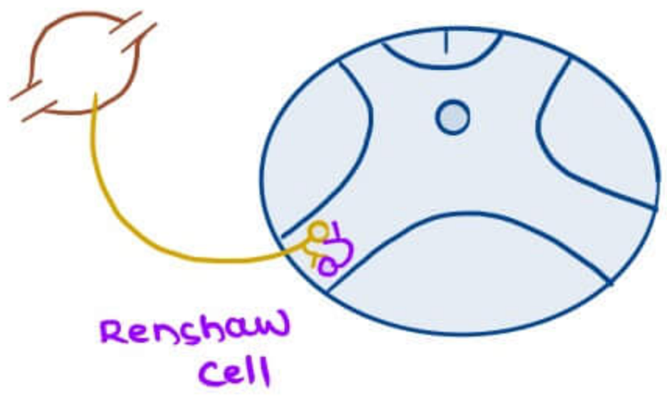
5. INHIBITION
   Direct → Axosomatic Synapse
   Presynaptic → ↓ release of excitatory NT
   → endogenous analgesia system
   Post synaptic
   → hyperpolarization of post synaptic membrane
   → endogenous analgesia system

SPECIAL TYPE

1. FEED FORWARD
   → seen in cerebellum (cerebellar learning)
   → Granule cell facilitatory on purkinje cell
      ↳ before that



2. RECURRENT OR RENSHAW CELL INHIBITION



→ inhibitory potential

→ PURPOSE

↳ delays muscle fatigue

↳ decreases the excitability of anterior motor neuron

→ shapens the signal to muscle

6. SUMMATION

→ EPSP

→ localised, depolarising potential (2-5mv)

→ not sufficient to create AP

→ multiple EPSP add ups and produce AP

EPSP	AP
→ localised depolarisatⁿ	→ propagated changed
→ greaded response	→ all or none law
→ monophasic change	→ biphasic change

Summation occurs by

TEMPORAL SUMMATION [Time]

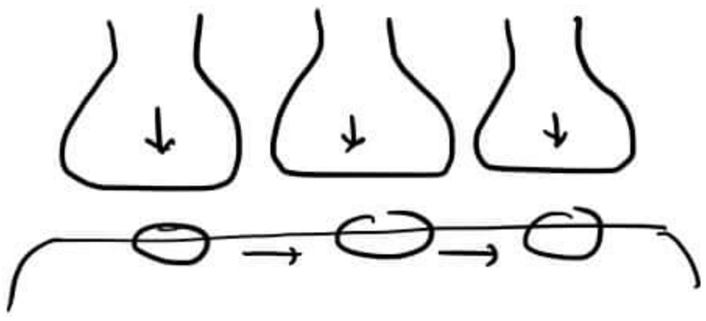
→ EPSP decays exponentially over time (15 m sec)

→ if one more happen in 15 m sec, Summation occurs

SPATIAL SUMMATION (Space)

→ EPSP occuring at a time are summated

→ Spacial summation has the inherent property of temporal summation

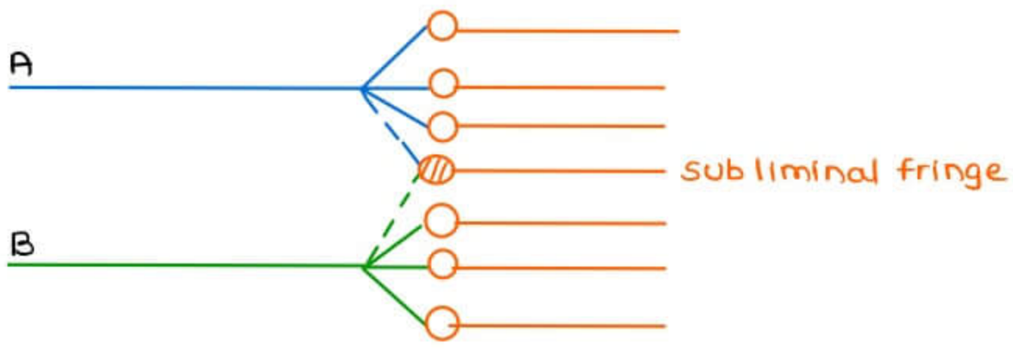


EPP → each EPP cause single contractⁿ

EPSP → Small amplitude summatⁿ required to cause AP (Trail & error method)

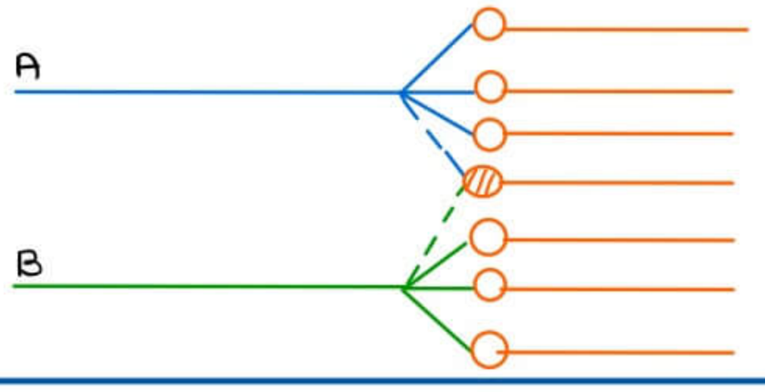
SUBLIMINAL FRINGE

→ combined stimulatⁿ achieves more response than individual stimulation



OCCLUSION

→ combined stimulatⁿ achieves diminished response

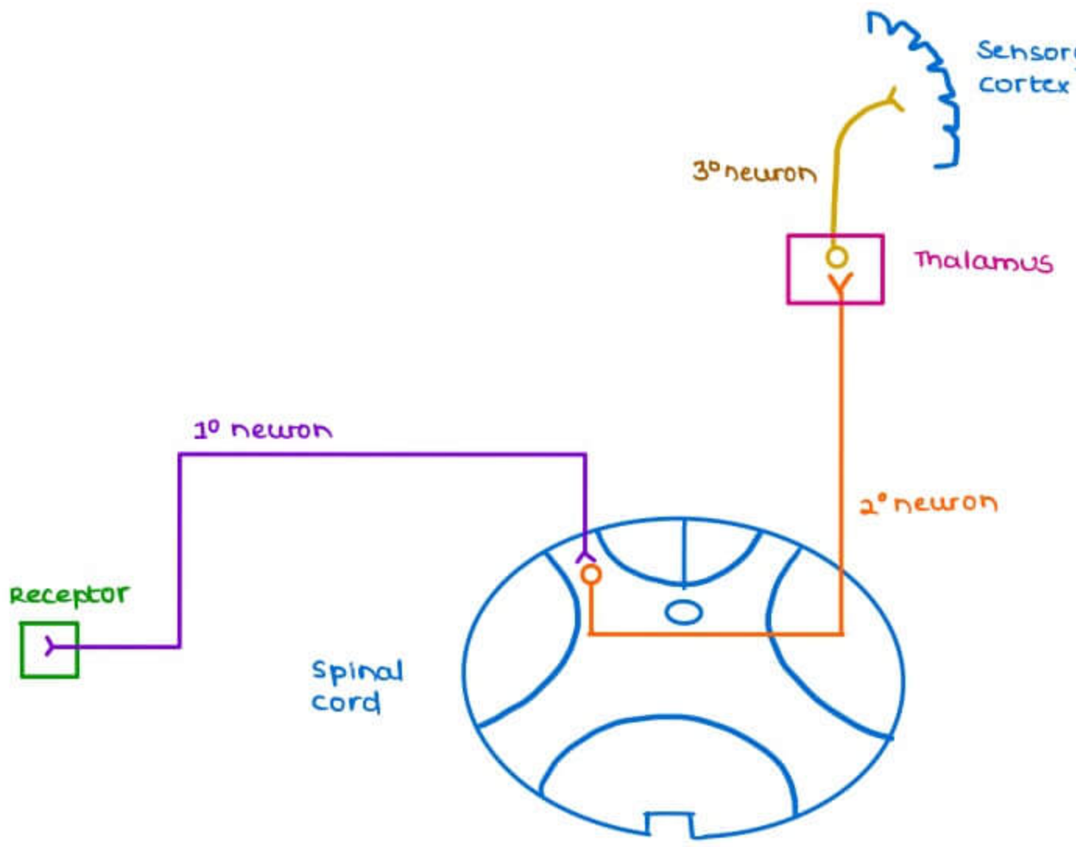


SENSORY SYSTEM

ORGANIZATION

→ functioning governed by

- 1° neuron → starts from receptor & enters the spinal cord
- 2° neuron → starts from spinal cord, crosses midline & ends on thalamus
- 3° neuron → starts from thalamus to the sensory cortex



→ THALAMUS is the OBLIGATE RELAY STATION for all general & special senses

Except OLFACTION

SENSES

GENERAL

1. Touch
2. Pain
3. pressure
4. Proprioception
5. Vibration

SPECIAL

1. Vision
2. Hearing
3. Taste
4. Hearing
5. Equilibrium

SPECIAL SENSES

→ contains specialized end organ

→ carried by cranial Nerve

GENERAL SENSES (Based on stimulus)

EXTEROCEPTIVE SENSES

→ source of stimulus is on external aspect of body

→ TELERECEPTORS

↳ source of stimulus is at a certain distance from the body

↳ Ex: Vision Hearing smell

INTEROCEPTIVE SENSES → Source of stimulus is deep inside the body

OLFACTION

→ meets other sensations at
  ↳ Amygdala
  ↳ Neo cortex

→ Gives the collaterals & potentiate other senses
  Ex: Taste → In common cold, taste can't be appreciated properly

THALAMUS

→ OBLIGATE RELAY STATION FOR all SENSES
→ Thalamic nuclei involving in motor functions
  ↳ Ventro Anterior
  ↳ Ventro Lateral
  ↳ Centro Median
  } connected ī cerebrum & Basal ganglia

LAWS → encodes intensity, duration, location & modality etc

DALE'S PRINCIPLE

→ applicable for entire nervous system
→ SAME NT IS RELEASED FROM ALL THE BRANCHES OF AN AXON

LABELLED LINE PRINCIPLE

→ encodes modality, location (to some extent)
→ EACH SENSORY MODALITY IS CARRIED BY A SPECIFIC TRACT IN CNS LOCATED IN A SPECIFIC PART OF CNS
→ Ex: Fine touch carried by dorsal columns

MULLER'S DOCTRINE OF SPECIFIC NERVE ENERGIES

→ NO MATTER WHAT FORM OF ENERGY IS APPLIED, EACH SENSORY PATHWAY CONVEYS THE SAME FORM OF ENERGY THAT IT SUPPOSED TO CONVEY

LAW OF PROJECTION

→ PHANTOM LIMB
→ NO MATTER WHERE YOU APPLIED A STIMULUS, CORTEX ALWAYS PROJECT THE SENSATION ONTO THE RECEPTOR FROM WHICH THE PATHWAY STARTS

→ Phantom pain sensation may disappear after 6 months
  ↳ CORTICAL PLASTICITY
    → Gradually impulses from amputed area diminishes
    → the dendritic geometry in cortex area changes & neurons shrink in size
    → Neurons of neighbouring area starts encroaching the area effectively & training of that area obliterated

INTENSITY DISCRIMINATION

→ Intensity discriminatn in CNS occurs by changing AP FREQUENCY

WEBER FECHNER LAW $S = K \times \log (I)$

S → magnitude of sensation felt
K → proportional constant
I → actual intensity applied

PERCEPTION FELT BY THE CORTEX ABOUT THE INTENSITY OF STIMULUS CHANGES ∴ LOGARITHMIC SCALE OF THE ACTUAL INTENSITY APPLIED IN PERIPHERY

Ex: K = 1, I = 10 } S = 1 × 1, S = 1 → If the percept^n felt is doubled, actual intensity is ↑ by 10 times

I = 100 → S = 1 × 2 = 2

STEVEN'S POWER LAW $S = K \times (I)^n$

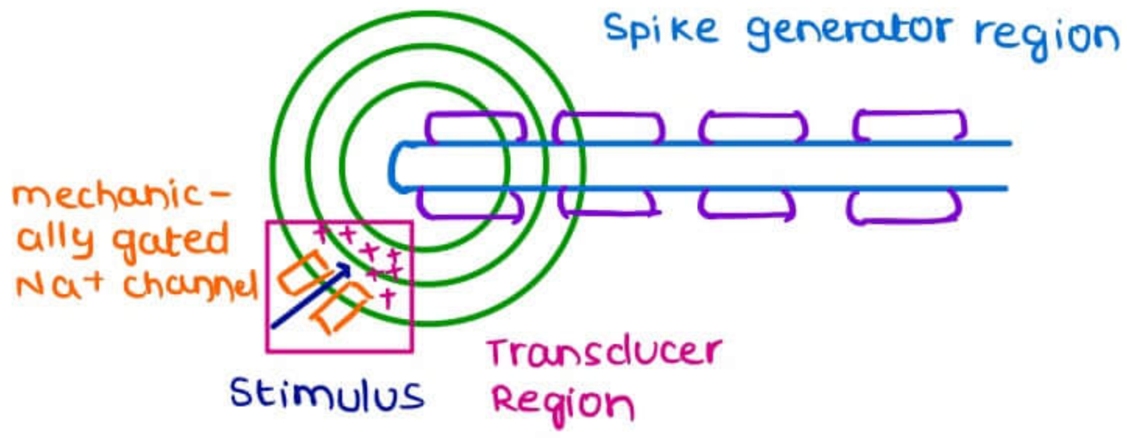
BELL MEGENDIE LAW → DORSAL ROOTS ARE SENSORY & VENTRAL ROOTS ARE MOTOR

RECEPTORS

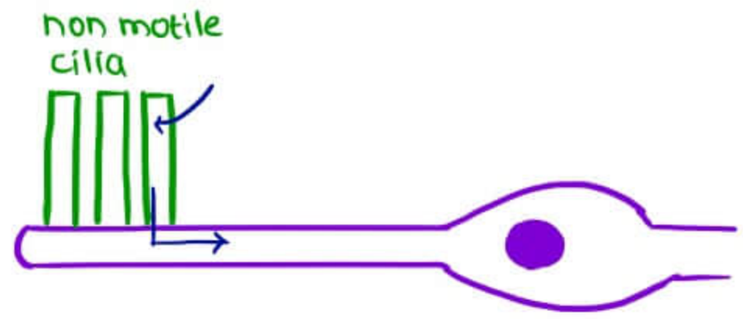
→ Biological transducers → converts any form of energy into electrical energy
→ end organs
→ Transducer & Spike generator region are at same cell for OLFACTION

PACINIAN CORPUSCLE

→ sensory neuron emerges from inside the corpuscle
→ 1st node of Ranvier is ∴in the corpuscle
→ 1st AP generated at 1st node of Ranvier (EXCEPTION)
→ Receptor potential should be > 10 mV, to generate a spike potential

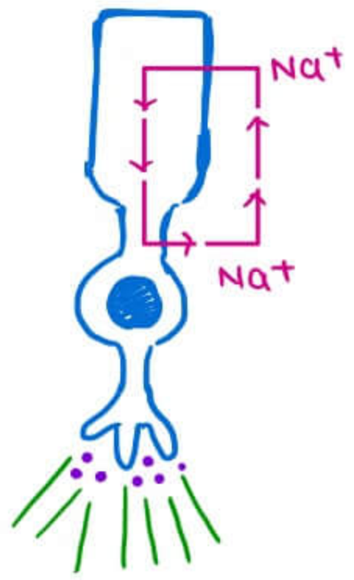


Olfactory neuron (bipolar neuron) →



→ for most of sensations, Receptor potential is depolarising potential, but
In case of VISUAL SENSE, ROD RECEPTOR POTENTIAL IS HYPERPOLARIZING POTENTIAL
↳ even in complete darkness, Na^+ current is moving from outer to inner segment & causes a steady Glutamate (NT) release at synapse

↳ When light strikes, Na^+ goes out but can't come back in



→ ROD HYPERPOLARIZED
→ ↓ Glutamate at synapse
→ Light is perceived

↳ Reason → Evolution development

→ Threshold for excitation for a single rod → 1 Photon
→ minimum threshold / detectable light for retina → 7 photons
↳ DARK NOISE → Asynchronised relase of NT from rods during dark
↳ A minimum of 7 rods fires synchronously then light is detected

→ minimum threshold for entire eye → 45 photons

CLASSIFICATION

1. MECHANO RECEPTORS
→ Meissner's corpuscle
→ merkel disc
→ Pacinian
→ Ruffini's

2. THERMO RECEPTORS
→ belong to TRP (Transient Receptor Potential) Superfamily
→ CMR (cold & menthol sensitive Receptor)

3. CHEMO RECEPTORS
→ Smell ®
→ taste ®
→ Glomus cell

4. ELECTRO MAGNETIC RECEPTORS → Rods & cones
5. NOCICEPTORS
→ belongs to TRP super family
→ vanilloid Receptor (TRP-V_1)
→ NOT FREE NERVE ENDINGS

ADAPTATION

→ Receptor responds to stimulus briefly
ī continued stimulus receptor response stops
→ ↓ the unnecessary burden to cerebral cortex

→ When continued stimulus removed, receptor responded briefly
↳ meant to detect change in the environment

→ TYPES

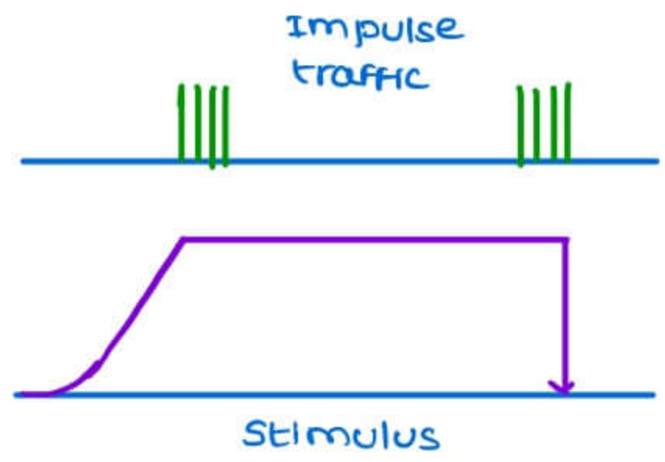
1. RAPIDLY ADAPTING / PHASIC RECEPTORS

→ Pacinian corpuscle

↳ Phasic receptor

↳ mechano receptor

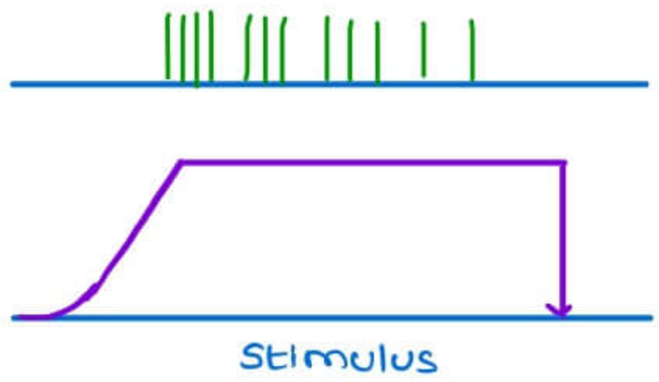
↳ best suited for vibration



2. SLOWLY ADAPTING RECEPTOR

→ MERKEL RECEPTOR

↳ helps in continuously Sending the important Sensory Information

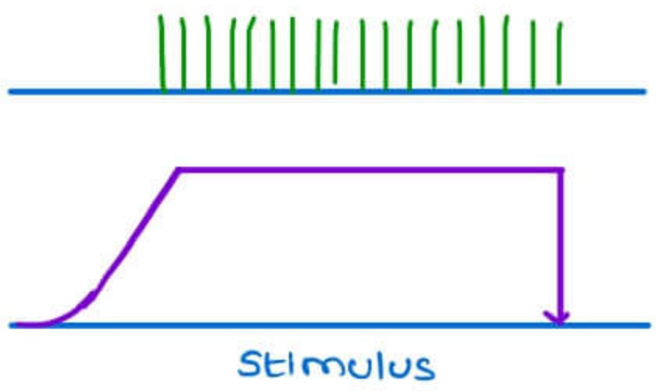


3. NON ADAPTING / TONIC RECEPTOR

↳ do not adapt

↳ helps to carry the very important Sensory information

↳ Ex: PAIN RECEPTORS



TEMPERATURE RECEPTORS

→ Tonic + Phasic receptors

→ For every 1°C steady ambient temperature, tonic discharge occurs

→ From 10°C - 30°C

→ for each 1°C, tonic discharge occurs by cold Receptors

→ From 32° - 42°C

→ for each 1°C, tonic discharge occurs by warm receptors

→ For sudden change of temperature, Phasic discharge occurs

↳ ↓ temperature, Cold receptors Fired phasically

↳ ↑ temperature, warm receptors fired phasically

↳ indicates the change in direction of temperature

→ 30°C - 32°C → THERMO NEUTRAL ZONE

→ > 45°C → PARADOXICAL COLD

↳ pain fibres alw cold receptors are fired

→ 20°C - 24°C → maximum firing Frequency OF cold receptors (Thermogenic shivering can be initiated)

MECHANO RECEPTORS

RECEPTOR	LOCATION	RECEPTIVE FIELD SIZE	SPEED OF ADAPTATION	SENSATION ENCODED
Merkel's DISC	Epidermis	Smallest	Slowly	Locatⁿ of touch
meissner corpuscle	Dermis	Small	Rapidly	speed of applicatⁿ of touch ↳ Flutter along the skin
Pacinian corpuscle	Dermis & Deeper tissues	Large	Very rapidly	vibratⁿ
Ruffini's corpuscle	Ligaments muscles Tendons	Large	Slowly	Deep pressure (Massage)

BRAILLE → meissner corpuscle > ruffini's corpuscle

RECEPTIVE FIELD SIZE

↳ area of skin from where sensory neuron collects information

↳ basis for 2 point descrimination

↳ smaller the size, better the 2 point discriminatⁿ

2 point discrimination

→ determined by receptor density also

→ Threshold is Least in fingertips (1-2 mm)

Threshold is more at back (50-60 mm)

↳ receptive field size is least & receptor density is more at fingertips

→ also determined by CORTICAL REPRENTATION

↳ Larger the representation, best the 2 point discrimination

→ it is needed for determination of TEXTURE

ASCENDING TRACTS

SPINAL CORD CROSS SECTION

→ central H shaped grey area

→ Anterior white column

Posterior white coloum

Lateral white column

1. DORSAL COLUMN SYSTEM

carries Fine touch (2 point discriminatn)
Pressure
Vibratn
Proprioceptn (conscious)

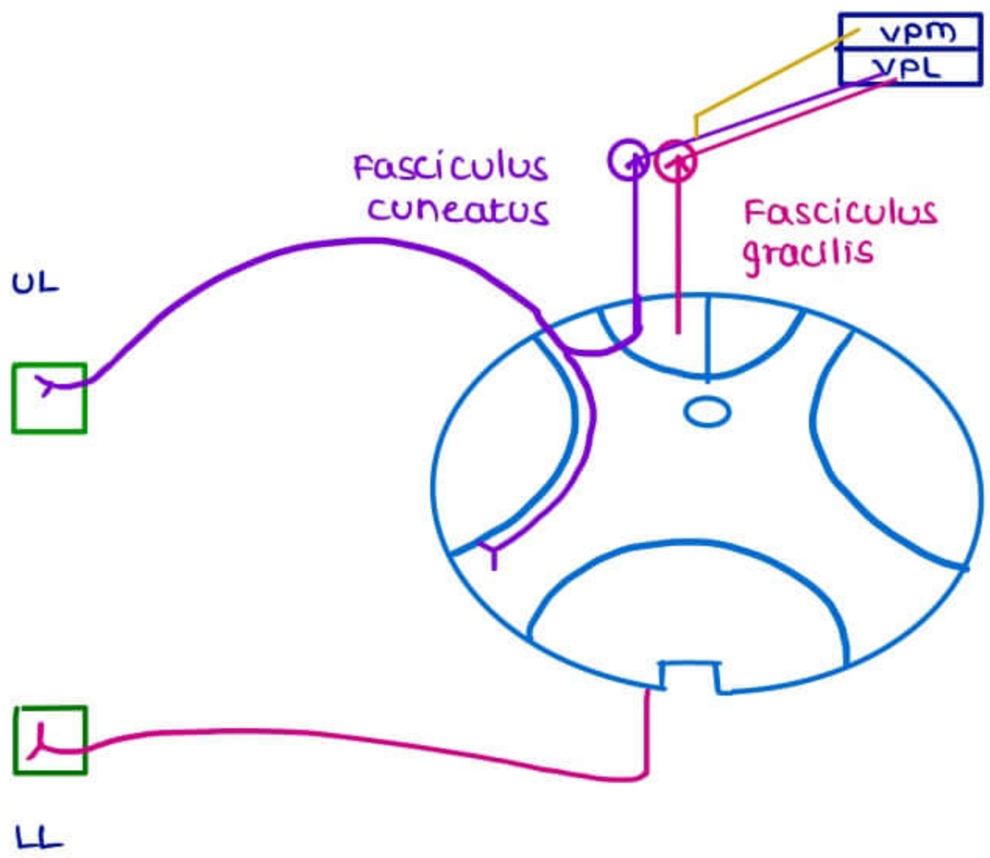
2. ANTERO LATERAL SYSTEM

carries crude touch
pain } by Lateral white coloumn
temperature
Tickle, itch
Sexual sensations

DORSAL COLUMN	ANTERO LATERAL COLUMN
Faster ↳ A_α, $A\beta$ ↳ 70 – 130 m/sec	relatively slow ↳ $A\delta$, C ↳ 5 – 30 m/sec
EPICRITING SENSATIONS ↳ need intact cortex ↳ First to disappear Last to reappear (32 – 52 wks) ↳ Vibratn sense lost at first	PROTOPATHIC SENSATION ↳ do not need intact cortex ↳ recover early (8 – 32 wks)
1° neuron enters the spinal cord runs on same side & ascend & upto upper medulla to end there	1° neuron enter the spinal cord & ends here itself

DORSAL COLUMN

FINE TOUCH



FINE TOUCH FROM UL

→ 1° neuron enters the spinal cord & divides into 2 branches
↳ one branch comes anteriorly & synapses in anterior horn cell
→ serves as REFLEX ARC
↳ other branch turns backwards & runs upward in dorsal white column

FINE TOUCH FROM LL

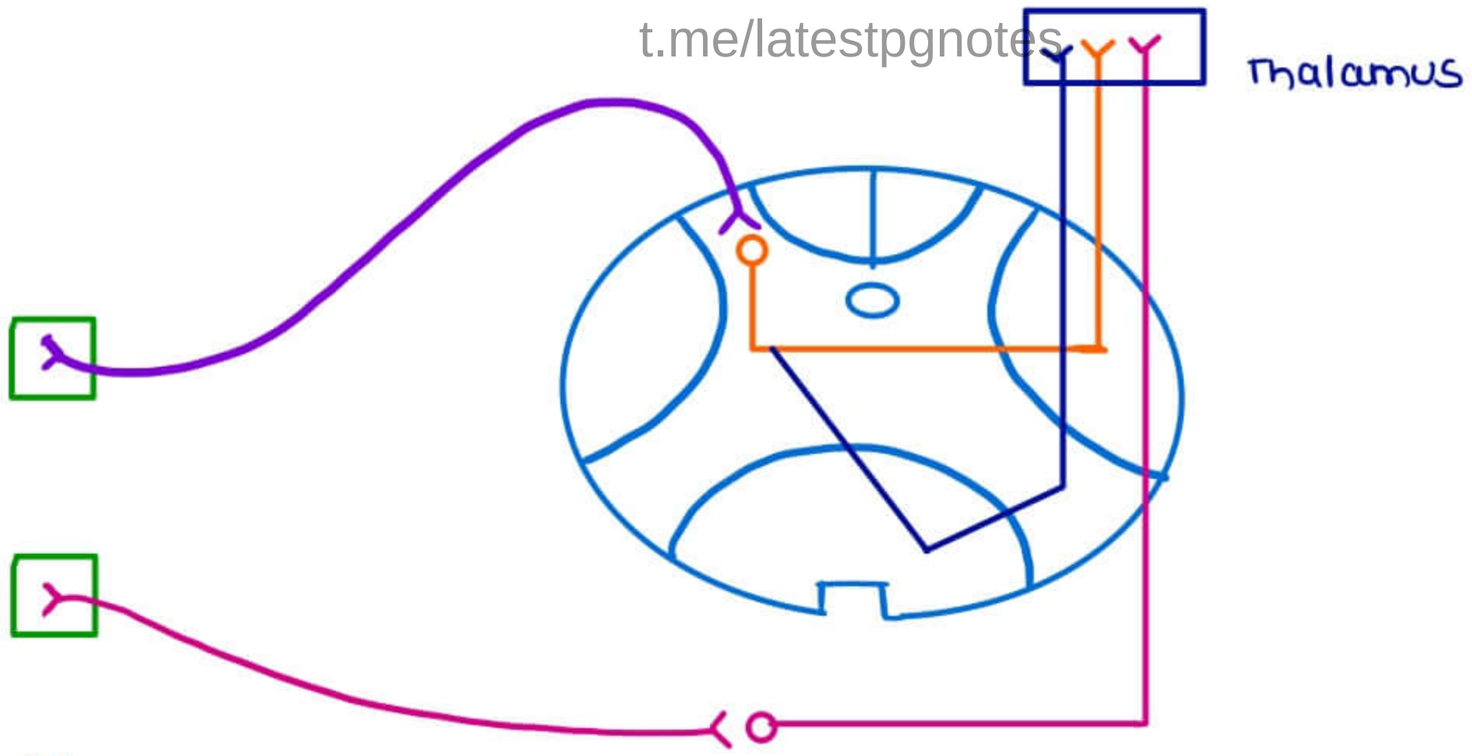
→ 1° neuron enter the spinal cord & starts running upwards through lumbosacral segments
  ↳ in the cervical Region, UL fibre push the LL fibre to the midline
  ↳ creating 2 distinct ascending tracts in white column
    FASCICULUS GRACILIS → bundle near the midline, coming from LL
    FASCICULUS CUNIATUS → bundle placed laterally, coming from UL

→ stereognosis is lost in the lesion of fasciculus cuneatus
→ faciculus gracilis, fasciculus cuneatus } Tract of GOLL & BURDACH (old name)
→ 1° neurons ends in upper medulla, in nucleus gracilis & nucleus cuneatus

→ 2° neuron
  ↳ starts in upper medulla & crosses midline & runs in medial lemniscus & joined by trigeminal nerve & ends in thalamus
    ↳ 2° neuron of dorsal column ends in ventro lateral nucleus
    ↳ Trigeminal nerve ends in ventro medial nucleus of thalamus

ANTERO LATERAL COLUMN

PAIN



PAIN FROM UL

→ 1° neuron enters the spinal cord & ends there
→ 2° neuron starts from dorsal horn & crossed midline in anterior commisure & ascends up as LATERAL SPIND THALAMIC TRACT to Thalamus

→ SYRINGOMYELIA
  ↳ cyst filled lesion in central canal
  ↳ grows anteriorly & damage pain & temperature fibres first

PAIN FROM LL

→ 1° neurons enter spinal cord and ends there
→ 2° neurons starts & crosses midline & runs upwards in lateral White column
→ UL fibre joins lower limb fibre & LL fibre pushed laterally

Arrangement of fibres in lateral white column (from lateral to medial)

1. LL
2. abdomen
3. UL

↳ in the tumor of lateral column, 1st sensation affected is → pain from opposite side of LL

CRUDE TOUCH

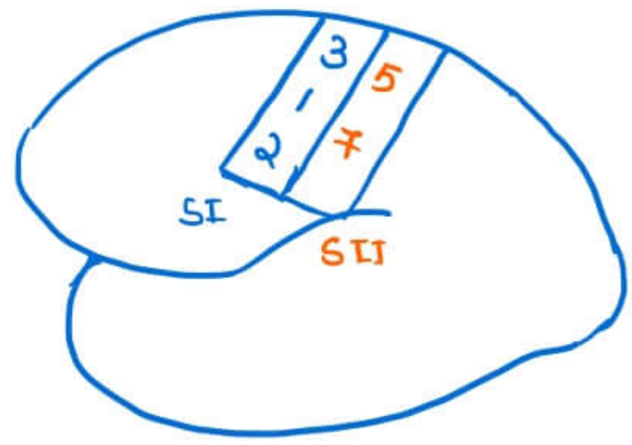
→ come to anterior white column & forms ANTERIOR SPINOTHALAMIC TRACT

VPL NUCLEUS → Relay nucleus for all the sensations

Ventro basal complex
Intra laminar nuclei } for pain sensation

SENSORY CORTEX

→ Area 3,1,2 → SI (somato sensory Area I)
→ Area 5,7 → S II (Secondary sensory cortex)



→ SI → concerned ī percept^{n} of sensations
→ SII → concerned ī analysis & interpretat^{n} of touch (stereognosis)

→ Body representation is contralateral, vertical & inverted
→ Largest representation → Lips & face

PARIETAL HEMINEGLECT SYNDROME

→ LESION OF posterior parietal cortex in non dominant hemisphere
→ Non dominant hemisphere is concerned ī spatio temporal co relation ī body parts
→ opposite half of body is neglected

PHYSIOLOGY OF PAIN

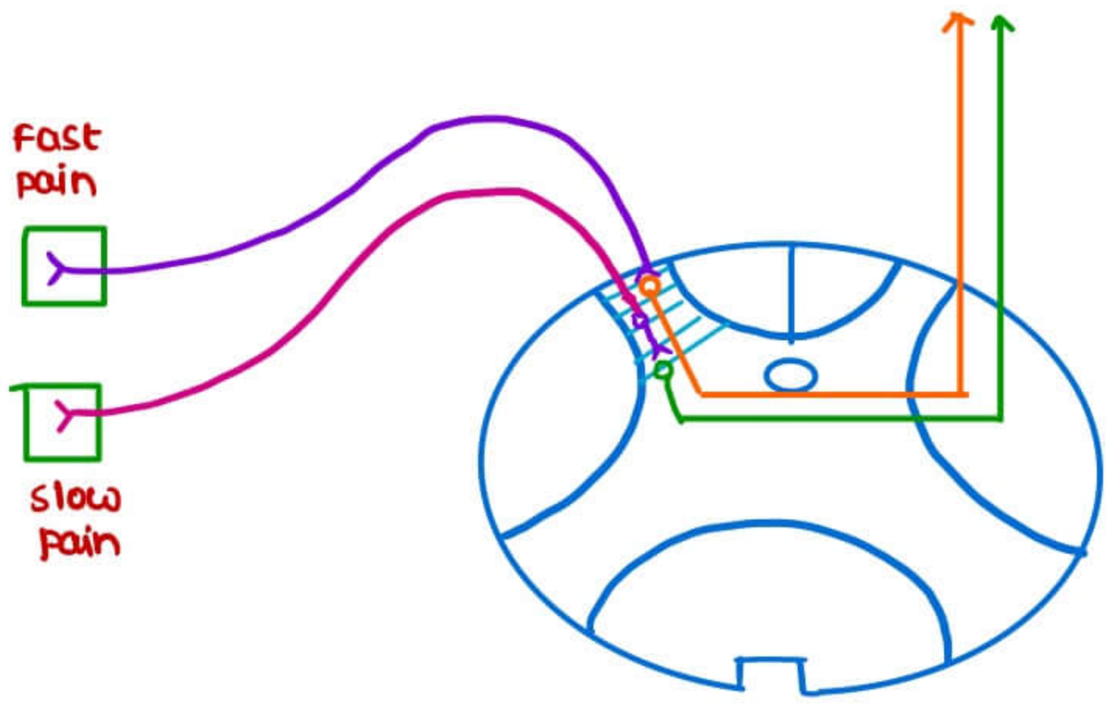
PAIN INSENSITIVE STRUCTURES	PAIN SENSITIVE STRUCTURES
Brain	vessels
cornea	meninges
Lung parenchyma	pleura
Liver parenchyma	Bronchi
Kidney	Heart
	pericardium
	Liver capsule
	Gall Bladder
	Bile duct
	ureter
	Bladder
	Urethra

→ Intestines
  ↳ not sensitive to sharp cutting pain
  ↳ sensitive to torsional pain

TYPES OF PAIN

1. FAST / 1ST / SHARP / ACUTE / PRICKING PAIN ($A\delta$)
2. SLOW / 2nd / DULL / CHRONIC / ACHING PAIN (C)

→ Pain carried by Lateral Spinothalamic tract
  Neospinothalamic tract carries fast pain
  Paleospino thalamic tract carries slow pain



→ Laminar organization present in dorsal horn of spinal cord
→ Fast pain carrying fibres end in Lamina 1 & 2° neuron start here & crosses midline & continues as Neospinothalamic tract
  NT is Glutamate

→ Slow pain afferents enters spinal cord & ends on Lamina 2 & 3 & another neuron to lamina 5 & the next neuron cross the midline & carried as paleospinothalamic tract

VARIETIES OF PAIN

Physiologic → starts from receptor
Pathologic → do not from receptor
  Neuropathic pain (nerve injury)

PHYSIOLOGIC

1. ALLODYNIA → non noxious stimulus gives pain sensation
   → Ex: Trigeminal neuralgia
2. NOCICEPTIVE → noxious stimulus giving corresponding degree of pain
3. HYPERALGESIA → noxious stimulus giving exaggerated pain

→ Allodynia & Hyperalgesia is due to reactivation of previous non-active receptors
→ Hyperalgesia seen mostly in inflammatory pain

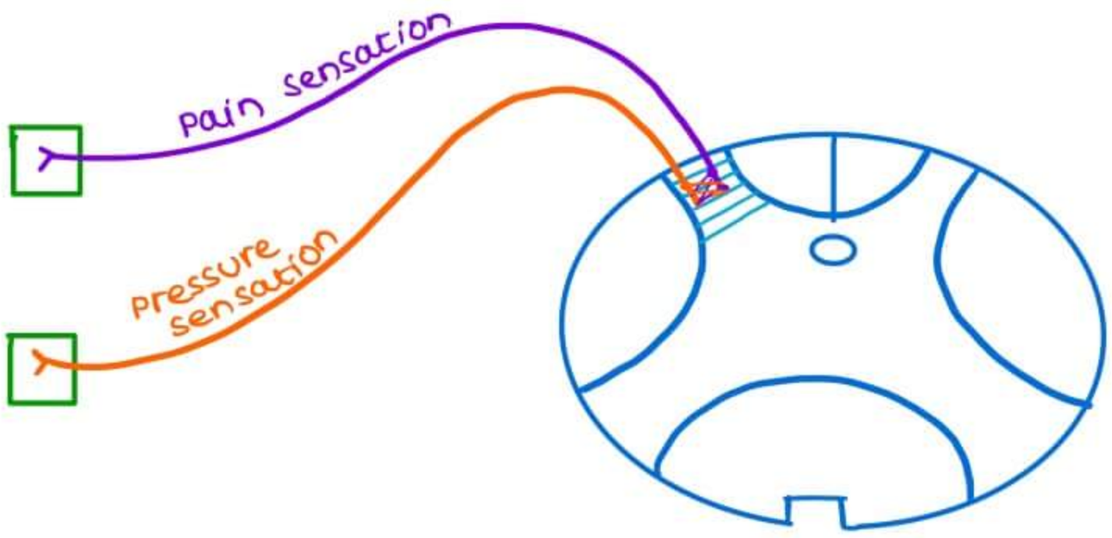
NEUROPATHIC PAIN

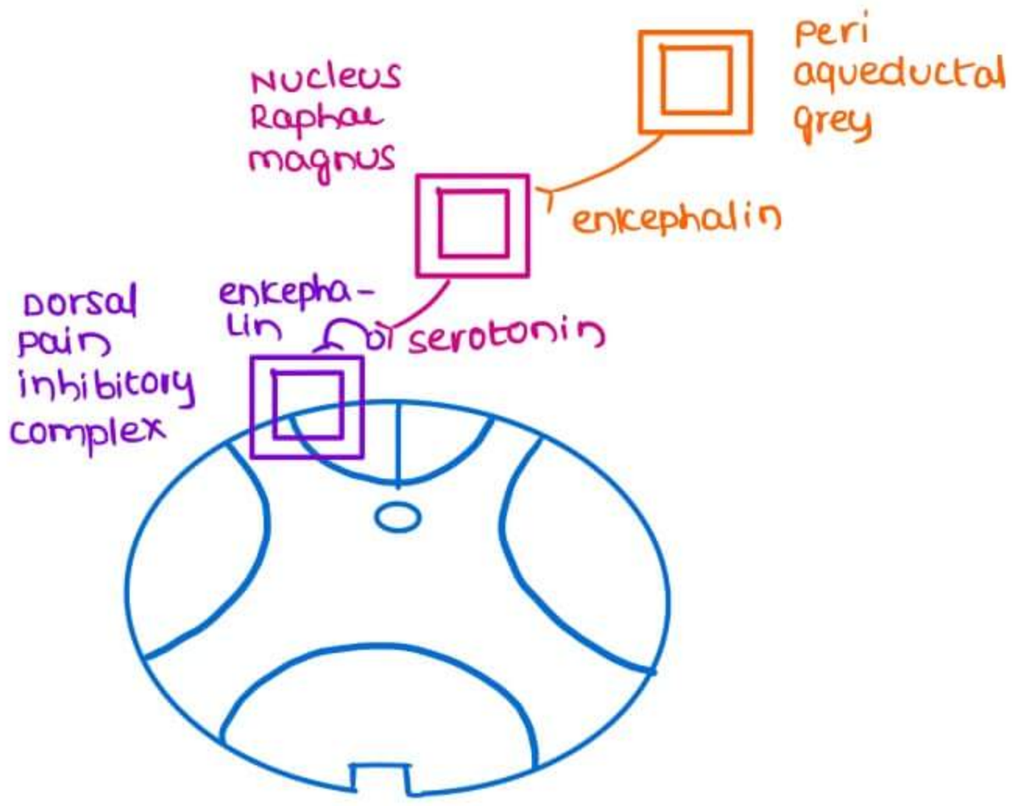
- → causalgia
- → Phantom pain
- → Post herpetic neuralgia
- → Trigeminal neuralgia

ANALGESIA SYSTEMS

GATE CONTROL THEORY OF PAIN

- → Accupressure therapy is based on this
- → Gate is substantia gelatinosa of Rolando (Lamina 2 & 3)
- → pressure sensation inhibits pain via collaterals in substantia gelatinosa





DESCENDING ANALGESIA SYSTEM

- → 3 COMPONENTS

1. PERI AQUI DUCTAL GRAY
   - ↳ projects on nucleus raphae magnus
   - ↳ has encephalic neurons
   - ↳ NT → enkephalin

2. NUCLEUS RAPHAE MAGNUS
   - ↳ projects Serotinergic neurons & ends on interneurons
   - ↳ NT → Serotonin
   - ↳ inter neurons forms Dorsal Pain inhibitory complex

3. DORSAL PAIN INHIBITORY COMPLEX
   - ↳ inter neurons NT → Enkephalin
   - ↳ Pre synaptic & post synaptic pain inhibition occurs
   - ↳ Encephalin has inhibitory effect on pain carrying afferents

ENDOGENOUS OPIOIDS | ENDOGENOUS CANNABINOIDS

ENDOGENOUS OPIOIDS

1. Endorphins
2. Enkephalins
3. Dynorphin

ENDOGENOUS CANNABINOIDS

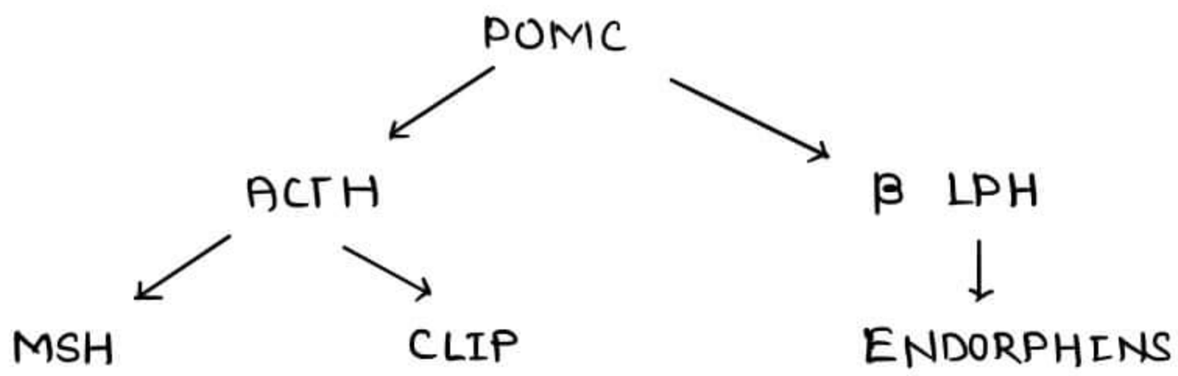
1. 2 - AG
2. Anandamide

→ act via CB receptors

CB_1 → also Euphoria

CB_2 → also Control of pain

Endogenous opioids



RECEPTORS

→ Endogenous opioids acts via μ, κ, δ

→ PREFERENTIAL BINDING

Endorphins → μ

Enkephalins → κ

Dynorphins → δ

→ Endorphin predominant Actions

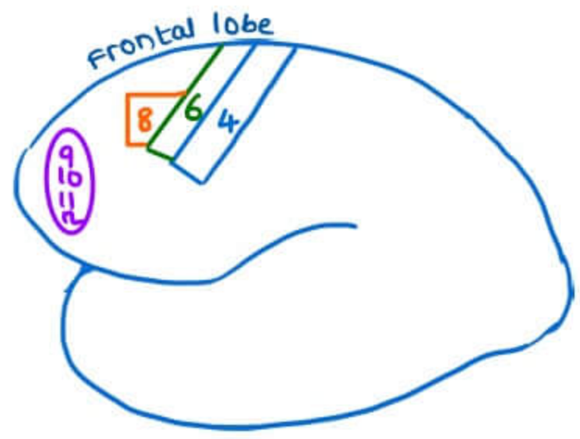
1. Meiosis
2. Constipation

μ	κ	δ
Analgesia	Analgesia	Analgesia
Meiosis	meiosis	
sedation	sedation	
Euphoria	dysphoria	
constipation	Diuresis	
Respiratory depression		
↑ GH Secretion		
↑ Prolactin Secretion		

MOTOR SYSTEM

ORGANIZATION

Area 4	Primary motor area
Area 6	pre motor & Supplementary motor area
Area 8	Frontal eye fields
Area 9,10, 11,12	Seat of intellegence in prefrontal cortex



BODY REPRESENTATION

→ CL , inverted

→ Motor Homunculus

↳ Greatest representat^{n} → Thumb, muscles of vocalisation & masticat^{n}

ORGANIZATION & FUNCTION

→ 1st impulse of voluntary movement is recorded at → Area 6

↳ Thought / idea starts here

→ 2nd impulse comes from Basal ganglia

↳ converts the abstract thought into voluntary movement

↳ Selects the desired movement

↳ Supress the other movement

↳ provide spontaneity & purpose to the movement

↳ provide proportion to the movement

→ 3rd impulse comes from CEREBELLUM

↳ provides the sequencing of muscle contraction

→ 4th impulse comes from AREA 4

↳ command will be formed in concerned muscles

↳ command sent down for execution

→ Sending down of command done by

↳ cortico spinal tract

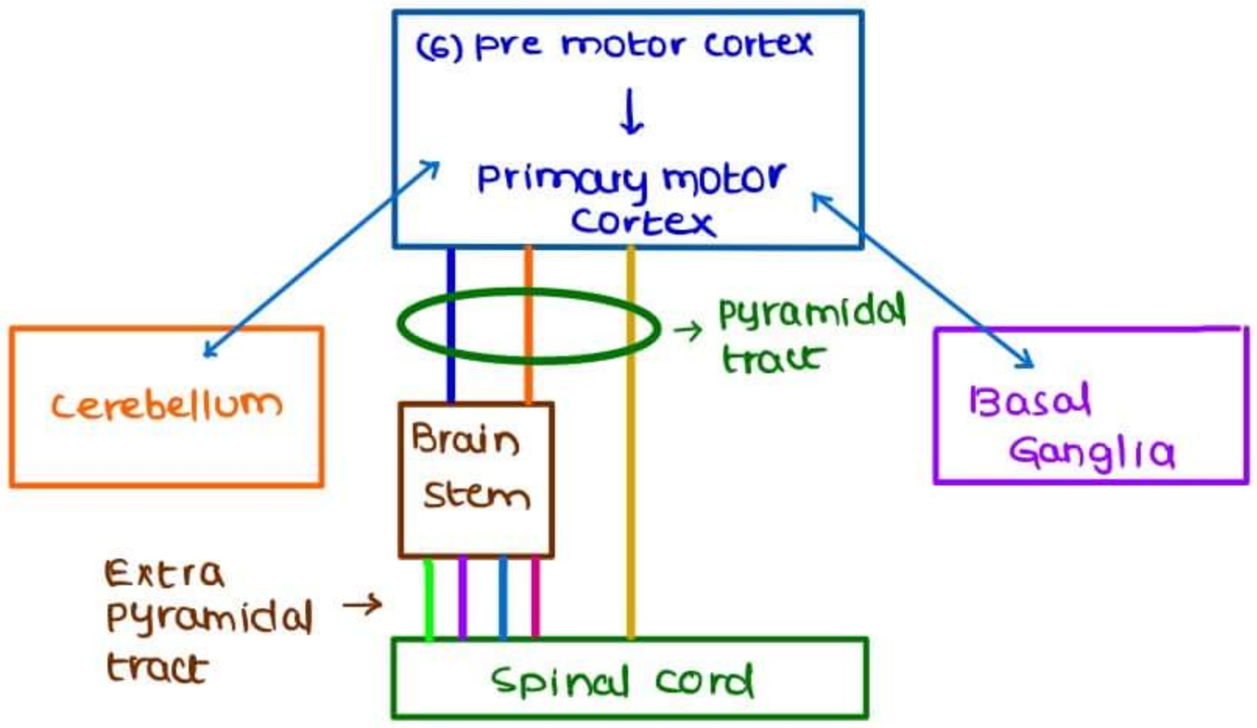
→ initiates the voluntary movements

→ controls distal muscle group

→ controls thumb (skilled voluntary movement)

PYRAMIDAL TRACT

1. cortico spinal Fibers
2. Cortico bulbar Fibers } cortex to Brainstem
3. Cortico nuclear Fibers



PYRAMIDAL TRACT

- ↳ corticospinal tract
- ↳ corticobulbar tract
- ↳ corticonuclear tract

EXTRA PYRAMIDAL TRACT

- ↳ vestibulospinal tract
- ↳ Reticulospinal tract
- ↳ Rubrospinal tract
- ↳ tectospinal tract

EXTRA PYRAMIDAL TRACT

→ all fibers outside the pyramids in medulla

1. vestibulo spinal tract
   - ↳ controls posture & Equilibrium
2. Reticulo spinal tract
   - ↳ controls trunk muscles

} controls axial muscles

3. Rubrospinal tract
   - ↳ controls proximal muscle tract
4. Tectospinal tract
   - ↳ Tectum → ROOF OF MID BRAIN
     Tegmentum → Floor of midbrain

↳ ROOF OF mid Brain Contains

CORPORA QUADRIGEMINA

- 2 Superior colliculi → part of visual pathway
- 2 Inferior colliculi → part of hearing pathway

↳ controls movements in response to visual & auditory inputs

EXTRA PYRAMIDAL SYSTEM

→ Extra pyramidal tracts + The cortical area that control those extra-pyramidal tracts + cortical areas connected t Basal ganglia

LATERAL MOTOR SYSTEM OF CORD

corticospinal tract
Rubro spinal tract
} runs on the lateral aspect of spinal cord

MEDIAL MOTOR SYSTEM OF CORD

Vestibulospinal tract
Reticulospinal tract
Tectospinal tract
} runs on the medial aspect of spinal cord

CORTICO SPINAL TRACT

ORIGIN

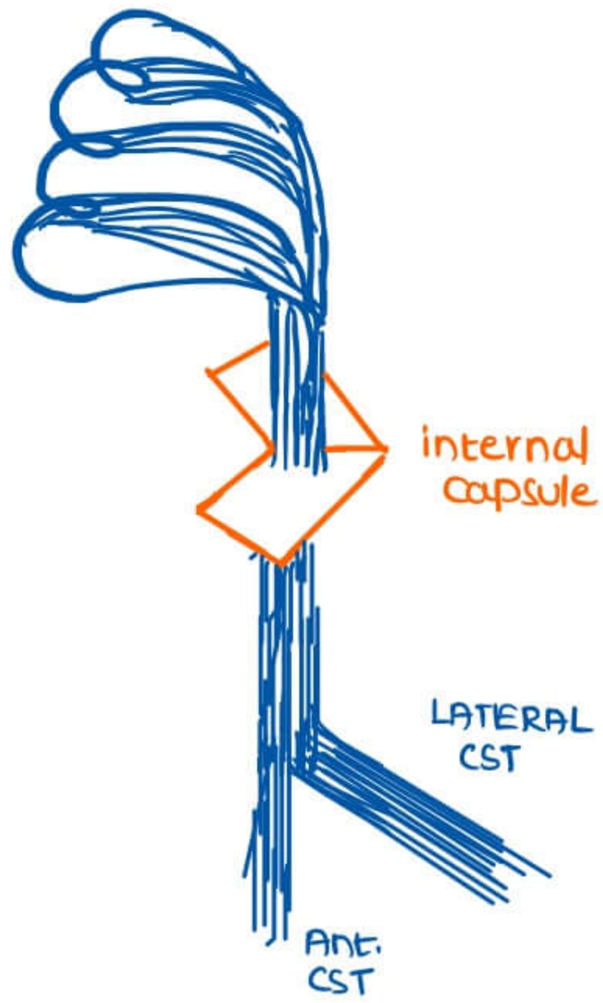
30% Fibers → Area 4

30% Fibers → Area 6

40% Fibers → Sensory cortex (Parietal lobe)
- ↳ involved in sensory motor integration

SOURCE

3% Fibers → PYRAMIDAL CELL
- ↳ large, heavily myelinated
- ↳ Large BETZ CELL
- ↳ most rapidly conducting (120m/sec)
- ↳ Facilitatory descending tract
- ↳ initiates voluntary movement



97% Fibers → Normal neural cells
- ↳ inhibitory

UPPER MOTOR NEURONS
- ↳ From motor cortex to spinal cord
- ↳ predominantly inhibitory to Lower motor neuron
  - → In UMN Lesions, HYPERTONIA & exaggrated tendon reflexes seen

LOWER MOTOR NEURONS → From spinal cord to muscle
- ↳ In LMN lesions, hypotonia, no tendon reflex present

COURSE
- → converge to make a bundle → CORONA RADIATA
- → runs down through ant. 2/3rd of post. limb of Internal capsule

- → 85 - 90% Fibers cross the midline in Lower medulla to reach opposite side
  - ↳ MOTOR DECUSSATION & enters spinal cord
  - Runs in the lateral aspect of spinal cord → LATERAL CORTICO SPINAL TRACT

- → 10 - 15% runs on same side on the anterior aspect of Spinal cord
  - ↳ ANTERIOR CORTICO SPINAL TRACT
    - ↳ at upper or mid thoracic level, these fibers also cross the midline

- → most of Fibers ends on Interneurons in the spinal cord
- → Pattern generator for walking → Spinal cord

UNCONCIOUS PROPRIOCEPTION

→ As muscle begin to contract, the moment to moment change of length conveyed from muscle to spinal cord & from spinal cord to cerebellum

→ carried by spino cerebellar tract

→ comparator function done by cerebellum & sends signals back to adjust the contractions

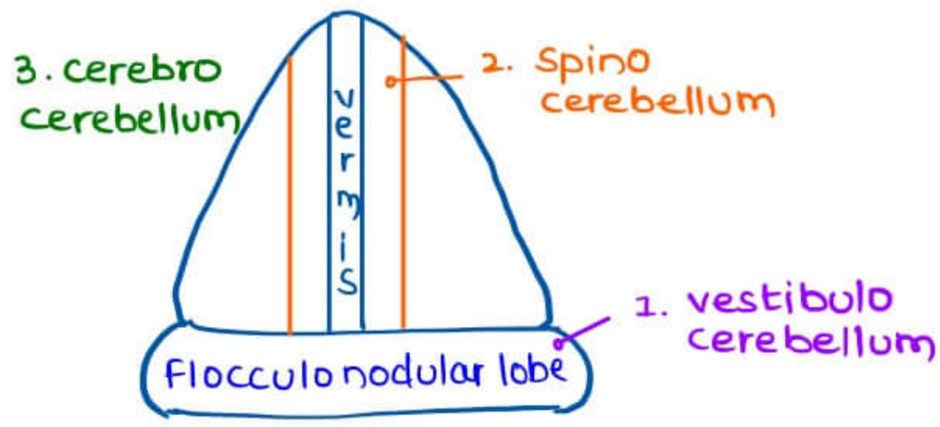
CEREBELLUM

→ connected ĩ cortex, spinal cord

→ Master co-ordinator of voluntary movements

BASAL GANGLIA

→ Exclusively connected ĩ the cortex



CEREBELLUM

FUNCTIONAL DIVISION

VESTIBULO / ARCHI CEREBELLUM

→ connected ĩ vestibular apparatus

→ oldest in evolution

→ controls the posture & equilibrium

→ controls vestibulo ocular reflex

SPINO CEREBELLUM / PALEOCEREBELLUM

→ connected to & fro ĩ spinal cord

→ co-ordinates blw muscle group

↳ movement become smooth & precise

→ damping function

→ controls alternate rapid movements

↳ lesion causes Adiadochokinesia

→ maintains muscle tone

CEREBRO / NEO CEREBELLUM

→ connects ĩ cortex

→ newer in evolutⁿ

→ α - γ CO-ACTIVATION linkage occurs here

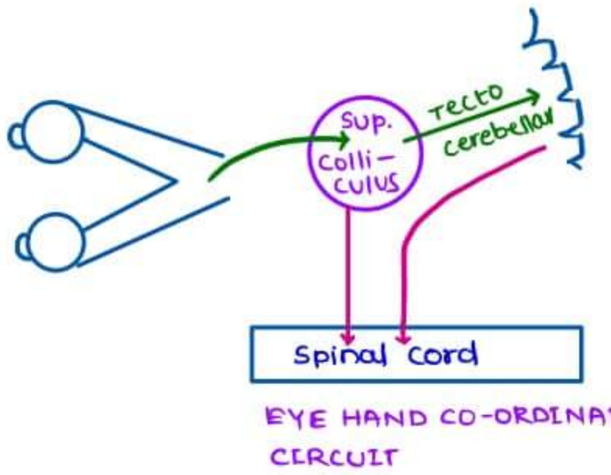
→ helps the cortex in planning & programming

→ provides sequencing of muscle contractⁿ to the cortex

CONNECTIONS

AFFERENT	FUNCTIONS
vestibulo cerebellar tract	Head orientat^{n} & rotation
dorsal spino cerebellar Tract	unconcious proprioception (particularly from Lower parts of body)
ventral spino cerebellar tract fastest ascending tract (120m/s)	carries 'EFFERENCE COPY' OF Anterior motor neuron
cuneo cerebellar tract	carries proprioceptive impulses from arm & neck
Tecto cerebellar tract	part of eye hand co-ordinat^{n} circuit
cortico ponto cerebellar tract (longest tract in brain)	conveys the intention of cortex regarding voluntary movement
Olivo cerebellar tract	converged input from multiple sources

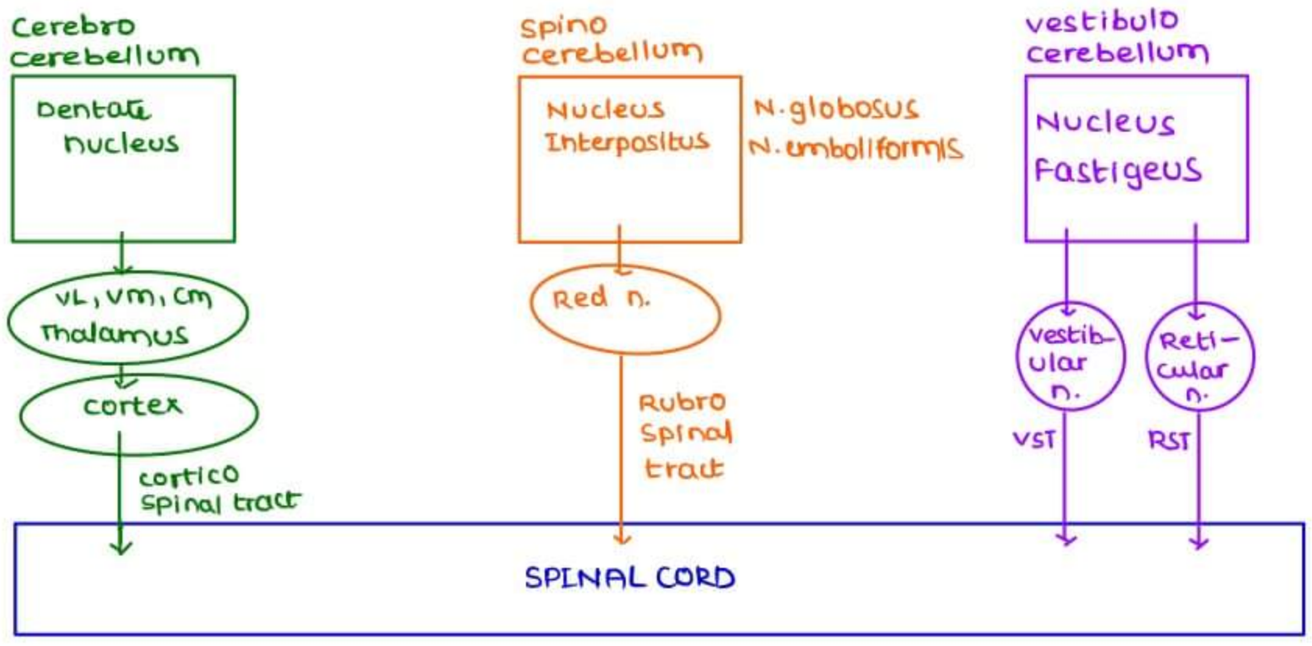
HISTOLOGY OF CEREBELLUM



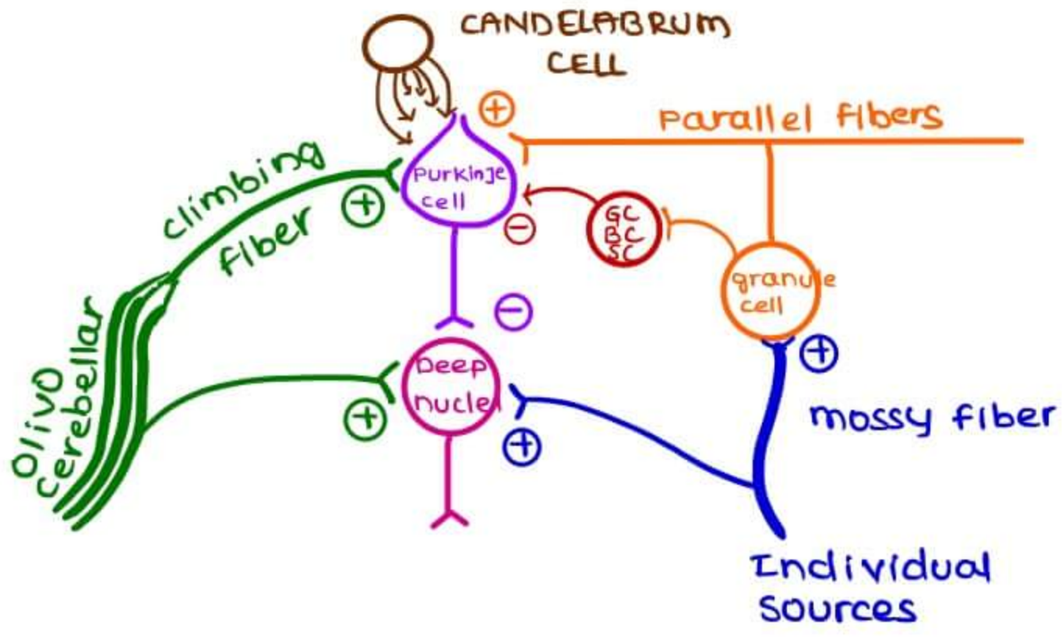
Eye hand co-ordination controls by Superior colliculus

DEEP NUCLEI

→ Efferents of cerebellum goes via deep nuclei



CEREBELLAR CIRCUIT



Inhibitory interneurons

- GC → Golgi cell
- BC → Basket cell
- SC → Stellate cell

DISORDERS OF CEREBELLUM

- → Ataxia
- → post pointing
- → Loss of muscle tone
- → Intention tremor
- → Romberg sign ⊕

Romberg test

ATAXIA

1. Sensory ataxia
   - → ↑ eyes open → Patient can perform the test
   - → ↑ eyes close → Patient can't perform the test

2. Cerebellar ataxia
   - → ↑ eyes open/close → Patient can't perform the test

BASAL GANGLIA

- → Subcortical masses of grey mater
  1. caudate nucleus
  2. Putamen
  3. Globus Pallidus
     - ↳ GP Externa
     - ↳ GP Interna
  4. Substantia nigra
     - ↳ Pars compacta
     - ↳ Pars reticulata
  5. Subthalamic nucleus / Body of Luy's

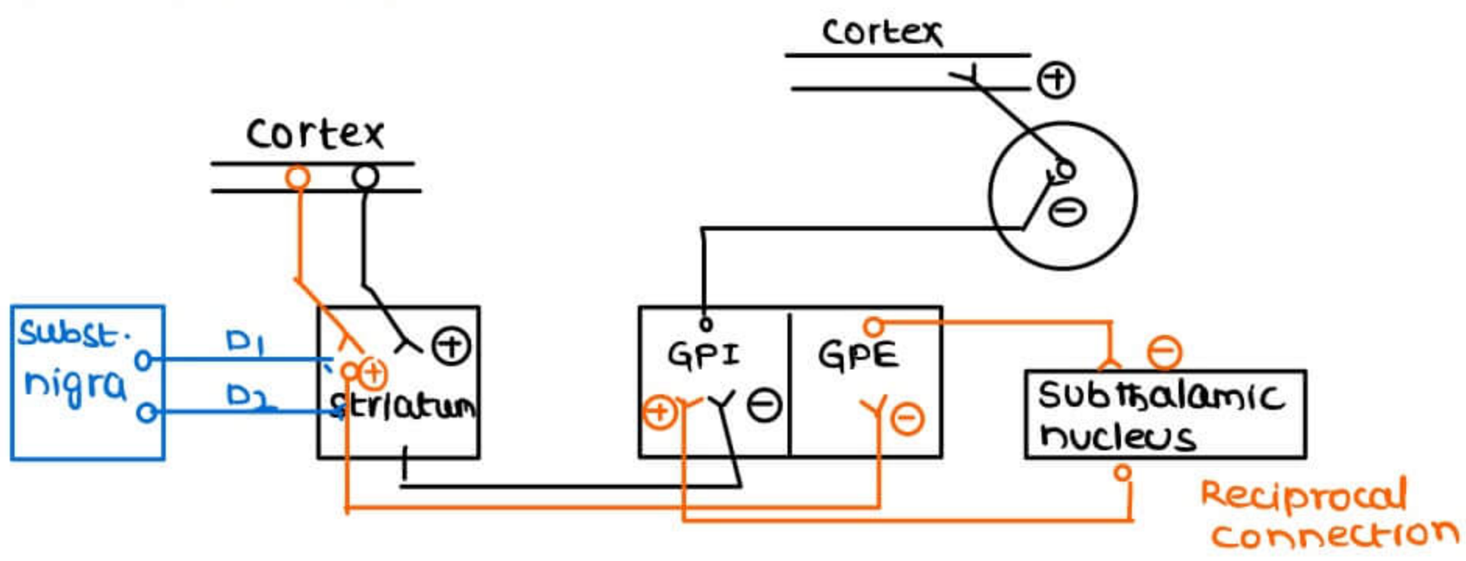
- → Functionally
  - → caudate nucleus, Putamen } Corpus striatum
  - → Globus pallidus → Pallidum
- → Anatomically, on either side of Internal capsule
  - → on one side → Caudate nucleus
  - → on another side → Lentiform nucleus
    - ↳ Putamen + Globus Pallidus.
- → In WILSON'S DISEASE, hepato lenticular degeneratⁿ dt excess copper depositⁿ

→ FEATURES

- → all afferents end in Striatum
- → all efferents emerge from Internal Globus pallidus
- → Fiber coming from cortex is excitatory
  Fiber reaching back to cortex is excitatory
  all others are inhibitory

→ CIRCUITS

1. DIRECT CIRCUIT



Pallido thalamic projection, have back ground tonic inhibitory activity
↳ Basis for Tremors at rest in Parkinsonism

Facilitates the movement by DISINHIBITION

2. INDIRECT CIRCUIT → Inhibition of movement

SUBSTANTIA NIGRA

- → not involved in the circuits directly
- → modulates the activity of striatal neurons → NIGRO STRIATAL PROJECTIONS
- → dopaminergic projection (D_1 & D_2)
- → D_1 → facilitates the direct circuit → movement facilitated
  D_2 → inhibitn of indirect circuit → movement facilitated

→ PARKINSONISM

- → degeneration of nigrostriatal tracts
- → bradykinesia

→ it is under control of Cortex by
  ↳ Strato nigral projection
  - → cholinergic projection
  - → reciprocal innervation
  - → anticholinergic drugs are given in parkinsonism

SUB THALAMIC NUCLEUS

- → controls associated movements of body (swinging of arms while walking)
- → Lesion leads to Hemiballismus

HUNTINGTON'S DISEASE

(Hyperkinetic)

→ dlt Huntington's gene
  - Trinucleotide (CAG) expansion disease

→ Intra striatal degeneratⁿ of GABAergic & Cholinergic neurons

CHOREOFORM MOVEMENTS → Lesion of caudate nucleus
TREMORS → lesion of pallidothalamic projectⁿ

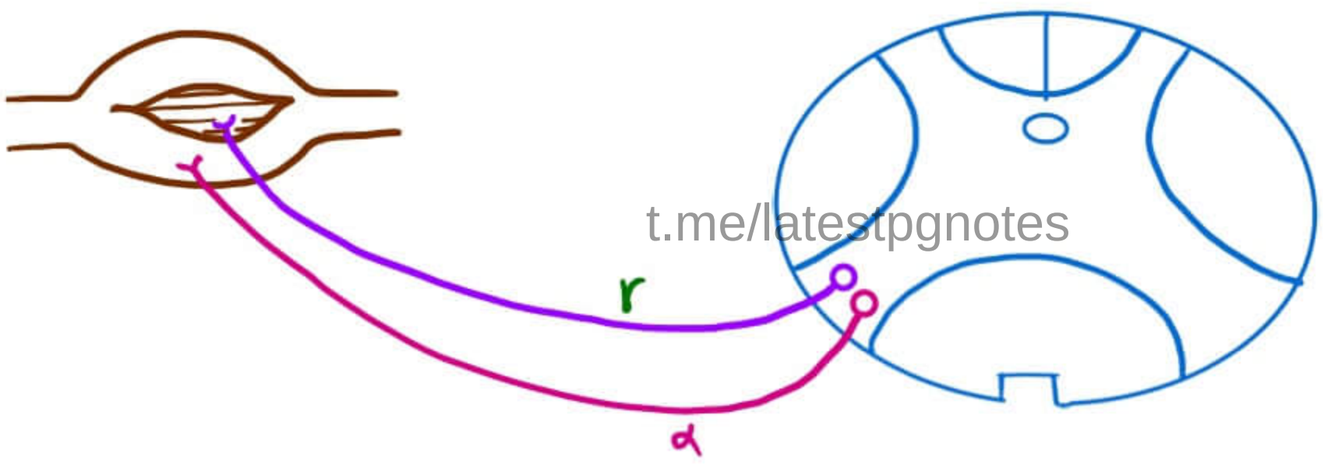
PARKINSONISM

(Hypokinetic)

LOWER MOTOR NEURON / ANTERIOR MOTOR NEURON

→ starts from spinal cord (Anterior horn) & goes to muscle

→ 2 TYPES
  1. α motor neuron
  2. γ motor neuron



→ MUSCLE FIBERS
  → Large extrafusal fibers on outside
  → Small intrafusal fibers near the belly of muscle
    ↳ connected τ extrafusal fibers τ surrounding glycocalyx
  → α motor neuron innervates extra fusal fibers
    γ motor neuron innervates intrafusal fibers

  → muscle contraction is dlt contractⁿ of extrafusal fibers
  → Intra fusal fibers
    ↳ forms proprioceptors

→ PROPRIOCEPTORS
  1. MUSCLE SPINDLE
    ↳ In the belly of muscle
    ↳ formed by intra fusal fibers
    ↳ detects the length of muscle when muscle is stationary
    ↳ detects rate of change of length

a. GOLGI TENDON ORGAN (GTO)

↳ present in tendon

↳ made up of tendon fibers

↳ detects tension in the muscle

↳ detects rate of change of tension

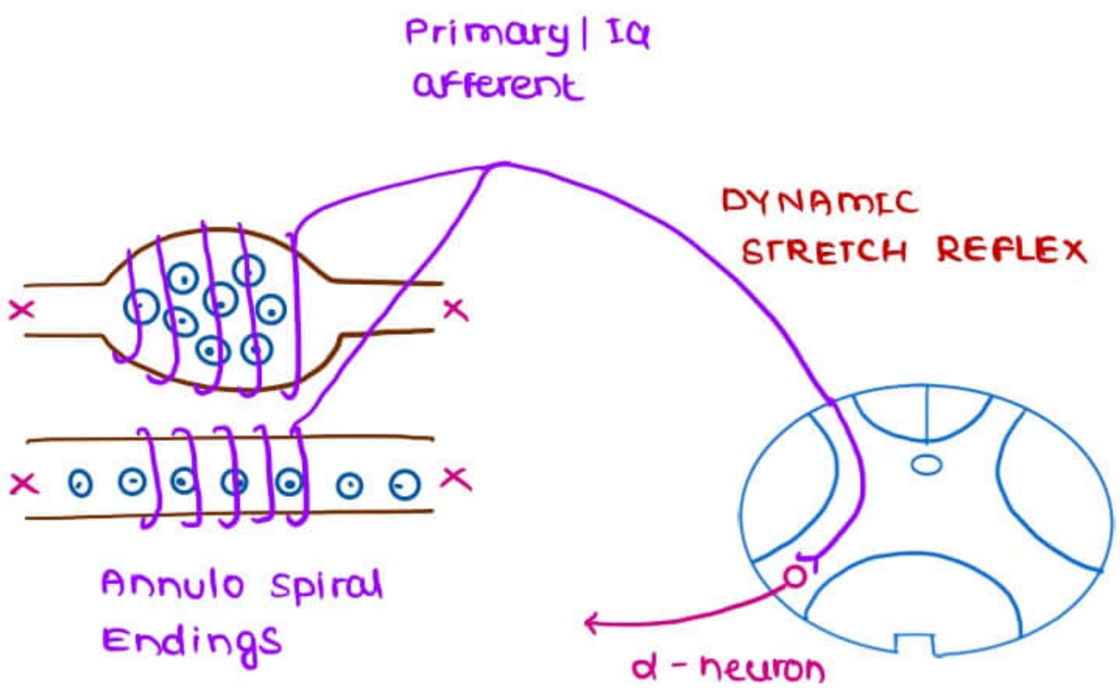
MUSCLE SPINDLE

→ 10-12 intra fusal fibers makes 1 muscle spindle

↳ 2-3 → nuclear bag fibers

↳ 8-9 → nuclear chain fibers

↳ ratio blw nuclear bag & chain fibers → 1:3



→ INNERVATION

↳ ANNULO SPIRAL ENDINGS

↳ comes from central portions of both

↳ both joins to form primary | Ia afferent

↳ enters the spinal cord & ends on α motor neuron, which inturn supply extra fusal fibers

↳ This is the circuit for DYNAMIC STRETCH REFLEX (Tendon | Knee jerk)

↳ Receptor for knee jerk → Muscle spindle

↳ γ MOTOR NEURON

→ maintains the excitability of muscle spindle by pulling the ends of intra fusal fibers

↳ 1. JENDRASSIK MANEUVRE

→ in case of not getting knee jerk properly, hooking of fingers, clenching of the teeth, ↑ γ motor neuron discharge to the muscle spindle & maintain the excitability

→ aids in obtaining proper knee jerk

↳ 2. α - γ LINKAGE

→ during continuous muscle contraction, muscle spindle gets UNLOADED

→ γ motor neurons helps in maintaining excitability

↳ FLOWER SPRAY ENDINGS

→ present at the ends of Nuclear chain fibers

→ Gives Secondary / Type II afferent

→ detects the static stretch of muscle

→ Reflex initiated by muscle spindle is Mono Synaptic reflex

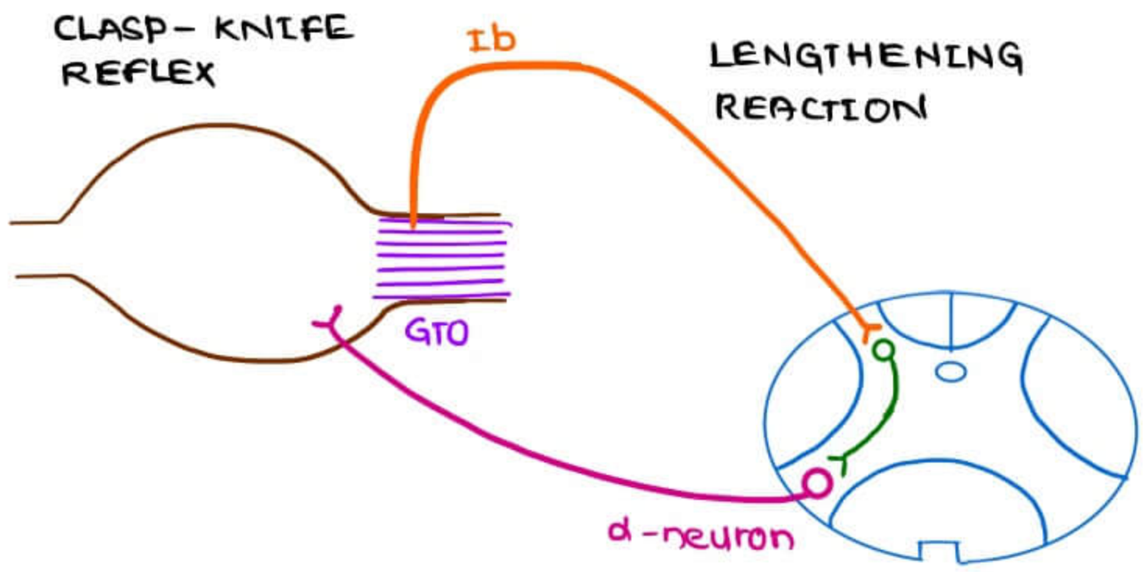
↳ excitatory to α - motor neuron

GOLGI TENDON ORGAN

→ situated in tendons at a ratio of 1 : 20

→ Ib Afferent arises from GTO

→ Ib enters the Spinal cord & ends on inhibitory interneuron, which inturn ends on α motor neuron



→ Reflex initiated by golgi tendon organ is disynaptic reflex

↳ always inhibitory to α motor neuron

↳ This is the basis for CLASP - KNIFE REFLEX

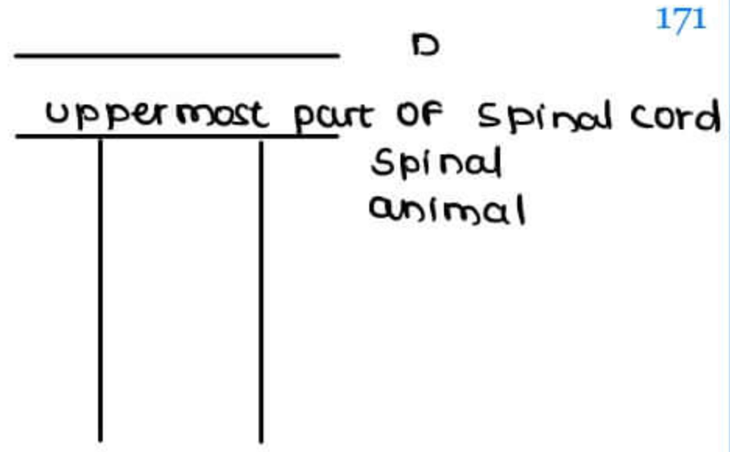
→ Spasticity seen in pyramidal lesions

→ LENGTHENING REACTION → muscle lengthens & relaxes completely

HYPERTONIAS

SPASTICITY	RIGIDITY
Seen in pyramidal tract lesion	Seen in Extra pyramidal tract lesion
Unidirectional	Bidirectional
involves one group of muscles (agonists)	involves both agonists & antagonists
velocity dependent	↳ Lead pipe rigidity → cog wheel rigidity
	not velocity dependent

POSTURAL REFLEXES



STRETCH REFLEX → most basic postural Reflex

STUDY OF POSTURAL REFLEXES

Spinal Animal → transection done at upper most part of spinal cord

Decerebrate animal → Transectn made in the mid collicular level
→ Spinal cord & vestibular nuclei retained

Advantages OF Studying from Experimental Animals

1. Study of reflexes can be done
2. Centre of reflex can be known

Mid brain / Thalamic Animal
→ Spinal cord, vestibular nuclei & red nuclei retained

Decorticate animal → A layer of cortex is removed

DECEREBRATE RIGIDITY → all extensors goes into rigidity
→ Seen in Lower animals

DECORTICATE RIGIDITY → Seen in human
↳ extensors of LL & Flexors of UL goes into rigidity

LOCAL / STATIC REFLEX
→ 1 or 2 spinal segments & 1 side of spinal cord involved

I. POSITIVE SUPPORTING / MAGNET REACTION
↳ on stimulating sole continuously Extensors activated & Limb acts as a rigid pillar → positive supporting Reactn

↳ Contraction is goes on increasing in the direction of Stimulus
→ Magnet Reaction

↳ Seen in spinal animal
↳ Centre is in spinal cord

2. NEGATIVE REACTION

→ Release from positive supportive Reaction

→ seen in spinal animal

centre is in spinal cord

SEGMENTAL STATIC REFLEXES

→ entire segment involved

both sides are involved

1. CROSSED EXTENSOR REFLEX / PHILLIPSON'S REFLEX

→ When one limb is flexed, opposite limb begins to flex

GENERAL STATIC REACTIONS

→ not seen in spinal animal

→ entire body is involved

→ animal aquired upright posture insecurely

1. TONIC NECK REFLEX

→ Looking below a table (flexion at Neck), posture maintained by

↳ extension at Hind limb

↳ flexion at Fore limb

→ Looking above a Shelf (Extension of Neck), posture maintained by

↳ Flexion at hind limb

↳ Extension at fore limb

→ centre is in vestibular nuclei

2. TONIC LABYRINTHINTHINE REFLEX

→ Animal on table & head drops → Extension of all 4 limbs

→ centre is in vestibular nuclei

RIGHTING REACTIONS

→ Chains of events

→ Seen in midbrain animals

→ Center is in Red nucleus

→ animal assumes the upright posture actively

NEED INTACT CORTEX

→ Optical Righting Reaction

↳ needs visual cortex

→ Hopping Reaction } cortex
Placing Reaction }

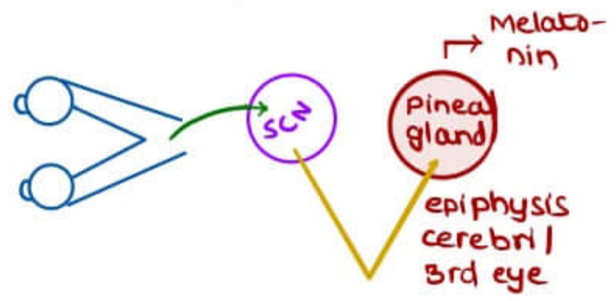
HIGHER FUNCTIONS

HYPOTHALAMUS

NUCLEUS	CONNECTIONS FIBERS/NT	FUNCTION	LESION
SUPRA OPTIC NUCLEUS	Osmoreceptors	ADH synthesis	central DI (Lack of ADH)
PARAVENTRICULAR NUCLEUS	Neuro Endocrine reflex	Oxytocin synthesis	Dalayed labour
SUPRA CHIASMATIC NUCLEUS	Retina	circadian Rhythm	Jet lag (Disturbed circadian Rhythm)
PREOPTIC NUCLEUS	Anterior neuron androgen sensitive Posterior neuron Estrogen sensitive	Sexual Function in males & females	loss of libido altered sexual preferences
ventro Medial Nucleus	CART	Satiety	Hyperphagia Obesity
Lateral hypo thalamic area	Orexigenic neurons / Glucostatic neurons	Hunger	anorexia
Lateral superior hypothalamic area	Osmo receptors	Thirst	Adypsia

If visual cues are removed, effect on circadian rhythm is
→ cycle length will increase

SCN → Link blw external enviroment & body (internal environment)



If visual cues are removed
↳ circadian rhythm is still maintained by body temperature
↳ circadian rhythm is prolonged (>25 hrs)

Periventricular nuclei	Limbic System	Reward & Rage Reaction	Timid animal
Most anterior Hypothalamus	Warm sensitive	Cutaneous vasodilatn & Sweating	Hyperthermia
most posterior hypothalamus	cold sensitive	Shivering	Hypothermia

HYPOTHALAMUS

→ Part of Diencephalon
→ concerned ↑ vegetative & visceral function
→ Highest seat for ANS control present here

CEREBRAL HEMISPHERES

→ In Right handed individuals Lt hemisphere is dominant
In Lt. handed individuals, both hemispheres are dominant

DOMINANT (Categorical) → concern ī Language function

NON-DOMINANT (Representational)

→ Concerned ī Spatio temporal co-relation ī each other
↳ lesion Leads to HEMINEGLECT SYNDROME

PLANUM TEMPORALE

↳ present in temporal lobe
↳ larger in dominant hemisphere
↳ Asymmetry exaggerated in musicians

LEARNING & MEMORY

LEARNING

→ aquisition of new information & skill → learning
Storage of the skill → memory

ASSOCIATIVE LEARNING

→ associates ī 2 or more events & Learns it

NON ASSOCIATIVE LEARNING → Learns from a single event

All types of learning & memory are presynaptic modulations Except Long term memory (modulatn of post synaptic neuron)

NON ASSOCIATIVE LEARNING – TYPES

1. Priming
2. Habituation → ↓ response to a stimulus after repeated stimulus
→ ↓ release of excitatory NT by presynaptic neuron
3. Sensitization → Life threatening/ imp. stimulus, the response is increased
→ ↑ release of NT by presynaptic neuron for a particular stimulus

ASSOCIATIVE LEARNING

CLASSICAL CONDITIONING (PAVLOV)

→ dog is presented ī food pellets, reflex salivation occurs (innate reflex)
→ unconditioned stimulus
↳ giving the food
↳ natural

→ conditioned stimulus
  ↳ ringing the bell
  ↳ Learning stimulus

→ conditioned stimulus, immediately followed by unconditioned stimulus
  ↳ Pairing occurs (should be done repeatedly)

→ Now salivath occurs even for conditioned stimulus alone

→ EXTINCTION occurs ∵ interference, gaping etc

OPERANT CONDITIONING (SKINNER)

→ Animal actively operate on environment & learns
  (Reflex response present in classical conditioning, no active learning)

→ After a while, positive reinforcement for reward & negative reinforcement for punishment learnt.

MEMORY

SHORT TERM & Intermediate term

→ Post tetanic potentiation
  ↳ stimulating synapse tetanically
  ↳ post tetanically, for stimulus extra NT is released

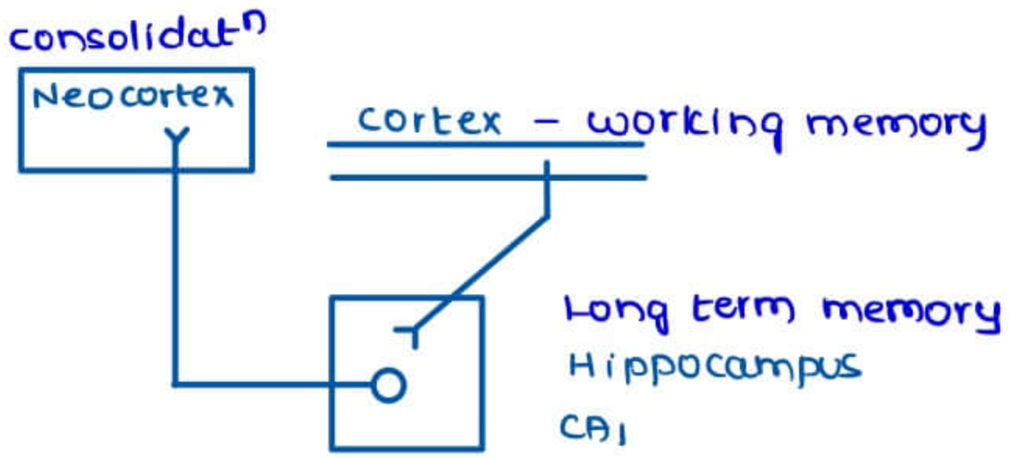
→ Pre synaptic facilitation
  ↳ pre synaptic facilitation leads to release of extra NT

LONG TERM MEMORY

→ LONG TERM POTENTIATION IN HIPPOCAMPUS
  → Structural changes in dendritic geometry
  → NT → Glutamate acts via NMDA receptors

→ Cortex develops a WORKING MEMORY
→ Working memory converted into long term memory in hippocampus
  ↳ by ↑ Synaptic transmission neurons on a long term basis
  ↳ NT → Glutamate
  ↳ Receptors → NMDA Receptors
  ↳ Sustained opening of NMDA Receptors ∵ continuous incoming of NT occurs in POST SYNAPTIC NEURONS (sustained influx of Ca^{+2} & sustained development of EPSPs in hippocampal neurons)
  → CONSOLIDATION occurs in neocortex

→ LESION OF HIPPOCAMPUS
  ↳ causes ANTEROGRADE AMNESIA
    ↳ not able to form long term memory from that point onwards



SLEEP & EEG

EEG

→ record of cortical potential, recorded from surface

→ Synaptic potentials (NOT ACTION POTENTIALS)

↳ EPSPs & IPSPs

WAVES

δ wave

→ 8 - 13 HZ

→ 

→ Waves of quiet Wakefulness i eyes closed & mind wondering

→ recorded from occipitoparietal region

→ temporory after images may be responsible

→ Recorded in Stage I of NREM sleep (all 4 δ waves)

β waves

→ 15 - 30 HZ

→ low amplitude & high frequency

→ 

→ Waves of alert wakefulness i eyes open & mind focussed

→ recorded from parieto frontal region

→ also recorded in REM sleep

↳ REM sleep also called as PARADOXICAL SLEEP

↳ all 4 β waves → REM sleep

↳ 2 α → 2β waves → EEG DESYNCHRONISATION (misnomer)

→ recorded in wakefulness

Tθ waves

→ 4 - 7 HZ

→ recorded in NREM | slow wave sleep (stage 1 & 3)

→ recorded in children from temporo parietal region

→ 

→ also recorded from hippocampus

δ WAVES

→ 0-4 Hz
→ Even if thalamo cortico projections are cut, these waves are recorded
→ responsible for arousing & alerting responses (Reticular system)
→ very slow frequency waves

→ recorded in Organic brain disease
→ also recorded in deep sleep, (stage 4 NREM sleep)
deep coma,
deeper planes of anesthesia

γ - OSCILLATION (30 - 50 Hz)

→ high frequency oscillation
→ recorded on very high mind activity

SLEEP

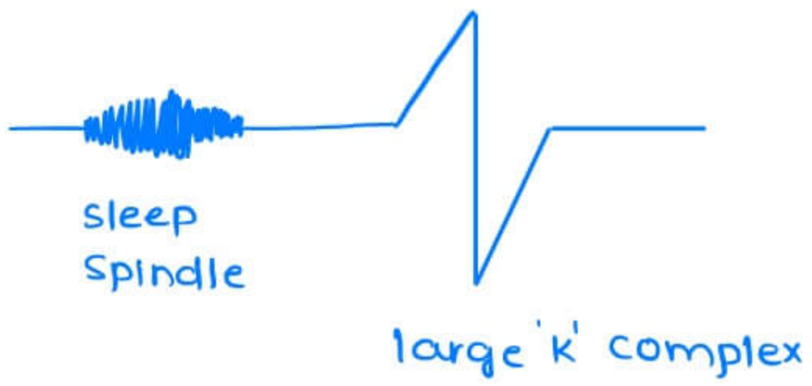
NORMAL SLEEP ARCHITECTURE

→ 120 min cycle
→ 4-5 cycle occurs in one sleep
↳ 90 min of NREM sleep (1,2,3,4) (Superficial to deep)
↳ 15-20 min of REM sleep (deep to superficial)

NREM (Non Rapid Eye movement) / SWS (Slow wave sleep)

→ 4 stages

STAGE I → α waves initially, Tθ waves later
STAGE II → classical EEG



STAGE III & IV → δ waves

REM SLEEP

→ Concommitants
1. Rapid eye movements
2. β waves recorded
3. HR & RR becomes irregular
4. loss of muscle tone (sleep paralysis)
↳ present through out body
↳ neck extensors maximally effected
↳ no loss of tone in Diaphragm, extra ocular muscles, middle ear muscles