17/1/22

BI3214 - ANIMAL PHYSIOLOGY I

Homeostasis

Its the mechanism that maintains a stable internal environment in the face of changing external conditions.

Example : Blood sugar level of humans is maintained b/w 70 - 100 mg per deciliter (100 ml) after 8h fasting
> 180 mg is dangerously high
< 50 mg is very very low (hypoglycemic coma)

Not just sugar, but also other constituents — ions, proteins, urea & glucose — in the blood and plasma is maintained at a typical range.

Na	135 - 155	mEq/L
K	3 - 5.5	mEq/L
Total protein	6 - 8	g/dL
Urea	10 - 25	mg/dL
Glucose	70 - 100	mg/dL

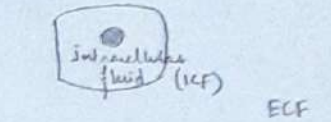
→ Temperature is a classic example

Even in the face of large external fluctuations, most cells in the body in the internal environment are exposed to fairly constant conditions.

* This phenomenon was discovered by Claude Bernard. He was a French physiologist, coined the term "milieu interior". "Constancy of internal environment is the condition for free & independent life."

* Walter Cannon - American physiologist. Coined the term 'homeostasis' and expanded the concept.

Salmon - example of chloride ion regulation.
Females migrate from seawater to freshwaters streams to lay eggs, and after hatching, the young ones go to the sea.
Despite huge variation in Cl^- conc of water, the conc in its blood remains constant.



	ICF	ECF	
Na	10	142	out → in
K	140	4	out ← in
Ca	0.0001	2.4	out → in
Cl	4	103	out → in
OSMOLALITY	281 mOsm/L	281 mOsm/L	

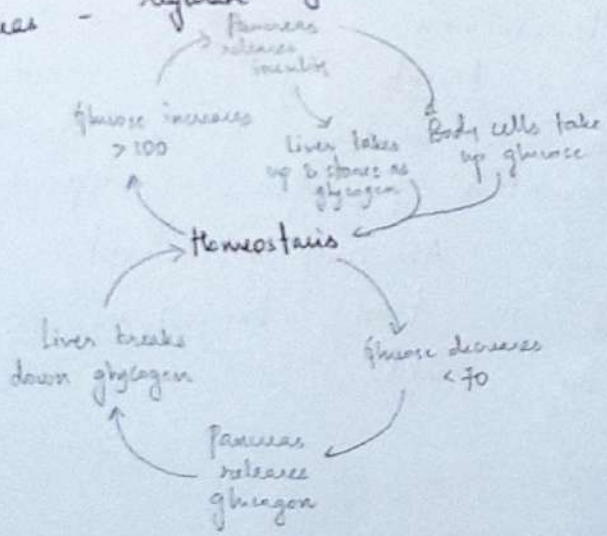
The chemical constitution of ICF and ECF is very different. The plasma membrane plays a very important role in maintaining this.

Osmolality is the same ⇒ water is in thermodynamic equilibrium across the membrane.
Changes in solute conc causes shift in water gradient & water diffuses until homeostasis is reached. This means the cell might shrink or burst.

281 mEq/L

Each cell benefits from homeostasis and in turn, each cell contributes its share toward maintainence of homeostasis

Homeostatic mechanism of major functional system
Lungs - provide oxygen, excrete CO_2
GI tract - provides nutrients
Kidneys - regulate ion conc in ECF, excrete urea
Liver & Pancreas - regulate glucose in ECF



Insulin: β cells
Glucagon: α cells
of Islet of Langerhans

Set point – desired or targeted value for an essential variable in a closed-loop feedback system

→ Control systems of the body

Brain receives input from sensory neurons and it directs effector organs to react so that homeostasis is maintained.

Eg: Temperature – too hot → blood vessels dilate, sweating
too cold → shivering, no sweating.

Brain is the control (thermostat) center, maintaining homeostasis.

So, homeostatic control systems have 3 components –

Receptors → Control system → Effectors

SET POINT

Regulated variable

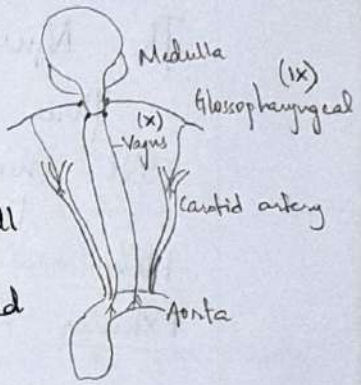
Control system compares the input with a particular set point and directs the effectors to act in the opposite direction of change

→ Regulation of arterial blood pressure

The baroreceptors on the aorta send information to the Medulla through the Vagus nerve. The receptors are stimulated by the stretch of the arterial wall

Wall is the mechanotransducer (?)

The pressure on carotid artery is sensed by Glossopharyngeal nerve



Lecture 02 – 19/1/22

→ Changes in physiology are responses to changes in environment

When T drops, hypothalamus detects it (based on blood T and thermoreceptors in the skin) and constricts blood vessels, and causes shivering to generate heat.

Hypothalamus also triggers higher cortical points which makes the individual seek warmth.

⇒ The set point for T is in the hypothalamus.

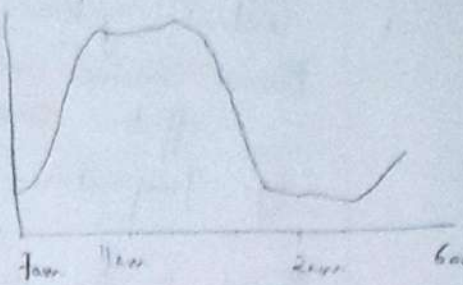
Similar set points are there for CO_2 & O_2 saturation, blood pressure and osmolality.

Based on osmolality (if increases), hypothalamus releases ADH which makes kidney absorb more water.

internally programmed to occur

Some changes in physiology are adapted to predictable environment changes such as diurnal cycles.

The core body temperature varies throughout the day because of the body's physiological activity.



The concentration of melatonin also varies regularly across the day.

11 am - 7 pg/mL

1 am - 60 pg/mL

Melatonin plays an important role in maintaining circadian rhythm.

Disruption of homeostasis

When cells begin to malfunction, homeostatic balance is disrupted - it leads to disease or cell malfunction which can be of 2 types: deficiency & toxicity.

The Muscle Physiology

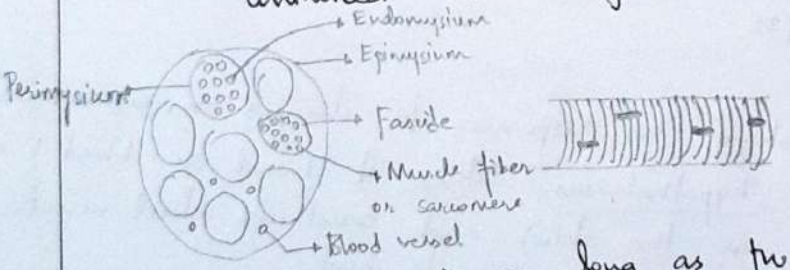
Three types of muscles - cardiac, skeletal, smooth

We need muscles to move the body & things inside the body

Flexor - biceps & other muscles that contract

Extensor - opposite of flexor (triep)

Skeletal muscles are attached to the bone and can be controlled voluntarily.



Fascicle is wrapped up by perimysium

10 - 100 μm diameter

Each muscle cell is as long as the muscle fibes (upto 30 cm long)

The muscle doesn't connect to bone directly, it connected through tendons (white matter)

Myoblasts come togethes and fuse to form a muscle cell which is multinucleate ie its a syncitium

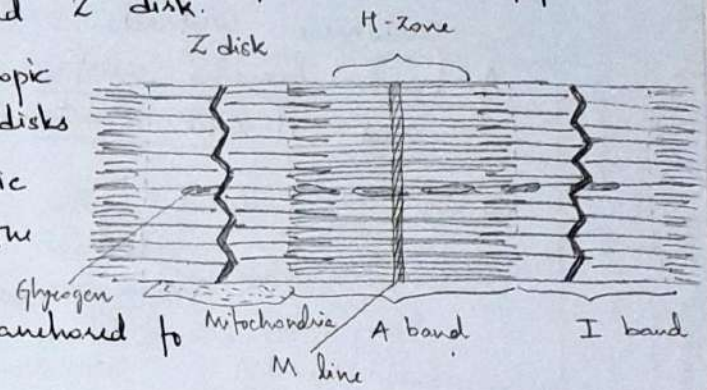
There's a satellite cell (myoblast) is a stem cell which activates for muscle growth and regeneration

Myosin - 1.6 μ, 12-15 nm across
Actin - 1 μ . 7-8 nm across

The muscle fibre is covered by sarcolemma and is filled with myofibrils in the sarcoplasm. The myofibrils have dark lines called Z disk.

A band - dark & anisotropic in between 2 Z disks

I band - light & isotropic has Z disk in the middle



The actin filaments are anchored to the Z disk.

The M line holds myosin fibers in the centre, which constitute A band.

The organisation is very geometric — in a cross section, each actin is surrounded by 3 mysin fibers and each myosin by 6 actin fibers.

T-tubule

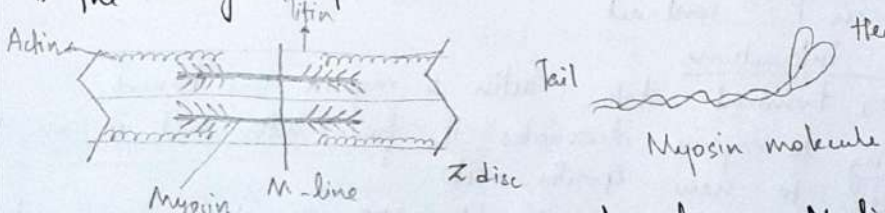
There are certain transverse tubule created by inversion of sarcoplasm. These tubules are along the Z-disks of the myofibres. The tubules have extracellular fluid in them, and they open at the other end. These tubules in the sarcoplasm are enmeshed by (or closely associated with sarcoplasmic reticulum).

20/1/22

Lecture 03

Organisation of skeletal muscle.

The length of sarcomere is the same for all mammals



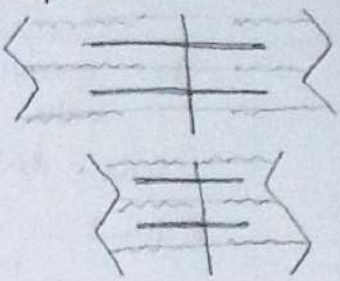
Thick filament - mypsin - anchored on M-line

Its organised with myosin heads on the outer side → cross-bridges between actin filaments.

Myosin is made of several subunits that ensemble in certain way

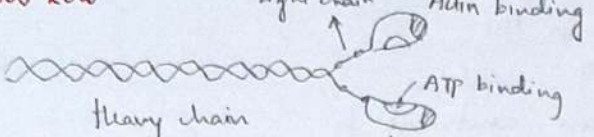
Actin filament is thin and its a helix made up of different proteins (troponin, tropomyosin)

Myosin heads attach to actin filaments and pull back so that filaments slide over one another and sarcomere contracts.



A band remains constant but I band and H-zone shorten

* They noticed that A band doesn't shorten whereas H zone & I band lengthen/shorten as cell shrinks/contracts.

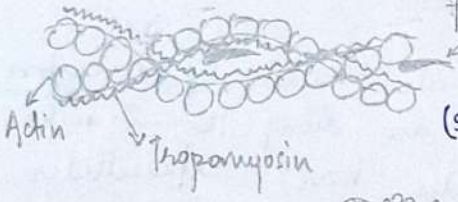


History - Sliding filament theory

1950s - Huxley & Niedergerke* Huxley & Hanson

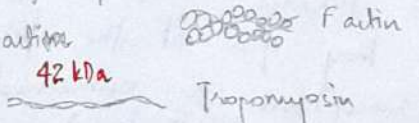
Force of contraction is generated by the cross-bridges of thick filaments attaching to thin & actively pulling them

The globular head domain has Actin binding site and an ATPase. It binds to actin, hydrolyses ATP and uses the energy to push the actin filament to the centre of the sarcomere.



Troponin binds to -

(subunits) Troponin I - Actin
Troponin T - Tropomyosin
Troponin C - Calcium ion



Tropomyosin covers the myosin binding site of the actin filament.

It prevents the binding of actin and myosin

When calcium binds to troponin, it pulls the tropomyosin away so that myosin binding sites on actin are exposed and it can bind to myosin so it can contract.

Molecular interactions

1. Rigor is a transient state : actin & myosin are bound
2. ATP binding to myosin dissociates it from actin and it can now bind to new G-actin site
3. Myosin ATPase hydrolyses ATP to ADP + P_i which remain bound to myosin.
4. Now myosin head moves to cocked position and binds to G-actin

The frequency at which muscles contract, the time period, varies from muscle to muscle.

5. Myosin binding to actin triggers rapidly releases of P_i and the power stroke. Actin is moved 10 nm towards the centre of sarcomere.

6. Myosin head is unbinds from ADP but remains bound to actin (i.e rigor or transient state)

Importance of Ca^{2+} ions

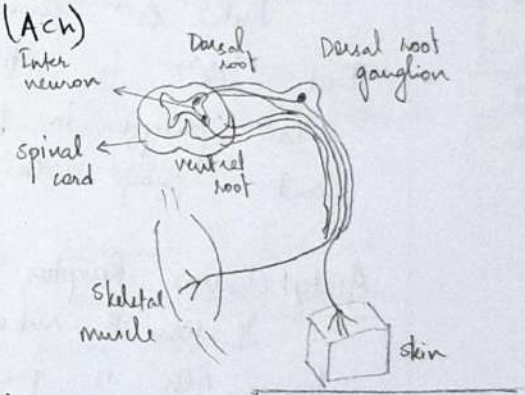
In a relaxed state, intracellular Ca ion conc. is very low ~ 10^{-7} M and muscle will only contract when Ca binds to troponin (TN-C) #

Sliding filament theory – myosin heads act independently but together and create tension incrementally
↳ not synchronised

Titin – very large molecule (upto 1 micron)
It functions as a molecular spring which is responsible for passive elasticity of muscle. There domains unfold when protein is stretched and refold when tension is removed. It connects Z disc to M line.

Neuromuscular junction

All skeletal muscles are stimulated to act by the neurotransmitter Acetylcholine (Ach)

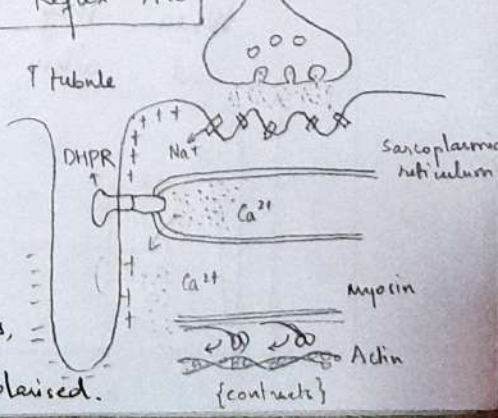


If the skin is pricked, its sensed by sensory neuron, processed by interneuron and a signal is sent to the motor neuron (whose endings innervate skeletal muscle) which releases Ach and makes it contract so hand (skin) is pulled away.

Reflex Arc

Excitation - Contraction coupling

The motor neuron is cholinergic
The receptor on the ~~sarco~~ muscle cell binds to both Ach & nicotine. Its a ligand gated Na channel, so when Ach binds, Na^+ rushes in and the membrane is depolarised.



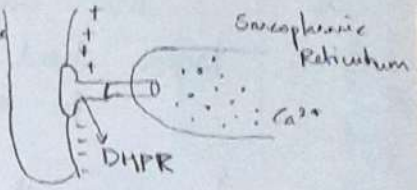
* Nicotinic - cholinergic receptor

Ca^{2+} + TN-C → leads to conformational change in TN and TM which exposes myosin binding sites on actin

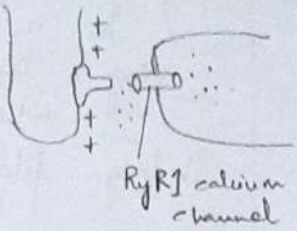
Lecture 4

24/1/22

- When Ach binds to the ligand-gated channel and Na^+ rushes in & initiates an action potential
- This depolarises the membrane and this action potential travels along the sarcolemma through the T-tubule.
- DHPR: Dihydropyridine Receptor – its a system of proteins in the membrane of the T-tubule. It is very closely bound to RyR calcium channel on the Sarcoplasmic Reticulum, filled with Ca^{2+}.



- When the action potential arrives, DHPR undergoes conformational change, which decouples RyR1 Ca^{2+} channel, so that Ca^{2+} floods the cytoplasm from the reticulum.

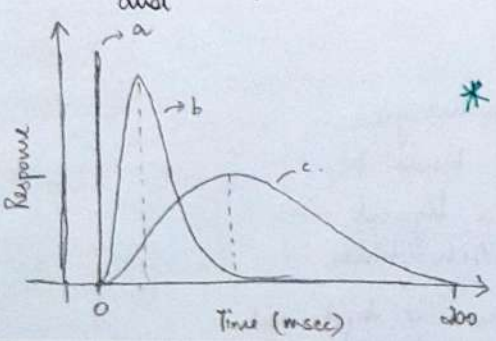


- This Ca^{2+} is now available for actin-myosin filament sliding which contracts the muscle. Cross-bridges go through several cycles as long as Ca^{2+} is bound to TN
- The Ach in the synapse is broken down by Ach Esterase, a protein on sarcolemma. Thus the action of Ach is stopped very quickly, so action potential is stopped and RyR1 Ca^{2+} channel closes.
- But Ca^{2+} is still in the cytoplasm. There are Ca^{2+} pumps in the sarcoplasmic reticulum which use ATP and pump Ca^{2+} from cytoplasm to SR.

Ca^{2+} is stored in SR as free ions & released with Calsequestrin along

Acetylcholine Receptor

It has 5 subunits – $2\alpha, \beta, \gamma, \delta$. The binding site for Ach is present on the 2 α subunits. When they bind, they undergo a conformational change and allow Na^+ to go inside the cell.



* a) Action potential on T tubule (1 ms)
b) Myoplasmic $[Ca^{2+}]$ (20 ms)
c) Twitch force – actin-myosin interaction (60 ms)

RyR : Ryanodine Receptor
Ryanodine - alkaloide (poisonous) in SA plant - used as insecticide
It binds to RyR tightly. At nanomolar level, it releases all Ca leading to massive contractions

When RyR1 opens, it changes cytoplasmic [Ca] from 0.01 μM to 1 μM.

DHPR stimulation at single site is enough to trigger the coordinated opening of entire group of RyR1, which increases the reliability of impulse transmission

Calsequestrin : Protein in SR that can bind to many Ca^{2+} molecules with low affinity - it maintains low free-Ca^{2+} ions in the SR

Myasthenia gravis (muscle channelopathy)
there, the patient experiences great weakness. Sometimes AChR receptors enter the blood, where its a foreign body. So, WBCs produce AChR antibodies, which now attack and degenerate AChR on the skeletal muscle (80% destroyed). So, the signal doesn't trigger muscle contraction which weakens the muscle

Treatment - drugs that inhibit AChE, so the Ach stays in the synapse for a long time, which stimulates the muscle.

At rest, insignificant amount of Ach release causes twitches. Non-depolarising muscle relaxants prevent AP by blocking N2 ACh receptors

Muscle Energetics
ATP has 3 functions -

- ATP binds to myosin and this detaches it from actin
- Hydrolysis of ATP that's bound to myosin cocks the myosin heads and prepares for power stroke
- ATP powers Ca channel which pumps Ca^{2+} from cytoplasm to SR.

Muscle stores glucose as glycogen and breaks it down through glycolysis when needed.

Also muscle needs a lot (lol!) of ATP. Creatine phosphate combines with ADP and gives ATP + Creatine. It acts as a buffer providing ATP.

3 ways of producing ATP in the muscle -
1. Phosphagen creatine phosphate
2. Anaerobic glycolysis (glycogen → lactic acid + ATP)
3. Aerobic catabolism. (phosphorylation)

DHPR (L type Ca channel)
DHP - used as DHPR blockers as treatment of hypertension

Lecture 5

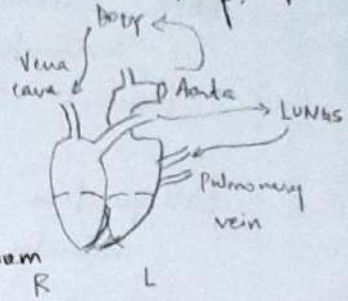
27/1/22

Cardiac muscle

Diameter : 10 μm
Length : 100 μm

This also has striations, like skeletal muscle, but unlike that, the muscle cells are branched and connected to one another.

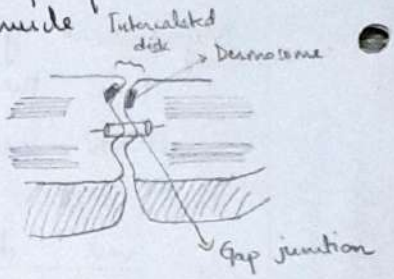
Also, cardiac muscle rolls and folds in on itself, its not attached to any bone.



The cardiac muscle cells are divided by intercalated disks - cell membrane with a lot of gap junctions

Cells can be multinucleate, forming syncitium

The internal cell structure - arrangement of filaments is similar to that of skeletal muscle



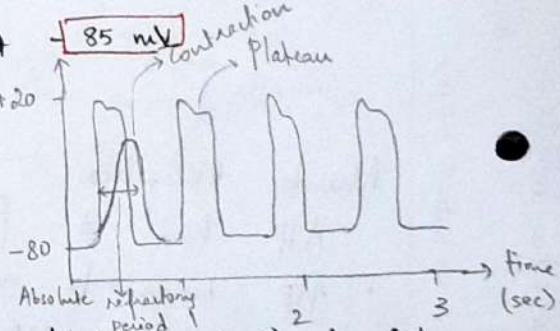
Gap junctions allow action potential to spread between cardiac cells by allowing passage of ions between cells, producing depolarization of heart muscle

The cardiac muscle also has T-tubules - but its 5 times greater in diameter ⇒ 125 greater in volume.

Membrane potential (resting) is about -85 mV

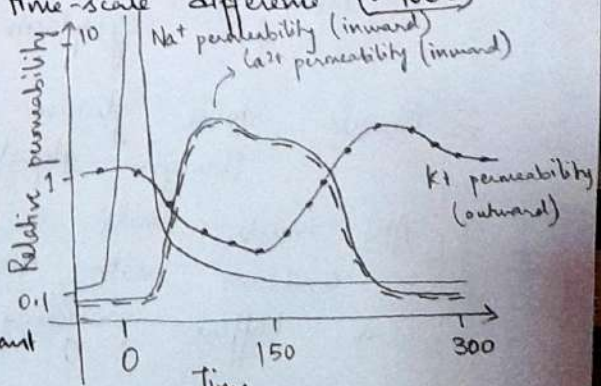
When depolarised, it goes to +20 mV

Membrane remains depolarised for 0.2 s in atrial & 0.3 in ventricular muscles



Exciting skeletal muscle - inject very dilute conc (10^{-5}) of ACh

When its stimulated, the depolarization & repolarisation happens in 0.3 ms ! huge time-scale difference (~1000)



Why plateau? - 3 types of channels -

1. Fast acting Na^+ channel - 0.1 ms
2. Slow acting Ca^{2+} channel (L-type) - slower to open & stays open for long time

It causes prolonged depolarization and the plateau. Also Ca^{2+} is important for muscle contraction.

RyR1 - skeletal muscle RyR3 - brain	Along with Ca^{2+} from SR, a large amount of Ca^{2+} also diffuse from T-tubule during action-potential (11)

3. K+ channel - the permeability decreases, which helps maintain the plateau. When Ca^{2+} channels close, K+ permeability increases rapidly, thus helping repolarization.

Excitation - contraction coupling

1. AP enters from adjacent cell
2. Voltage-gated Ca^{2+} channels open, Ca^{2+} enters cell
3. It induces Ca^{2+} release through RyR2 channel (not mechanically connected to DHPR)
4. Local release causes Ca^{2+} spark. Summed Ca^{2+} sparks create Ca^{2+} signal
5. The signal initiates actin-myosin contraction. Relaxation occurs when Ca^{2+} unbinds
6. Ca^{2+} is pumped back into SR using ATP
7. Some other Ca^{2+} is sent out of the cell using a Ca^{2+} - Na^+ Antiport system. (Na^+ gradient is maintained using Na^+ - K^+ - ATPase)

RyR2 - calcium induced calcium release

T-tubule: contains very charged mucopolysaccharide → After the plateau it gets cut off
that bind & store abundant Ca^{2+}, keeping the always available (during action potential).

Hypertension - High BP treatment
L-type calcium channel blockers are used as cardiac antiarrhythmics or antihypertensives. Commercial drug: Nifedipine)
It reduces Ca^{2+} going in, controling muscle contraction.
Digoxin — inhibits Na^+ - K^+ pump.

T-tubule - allows Ca^{2+} to to go to the interior of the muscle cell and trigger contraction.

Structure of the heart → sits on top of diaphragm, left of the midline, within mediastenum
Double circulation - Pulmonary and Systemic circuit

RA → RV → Pulmonary artery → Lungs → Pulmonary vein → LA → LV → Aorta → Body → Vena cava → RA

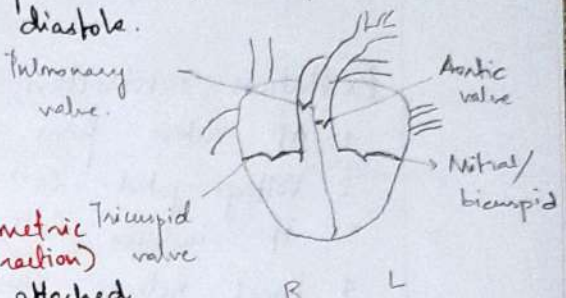
The amount of blood pumped into pulmonary (20%) & aorta is equal to blood that comes in from vena cava and pulmonary vein.

Lecture 6

31/1/22

When the atria receive blood, they expand a little. The blood comes in at very low pressure (2-4 mm Hg).

When the atria contract, the mitral/bicuspid and the tricuspid valve open because of atrial systolic pressure and because ventricles are in diastole.



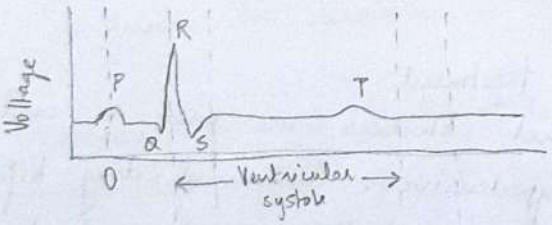
Between closing of bicuspid valve and opening of aortic valve, the left ventricle is completely sealed for ~~0.5~~ 0.05 seconds. (Isovolumetric contraction)

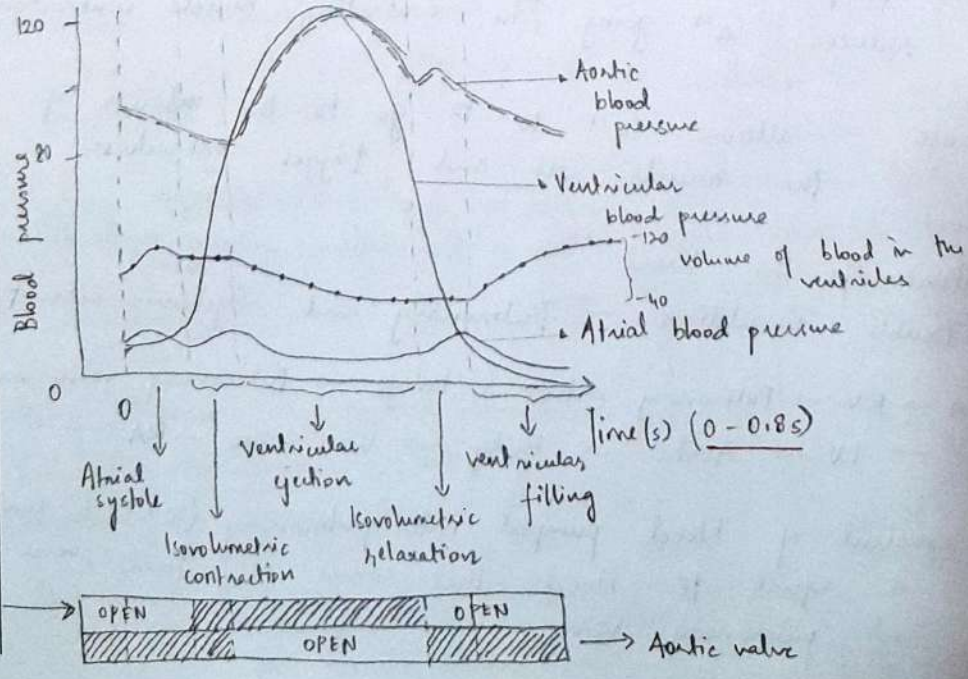
The walls ~~are~~ of the AV valves are attached to tendons (chordae tendonii) which are anchored to the papillary muscles of ventricles. When ventricle contracts, the valves are closed so that blood doesn't go back to the atria.

The Cardiac Cycle

We start with atrial systole.

P - Depolarisation of atria
QRS - Depolarisation of ventricles
T - Repolarisation of ventricles





Semilunar valves do not have to be strong - they don't need to be anchored by tendons.

Pulmonary & aortic valves

* Papillary muscles contract with ventricles — they pull the cusps of the valves inward to prevent their bulging too far into atria. If it bulges too much, it can leak severely & cause cardiac incapacity

- When atria contracts, and bi-/tricuspid valves are open, blood goes into ventricles.
- Then, bicuspid & aortic valve are closed and ventricle ~~closes~~ contracts ⇒ The pressure rises rapidly. When it goes > 80 mmHg, the blood goes into the aorta, because the pressure is more.
- Then ventricles relax, and blood pressure decreases below atrial BP so that blood can flow from atria to ventricles

End diastolic volume (left ventricle) ~ 110 - 120 ml
End systolic volume (left ventricle) ~ 40 - 50 ml (residual blood)
Stroke volume output ~ 70 ml
Cardiac output (left ventricle) ~ 5-6 litre/min
Ejection fraction : $70/120$ ~ 60%.

When heart is beating strongly, the end-systolic volume can decrease (~ 20 ml) and end diastolic volume can increase (~ 150 - 180 ml), and the heartbeat also increase. Thus, stroke volume output can be increased to more than double.

Cardiac output = Stroke volume x heartbeat

The atrioventricular and semilunar valves prevent the backflow of blood when heart contracts.
Semilunar valves close due to backflow, but AV valves are thin and need the support of tendons.

Function of papillary muscles - (slide) *

The ventricular wall of left ventricle is much thicker than the right one. The LV has to generate a lot more pressure to pump the blood throughout the body, whereas RV has to pump to the pulmonary circuit.
Although walls are thicker / thinner, the volume of both ventricles is the same

Velocity of blood ejection through aortic & pulmonary valves is much greater because they have smaller openings.

2/2/22

Lecture 7

Cardiac conduction system

Group of specialised cardiac muscle cells in the walls of the heart that send signals to the heart muscle causing it to contract.

Its very important for the heart to contract synchronously and rhythmically. for blood to flow from one part to another.

Main components – muscle tissue that behaves like neurons

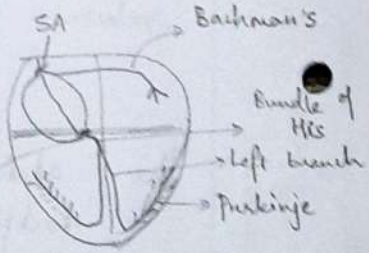
* Sino Atrial (SA) node – in Right auricle
* Atrio Ventricular (AV) node – in b/w RA and RV
* Internodal pathway – Anterior, Middle & Posterior pathway b/w SA & AV node
* Bachman's bundle – from SA node to LA → left atrium
* Bundle of His & bundle branches – conduction pathways to ventricles & Purkinje fibres

SA node can excite itself rhythmically.

Each cardiac cycle is initiated by spontaneous generation of AP in the SA node

SA node → AV node → bundle branches : delay of 1/10th of second

This allows atria to pump blood into the ventricles before they contract.



The heart consists of fibrous non-conducting tissue b/w atria & ventricles, which blocks conduction of any AP between muscle of atria and ventricles. The only allowed pathway for conduction is the Bundle of His, which conducts signal from AV node to Purkinje fibres.

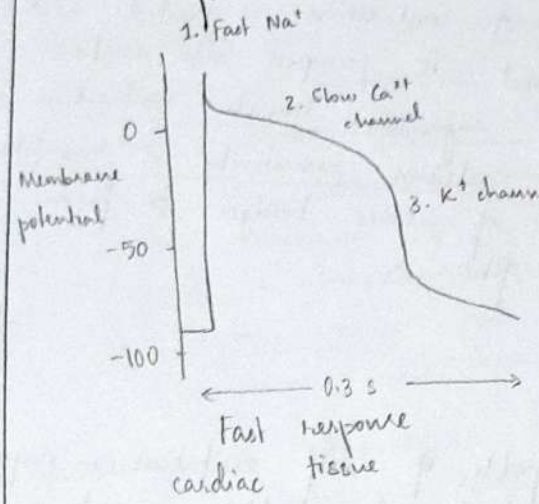
Intrinsic discharge rates –

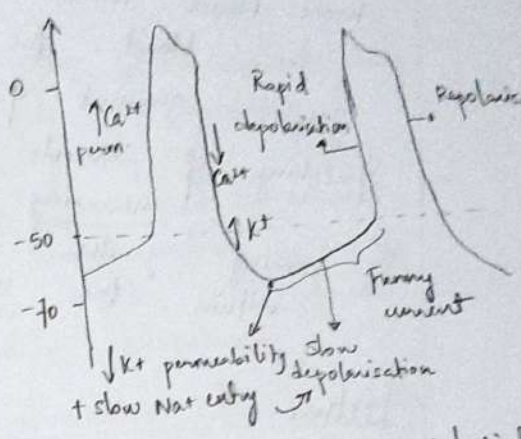
SA node	70 – 80 /min
AV node	40 – 60 /min
Purkinje fibres	15 – 20 /min

SA node acts as the pacemaker which sets the heartbeat

Different parts of muscle contract with a slight delay, but within 0.2 seconds of stimulation by SA node

SA node fires at the end of atrial diastole, just before systole





Self-excitation of SA-node

The cells of SA node has some special Na^+ channels which open when the cell hyperpolarises.

Resting potential is -60 mV, so when plasma membrane goes to -85 to -90 mV, there Na^+ channels open and cause slow depolarisation. One membrane potential crosses -50 mV, L-type Ca^{2+} channels open and action potential happens.

K^+ channels open which start repolarising the membrane and when hyperpolarised, the special Na^+ channels (funny channels cuz they're unusual) open triggering slow depolarisation.

The transfer of blood electrical signal is slowes along the Bundle of this because we need a slight delay b/w contraction of atria and ventricles.

Frank - Starling mechanism - intrinsic regulation of heart pumping

When the body needs more oxygen, heart pumps more blood by increasing the volume of blood per each pump and the rate of pumping.

Ability of heart to adapt to the changing volumes of inflow blood is called Frank-Starling mechanism. When more blood comes in, the muscle stretches to accommodate the blood, the force of contraction is greater and so greater amount of blood is pumped into aorta.

Stretching of muscle fibers augments muscle contraction by increasing the calcium sensitivity of myofibrils, * causing greater number of cross bridges to form within the muscle fibers.

3/2/22

Lecture 8

The mammalian heart is capable of self excitation — myogenic. But it beats at a constant rate, which is not enough in a changing environment.

The Autonomous NS regulates the beating of the heart.

Heart has dual nerve supply — sympathetic and parasympathetic.

Parasympathetic — SA node, AV node, atrial muscles

Sympathetic — SA node, AV node, atrial & ventricular muscles

The nerves arise from nuclei in medulla oblongata.

Dorsal motor nucleus of vagus — fibers from here form the vagus nerve which synapse onto a parasympathetic ganglia, and from there, post ganglionic fibers innervate the heart. This is part of parasympathetic circuit.

Preganglionic fibers and post-ganglionic fibers are both cholinergic. So parasympathetic system releases Ach on the heart.

Cardioacceleratory center (sympathetic) — nerve fibers from here come down the spine, synapse at sympathetic trunk ganglion. Long post-ganglionic fibers innervate the heart, especially ventricular muscles and releases norepinephrine / noradrenaline

* β - adrenergic receptor

- Half-life of { epinephrine, norepinephrine – 11 sec; insulin – 6 mins; Growth hormone – 1.5 h; Steroidal hormone – several hours.

Sympathetic NS control

- If stimulates the heart – increases heart rate from 70 to 180 beats per min. It also increases the force of contraction, so total cardiac output increases by 2 to 3 times.

Norepinephrine and heart contractility

Binding of NE to receptor* initiates cAMP (2° messenger system) which activates protein kinase which phosphorylates –

1. Slow Ca^{2+} channels, promoting Ca^{2+} entry
   This stimulates SR to release Ca^{2+} (Ca induced Ca release)
2. Myosin – increasing myosin cross bridge cycling
3. Ca^{2+} uptake pump removing more rapidly Ca^{2+} from sarcoplasm and hence speeding relaxation.

Stimulation of Sympathetic NS, stimulates adrenal medulla which releases epinephrine and norepinephrine hormones, which further stimulates the heart further.

Angina pectoris

Coronary circulation – it supplies blood to the heart.

Progressive constriction of coronary arteries causes cardiac pain which is called angina pectoris. It appears when load on the heart is too great in relation to available blood flow.

The pain is felt in the left shoulder, chest, left hand arm. when they exercise or experience intense emotions

Treatment with drugs –

1) Nitroglycerine & other nitrate drugs
2) Beta blockers – they block β-adrenergic receptor which slows down the beating of the heart and with less force.

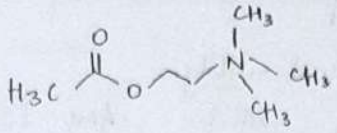
Propranolol – clinically significant beta blockers used to treat AP & high BP discovered by James Black 1962

Ca^{2+} blocker – for hypertension

Parasympathetic NS control

Vagal (parasympathetic) stimulation causes release of Ach which causes decrease in rhythm of heart & slows down beating of heart to half the normal
So continuous sympathetic stimulation is necessary to maintain normal levels of heart beat.

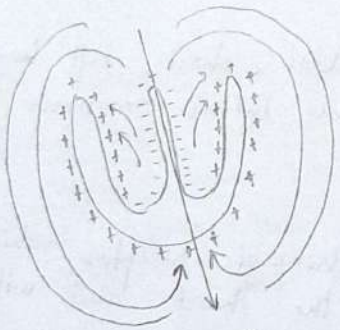
Ach :



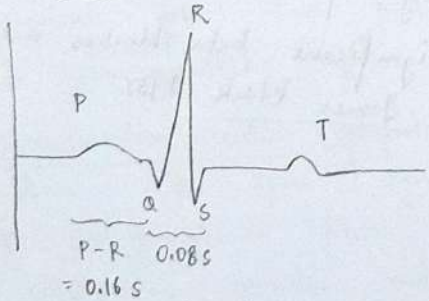
- Nicotinic cholinergic receptor — made of 5 subunits. When Ach binds, the associated channel opens and allows Na^+ and Ca^{2+} ions to go into the cell. (Skeletal muscle).

- Muscarinic cholinergic receptor - single protein, 7 transmembrane domains
It is a GPCR — when Ach binds, it triggers other downstream processes.
These receptors are found in the heart (M_2 muscarinic receptor)
When Ach binds, G protein cleaves from this receptor and binds to a kind of K^+ ion channel, causing it to open, so K^+ ions go out, causing hyperpolarisation.
This inhibits the SA node cells — heart becomes more refractory to contraction and rate of heartbeat slows.

Ach also suppresses the opening of funny channels.



When SA node simulates, the interventricular septum is depolarised for a fraction of a second before the walls of ~~ea~~ ventricle.
This causes a typical current which is measured by ECG.



- P wave starts with stimulation by SA node
- P wave is along the depolarisation of atria
- Q : ventricular excitation begins
- QRS : ventricular excitation complete
- T wave : repolarisation of ventricles.

Arrhythmia and other points in the last 5-6 slides.

7/2/22

Lecture 9

Hemodynamics

↳ principles that govern blood flow in the cardiovascular system.

5,000 ml of blood flows in and out of heart and lungs.

Left heart pumps blood to organs with pressure of ~104 mm Hg –

Skeletal muscle – 1450 ml/min (25%)

GI system – 1250 ml/min (25%)

Kidney – 1000 ml/min (20%)

Brain – 5-10%

Coronary – 5%

Skin – 5%

The blood in the veins is at a low pressure of ~4 mmHg.

The blood flow to different organs can vary greatly depending on the requirement: post meal – GI tract, high temp – skin.

Microvessels of each tissue continuously monitor tissue needs (O_2, CO_2, nutrient & waste products' level) and act on local blood vessels to modulate blood flow. Control of circulation is also regulated by autonomous NS.

Blood vessels

Elastic arteries – conducting vessels

Muscular arteries – distributing vessels

Arterioles – resistance vessels

Capillaries – exchange vessels (with Precapillary sphincters)

Veins – capacitance vessels

Arteriovenous anastomosis – direct connection b/w small arteries and small veins. Found in glabrous skin (palms & soles)

Arteries have thick walls to withstand pressure, but it contains lesser volume of blood. Its made of tunica externa, tunica media (smooth muscles & tunica interna) and inner endothelial cells.

Veins have thinner walls, it can expand. At any time, veins contain 80% of blood They also have valves, so the blood doesn't go back.

Arterioles can greatly constrict or dilate to modulate blood flow. Is innervated by sympathetic adrenergic nerve fibers. Smooth muscles of arterioles (in skin & splanchic vasculature) have α_1 adrenergic receptors — which when stimulated cause constriction of smooth muscles, reducing blood flow.

α_1, β_2 receptors

β_2 adrenergic receptors in skeletal muscle vasculature cause dilation which increases blood flow.

Blood vessels without dual innervation

Splanchnic vessels are just innervated by sympathetic NS which release norepinephrine. At resting condition, the nerve fires at faster rate, releases NE, which keeps the vessels contracted when we eat food, the rate of firing decreases, which dilates blood vessels and increases blood flow.

#veins collapse in the cross-section because it doesn't have thick walls & very low pressure inside

Endothelium

The innermost layer of vessels & heart in vertebrates is made of endothelial cells. They secrete some compounds into the blood, such as prostaglandins & nitric oxide which affects contraction & relaxation of smooth muscle. They also synthesize hormones from precursors and can terminate hormone action by degrading them.

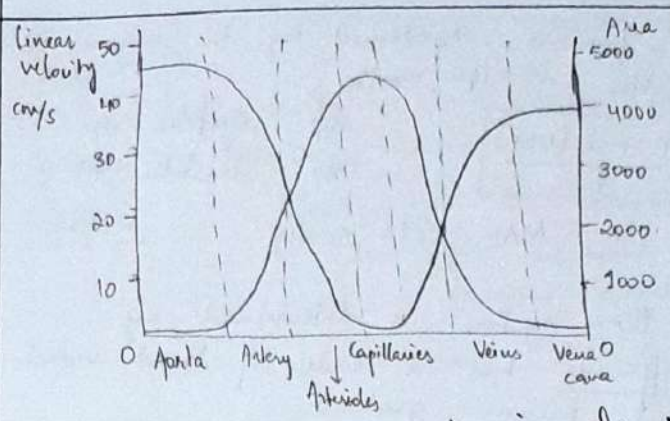
Tunica media (composed of smooth muscle) is largely responsible for regulating circulatory dynamics.

Vasodilation: increases diameter, decreases resistance

Vasoconstriction: decreases diameter, increases resistance to blood flow.

Veins: Act as reservoir of blood. Smooth muscles are innervated by sympathetic nerve fibers: α_1 adr. rec
Increase in activity causes constriction & reduces capacitance.

splanchnic - visceral
somatic - skeletal

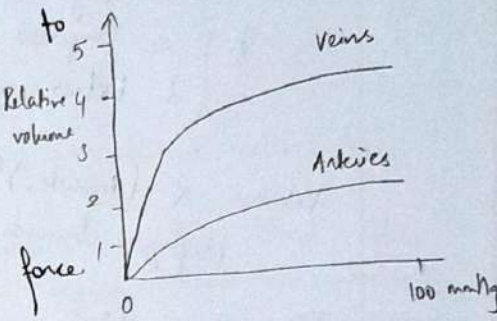


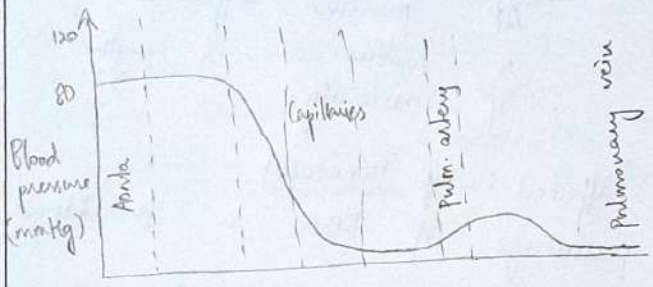
Aorta – 33 cm/s
Capillary – 0.3 mm/s

The velocity of blood is inversely proportal to vascular cross-sectional area because the same amount (volume) of blood must go through each segment.

Compliance : ability of a hollow organ to distend & increase volume with increasing transmural pressure.

Also tendency of a hollow organ to resist recoil toward its original dimensions on application of compressing force.





Pressure in veins & pulmonary system is much lower

Pressure in capillaries –
35 mmHg (arterial side)
10 mm Hg (venous side)
This pressure helps leaking out of nutrients through porous capillaries.

Pulmonary artery : 25/8
Capillaries : 10 mmHg
Pulmonary vein : 8 mmHg

Arterial pressure pulsations

The aorta is distensible – when heart pumps the blood, it goes into aorta, which distends & when heart is in diastole, the walls recoil which propels the blood forward. This decreases the pulsatile nature of blood flow and its converted to a steady flow through the capillaries.

Pulse pressure = SBP – DBP

Auscultatory method of measuring arterial blood pressure — using stethoscope and sphygmomanometer.

Mean Arterial Pressure

It is the perfusion pressure experienced by the organs in the body

MAP should be b/w 65 - 100 mmHg

$$MAP = \frac{SBP + 2(DBP)}{3}$$

SBP : systolic BP
DBP : diastolic BP

For 120/80 mmHg, MAP = 93 mmHg

Blood flow through the system is determined by —

1) Pressure difference b/w 2 ends of blood vessel
Also called pressure gradient

2) Vascular resistance, which is determined by :-

* a. Length & diameter of individual vessels
* b. Organisation of vascular network
* c. Physical characteristics of the blood (viscosity)
* d. Extravascular mechanical forces acting on the vasculature

Volume $\propto$ (diameter)^3 ⇒ small changes in diameter cause large changes in amount of blood that flows.

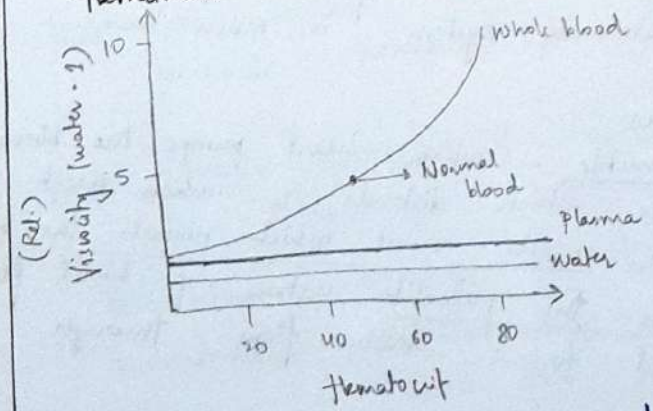
Poiseuille's Law

$$F = \frac{\pi \Delta P r^4}{8 \eta l}$$

F : Flow of fluid
ΔP : pressure difference
r : radius
l : length
η : viscosity

Viscosity of blood is affected by hematocrit

hematocrit : volume percentage of RBCs in the blood



Plasma is 1.8 times as viscous as water and normal whole blood is 3 times as viscous.

Its mainly due to proteins and RBCs.

Fluid column effect — BP in a standing man
Varicose veins — disfigured valves and backflow of blood

Lecture 10

Why don't capillaries burst under pressure?

Pressure in capillaries ~ 30 mmHg on artery side

Laplace law: Tension in the tube is directly proportional to radius of the tube ⇒ walls of small arteries can withstand pressure, whereas large arteries need thicker walls.

$$T = r \cdot \Delta P$$

So, capillaries can withstand high P with thin wall because tension experienced is v. low due to small r.

Method of measuring blood flow

Doppler flowmeter – a piezoelectric crystal emits ultrasound freq and detects the reflected freq & measures the rate of flow based on that.

Microcirculatory bed

- Capillaries are made up of single layer of endothelial cells – they don't have smooth muscles.
- There are also precapillary sphincters, which regulate blood flow into the capillaries, to give the organ minimum amount (local) of blood it can work with. Regulated by sympathetic NS & chemicals
- There are 10-100 capillaries per capillary bed
- Capillaries themself don't contract, but they are restricted by sphincters which make the capillaries active & inactive based on the requirements of the downstream tissue

Capillary exchange

O_2, CO_2 can diffuse freely

Water and water soluble particles are also exchanged easily through water pores.

Plasma proteins can't cross.

Other proteins are actively transported through vesicles in the endothelial cells

Capillaries in different tissues have different permeabilities.

Types of capillaries

Continuous

Found in brain (Blood brain barrier)

Fenestrated

Muscles x Kidney, intestine
Med level of (pores)
permeability

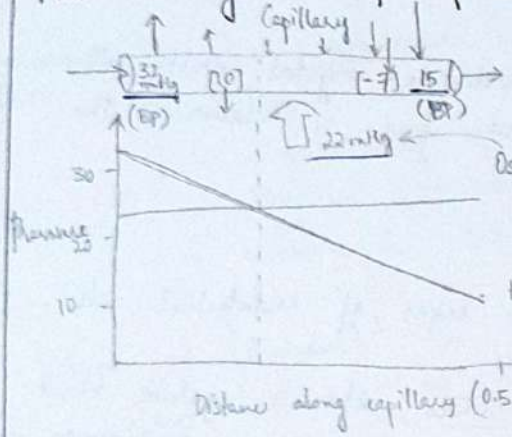
Sinusoid / Discontinuous

Liver (cuz it synthesizes proteins which need to be taken up)

Also bone marrow, where RBCs are produced

Lymph nodes, spleen, adrenal gland

Fluid exchange in capillary walls : Starling-Landis



hydrostatic pressure is high in the arteriole side & decreases along the length.

So, a lot of water leaves the capillary initially bcuz of pressure. This increases the osmotic pressure. when osm. P is more than hydrostatic P, water starts coming inside.

So there's a ~~lot of~~ microcirculatory system in every capillary.

But not all of fluid comes back, some of it remains in the interstitial fluid, and flows into the lymphatic system.

Blood brain barrier

The capilleries in the brain are made of tightly attached endothelial cells that are surrounded by astrocyte foot processes.

If the brain needs anything, it is transported through carriers.

This needs to be kept in mind while desinging drugs for brain diseases.

Starling-Landis : Blood plasma initially loses blood but regains volume in the final segments (due to osmotic P) → Hydrostatic P.

Regulation of Circulation

Blood flow is regulated at each tissue get required amount of blood required this involves —

a. optimal regulation of cardiac activity & BP
b. adequate perfusion of all organs
c. shunting blood to active organs from inactive ones as or to not overtax the heart

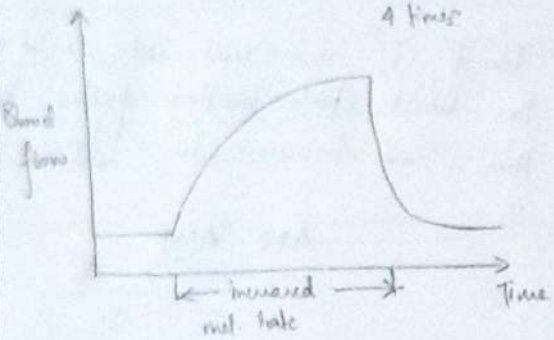
Its regulated by changing diameter of blood vessel. Muscle tone changes in response to —

Muscle tone changes due to —

* 1) local stimuli
* 2) Humoral signals
* 3) Neural signals (sympathetic system)

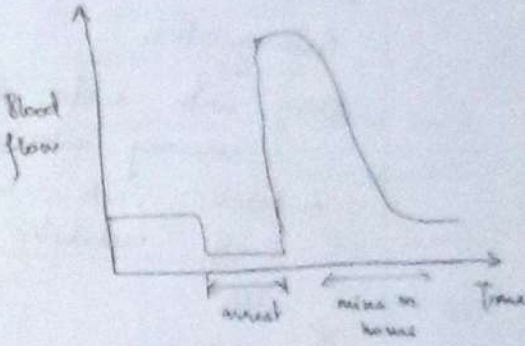
Active hyperemia

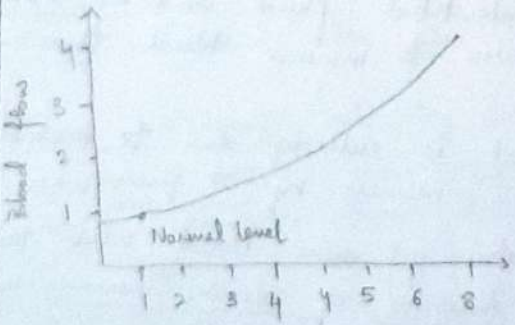
Increase in blood flow due to increased use of O_2 by tissues.



Reactive hyperemia

When blood supply is blocked for short time. then unblocked. blood flow increases immediately by 4 times





Increase in metabolism by 8x increases blood flow by 4x

Blood flow at rest

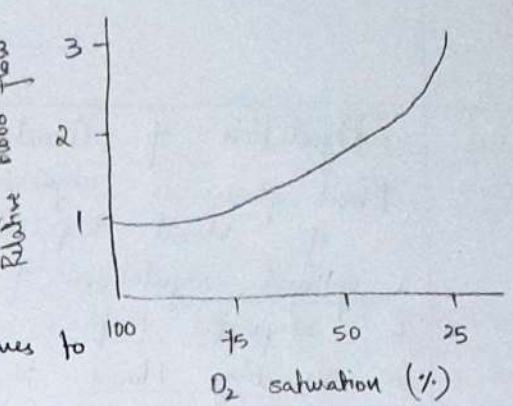
Liver	25%	83%
Kidneys	20%	
Muscle	20%	
Brain	18%	
Skin	7%	
Heart	5%	→ increased metabolism ⇒ it consumes a lot of O_2.
Bone marrow	5%	

When tissue becomes highly active such as when exercising, 87% of blood flow is redirected to muscles. at cost of other organs.

Acute local blood flow regulation based on O_2 availability.

O_2 could be low due to
- high altitude
- pneumonia
- CO poisoning (inhibits O_2 transport by Haemoglobin) *
- Cyanide poisoning (inhibits ability of tissues to use oxygen)

Blood flow increases when O_2 saturation level goes down due to:



Autoregulation (local) of blood flow

Autoregulatory mechanisms help maintain constant blood flow to certain organs when blood pressure changes. (eg. renal vessels constrict when BP increases)

It also functions to regulate flow in response to metabolic activity of the organ.

10/2/22

Lecture 11

Autoregulation

Along with aorta, oxygenated blood is also sent into right & left coronary arteries. Say, the heart starts beating faster. When metabolic rate increases, there's an increase in local conc. of metabolic products -

- CO_2
- H^+
- K^+
- * Adenosine
- * ADP, AMP

These metabolites go into interstitial fluid and are detected by arteriole, which dilates to increase blood flow and provide O_2 conc.

Blood flow to brain & heart is entirely due to metabolic products. Blood flow can increase by 5 times when required (eg. heart & skeletal muscle also get more blood when they're functioning a lot. The diameter of arterioles increases and capillaries become perfusive (sphincter released).

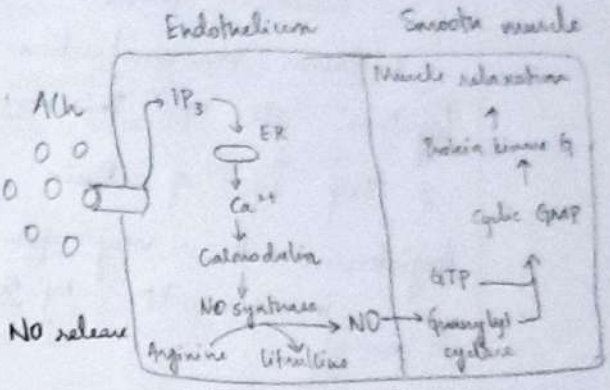
Capillaries are always perfused in the heart. When myocardium needs more O_2, the cells release ATP into extracellular fluid, which breaks down to form adenosine. Adenosine acts on the smooth

muscles of arterioles and triggers the purinergic receptors.
A2 receptor on the vascular smooth muscle is a GPCR, which increases activity of Adenyl cyclase → increased cAMP → relaxation
This dilates the arterioles.

A1 purinergic receptor on SA & AV node is also GPCR but here, it decreases the activity of AC → decreased cAMP which decreases chronotropy (freq/ heart beat decrease) and decreases dromotropy (conduction speed of action potential b/w SA & AV node)
This is done because heart itself is not getting enough O_2, so heart slows down before it collapses.
All of this is just local control — muscle talking to muscle.

Nitric oxide (NO)

Its a vasodilator released from healthy endothelial cells
Its a lipophilic gas — NO Synthase (NOS) synthesizes NO from arginine
Secretory action of endothelial cell was discovered when it was observed that if endothelium was scraped off, the arterioles couldn't dilate.



NO mainly acts on local tissues.
Agents like ACh, thrombin, serotonin, ADP & bradykinin promote release of NO.
Mechanical stimuli - sheer stress on the endothelial cells also trigger NO release

Viagra - sildenafil acts by inhibiting cGMP-specific phosphodiesterase type 5 (PDE5), an enzyme that promotes degradation of cGMP, which regulates blood flow in the penis. Thus the vessels remain dilated & blood flow is increased.

1998 Nobel was awarded for discoveries concerning NO as a signalling molecule in the cardiovascular system.

NO activates soluble guanylate cyclase in vascular smooth muscles which converts GTP → cGMP relaxes ↓ blood vessel (upstream)

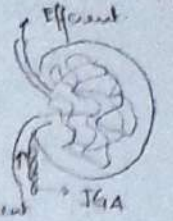
① Receptor stimulated

② Flow-stimulated NO production

Local blood flow regulation in kidney

For ultrafiltration in Bowman's capsule to happen, the blood pressure should be > 50 mmHg. If it starts decreasing, the Renin-Angiotensin mechanism regulates BP.

Renin is secreted by Juxtaglomerular kidney cells which sense changes in renal BP via stretch receptors in vascular walls.



Angiotensinogen is a protein produced by the liver that is present in the blood

Renin acts on Angiotensinogen & cleaves it to produce 10 aa peptide called angiotensin I. It is inactive by itself.

Circulating in the blood, it comes across Angiotensin-converting enzyme (ACE) in endothelial cells, which cleaves two aa to make angiotensin II.

Angiotensin II acts on —

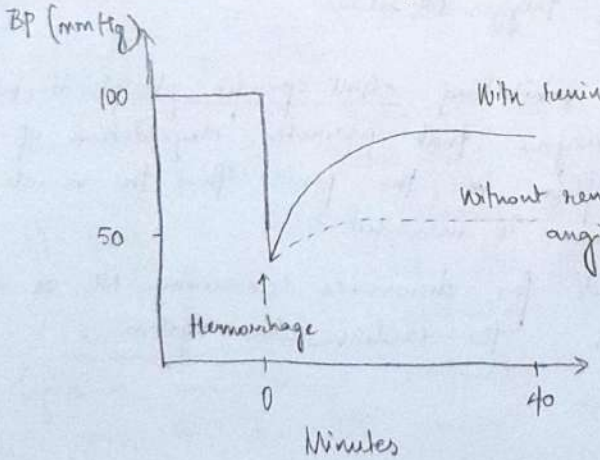
Effects of angiotensin II *

1. Adrenal cortex → ↑ Aldosterone → ↑ Na^+ reabsorption : which increases water retention, increasing ECF volume
2. Increases Na^+ - H^+ exchange, which also increases Na^+ reabsorption
3. Increases thirst
4. Causes vasoconstriction ⇒ increased total peripheral resistance (TPR)

Together, all of this increases the blood pressure

≠ Half life of Renin ~ 20 mins, Angiotensin II ~ 1-2 mins

Angiotensin II - very powerful vasoconstrictor : 1/10⁶ g can increase BP by 50 mm Hg



ACE2 receptor is found in the lungs (pulmonary circulation). Sars-Cov-2 virus enters through ACE2

14/2/22

Lecture 12

ACE - found in endothelium of lungs

If ACE is inhibited, Angiotensin 2 will not be produced
ACE inhibitors decrease Blood pressure by decreasing tension of blood vessels & blood volume.

Eg: Captopril - ACE inhibitor

So, ACE inhibitors, Beta blockers, Calcium channel blockers and long acting nitrates are prescribed in combination, based on patients need.

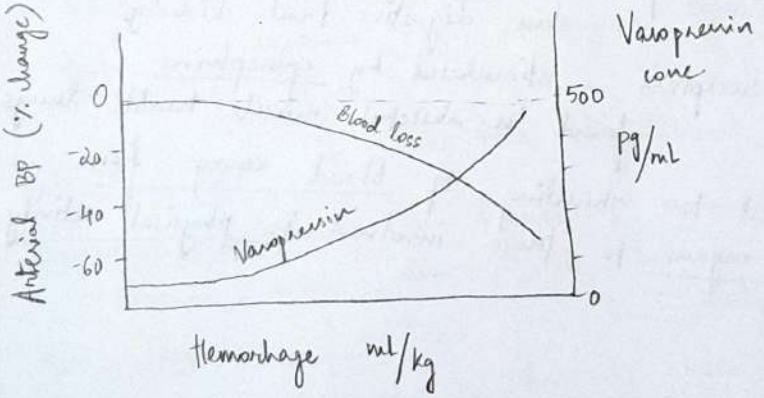
Vasopressin (Anti Diuretic Hormone)

Also a vasoconstrictor. Its a neurohormone - formed in hypothalamus & released by posterior pituitary gland
Its a nanopeptide that's released into the blood stream.
Normally, vasopressin levels are low, but after hemorrhage, it can rise to increase BP by 60 mmHg

Effects of Vasopressin

It has two types of receptors

* V1 receptor : in the smooth muscle of blood vessels
  Its a GPCR, which constricts wall
* V2 receptor : in the kidney, when stimulated it increases water reabsorption.

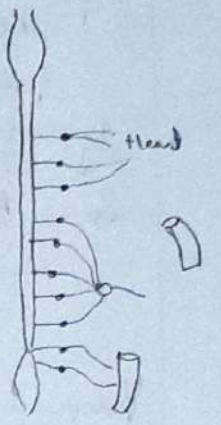


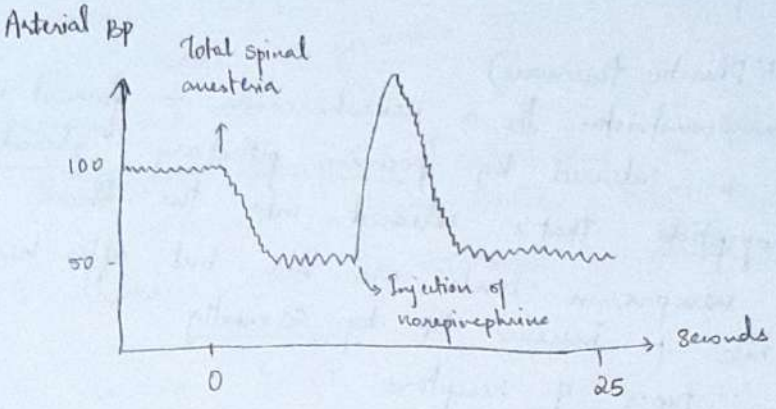
Endothelin

A powerful vasoconstrictor released from damaged endothelium
It's a 21 aa peptide that's released when endothelium is damaged, which constricts vessels and prevents blood vessels.

Nervous Regulation of Circulation

Almost all blood vessels are innervated by post-ganglionic fibers of sympathetic NS and they release norepinephrine
They are also affected by epinephrine & norepi released by adrenal medulla





Effect of NE on arterial BP

Preganglionic fibers (cholinergic) of sympathetic NS stimulate adrenal medulla cells to release epinephrine & NE, where epinephrine dominates (about 80%).
They act on adrenergic receptors which are present everywhere

α1-adrenergic receptors – more sensitive to norepinephrine
skin, digestive tract, kidneys.

β2-adrenergic receptors – stimulated by epinephrine
found in skeletal muscle, heart, lungs

The net effect is shunting of blood away from visceral organs to those involved in physical activity.

* by changes in intracranial pressure

Control of special circulation

Circulation	Vasoactive metabolites	
Coronary	Hypoxia, Adenosine	Local > sympathetic
Brain	CO_2, H^+	Local control > sympathetic control (→ flow of blood to different parts of brain is closely regulated *)
Skeletal muscle	Lactate, CO_2, K^+, Adenosine	Local (during exercise) = Sympathetic (emergency)
Skin	–	Local << sympathetic (temp)
Pulmonary	Hypoxia	Local >> sympathetic
Renal	–	Local (glomerular) >> sympathetic

Baroreceptors

Present in aorta & carotid, they carry information to the medulla

The regulation happens within seconds – when body posture changes, the arteries are quickly adjusted so that blood flow to brain is regulated.

When you stand up, BP in head changes & in turn, there's a strong sympathetic surge so When blood pressure increases, the frequency of action potentials that it produced by baroreceptors increases. This is received by adjusted nucleus of tractus solitarius in the medulla.

Glossopharyngeal, Vagus

And it regulates BP through sympathetic & parasympathetic NS

Role of oxygen in Long-term Regulation

Role of long-term * O_2 reduction

Increased vascularity in tissues of animals that live at high altitude, where atm O_2 is low

Also, number of RBCs in the body increases.

* Fetal chicks hatched in low O_2 have twice as much tissue blood vessel conductivity as is normally true

* Similar changes are observed in premature babies, when they're taken out of oxygen rich chambers.

Lecture

Lymphatic System

Lymph consists of water, nutrients, proteins and WBCs. They drain into the lymphatic system. [5% of blood in capillaries]

extracellular fluid that's not reabsorbed by the blood

Starling hypothesis becomes important — i.e most of plasma is reabsorbed but not all. Exchange of fluids mainly happens through diffusion.

Lipid soluble substances can diffuse directly through cell membrane of endothelial cells. eg. O_2, CO_2

Water soluble substances only diffuse through intercellular pores in the endothelium. Eg. Na^+, Cl^-, glucose

Order of lymphatic vessels

Capillaries → Collecting vessels → Lymph nodes → lymph trunks → Lymph ducts empty into the veins of the neck

Lymph nodes are scattered along collecting vessels.

The flow of fluid is driven by interstitial pressure caused by continuous oozing out of fluid from blood capillaries.

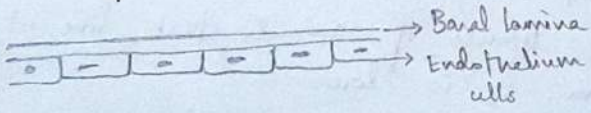
Important function: lymph returns proteins to the blood from the interstitial space — would dies in 24 hrs if this doesn't happen

The terminal lymphatic capillaries are blind ended and fluid can easily diffuse into it. Sac-like terminal lymphatics are suspended in the interstitium

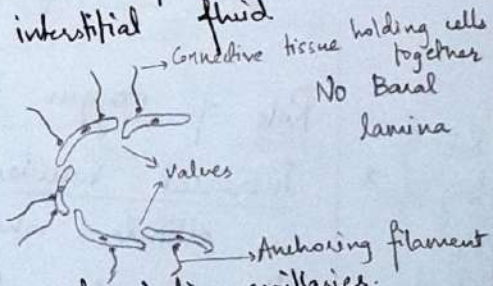
Human circulatory system processes 20 L of blood in the day 17 L is reabsorbed by capillaries, while 3 L of fluid is returned to the blood by lymph. (120g of protien) colloid

Recycling protiens is essential for maintainance of blood osmotic pressure gradient b/w plasma & interstitial fluid.

Oncotic [Colloid osmotic] pressure — exerted by protiens in blood vessels plasma, which tends to pull water into circulatory system



Blood capillary



No basal lamina (its very discontinuous) in lymphatic capillaries.

Lots of gaps between cells ← Endothelial cells are arranged s.t. blood can flow in easily.

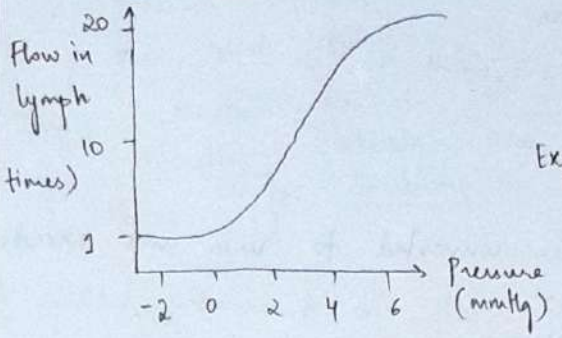
But if intracapillary pressure increases, then the gap between cells closes so it can't flow out — acts as valves.

In lymphatic collecting vessels, endothelial cells are more tightly arranged and fluid can't move b/w cells or out of lymph vessel.
Also, they're covered by continuous basal lamina, unlike lymph capillaries

The flow of fluid through lymph vessels is also helped by smooth muscles — if pressure inside increases, the smooth muscle stretches and when they stretch, they also constrict, which drives the flow of fluid

Stretch-mediated active contractions

Myogenic response

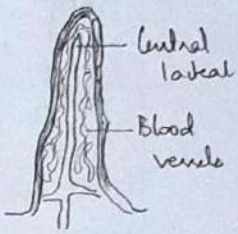


Principal driving force for entry of fluid into terminal lymphatics is pressure of Interstitial Fluid (PIF)
Expansion of interstitium also causes anchoring filaments to pull open the terminal lymphatic.

Protien conc in — interstitial fluid : 2 g/dL
lymph (livers) : 6 g/dL
GI tract : 3-4 g/dL

All lymph collects into lymphatic duct in the thorax which then empties into veins

Lymphatic system is also a major route for absorption of nutrients, especially fat, from the intestine.
Soluble nutrients (sugars, protiens) are absorbed by blood vessel. The absorbed fat is carried through lymph system and emptied into the veins.



Villi

Lymph nodes and lymph gland

They're distributed throughout the body. They are garisons of B, T & other lymphocytes. lymph nodes act as filters or traps for foreign particles and lymphocytes are ~~more~~ activated for the immune response
When an antigen is recognised, an immunological cascade begins involving activation and recruitment of more and more cells, and production of antibodies and cytokines.
lymphatic system is responsible for carrying cancerous cells between different parts of body, called metastasis. Intervening lymph nodes can trap cancer cells, if they're not successful in destroying them, nodes become sites of secondary tumor

Elephantiasis — parasitic worm Wuchereria bancroftii infects lymph nodes and blocks flow of lymph through the body, resulting in chronic edema in lower torso.

Renal Functions

Main functions

Kidney functions:
1) Regulation of water, inorganic ion balance & acid-base balance
2) Removal of metabolic waste product
3) Removal of foreign chemicals from blood & their excretion
4) Gluconeogenesis
5) Production of hormones / enzymes
   - Renin : water balance
   - Erythropoietin, Vitamin D3 (calcitriol)
   - Vitamin D3

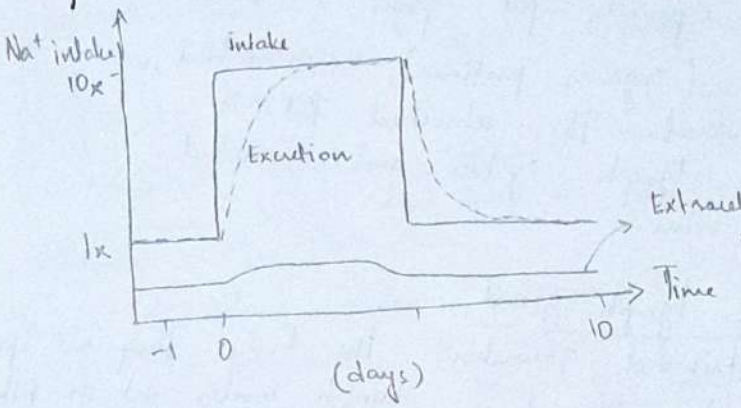
Excretory function

- Metabolic waste products are converted to urea and excreted from urine. Others include – (helps in transiently holding ATP)

Excretory products:
- Creatinine from muscle creatine
- Uric acid from nucleic acids
- Bilirubin : end product of haemoglobin breakdown
- Metabolites of various hormones & drugs

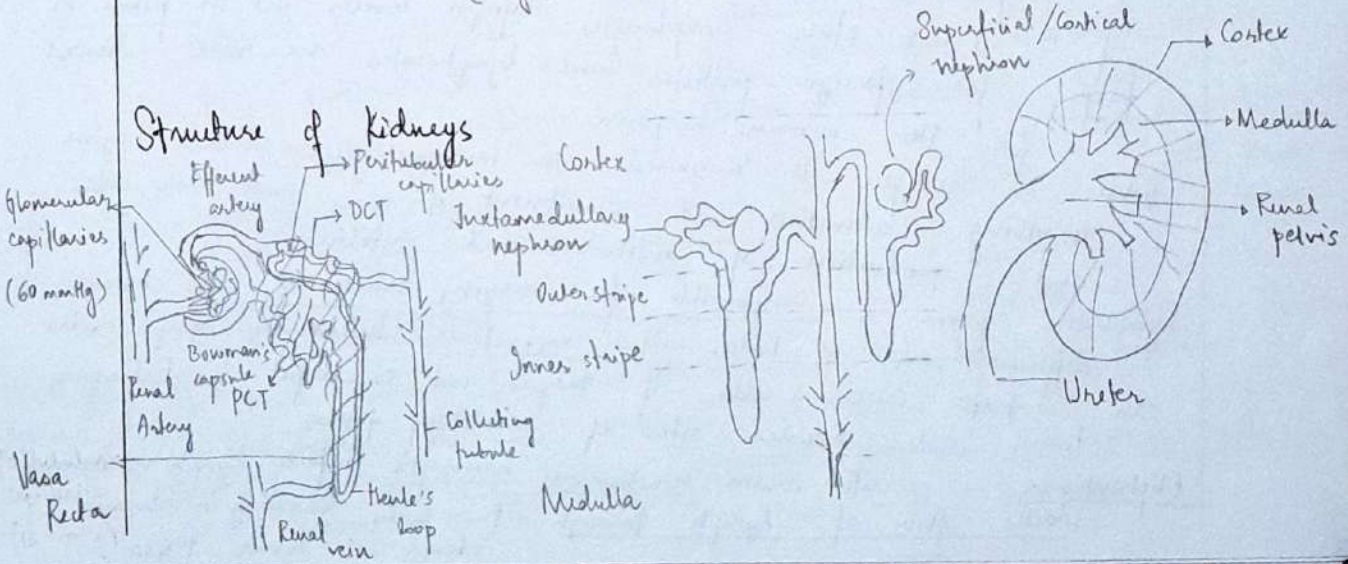
- They are eliminated from the body soon as they are produced

Excretion regulates wide changes in ion balance



→ doesn't change much even though Na+ intake is 10 x

Structure of Kidneys



Blood flow to the kidneys is 22% (1100 mL/min). Renal artery enters through the hilum & branches progressively till it gives & rise to glomerular capillaries where large amount of fluid and solutes (except proteins) are filtered. Efferent arteriole gives rise to a second capillary network (peritubular capillaries) that surrounds the renal tubules.

High hydrostatic pressure (60 mmHg) in glomerular capillaries helps filteration, whereas low P (13 mmHg) in peritubular capillaries allows for reabsorption.

17/2/22

Lecture 14

Superficial / Cortical nephron - smaller, thinner tubule
Juxtamedullary nephron - longer, thin's loop covered with vasa recta

Glomerulus & Renal corpuscle

The capillaries in glomerulus are fenestrated, which allows large amt. of solute-rich fluid to pass through.
Inner layer of glomerulus contains highly modified branching epithelial cell called Podocytes.

Podocytes have foot processes that surround the basement membrane of the capillaries. The cleft b/w foot processes are the filtration slits. Podocyte supports the capillaries.

So, 3 layers - fenestrated endothelium, basement membrane, podocytes

Glomerular mesangial cells - smooth muscle cells that help regulate blood flow in capillaries.

The basement membrane is negatively charged - this repels large proteins (usually negatively charged) are repelled & kept in plasma. Whereas positively charged molecules (dextran) are filtered easily

Filterate contains
1) All electrolytes (Ca^{2+} is usually associated with large proteins)
2) Metabolites & metabolic waste
3) Non-natural substances
4) Lower weight proteins and peptides

Filterability

Water, Na^+, Glucose - 1.0
Myoglobin - 0.75
Albumin - 0.005

Filterability is inversely related to the molecular size

Glomerular Filteration Rate (GFR) is 20% of renal plasma flow. 1100 ml/min blood flows to the kidney, whereas GFR is about 120 ml/min.

Urine formation : Glomerular filteration, Tubular Reabsorption, Tubular Secretion

The filtrate from glomerulus is called pre-urine From this, useful substances are reabsorbed, whereas other unwanted metabolites are secreted

Urine formation rate = Filteration − Reabsorption + Secretion.

How products are treated

A. Filteration only : Creatinine, ~~urea~~, uric acid
B. Filteration + partial reabsorption : Electrolytes (K^+, H^+), urea (half is reabsorbed)
C. Filteration + complete reabsorption : amino acid, glucose, HCO_3^-, Na^+ (mostly), Cl^-
D. Filteration + secretion : metabolites

Phosphocreatine serves as rapidly mobilizable reserve of high-energy phosphate in skeletal muscle & brain

Phosphocreatine → (spontaneous) Creatinine + Phosphate

Creatinine is entirely excreted out. Healthy person : 0.7 − 1.2 mg/dL
If filtering of kidney is deficient, creatinine blood levels rise − its used to calculate Creatinine clearance (CrCl)

Outward force - glomerular hydrostatic pressure : +60 mmHg
Inward - colloid osmotic pressure (oncotic) : −32 mmHg
Inward - capsular hydrostatic pressure : −18 mmHg
} Pressures

∴ Net filteration pressure = 10 mmHg

In some pathological states associated with obstruction of urinary tract (kidney stone), the Bowman's capsule pressure can increase, causing reduction in GFR, which can damage the kidney. This is called hydronephrosis.

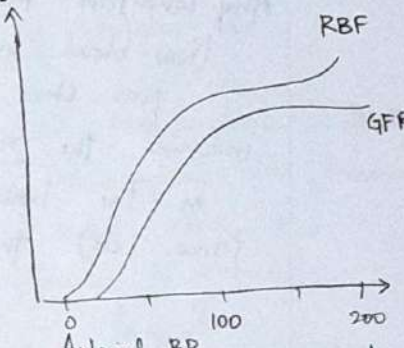
	Pressure (mmHg)	
Renal artery	100	pressures
Afferent arteriole	60	
Glomerulus	59	
Peritubular capillaries	18	
Renal vein	4	

⇒ There's a strong outward force in glomerulus pushing fluid out

Autoregulation of Renal blood flow & GFR

Blood pressure is very important to be maintained for proper GFR

It makes sure that GFR & RBF is relatively constant with variation in BP.

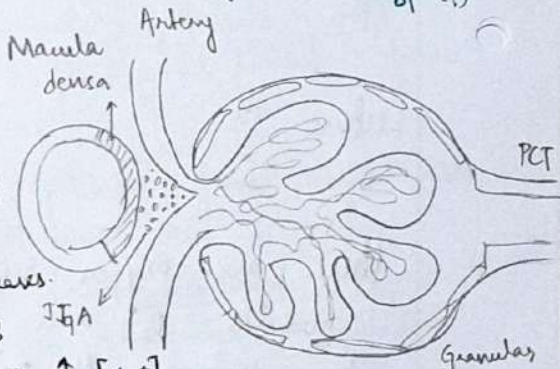


In response to increased flow of tubular fluid in thick ascending limb ⇒ increased BP (?)

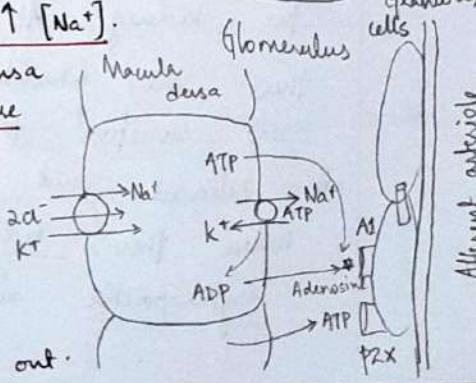
The Bowman's capsule is close to DCT.

Macula densa is a collection of epithelium cells at junction of ascending limb and DCT.

Macula densa sits at the angle between afferent & efferent arterioles



1. When BP increases, filteration rate increases. ⇒ reabsorption decreases. This causes fluid at the macula densa to have ↑ [Na+].
2. This increases uptake of NaCl by macula densa via NKCC2 symporter. This leads to increase in ADP :: cell pushes Na+ out & K+ in.
3. The osmolality in the cell increases, so water comes in. ATP escapes through stretch activated anion channel
4. ADP is converted to adenosine & ATP is also out.



5. Adenosine acts on Adenosine A1 receptors & ATP binds to P2X (purinergic) receptors on the smooth muscle cells surrounding afferent arteriole, both of which release Ca^{2+}

6. Increase in intracellular Ca^{2+} induces vasoconstriction of afferent arteriole, thereby returning GFR to normal levels.

* A2A receptors - coronary artery vasodilation

Erythropoietin

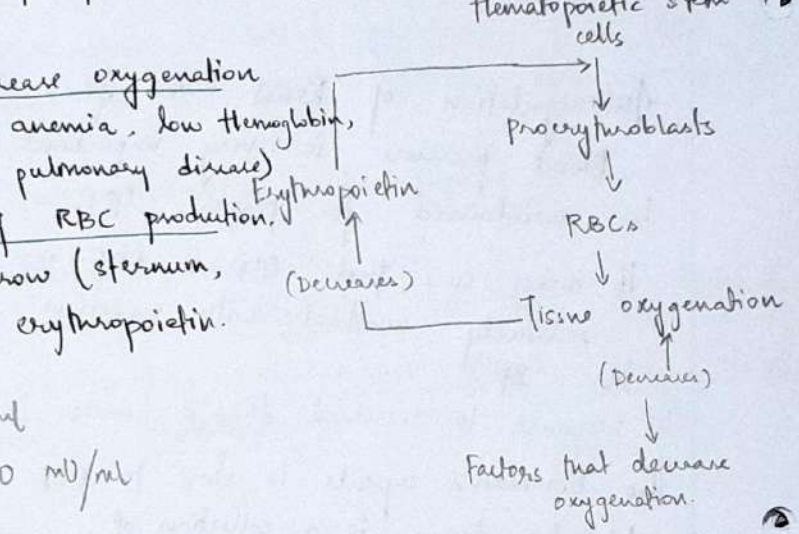
Also called haemopoietin, its a hormone that stimulates RBC production in low oxygen conditions. Its a large glycoprotein

Hypoxia causes marked increase in erythropoietin production

Its produced by interstitial fibroblasts in renal cortex, which are in close association with peritubular capillary.

About 10% of erythropoietin is produced in the liver.

Any condition that decrease oxygenation (low blood volume, anemia, low Hemoglobin, poor blood flow, pulmonary disease) increases the rate of RBC production in the bone marrow (sternum, femur etc) through erythropoietin.



Normal - 10 mU/ml

Hypoxic stress - 10,000 mU/ml

Lecture 15

21/2

There are oxygen receptors in the carotid that tell the medulla O_2 conc in blood. O_2 receptors are also present in the kidney. At the edge of medulla and cortex in kidney, there are fibroblasts which secrete erythropoietin. Fibroblasts are sensitive to O_2 level in blood, if it decreases, erythropoietin is released and it acts on bone marrow.

When there's kidney failure, you should also give erythropoietin, along with dialysis.

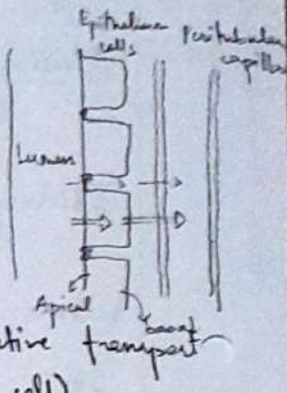
Na^+ reabsorption is driven by —
1. Chemical gradient : intracellular Na^+ - 12 mEq/L ; tubular fluid - 140
2. Electrical gradient: -70 mV intracellular potential

Urine formation

After filteration in Bowman's capsule, the filtrate goes through PCT, loop of Henle, DCT & Collecting tubule

Reabsorption occurs in PCT

Peritubular capillary lies very close to PCT. Water, ions and other solutes are absorbed here



They can be transported through cell membranes of epithelium cells (transcellular) or through junctional spaces b/w cells (paracellular).

When transported through cell, it can be very active transport or passive transport (channels on basal side of cell)

The cells of PCT are very thick. 65% of solutes are reabsorbed at this level

PCT has high capacity for active & passive reabsorption — they have extensive brush borders (microvilli) on the apical side (luminal). They also have a lot of mitochondria on basal side. Also there's a labirynth of proteins systems & channels that helps transcellular transport

Peritubular capillaries are like venous ends of other capillaries because efferent capillary has higher osmotic pressure — there's a net reabsorptive force that moves the fluid and solutes from interstitium into the blood

Na^+ is actively transported to the capillaries from basal side of the tubular epithelium cells. So Na^+ come in the tubular epithelium cells is low and there's an electrical gradient (resting membrane -70 mV). So Na^+ moves into the cells & its transported to capillaries.

Cl^- ion follows Na^+ to maintain the charge. Water also follows these ions to maintain osmotic pressure.

paracellular route

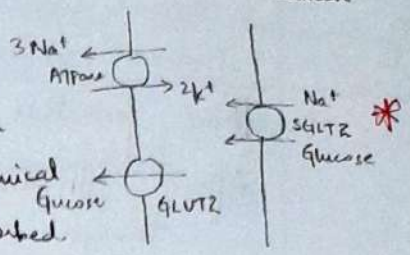
Na^+ is passively reabsorbed by an Na^+-Glucose symport system

There are different symport systems for amino acids, other ions, vitamins etc

Secondary (active) transport

Sodium-glucose transporters (SGLT2) help reabsorb Na^+, glucose from lumen of PCT

Glucose gets a ride along with Na^+ which is being transported along the electrochemical gradient. Similarly amino acids are also reabsorbed.



Glucose and amino acids exit the cell through facilitated diffusion (GLUT2 channel) i.e. passive transport into the blood
↳ Basal membrane

Kidney : weight = 0.5% | ATP usage = 10%.

GLUT transports glucose from high conc to low conc

23/2/2022

Lecture 16

SGLT family

It has 14 transmembrane domains. It processes co-transport of Na^+ & Glucose

SGLT1 - intestine, heart, kidney
SGLT2 - kidney (PCT)
SGLT3 - intestine, liver, spleen, muscle

GLUT - bidirectional, 12 TM, channel

Primary active transport is linked to ATP hydrolysis

The main transporters are —

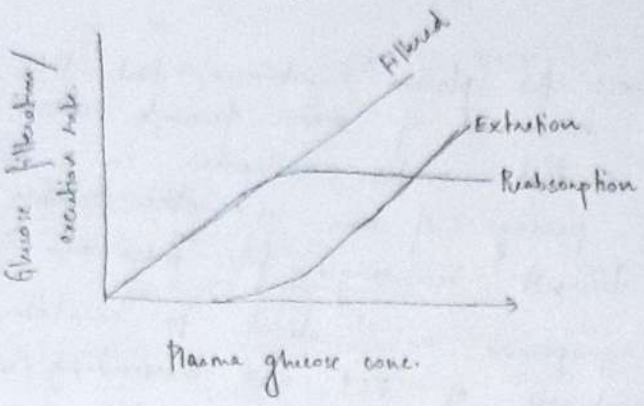
Active transporters *
a) $Na^+ - K^+$ ATPase
b) Hydrogen ATPase
c) Hydrogen Potassium ATPase
d) Calcium ATPase

Pinocytosis — active transport mechanism for reabsorption of proteins

Protein first attach to microvilli and this portion invaginates to form a vesicle. Once inside the cell, this protein is digested and amino acids are transferred to the capillaries.

Transport Maximum for Actively Reabsorbed substances

SGLT channels are the bottleneck - if plasma glucose conc increases more than the transport can maximum, then the conc of glucose & Na+ excreted will increase



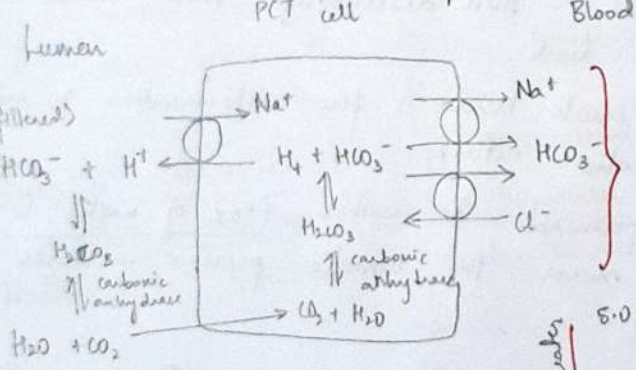
The same is true for other substances that are reabsorbed -

- Phosphate
- Sulfate
- Lactate
- Plasma protien
- Amino acids

Passive water reabsorption by osmosis is coupled mainly to Sodium reabsorption. Large fraction of water transport mainly occurs through tight junction

Reabsorption of HCO_3^-

Bicarbonate is very important for maintaining pH of blood and extracellular fluid



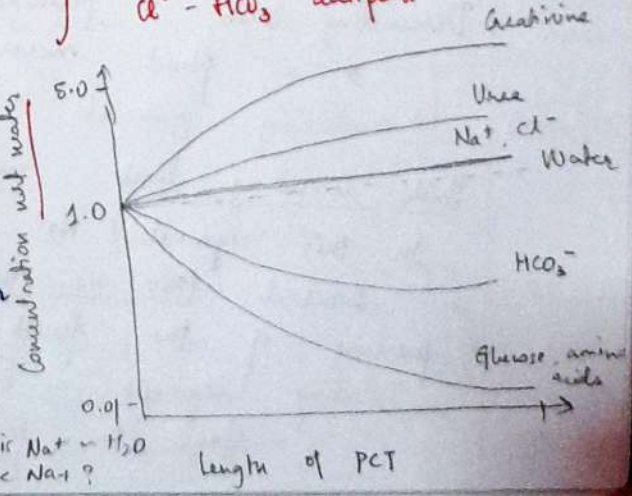
: How HCO_3^- is reabsorbed in nephron

$Na^+ - HCO_3^-$ symport

$Cl^- - HCO_3^-$ antiport

Relative reabsorption of solutes:

Chloride, urea & other solutes passively diffuse through paracellular pathway.



Why is $Na^+ \sim H_2O$ & as $\propto$ Na^+?

Secretion of organic acids & bases by PCT

They secrete bile salts, oxalate, urate & catecholamines into the lumen through a symport or antiport system

This poses a problem because certain drugs (penicillin, aspirin) are also rapidly excreted by the kidney. Its hard to maintain therapeutically effective drug conc.

Aquaporins

Some water can cross the plasma membrane, but this can't account for rapid movement of water through cells.

Aquaporins selectively conduct water molecules in & out of cell while preventing passage of ions and other solutes

Water travels the channel in single file. There are 13 types.

Different types of aquaporins are localized to basolateral and apical membrane of PCT and descending limb of loop of Henle, & collecting duct.

[Ascending limb & DCT are impermeable to water]

In PCT, water moves rapidly along osmotic gradient to establish ~~active~~ isotonicity.

Henle's loop

It has 3 components : thin descending, thin ascending and thick ascending limb.

Thin segments: no brush border, few mitochondria & minimal metabolic activity

Descending limb is permeable to water (20% of water is reabsorbed)
↳ so as fluid moves, the osmotic pressure increases.
↳ moderately permeable to solutes

Thick ascending limb : impermeable to water. This concentrates the urine.
In this segment, Na^+, Cl^-, K^+, Ca^{2+}, HCO_3^- — ions are absorbed (25% are reabsorbed). This decreases the osmotic pressure of the fluid inside the loop.

Diluting segment — because ions are reabsorbed but water stays the same

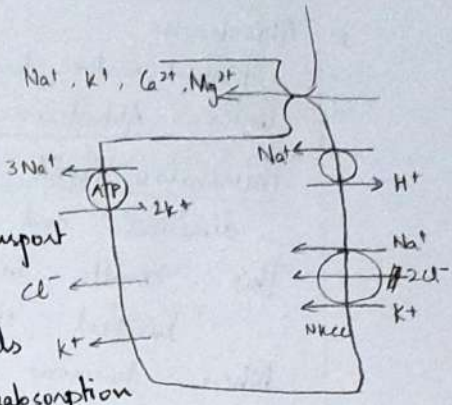
Loop diuretics – NKCC symporter (loop of Henle)
Thiazide diuretics – NaCl symporter (DCT)

Mechanisms in thick ascending limb (TAL)

Low Na^+ in the cell provides suitable gradient for Na^+ to be in the cell.

Na^+ is pumped through NKCC channel on the apical side

Na^+ gradient is used to propel the co-transport of K^+ & Cl^-



Furosemide → Loop diuretics – it acts on these channels and inhibits them so that ion reabsorption is hindered such that more water is lost in the urine.

Specifically, furosemide blocks Cl^- binding. These diuretics are used to treat high BP.

NKCC2 is major transport protien by which Na^+ is reabsorbed from urine and into cells

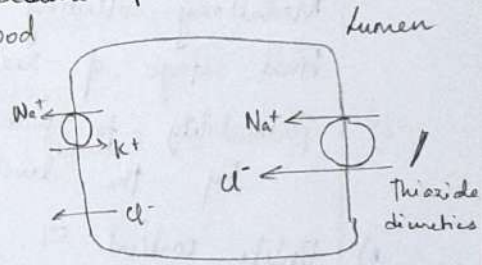
⟹ Early Distal Convoluted Tubule

Early part has Macula densa, forms part of JGA, and provides feedback regulation over blood flow to nephron

Early DCT also reabsorbs most of ions but its impermeable to water and urea

It's also called the diluting segment because it also dilutes the tubular fluid

Thiazide diuretics act on DCT and inhibit sodium-chloride symporter leading to retention of water in urine



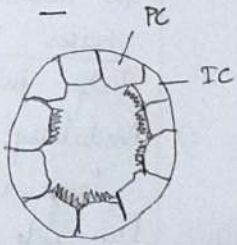
24/2/22

Lecture 16 17

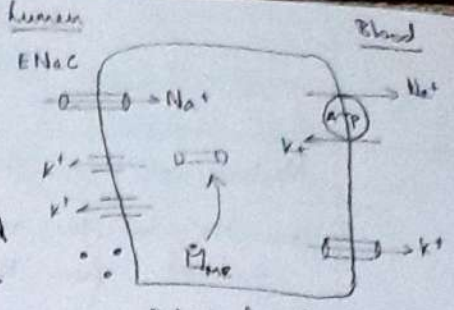
Late distal collecting tubule

There are two type of cells in these tubules – Principal cells and Intercalated cells.

PC & cortical collecting are main target for aldosterone which increases Na^+ permability on luminal side, thus increasing Na^+ reabsorption.



Epithelial Sodium Channel (ENaC) on the luminal side allows Na^+ to be absorbed by epithelial cell



* Aldosterone

Steroidal cortex hormone produced by adrenal cortex. Aldosterone enter PC & stimulates mineralocorticoid ho receptor (MR), which dimerises and activates a transcription pathway.

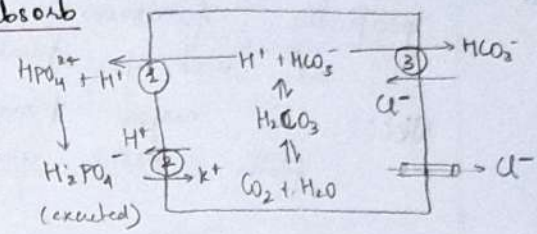
This results in insertion of more ENaC channels on the luminal side of PC.

When hormone signal goes away, ENaC are withdrawn from the membrane.

Intercalated cells (IC)

IC function

They avidly secrete H^+ and reabsorb HCO_3^- and K^+ ions



① Its done through hydrogen ATPase on the luminal side.

② They also have H^+-K^+ ATPase, which is an antiport system on luminal side

③ There's also an Anion Exchanger cell (AEC1) which exchanges HCO_3^- and Cl^-, which allows for absorbing HCO_3^-

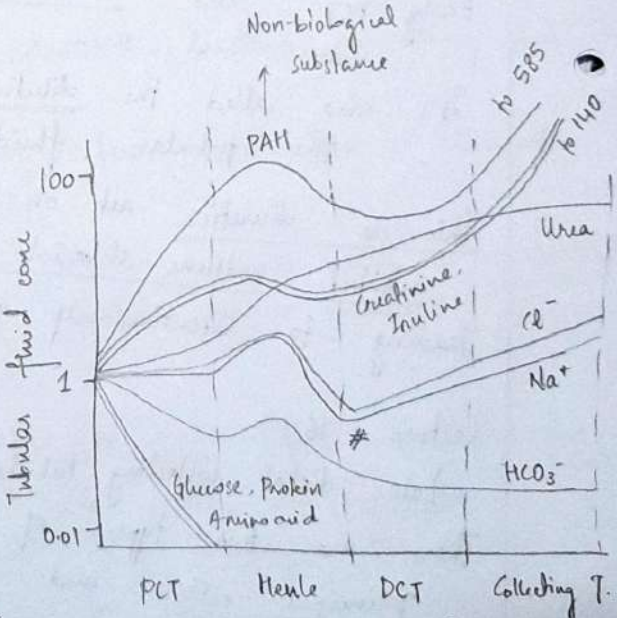
Medullary collecting duct

Final stage of reabsorption.

a) Permeability to water is controlled by the level of ADH

b) Unlike cortical CT, medullary CT is permeable to urea. Some tubular urea is reabsorbed into the medullary interstitium, which raises osmolality in region & helps in concentrating urine

c) Medullary CT secretes H^+ against a large conc gradient. Plays a key role in regulating acid-base balance



\# Because filtrate enters ascending limb where Na^+ are reabsorbed and water is also reabsorbed

Hormonal control of Tubular reabsorption

Hormone	Site of Action	Effect: Reabsorption	Effect: Excretion
Aldosterone	Collecting tubule & duct	↑ Na^+, H_2O	↑ K^+
Angiotensin II	PCT, Ascending loop / DCT, CT	↑ Na^+, H_2O	↑ H^+
ADH	DCT, Collecting tubule & duct	↑ H_2O	
Atrial natriuretic peptide	DCT, CT & duct	↓ Na^+	
Parathyroid hormone	PCT, Ascending loop/DCT	↓ PO_4^{3-}	↑ Ca^{2+}

Angiotensin II increases Na^+ & H_2O reabsorption

It is produced where there's low BP and it helps ultimately increase BP. It has 3 main effects —

1. It stimulates aldosterone production in adrenal cortex
2. Constricts efferent arteriole, which decreases BP in peritubular capillary (lesser than 12 mm Hg) and also increases filtration fraction in glomerulus (which increases conc of proteins & solutes osmotic pressure in the capillaries). Together, this increases reabsorptive force & hence reabsorption of H_2O & Na^+
3. It directly stimulates Na^+ reabsorption in PCT, loop of Henle, DCT and collecting tubules. It directly stimulates $Na^+ - K^+$ ATPase pump on basal side. It also stimulates (NHE) $Na^+ - H^+$ exchanger on the luminal side, especially in PCT. Also stimulates $Na^+ - HCO_3^-$ co-transporter on basal side

\# The Angiotensin II receptors are on both (luminal & basal) sides

Na^+ reabsorption : PCT - 67%
Thick asc. limb - 25%
DCT - 5%
CT - 3%

excretion : < 1%

Lecture 18

28/2/22

Regulation of Extracellular fluid osmolarity & Na^+ conc

Kidneys also maintain osmolarity of fluids in the body.
They excrete excess water by forming a dilute urine.

Osmolality of blood : 300 mOsm/L

When there's excess water, kidneys can excrete urine of 50 mOsm/L and when there's deficit of water, urine extracted can be ~ 1200 - 1400 mOsm/L

The ascending limb of Henle's loop and DCT, the urine is diluted by reabsorbing NaCl.

Concentrating urine beyond body fluid becomes very important for terrestrial animals in order to conserve water

Kidney manages to excrete large amounts of excess water by reabsorbing solutes while failing to reabsorb water in DCT and collecting tubule

Regulation of urine formation in kidney allows maintainance of homeostasis of body fluid osmolality.

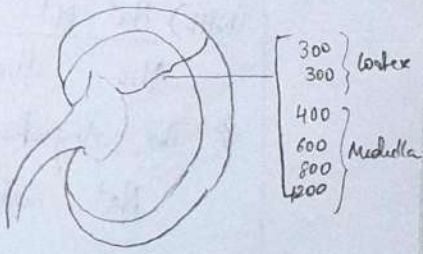
Min volume of urine excretion for human : 500ml but this has to be replaced by diet.

Extreme example : Australian hopping mouse - 10,000 mOsm/L urine
Beaver - 500 mOsm/L

Osmotic gradient in Renal medulla

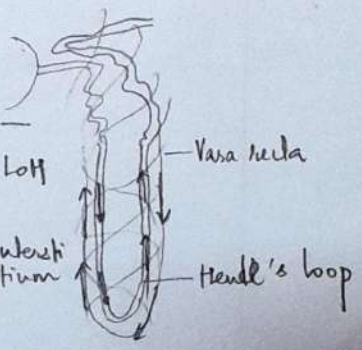
There are 2 types of nephrons - cortical (80%) and juxtamedullary (15-20%) nephrons

The Henle's loop and vasa recta of JXM nephrons goes deep into the medulla & countercurrent mechanism helps concentrate the urine



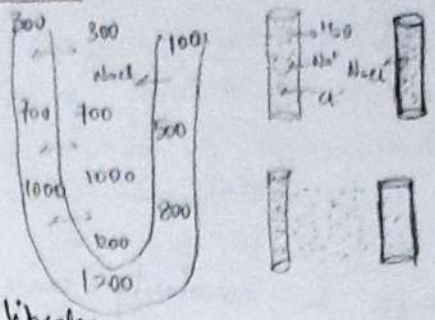
Factors that build up solute conc. in renal medulla —

1. Active transport of Na^+ & other ions from a) TAL of LoH and b) Collecting duct
2. Facilitated diffusion of urea from CD → medullary interstitium
3. Diffusion of only small amounts of water



Countercurrent exchange preserves hyperosmolarity of Renal medulla
1) Medullary blood flow is low – minimizes solute loss
2) Vasa recta serve as counter-current exchangers – minimizing washout of solutes.

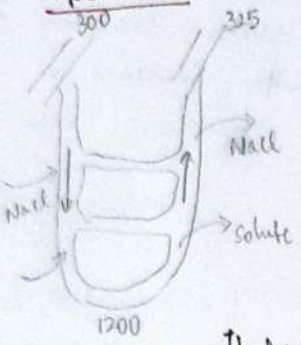
Single effect in loop of Henle



Thick walls in ascending limb are impermeable to water

Active transport of Na^+, $NaCl$ out of Asc. limb dilutes the fluid in Asc limb whereas it increases (as it equilibrates with EC fluid and) in Descending limb.

Single effect: Difference in osmotic pressure & NaCl conc. b/w Asc. limb & (adjacent interstitial fluid and desc. limb fluid)



Vasa recta is highly permeable to water and solutes. So the osmolality of blood varies with that of interstitial fluid. So, when blood leaves through vein, the osmolality is about the same – it has to be.

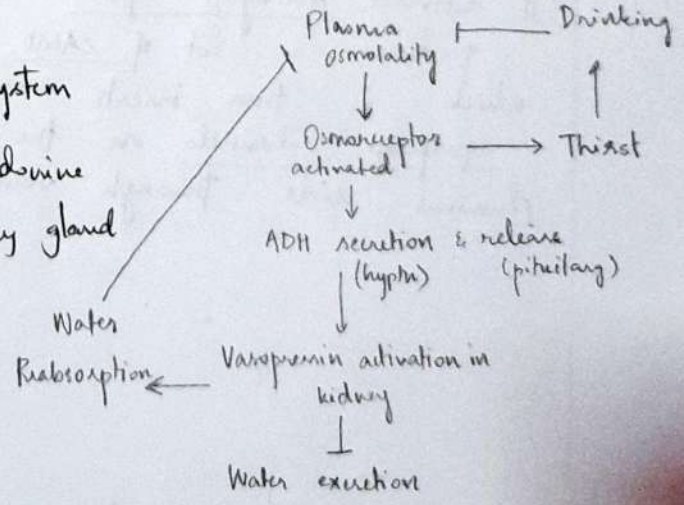
That's why fluid in loop of Henle needs to be first concentrated and then diluted

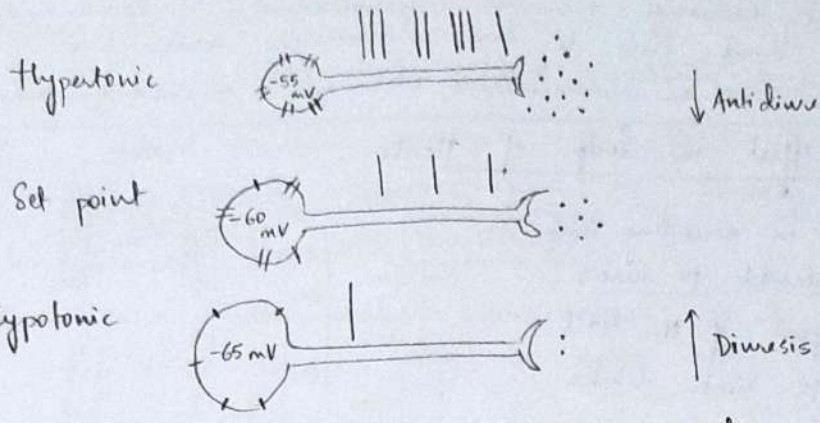
The cells in medulla also have osmolality of ~1200 (same as ECF)
They have high intracellular conc. of organic osmolytes of metabolic origin such as polyhydric alcohols and methylamines. This balances the high NaCl conc in the ECF

Osmoreceptor - ADH feedback system

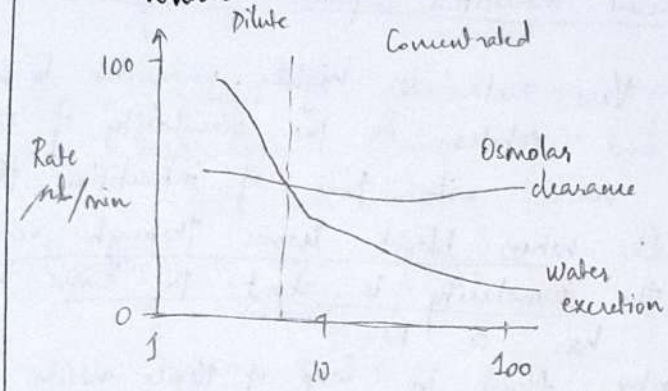
ADH / Vasopressin is a neuroendocrine hormone released by pituitary gland

Osmoreceptors are present in the hypothalamus





Changes in osmolarity cause inverse changes in cell volume. Shrinkage activates non-selective cation channels (NSCCs) which depolarizes the cell and increases firing rate, which increases the release of vasopressin.



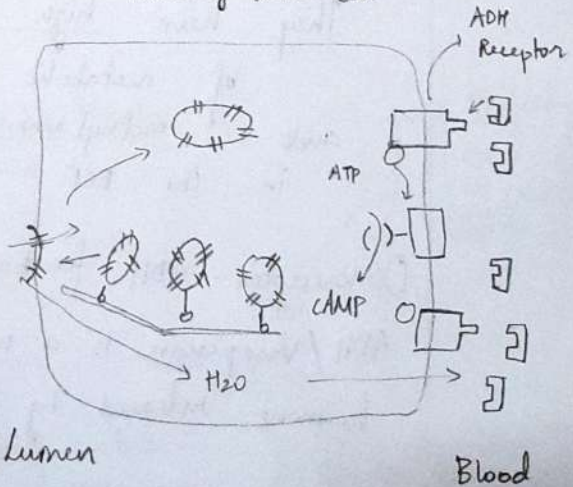
Water excretion decreases with increase in vasopressin.

This is achieved by regulating aquaporin channels in the collecting duct.

Hydrated — no aquaporins

Dehydrated — active aquaporins

Vasopressin binds to its receptor on CT cells, which is a GPCR. It activates Adenylyl cyclase which produces a lot of cAMP, which in turn inserts more aquaporin channels on the luminal side through vesicles.



Urea transport in the kidney

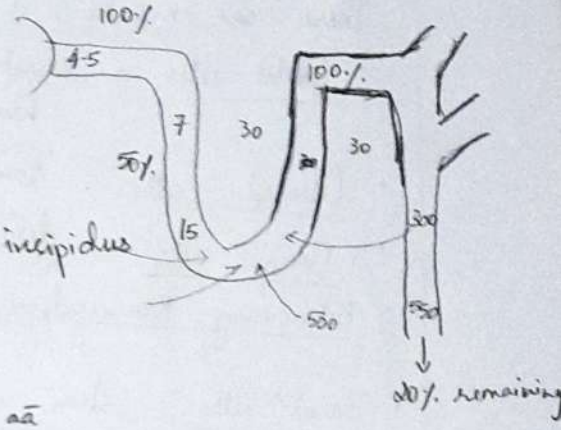
Out of 50 g urea filtered, 25-40 g are excreted.

Reabsorption (PCT, CT) and active secretion (Henle loop) leads to urea circulation b/w lumen of nephron and medulla, which is important for urine concentration.

Urea level is high in DCT, but it is absorbed in CT to reabsorb water as well

DCT walls are not permeable to urea.

Slides at the last.



No ADH production: central diabetes incipidus

Desmopressin : vasopressin-like

Atrial Natriuretic peptide (ANP) – 28 aa

secreted by heart muscle cells (atria)

powerful vasodilator

ANP reduces water & NaCl, thereby decreasing blood volume

ANP inhibits ENaC – antagonistically to Aldosterone

Lecture 19 2/3/22

Physiology of Respiration

Right and left ventricle pump the same amount of blood into the pulmonary as well as systemic circulation.

Pulmonary blood vessels are larger, and have thinner & more elastic walls.

Lungs

The airway branches 23 times from trachea to the alveoli.

Lining of lungs / airway -

There are mainly 5 types of cells -

- Goblet cells : secrete mucus which keeps the lining moist and humidifies inhaled air
- Ciliated cells : transports particulate matter to pharynx & oesophagus
- Clara cells : detoxify harmful substances
- Pulmonary Neuroendocrine (PNE) cells : sensitive to O_2, CO_2, air pressure, H^+ ions etc.
- Basal cells : stem cells which differentiate into other cells.

Respiratory pathway

The trachea is supported by horseshoe shaped cartilaginous ring, which allows trachea to change its diameter.

Cartilage ring becomes smaller along with trachea

Walls of pathways contain smooth muscles, they are innervated by SNS and PsNS. β-adrenergic receptors on smooth muscles (SNS) are stimulated by epinephrine (released by adrenal medulla) and this dilates the airways.

PsNS releases Ach which activates muscarinic receptors, which leads to contraction and constriction of airways.

The terminal bronchioles end in sac-like structures called alveoli. Its where gas exchange occurs. The lumen of alvedic are interconnected so that air pressure is maintained.

300 million alveoli - 40 m² of exchange area

Anatomical dead space - all the airways where gas exchange doesn't take place

With every inhalation, lungs & every alveolus expand.

Alveoli

It has type I cells - which form the alveolar wall

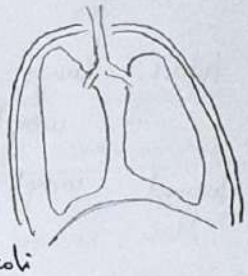
type II cells - 10% of cells which secrete surfactant.

There are also phagocytic macrophages which phagocytose debris

Histology of alveolus - sac + alveolar duct.

Movement of Air in and out of lungs

Lungs are essentially floating in the thoracic cavity. They are like balloons, they collapse when there's no force keeping them inflated.



Ventricular flow is driven by ΔP between alveoli and the atmosphere.

Contraction of diaphragm, external intercostal muscles and lifting up of clavicle increases volume of thoracic cavity by 20%, which decreases pressure during inspiration

20% increase in volume.

Expiration results from passive elastic recoil of the lungs

Phrenic innervation of diagram

Spinal nerves from cervical vertebrae (C3, C4, C5) combine and form the right and left phrenic nerves.

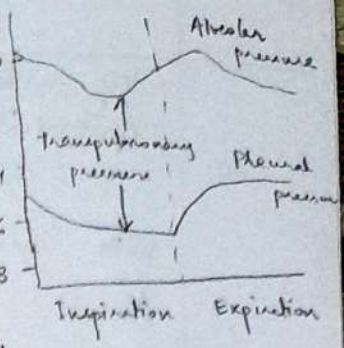
They carry rhythmic pulses from the medulla to the diaphragm.

Transection above C3 is fatal, but below C5 is not fatal because innervations to diaphragm remain intact.

External intercostal muscles are innervated by intercostal nerves from thoracic segment

Thoracic cavity

The lungs are covered by visceral (inner) and parietal (outer) pleura, with a cavity between the 2 layers that is filled with lymph. The pressure in this cavity is substantially negative - lymph is sucked out?



When we inhale (because of increase in volume) the pressure in the lung decreases & it increases during exhalation.

When pleural pressure shifts from -5 to -7.5 cm H_2O, the lungs should take in 500 ml of air.

Compliance of lungs - extent to which lungs will expand for each unit increase in transpulmonary pressure.

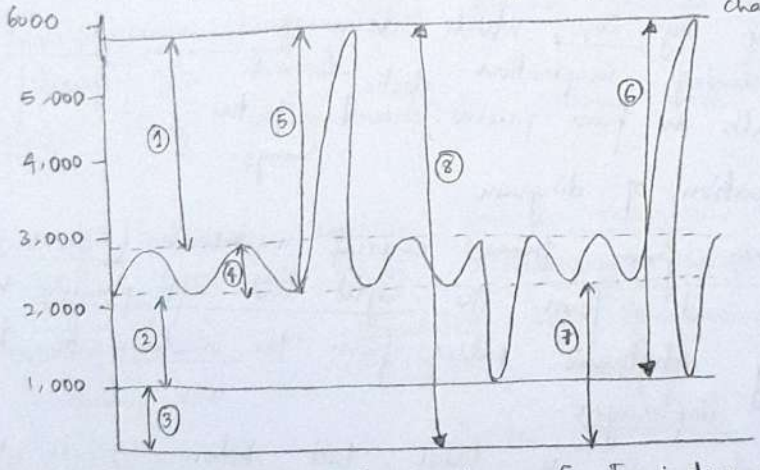
When lungs are infected, fibroblasts multiply & covers lung surface. So compliance of lungs decreases.

Normal compliance : 200 ml per 1 cm H_2O of transpulmonary pressure

More energy is required to breath

Spirometry - Recording changes in pulmonary volume and capacities

The volume movement of air in and out of lungs can be measured using spirometer (drum inverted over a chamber of water & counter balanced by a weight)



1. Inspiratory Reserve volume (~3500 ml)
2. Expiratory Reserve volume (~1200 ml)
3. Residual volume (1000 ml)
4. Tidal volume (500 ml)
5. Inspiratory capacity
6. Vital capacity (~4800 ml)
7. Functional residual capacity
8. Total lung capacity

Vital capacity can be used to differentiate lung diseases

Volume of alveolar air replaced by new air with each breath is only 1/7th of the total, so multiple breaths are required to exchange alveolar air.

This is because atm. air temperature could be very different and its not a good idea for alveoli to come in contact directly with really warm/cold air.

Functional residual capacity is 2300 ml, but only 350 ml of new air comes into alveoli with each breath.

Slow replacement of air also prevents any sudden changes in gas concentrations in blood

In terminal bronchioles, air not flows through convection, but in the alveoli, it diffuses through motionless air

Surface tension and Alveoli

Water has some surface tension – even in alveoli, water is trying to contract. This attempts to force the air out of alveoli and collapse. Net effect causes an elastic contractile force of the entire lungs, called surface tension elastic force

Surfactant greatly reduces ST of water. Surfactants are secreted by type II epithelial cells. Surfactants are a complex mixture of phospholipids, proteins & ions. This reduces ST to 1/12th to 1/2th of original ST

It is important at birth. In fetus, (inside womb), lungs remain collapsed. After birth they expand, & surfactants keep them from collapsing. When babies are born premature, they wouldn't have produced enough surfactant. Surfactant therapy reduces child mortality.

Lecture 20

3/2/22

Salbutamol – stimulates β-adrenergic receptors and relaxes bronchioles

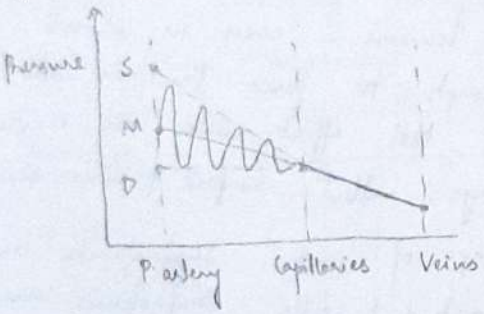
Pulmonary circulation

Pulmonary arteries are short, but have larger diameter. Their wall thickness is 1/3rd that of aorta. They are distensible and have large compliance

Blood volume that goes into lungs is 450 ml i.e. 9% of blood

Right ventricle pumps blood to pulmonary arteries (pressure: 24/9)
In capillaries of lungs, pressure is 10 mmHg & then the blood is brought back to left auricle

Pressure in systemic capillaries is 30 mmHg, twice that of pulmonary capillaries. Because of this pressure, some amount of fluid leaks out of the capillaries. But too much fluid shouldn't leak out – this will drown the lungs by seeping into the alveoli. So, the pressure is maintained at 10 mmHg.



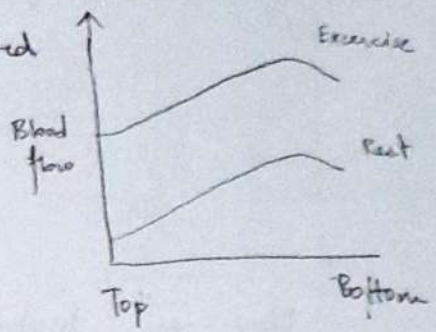
Effect of diminished alveolar oxygen on local alveolar blood flow

When alveoli detect lower than normal O_2 levels, the adjacent capillaries constrict (as opposed to systemic capillaries which dilate). This increases resistance to blood flow. If some alveoli are poorly ventilated, then it's better to redirect bloodflow to alveoli that are better aerated.

Some compound (vasoconstrictor) is released from local lung tissue – not well known.

Blood flow to different parts of lung

Because of gravity, more air is circulated at the lower part of lungs than top part. So blood flow to top of lungs is lesser that flow to lower part.



When left ventricle can't pump the blood well, blood stagnates at the left auricle and in the pulmonary veins. This increases blood pressure in the pulmonary capillaries, which is dangerous. Also, this increases pressure on the ~~left~~ right ventricle - increased load on left heart

Lymphatic system in the lungs

You need an efficient lymphatic system around every alveoli which drains excess fluid and doesn't let it accumulate

The lymph nodes are maintained at negative pressure

~ 26 min

Lymphatics are also present near the pleura.

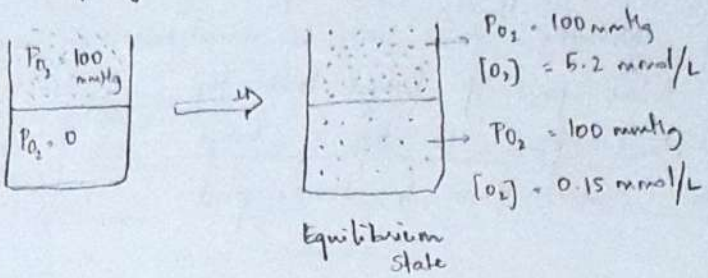
↳ With every heart beat, this helps push the lymph towards the heart

Negative force is always required on the outside of lungs to keep them expanded. This negative force is provided by pleural space, which is caused by pumping of fluid from pleura to lymphatics. Pleural fluid should be at minimum -4 mmHg, lymphatics are at -6-7 mmHg, so that extra fluid is 'sucked out' and the lungs don't accumulate any fluid

Physical principles of gas exchange : Diffusion

Gases are exchanged through diffusion.

Behaviours of gases in solution



When gas dissolves in fluid, pressure equilibrium is reached, which is not the same as conc. equilibrium

Partial pressure = $\frac{\text{Conc of dissolved gas}}{\text{Solubility coefficient}}$: Henry's Law

Pressure difference causes net diffusion of gases through fluids

Diffusion coefficient

Factors (other than ΔP) that affect diffusion —

1) Solubility of gas in fluid
2) Cross-sectional area of fluid (capillary diameter)
3) Distance through which gas must diffuse
4) Molecular weight of gas } constant
5) Temperature of fluid

We consider diffusion coefficient of O_2 is 1. Relative diffusion coefficients

CO_2	20.3
CO	0.81
N_2	0.53
He	0.95

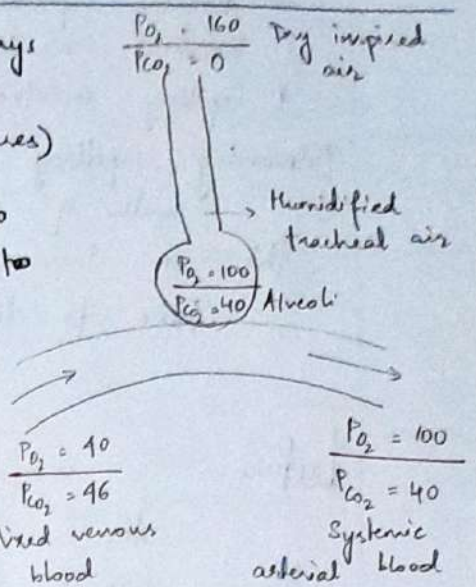
Total pressure of air at sea level - 760 mmHg

Partial pressure of O_2 - 160 mmHg, N_2 - 600 mmHg } in the air

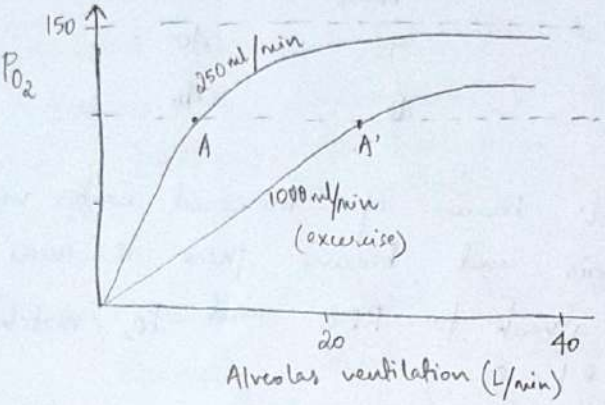
The partial pressure of O_2 and CO_2 changes as air enters the lungs, and later the capillaries.

The P_{O_2} in tracheal & bronchial airways is lesser because the air is humidified (conc. of water vapour increases)

Cell membranes are completely permeable to passage of O_2 & CO_2. Gases have to cross two cell membranes & basement membrane to go into RBC / expired



Ventilation



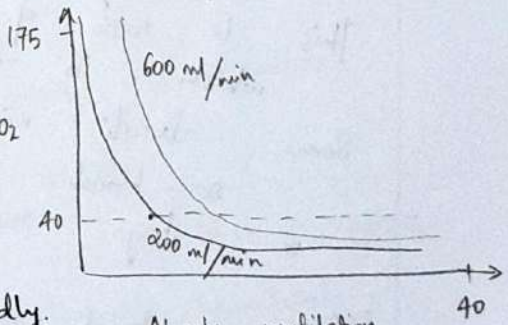
: Effect of alveolar ventilation & rate of O_2 absorption on partial pressure of O_2 in the alveoli.

The curve changes based on O_2 absorption rate.

A : 4.2L of alveolar ventilation A' : ~20 L/min

During exercise, alveolar ventilation should increase by four-fold to maintain the same level of partial pressure in the alveoli.

It's important to maintain partial pressure of gases in alveoli because its important to maintain the pressure difference so that the gaseous exchange occurs rapidly.



Alveoli

300 million alveoli in two lungs, each diameter : 0.2 mm

Capillaries form network in between alveoli.

Collectively, these membranes are called Respiratory / Pulmonary membranes

Respiratory membrane —
1. Fluid lining the alveoli
2. Alveolar epithelium cells
3. Basement membrane (alveolar & capillary)
4. Capillary endothelium cells.

Pulmonary capillary diameter : 5 microns ⇒ RBCs touch the walls of capillaries & must squeeze through them. (diameter – 7 μm)
This too increases the rapidity of diffusion since gases don't have to diffure through a lot of plasma.

21/3/22

Lecture

	Air	Alveoli	Arterial blood	Venous blood
PO_2	159	100	95	40
PCO_2	0.2	40	40	46

P_{O_2} decreases in alveoli because of increased water vapours in humidified air and because there is more CO_2
O_2 diffuses from alveoli to RBC and P_{O_2} matches / balances within 0.1 sec.

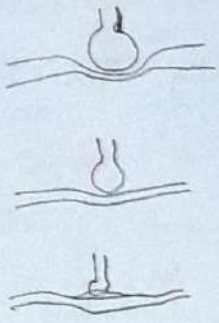
Every hour, we take in 4.2 L of air and during this time, 5 L of blood flows through the lungs.

Ventilation / Perfusion Ratio
This is ratio of ventilation rate (4.2) to perfusion rate (5) which in a normal person is 0.8.
Some alveoli might be impaired in gaseous exchange, so blood flow can be restricted (perfusion rate ↓ s) or stays same.

Pulmonary arterial pressure is normally sufficient to maintain perfusion. If this P or alveolar pressure decreases, then the capillaries will collapse
They collapse when we're blowing air into balloons.

Effect of gravity on ventilation / perfusion

A: alveolar
a: arterial
v: venous



Zone 1 — $P_A > P_a > P_v$ ⇒ capillaries will be compressed reducing blood flow
$P_a < P_A$ due to gravitational effect

Zone 2 — $P_a > P_A > P_v$ — blood flow is driven by $P_a - P_A$, not $P_a - P_v$
$P_{a_3} > P_{a_2} > P_{a_1}$

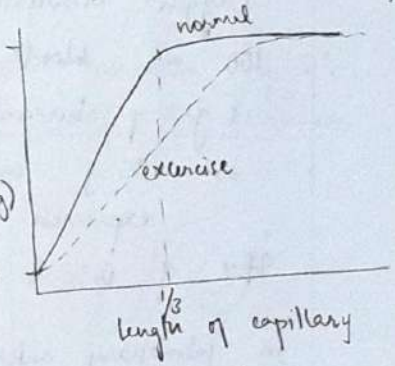
Zone 3 — $P_a > P_v > P_A$
here, gravitational effect has increased P_a and P_v, and blood flow is driven by $P_a - P_v$. In zone 3, capillary flow is highest

Transport of O_2 and CO_2 in blood & tissue

Presence of Haemoglobin in RBC allows them to transport 30-100 times more O_2 than dissolved O_2 in water of blood.

During exercise, blood flow increases ⇒ perfusion rate increases.
Normally, blood is saturated with O_2 when it crosses only 1/3rd of the capillary. This is a safety factor — if alveolar pressure decreases or perfusion rate increases, even then the blood will be saturated. #

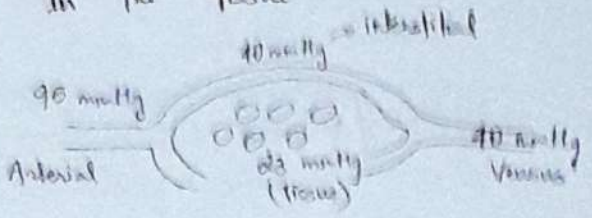
During exercise — Diffusion capacity increases 3X (capillaries ↗)
1) dormant alveoli are opened up to increase surface area of O_2 diff.
2) Better match b/w ventilation and perfusion



O_2 is supplied to lungs (bronchi) through bronchial arteries which branch off from aorta this provides O_2 to cells of lung & the deoxygenated blood goes into vena cava, and some of it (shunt blood) goes into pulmonary vein. This mixture of venous blood decrease P_{O_2} from ~100 mmHg to 95 mmHg

Similar curve when X axis is alveolar ventilation rate

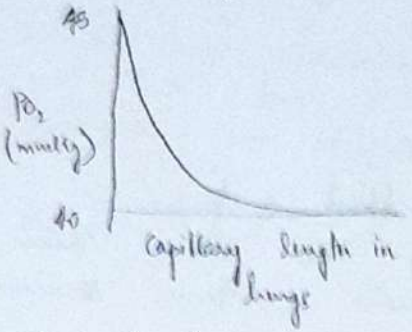
In the tissue

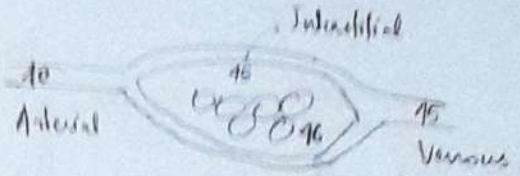


Mitochondria can function at v low P_{O_2} — even 0.5 mmHg !
what about the aerobic bacteria that evolved?

Even in venous blood, P_{O_2} = 40 mmHg. This is also a safety factor

→ Diffusion of O_2





CO_2 dissolves in water better than O_2

* 40 ml of CO_2 dissolves in 100 ml of water. This is important for maintaining the pH of blood. 1 ml of CO_2 is released in the alveoli.

23/2/22

Lecture 22

Oxygen dissociation curve

100 ml blood has 15 g of haemoglobin

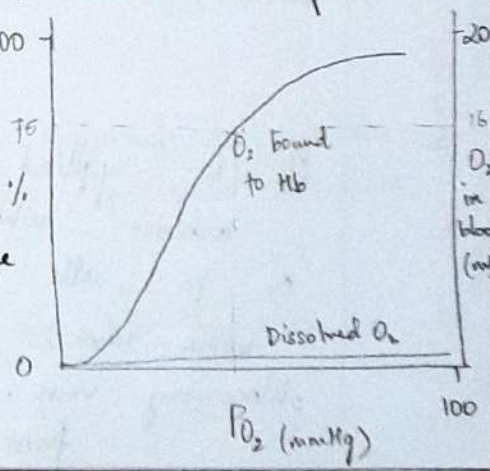
1 g of haemoglobin binds with 1.34 ml of O_2

⇒ 15 g can bind to 20 ml of O_2 — this is expressed as 20 volume per cent.

97% of O_2 is transported in Hb & 3% dissolved in plasma.

In pulmonary arterial blood, P_{O_2} = 40 mmHg, it has 15 ml of O_2 or 75% Hb saturation

⇒ There's a lot of reservoir O_2 in the blood in case the person starts exercising



Even when atm. P_{O_2} decreases, the buffer effect of Hb maintains almost constant tissue P_{O_2}.

If the curve was linear, the decrease in P_{O_2} would cause significant decrease in blood P_{O_2}. This sigmoid O_2 saturation curve is very beneficial.

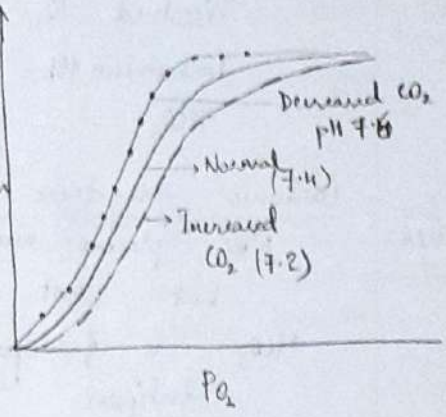
Even during strenuous exercise, the venous blood carries 10 - 15 g% of O_2.

Factors that affect O_2 - Hb dissociation curve.

If CO_2 conc increases, the affinity of Hb to O_2 decreases, so the HbO dissassociates from O_2 in the tissue very quickly.

The converse is true in lungs - Hb binds tightly to O_2 because CO_2 conc is less.

This was discovered by Christian Bohr - so its called Bohr effect.

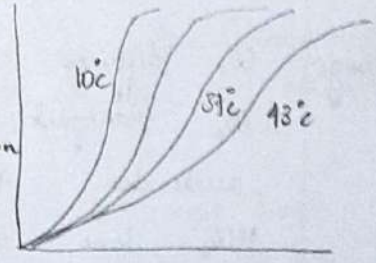


Shift during exercise

During exercise, the temperature of muscle increases by 2°C.

When temperature increases, the affinity of Hb decreases, so it releases more O_2 in the muscles.

When T is low, metabolic activity is low ⇒ less release of O_2 is sufficient



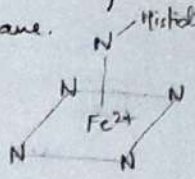
Binding of Hb - O_2

One molecule of Hb can bind to 4 O_2 molecules

There's an Fe ion surrounded by 4 N atoms in the heme ring.

α - 141 aa β - 146 aa

The N atom of Histidine amino acid in the α/β chain binds to Fe^{2+} ion from the top of plane.



When first O_2 molecule binds to Fe ion, the histidine pulls the iron towards the inside. This conformational change increases the O_2 binding affinity of neighbouring heme groups

The affinity of last heme group to O_2 is 300 times more than the affinity of first heme group to bind with O_2. This phenomenon is called Cooperativity.

Hill's coefficient : measure of cooperativity. 1 means no cooperativity or independent binding. Values >1 ⇒ positive cooperativity & values <1 ⇒ negative cooperativity. Hill coefficient of O_2 - Hb is 2.3 - 3.0.

Transport of CO_2 in blood — 4 ml / 100 ml of blood.

Dissolved CO_2 - 7% of CO_2

Carbamino Hb - 23%

HCO_3^- - 70%

In tissues: Carbonic anhydrase is present in RBCs, not the plasma. RBC plasma membrane is permeable to HCO_3^- and CO_2, but not H^+

HCO_3^- is transported out by chloride shift i.e. $HCO_3^- - Cl^-$ antiport system. (anion exchanger)

The proteins in RBCs mop up the H^+ so that pH is not disturbed so much.

O_2 also influences the affinity of Hb to CO_2.

In lungs: CO_2 diffuses from blood to alveoli because of ΔP_{CO_2}.

CO_2 transport is influenced by pO_2. Carbonic anhydrase accelerates $H_2CO_3 \rightarrow H_2O + CO_2$ by ≈5000 times.

HCO_3^- ions are transported into RBC by Reverse chloride shift through bicarbonate - chloride carrier protein.

Haldane effect: When P_{O_2} is ↑ (lungs) · O_2 binds with Hb & makes it a stronger acid - (#3)
1) This displaces CO_2 from carbamino-haemoglobin
2) It also releases H^+ which combines with HCO_3^- ⇌ $H_2O + CO_2$

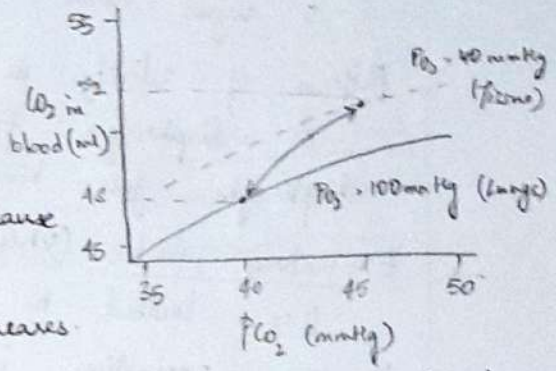
RBCs have a lot of Anion exchangers (glycoprotein)
Arterial blood - 7.4 Venous blood - 7.36.
Lower pH facilitates chloride shift - does this mean higher pH ⇒ reverse chloride? Isn't this the cause and not effect?

Fetal haemoglobin is more efficient than adult haemoglobin because 2,3-DPG is less & can pick up O_2 from mother's Hb within O_2 affinity

CO_2 dissociation curve (Haldane effect)

How O_2 influences: binding of O_2 displaces CO_2 from the Hb.

P_{O_2} varies in the body, and this affects CO_2 dissociation curve



CO_2 binds to Hb in tissue (because low P_{O_2}) and it is displaced in the lungs when P_{O_2} increases

Because the curve has shifted, the blood picks up 4 ml more of CO_2 from tissues.

2,3-diphosphoglycerate (DPG) present in RBCs and binds to deoxygenated Hb and allosterically decrease their affinity to O_2, making them release O_2 near respiring tissue

Lecture 24/3

Control of Ventilation

The P_{O_2} & PCO_2 in the alveolus have to be maintained for proper gaseous exchange, so that gas exchange in tissues is maintained.

So respiratory activity is highly responsive to changes.

To regulate respiration we need sensors for (chemoreceptors) O_2, CO_2 and pH (H^+ ions) in the brain, in medulla oblongata.

Along with chemoreceptors for O_2, CO_2 & H^+ we have mechanoreceptors in lungs and control centers in brain stem which direct the activity respiratory muscles.

Voluntary control from the cerebral cortex can temporarily override the brain stem (eg. breathholding)

Neural control of Respiration

→ **Inspiratory center**

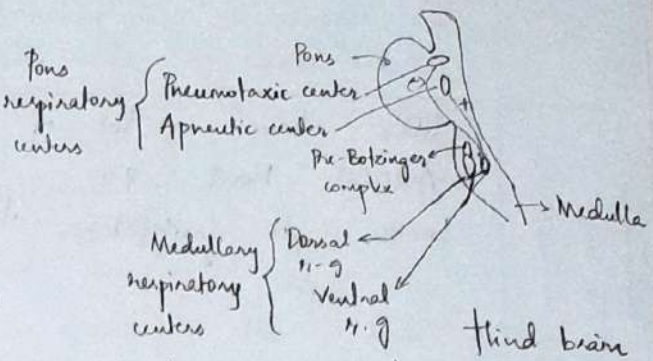
It is located in DRG (dorsal respiratory group) in medulla.

It controls the basic rhythm for breathing by setting the frequency of inspiration.

It sends its motor output to diaphragm via phrenic nerve.

It receives input from chemoreceptors (through glossopharyngeal & vagus nerve in aorta & carotid) and mechanoreceptors in lungs.

Pattern of activity in phrenic nerve – a burst APs, so diaphragm flattens & the quiescence, when diaphragm goes back to its original shape



→ **Expiratory center (VRG)**

It's located in the ventral respiratory group

Usually expiration is passive, so these neurons are inactive when we're sitting / sleeping. They're active during active expiration. They innervate internal intercostal muscles.

→ Apneustic center

It increases the inspiration period. Apneusis is characterised by severly prolonged inspiratory center. inhale?

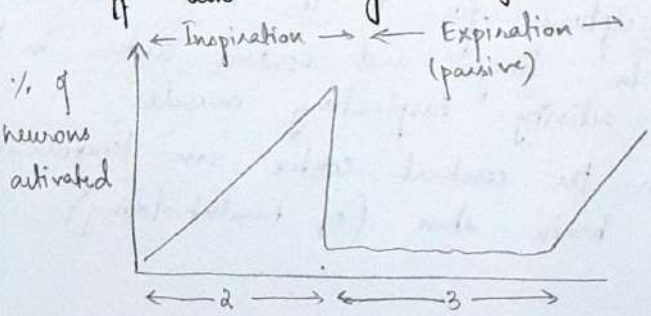
Stimulation of these neurons excites the inspiratory center, prolonging APs in phrenic nerve

→ Pneumotaxic center

It turns off inspiration by inhibiting the inspiratory center (stops APs in phrenic nerve)

It limits tidal volume and regulates breathing rate. (increases)

It acts antagonistically to apneutic center.



Slow activation of neurons allows for us to breathe is slowly & deeply, allowing maximum gas exchange

External intercostal muscles & diaphragm are activated during inspiration & they relax passively during expiration.
Internal i.c. muscles are active during expiration.

→ Pre-Botzinger complex
It controls routine breathing rhythm and also sighs & gasps.
It keeps firing without any inputs — central pattern generator. So it is now believed that this is the point of central regulation of respiration.

Hering-Breuer inflation reflex
This is triggered to prevent over-inflation of lungs.
When mechanoreceptors in lungs are activated by stretch, they send signals to DRG & Apneustic center.

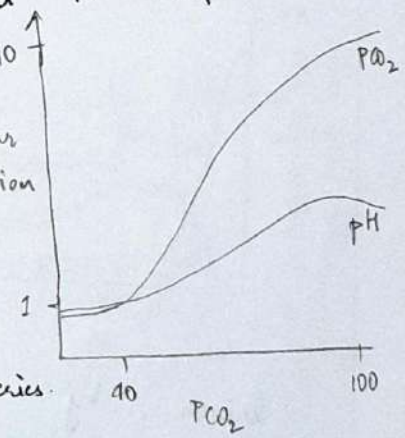
Chemical control of Respiration

CENTRAL
CO_2 concentration mainly regulates respiration rate. O_2 levels don't have direct control.

H^+ & HCO_3^- ions cannot pass the blood brain barrier. CO_2 goes from blood to CSF where

$$H_2O + CO_2 \rightleftharpoons HCO_3^- + H^+$$

This increase in H^+ (or decrease in pH) is detected by chemoreceptors & it is conveyed to DRG
This increases ventilation rate

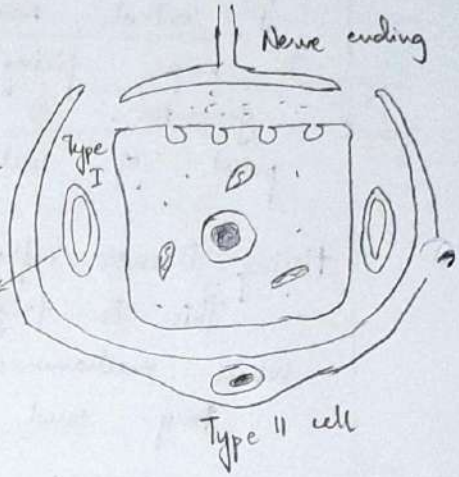


PERIPHERAL: Chemoreceptors detect PO_2 in blood
These chemoreceptors are present in carotid and aortic bodies, which are located on carotid & aortic arteries.

Each of the chemoreceptor bodies receives its own blood supply through a minute artery directly from the trunk. The blood flow through these bodies is 20x the weight of bodies ⇒ percentage of O_2 removed is virtually 0.

These bodies are 2mm in diameter. They transmit info through glossopharyngeal and vagus nerves. They respond to pCO_2, P_{O_2}, & pH.

Structure



Type I : Glomus cell
- sensitive to local changes in O_2, CO_2
- has prominent cytoplasmic granules (DA, NE, ACh, neuropeptides)
- Closely associated with neurons

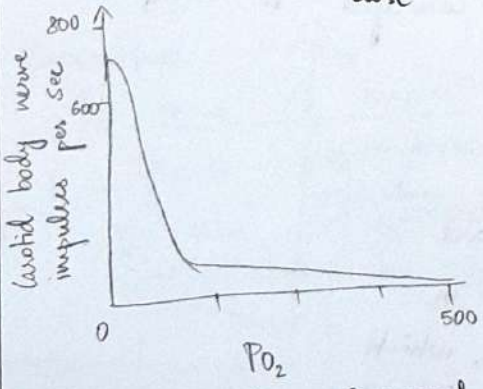
Type II : Sustencular cell
- Interstitial cell wraps around glomus & nerve endings
- function ?

Glomus cells have high metabolic rate & good blood perfusion, so they're sensitive to changes in P_{O_2}, P_{CO_2}

They're derived from neural crest.

They have **O_2-sensitive K^+ channels**

↓ O_2 ⇒ K^+ channels close → membrane depolarises → voltage-gated Ca^{2+} channels open → Neurotransmitters released



When O_2 tone falls below normal, chemoreceptors are strongly stimulated which increases ventilation rate.

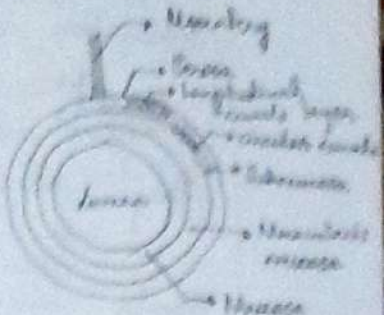
During exercise, P_{O_2}, P_{CO_2} & pH levels remain nearly constant because alveolar ventilation increases, driven by increased O_2 consumption.

Lecture

General principles of Gastro-intestinal function

Anatomy of gastrointestinal wall

The intestine is folded up and held in the peritonial cavity. They are held by mesentery, through which blood vessels and nerves connect to the gut



4 layers —

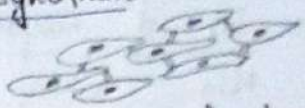
Layers
1. Serosa
2. Outer longitudinal, inner circular muscle layer
3. Submucosa
4. Mucosa

Smooth muscles

No striations because actin-myosin filaments are not arranged as geometrically as in skeletal or cardiac muscle

Its a tapering, spindle-shaped short cell. (200-500 μm in length)

Gastrointestinal muscle wall acts as syncitium — because muscle cells are connected to each other through gap junctions which allows for low-resistance movement of ions from one muscle to another.



Gap junctions are made of protein channels with 6 subunits

On the surface of smooth muscle cells, there are certain depressions called caveoli

Somatic motor reflex

Autonomic motor reflex

In autonomic motor reflex, the motor neuron synapses at the autonomic ganglion, and the post-ganglionic fiber innervates the smooth muscle

Innervation of smooth muscle: the axon ending of post-ganglionic fiber has varicosities (small swellings) which release NTs when stimulated.

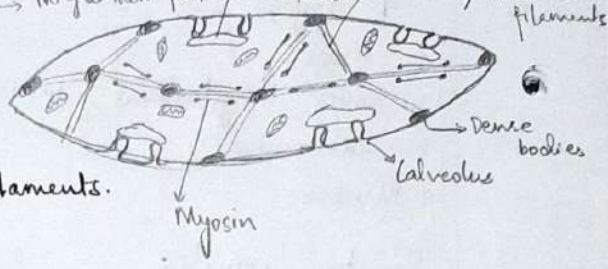
They release many NTs — ACh, bradykinine, dopamine, histamine and others.

Also support visceral function

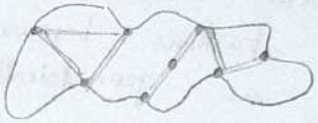
Smooth muscles are found in walls of hollow organs, single-nucleated & they have no large sarcoplasmic reticulum or T-tubules.

Z disks ⇒ Dense bodies are a composition of many proteins that anchor actin filaments, which lie alongside myosin filaments.

→ Alpha-actinin → Actin
Vinculin → integral membrane prot



Caveoli (considered rudimentary structures like T-tubules) are associated with sarcoplasmic reticulum. The caveoli have a lot of receptors for all the NTs — when stimulated, this causes Ca^{2+} release from SR & Ca^{2+} entry from extracellular fluid. The contraction is caused by actin sliding over myosin.



Contracted smooth muscle

→ can produce more force per cross-sectional area

Smooth muscles act at a much longer timescale, but it's tireless. Calcium pump is required for smooth muscles to relax — this pump is slow acting, so smooth muscle remains contracted for several minutes.

They use relatively less ATP because cross-bridge cycling is 1/10th to 1/300th of that of skeletal muscle

Phasic contraction: Alternating contraction & relaxation (skeletal muscle)

Tonic contraction: Continuous contraction in smooth muscles
Eg: Oesophagal valve remains contracted for ~30 mins after eating food

Reverse stress relaxation: Ability to return to its original force of contraction minutes after it has been elongated

Smooth muscles can have 2 types of structures —

1) Single unit : muscle cells are connected by gap junctions, which makes so electrical signals can pass from one cell to another.

2) Multi-unit : No gap junctions b/w cells — each of them can contract independently.
Eg: erector muscles of hair, muscles of iris

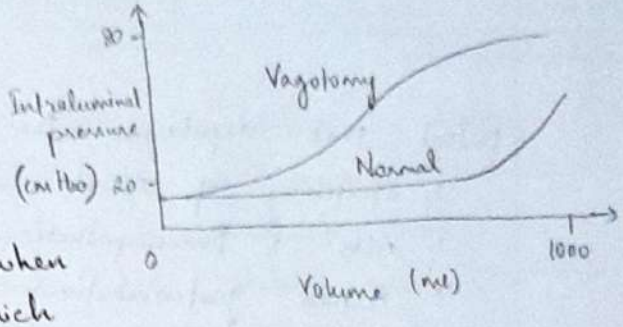
30/3

Lecture

Stress-relaxation of smooth muscle

Under normal conditions, as volume increases, the pressure remains constant

This is because the smooth muscle relaxes when there's increased volume, which maintains the pressure



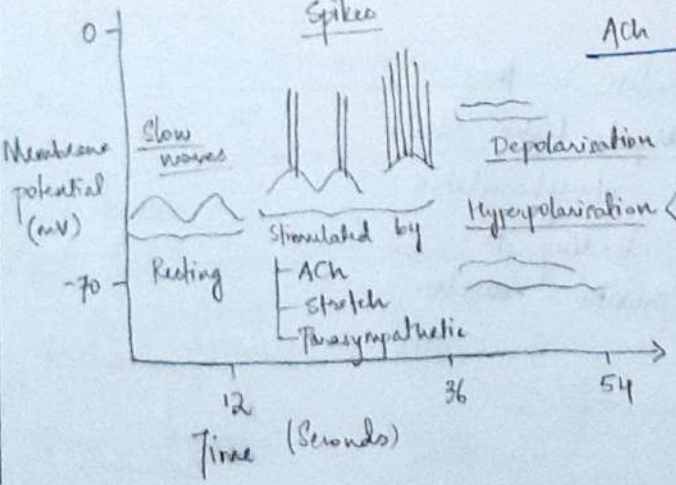
Vagotomy : when vagus nerve is cut, pressure increases when volume increases. i.e. stress relaxation is not happening.

Vagus nerve transmits information about increased load in the stomach to the brain.

Similar stress relaxation also occurs in the urinary bladder

Membrane potential in smooth muscle

* Smooth muscles have muscarinic ACh receptors which excites them, and triggers APs / spikes



* Slow waves cause gastrointestinal contractions to occur rhythmically

Δp : 5-15 mV f : 3-12 /min

Spike potentials

They are triggered when V_m > -40mV — they last 10 - 20 ms, very long compared to skeletal muscle / nerve

In unitary smooth muscles, APs are similar to skeletal muscles. Spikes last few ms, but there are also APs with plateau which lasts for seconds

Ion channels in smooth muscle.

Smooth muscles have more voltage gated Ca^{++} channels than Na^+ channels — this results in prolonged AP

When smooth muscle is stretched sufficiently, spontaneous APs are generated, which makes it contract

Factors that depolarize the membrane —

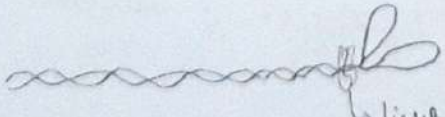
1. Stretching of muscle
2. ACh & Parasympathetic nerves that secrete ACh
3. Certain gastrointestinal hormones

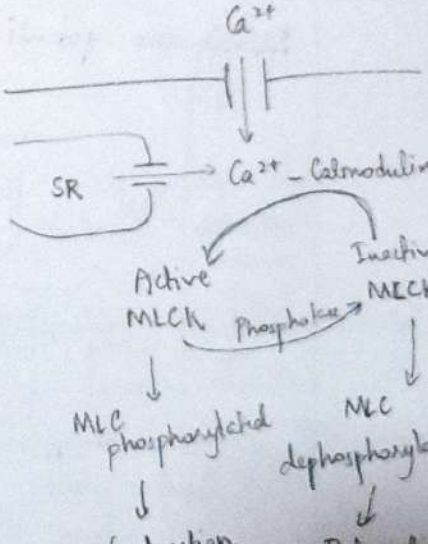
Norepinephrine & Sympathetic NS inhibits smooth muscles. They inhibit by closing Na^+ & Ca^{2+} channels, which prevents depolarisation.

Blood flow in capillaries is regulated by pre-capillary sphincters and upstream arteriole smooth muscles. The tissues release adenosine / NO / excess CO_2 or H^+, lactate which act as vasodilators to relax smooth muscles upstream so that blood flow to the tissue is increased

Contraction

Ca^{2+} binds to calmodulin & the complex activates Myosin Light Chain Kinase (MLCK). MLCK phosphorylates myosin light chains, leading to contraction of smooth muscle.



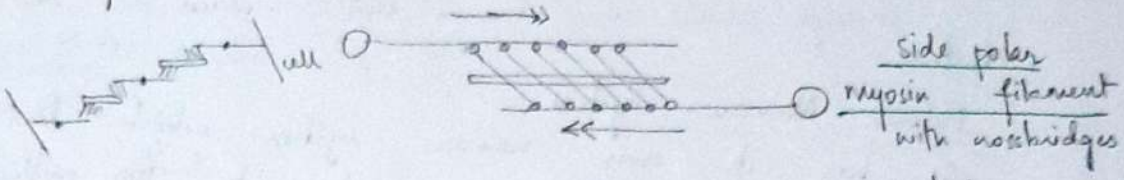


Dephosphorylation happens through MLC phosphatase

In skeletal muscles, tension can be maintained only if cross-bridges continuously bind & unbind, using ATP for each cycle

Smooth muscle doesn't have troponin, so calmodulin regulates contraction.

Ach stimulates muscarinic receptor, which is a GPCR. It activates a membrane protein Phospho C, which converts PIP2 to IP3. IP3 stimulates Ca^{2+} release from sarcoplasmic reticulum.



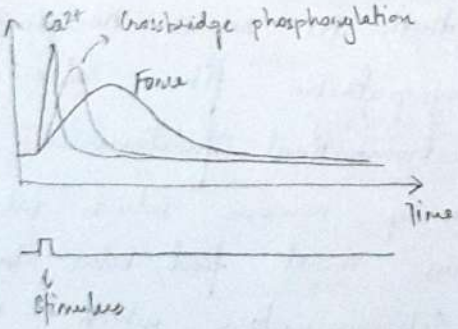
In smooth muscles, there's side-polar filament sliding — same myosin pulls opposite actin in opposite directions. This allows smooth muscles to contract from 100 to 300, as compared to skeletal muscle (100 – 80).

Smooth muscles respond to vasodilators — excess CO_2, H^+, NO

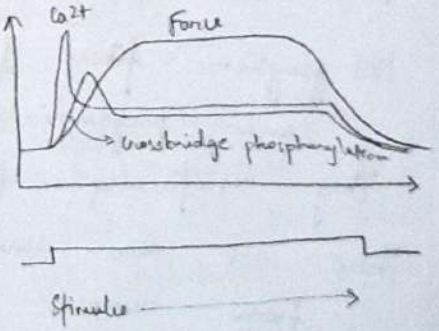
Some smooth muscles can stay contracted for long period of time without expending energy.

The rate of cross-bridge cycling drops radically when contraction is prolonged — this is called latch formation. This reduces energy expenditure to minimal levels.

Phasic contraction



Tonic contraction (latch contraction)



In tonic contraction, muscle goes to latch state i.e. cross bridges remain phosphorylated. Possibly by reducing the activity of both MLCK & MLCP, which slows down cross-bridge cycling rate

Stress relaxation — latching decreases.

Innervation of GI tract

It is innervated by autonomic nervous system extrinsically.

- Peristalsis and release of gastric juices is broadly under the excitatory control of parasympathetic NS which comes from Medulla Oblongata & Sacral nerves. It releases Ach.
- Sympathetic NS comes from thoraco-lumbar region (T5 - L2) There nerves release norepinephrine — which inhibits — 1) smooth muscles directly 2) (major extent) enteric nervous system — which can stop all gastric activity/movements 31/5

Lecture

Enteric Nervous System

GI has its own nervous system which lies entirely in the wall of the gut with 100 million neurons (about the same as spinal cord).

It controls gastrointestinal movements and secretion.

Its composed of two plexuses —

1. Myenteric or Auerbach's plexus — outer plexus present b/w longitudinal & circular muscle layers. very important for peristalsis (leads to increased tonic contraction, increased rate and intensity of rhythmic contractions
2. Submucosal or Meissner's plexus — inner plexus in the submucosa which controls secretions. local blood flow and finer movements of GI tract.

These two plexuses are innervated by Autonomous NS.

Post-ganglionic fibers of Sympathetic NS release norepinephrine and preganglionic Parasympathetic fibers release Ach.

They significantly affect gastrointestinal functions.

There are also some sensory neurons which take info from mucosa to brain about food/bolus in the intestine.

They could be mechano/chemoreceptors which send information over the Vagus nerve, to spinal cord & prevertebral SNS ganglia

Peristalsis : occurs by alternate contraction of circular and longitudinal muscles along the length.

Various neurons in myenteric plexus (Substance, Enkephalin, Calbindin etc) release - 12 different NTs

Saliva – keeps mouth moist, dissolves food components → taste
α-amylase – starch digestion
IgA & lysozyme – part of immune defence system

(73)

Secretory functions of Alimentary Canal

Two types of secretions along the GI tract –
- digestive enzyme
- mucous secretion – for lubrication, protection of parts of inner wall (prevents contact with food), buffering pH, makes fecal particles stick (glycoproteins) to one another

It is present everywhere – can be thick/dense in some places.
Mucus secreted by goblet cells.

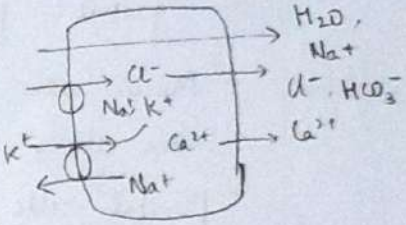
Dehydration → ↓ saliva secretion → makes mouth dry → thirst

Salivary glands

3 pairs – Parotid, Sublingual, Submandibular
Produces saliva of particular pH with α-amylase.
Saliva is secreted by salivary gland acini. It happens in two steps –

Rate: 0.1 – 4 ml/min

1. Acini secretes primary saliva similar in composition to plasma



There's steady leakage of K^+, Na^+

Transcellular Cl^- secretion: Cl^- is actively taken up into cell through NKCC channel
Cl^- along with HCO_3^- is co-transported into the lumen.
Lumen-negative transepithelial potential (LNTP) drives paracellular Na^+ transport. This is now 281 mM

2. Ductal cells reabsorb a lot of NaCl from the primary secretion, so that osmolality of saliva is ~ 100 mOsm, so that salt-taste buds remain sensitive and are not habituated to ↑ saltyness

NE – triggers viscous saliva w/ ↑ mucin
ACh – watery saliva, increased enzyme

Stimulation of saliva secretion
Salivant stimuli – smell, taste, mastication etc
Stimuli goes to hypothalamus & the salivary center, which stimulates salivary glands to secrete more saliva

Neurons release ACh. With aid of muscarinic cholinoreceptors & IP3, ACh increases intracellular / cytosolic Ca^{2+} conc.

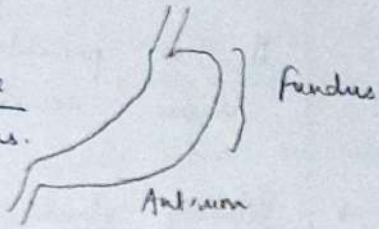
This increases increases luminal ion conduction, resulting in watery saliva with increased salivary enzymes.

Also causes contraction of smooth muscles, which leads to emptying of the acini

Stomach

It is thrown into folds called Rugae

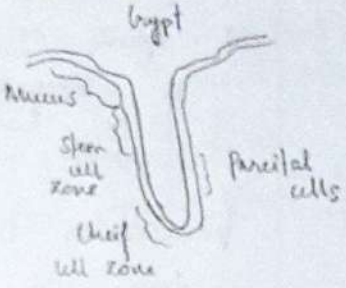
Bound by oesophagal & pyloric sphincters.



In the wall of muscle, between submucosa and circular muscle layer, there's a layer of oblique muscles.

In the mucosa, there are long tunnels, also called gastric pits, which have gastric glands

- Mucus cells
- Stem cell zone : to replace lost cells
- Parietal cells : produce HCl
- Chief cell : secrete pepsinogen.

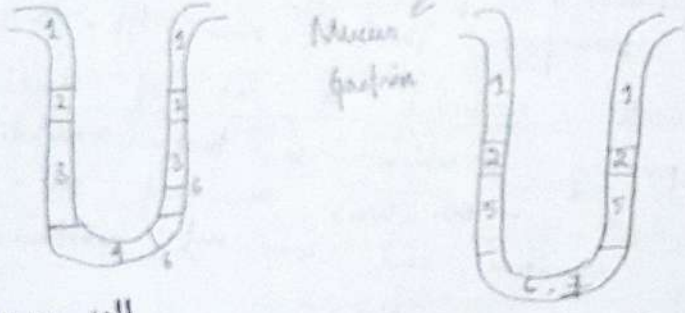


Oxyntic gland (Fundus)

HCl
Pepsinogen
IF
Mucus

Pyloric / Antral gland (Antrum)

Mucus
Gastrin



1. Mucus cell
2. Stem cell
3. Parietal cell
4. Chief cells
5. G cells - produce Gastrin - peptide hormone
6. ECL cell - secrete histamine - paracrine* signalling molecule
7. D cells - Somatostatin inhibiting hormone

* histamine locally signals parietal cell to secrete more HCl

(?) ECL : enterochromaffin

Chloride shift?

Parietal cells also secrete Intrinsic factor → important for B12

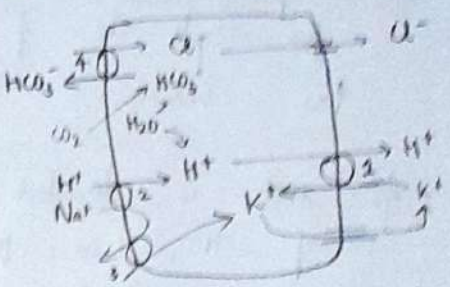
Near the pyloric sphincter, there are a lot of mucus cells

$H^+ - K^+$ ATPase in Apical side of parietal cells

It secretes H^+ into the lumen & takes in K^+ using ATP.

Refer to the diagram –

1. $H^+ - K^+$ ATPase
2. $H^+ - Na^+$
3. $Na^+ - K^+$ ATPase
4. Anion exchanger



Canaliculi – deep infolding / channel which increases the surface area for secretion. These channels open into the lumen, so HCl is secreted there

1/1/20

Lecture

- For H^+ that goes into lumen, HCO_3^- molecule goes into blood. After food, blood in the stomach has 4-5x more than normal level
- Most common chloride channel is mediated by GABA – γ-amino-butyric acid. One Cl^- ion reaches the lumen for each H^+ ion secreted

CFTR – another type of chloride channel

- Canaliculi have brush border, which increases surface area even more. Tubulovesicles fuse with membranes of canaliculi & increase no. of pumps & channels

Resting

Stimulated

- Parietal cells are stimulated by –

Gastrin, ACh, Histamine

Enterochromaffin cells : secrete histamine in oxyntic glands, to stimulate parietal cells in a paracrine pathway (m/mm)
Rate of secretion of HCl is directly controlled by ECL.
Histamine also stimulates production of gastrin (formed in antral part)
ECL cells are stimulated by 1) ACh 2) Gastrin

Cells of stomach are protected by thick mucus layer, where the pH is ↑, as compared to the middle of the lumen, which is pH 1-2.

As HCl is ~~directed~~ secreted in lumen, there's a rush of HCO_3^- in the associated circulatory blood called Bicarbonate flood

G cells secrete gastrin - it can have 34 or 17 aā
its a polypeptide

Regulation of gastric acid secretion.

1. Mechanical stimulus makes parietal cells in fundus release HCl.
2. This lowers the pH - This chemical stimulus makes G cells secrete gastrin in the antral part
3. Gastrin in turn activates - a) Parietal cell to release HCl
b) ECL cell to release histamine to stimulate ↑ → H_2 receptors
4. Vagus nerve releases ACh which acts on Parietal cell and ECL cells
5. It also releases CGRP (Calcitonin gene related peptide) which stimulates D cells to release SIH (Somatotrophin inhibiting hormone). SIH inhibits G cells and ECL cells.
This prevents secretion of too much HCl.

Why don't our digestive acids corrode our stomach lining? * lipophilic

SciAm article

Pharmacology of antacids

1. H2 Receptor antagonists (Cimetidine) – it blocks H2 receptors on parietal cell, decreasing production of HCl. This was popular till 1990s.

2. Proton pump inhibitors (PPIs - eg. omeprazole) – it inhibits proton pump. When omeprazole enters parietal cell* it gets protonated and activated. Active form binds to gastric proton pump, deactivating it.

Parietal cells also secrete Intrinsic Factor (IF)

IF is a glycoprotein. Two vitamins – B9 (folic acid) and B12 (cobalamin) are essential for nucleic acid synthesis (.. thymidine triphosphate) in the RBC production.

IF binds to Vitamin B12 and protects it from getting digested in the stomach. It's later absorbed in the ileum and transported to liver.

Pernicious anaemia – autoimmune disease where IF is not secreted ⇒ RBC production is inhibited.

Secretion and Activation of Pepsin

Cheif cells secrete inactive pepsinogen – it gets activated when it comes in contact with HCl. It degrades proteins into peptides. – cleaves b/w hydrophobic & aromatic aa.

Regulated by –

1. Stimulation of cheif cells by ACh from Vagus or Enteric NS
2. Stimulation of peptic cell in response to acid in the stomach

Ghrelin – peptide hormone that stimulates food intake & body weight gain – important for energy homeostasis.

When fasting, ghrelin is released by stomach, it goes into blood & triggers centers in hypothalamus which activates foraging behaviours. Ghrelin secretion goes down after feeding.

Lecture 6/4/22

Pancreas

It also made of several acini that secrete pancreatic juice

Cystic duct from gall bladder + Hepatic duct → Bile duct

Bile duct combines with pancreatic duct and ends into the duodenum, controlled by a sphincter

Zymogen granules – also called pro enzyme, it's the inactive precursor of an enzyme. Pancreas secretes zymogens to prevent enzymes from digesting cellular content

Pancreatic digestive enzymes –

Trypsin, chymotrypsin & carboxypolypeptidase – digests peptides

Amylase

Lipases

Activation

Enterokinase is an enzyme associated with small intestine wall that converts trypsinogen to trypsin.

Further, trypsin itself will convert more trypsinogen and chymotrypsinogen to activated enzymes.

Pancreatitis

Inflammation of pancreas occurs when activated proteases start digesting the pancreatic tissue itself.

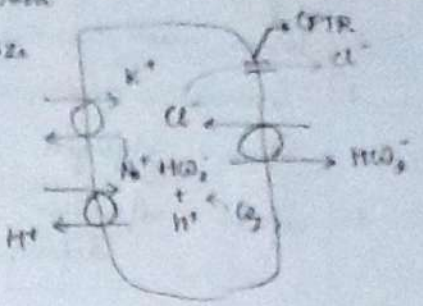
Most common cause is blockage of the hepatopancreatic duct due to gallstones, which blocks the flow of pancreatic juice

Aquaporins

Secretion of HCO_3^- ions into pancreatic juice

5x HCO_3^- ions as that of blood plasma Blood is secreted in pancreatic juice to neutralize HCl. HCO_3^- and water is secreted by epithelial cells of ducts.

Lumen



Cystic fibrosis transmembrane regulator (CFTR) : ion channel that transports Cl^- ions across the membrane

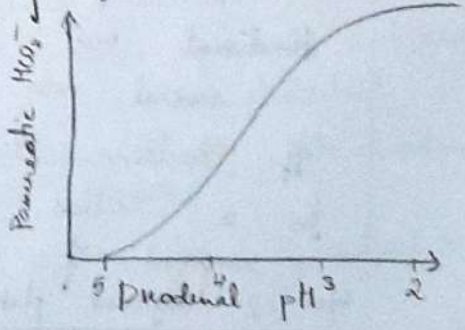
Cystic fibrosis - genetic disorder with a defective in CFTR gene
It causes the body to form unusually thick mucus because Cl^- ions are not going out ⇒ not drawing out water
It can result in serious respiratory & gastrointestinal manifestations.

Control of secretion

When food comes to duodenum, it first recognises the acidity of the chyme. In response, the duodenum epithelial cells secrete two peptide hormones -
1) Secretin 2) CCK (cholecystokinin)
These hormones enter the blood and secretin stimulates secretion and release of a lot of HCO_3^- and CCK activates pancreatic enzymes to be released.

Pancreatic acinar cells are stimulated by secretin, CCK and ACh (postganglionic parasympathetic fibers).

When contents are more acidic, HCO_3^- output is also increased



(5) Lecture 7/4/22

Liver functions

1. Package of fatty acid to be stored & transported
2. Synthesises plasma proteins
3. Forms non-essential amino acids
4. Converts ammonia to urea
5. Stores glycogen & regulates blood glucose homeostasis
6. Stores vitamins, removes iron, degrades hormones and detoxifies substances

Coeliac artery: branch of dorsal aorta that carries blood to the liver. It carries oxygen to hepatic cells

Lymphatics in the digestive system transport lipids & fats. Fatty blood is transported to the liver via lacteal system.

Hepatic portal system: carbohydrates and amino acids absorbed and transported to liver via the hepatic portal system — veins that go from intestine to liver.

This removes blood enters into a capillary network in the liver — is rich in glucose & amino acids, but not in pO_2.

The liver processes this blood, decides what do with the nutrients. It sends the required nutrients into circulation by sending the blood into inferior vena cava.

Liver — largest organ in the body: 1-5 kg in adult

Functional unit: liver lobule — cylindrical structure several mm in length and 0.8 - 2 mm in diameter

It contains 50,000 — 100,000 lobules.

In a section, lobules look like hexagons. Lobule is composed of cellular plates — each plate is 2 cells thick & b/w 2 adjacent plates lie bile canaliculi that empty into bile duct

At every corner of the hexagon lobule, there are 3 blood vessels –

1. Branch of the celiac artery : blood from the artery will flow towards the center of the lobule.
2. Hepatic portal vein from the intestine : blood from here also flows through capillaries towards the center of lobule where the central vein is located.
   Blood from central veins → hepatic vein → vena cava
3. Bile duct : bile secretion from hepatocytes (on opposite side of capillaries) goes into bile ducts, away from the center.

The cells in the lobule are arranged as plates directed radially outwards.

~1000 ml from portal vein & ~300 ml of blood from artery passes through the liver every minute.
This is about 27% of cardiac output.

Liver cirrhosis greatly reduces blood flow in the liver
Fibrosis / cirrhosis is caused by drinking alcohol due to growth of connective tissue.

Biliary Secretion
Bile is secreted in two stages & it helps in emulsification of fats.

1) Initial secretion by principal cells / hepatocytes : main components are bile acids, cholesterol – secreted in bile canaliculi
   Bile acids emulsify fats into minute particles. Bile also serves as a means for excretion of waste products – bilirubin & excess cholesterol
2) Second secretion stage :
   Bile flows into larger ducts & empties directly into duodenum or is stored in the gall bladder
   (It is stimulated by secretin. → there, Na^+ & HCO_3^- are added to the secretion by epithelial cells

Gallbladders have receptors for CCK, which helps in effective emptying of bile by stimulating contraction of wall and relaxation of sphincter of Oddi

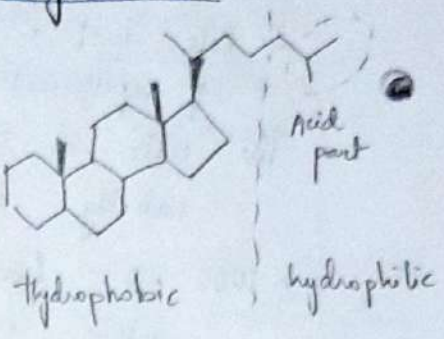
CCK also stimulates cells of pancreas

Main components of bile — water, bile salts, bilirubin, cholesterol and ions

Gall bladder reabsorbs a lot of electrolytes and water to concentrate the bile salts in the bile.

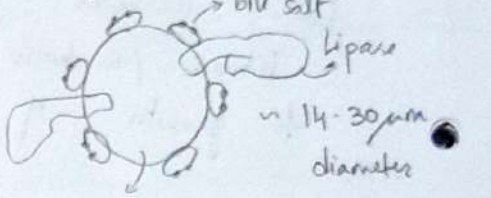
Bile acids — <u>Cholic acid</u> & <u>Chenodeoxycholic acid</u>

They are synthesized by oxidation of cholesterol. They might also be conjugated by aā - glycine, taurine to form bile salts



Liver synthesizes 6g of bile salts

- They have detergent action on fats - breaks them down to minute particles so they can be digested & absorbed
- They aggregate around droplets of lipids ~~and~~ to form <u>micelles</u>.
- These micelles of <u>fatty acids, lipids</u>, & <u>cholesterol</u> are easily absorbed by the small intestine.
- Dispersion into micelles also increases the surface area for lipases to act on
- This also allows for absorption of fat soluble vitamins.



Enterohepatic circulation

Bile salts are also <u>reabsorbed</u> and returned to the liver - <u>2-4 g recirculates</u> <u>6-10 times a day</u>. Only 0.6 g / day is excreted.

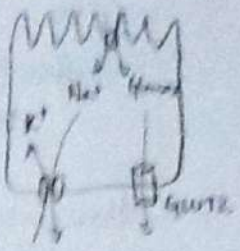
Absorption in small intestine

Nutrients are absorbed through villi & fatty acids through lacteal (lymph ducts).

Absorption of glucose

SGLT - sodium glucose symporter (apical side)

GLUT2 - glucose transporter on basal side



Absorption of amino acids

Proteins are digested by proteases; amino acids are absorbed by active transport into cells, and leave the cell by facilitated diffusion & enter capillary

Absorption of fats

Bile salts emulsify fats and create micelle

Fatty acids & monoglycerides are absorbed and repackaged to form chylomicrons, which are extruded from epithelial cells and enter lymph

M/H

Lecture

Introduction to endocrine physiology

This is another way of communication across the body.

In neurons, this happens over relatively short distance and timescales. Endocrine signalling through hormones occurs over long distances and timescales.

There are also neurosecretory cells - eg. Vasopressin secreted by hypothalamus.

There also exist paracrine and autocrine signalling system

Chemistry Structure and synthesis of hormones

There are 3 classes -

1. Proteins or peptides: anterior & posterior pituitary, pancreas, parathyroid gland & other glands secrete peptide hormones.

2. Steroids: secreted by adrenal gland (cortex) (cortisol & aldosterone), ovaries, testes & placenta (estrogen, progesterone, testosterone) derived from cholesterol

3. Derivatives of tyrosine : adrenal medulla (epinephrine & NE), thyroid gland (thyroxine & triiodothyronine)

Hormones determine cellular target action by binding to specific target receptors. Receptors maybe present on cell surface, cytoplasm or the nucleus.
Protein hormones have receptors on the outside & soluble hormones (steroids) have receptors inside

Hormones are transported through blood. Hormones redistribute rapidly throughout extracellular fluid and are not preferentially directed towards target tissue

Hormone half-life

Amines	2-3 mins
Thyroxine	6.7 days
Polypeptide	1-40 mins
Steroids	1-120 mins

Half-life : time taken for conc. of hormone in blood to reduce to half its conc.

Clearance from blood depends on rapidity with which it can escape to extravascular rate and its rate of degradation.

Half-life is not the same as duration of hormone effect. Hormone response may persist well after the hormonal conc. have returned to basal level.

Protein binding

Peptide hormones travel freely in blood. Steroid & thyroxine circulate in blood along with a carrier protein, generally globulins. This is reversible - so bound & free hormones are in equilibrium

Binding to carrier protein increases the half-life because it reduces chance of degradation or diffusion out of blood stream.

Bound hormone represents a reservoir for hormone and serves to buffer acute changes in hormone conc.

Hormone degradation

Hormones in blood are degraded at a constant rate, and are not subject to regulation.

Peptide hormones are degraded in liver.

Inactivation may also involve changing structure & solubility of hormone, so they can be excreted easily.

Regulation of hormone secretion : Negative feedback

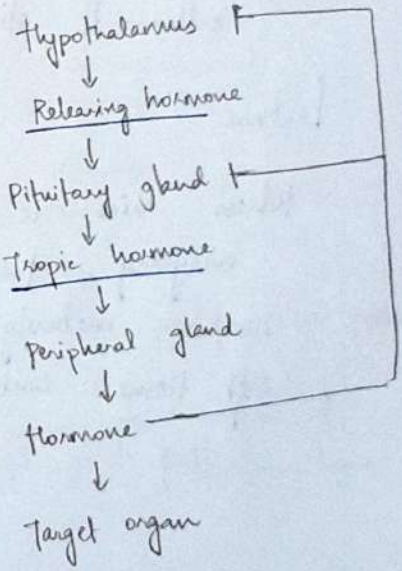
Eg. Fall in glucose levels is detected by α-cells of pancreas, & they release glucagon which acts on liver to release glucose & maintain homeostasis. Higher level of glucose inhibits glucagon

⇒ Hormones produce biological effects that directly or indirectly inhibit their further secretion.

This is Response-driven negative feedback.

The other pathway is endocrine axis driven negative feedback

Hypothalamus (LHRH) & pituitary (LH) secrete hormones to stimulate endocrine glands (testes - testosterone) to release hormones, which in turn blocks / inhibits pituitary, stopping further secretion.



Pituitary Gland

During development, some tissue from roof of mouth breaks off and forms the anterior lobe of pituitary gland — this is site of secretion of several hormones (7H).
The posterior lobe is formed by nervous system & its the site of release of vasopressin.

Secretion of anterior pituitary —

- Thyroid stimulation hormone (TSH) — thyrotropes
- ACTH (Adreno cortico tropic hormone) — corticotropes
- GH (Growth hormone) — Somatotropes
- FSH / LH (follicle stimulating / Leutanising hormones) — gonadotropes
- Prolactin — lactotropes
- MSH in some animals

Hormones released by hypothalamus & carried to pituitary through a capillary system / portal system

Growth hormone

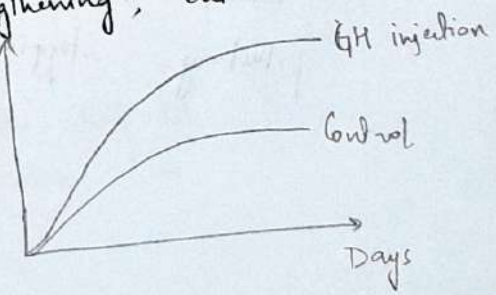
191 amino acids. More than 1/3rd of ~~other~~ cells of AP release & secretes GH. They stimulate growth of all tissues — especially early bone & muscle cells. It stimulates cell growth & cell division.

13/4

Lecture

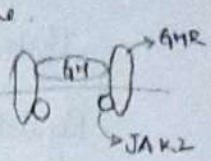
When mice is injected with extra growth hormone everyday, the animal grows much larger. As it reaches maturity, bones stop lengthening, but soft tissues continue to grow.

Half life : 20 mins



GH → GH receptor → Cytosolic Janus Kinase 2 (JAK2) → catalyzes the phosphorylation of receptor & other tyrosine residues

Growth hormone receptors are present everywhere, on all cells. The receptors are like dimers – they are stimulated by GH and further phosphorylate tyrosine.



Metabolic effects

1. Increased rate of protein synthesis
2. Increased metabolication / mobilization of fatty acids
3. Decreased rate of glucose utilization

Its effects are opposite to that of insulin. GH promotes protein synthesizing enzymes and inhibits degrading enzymes.

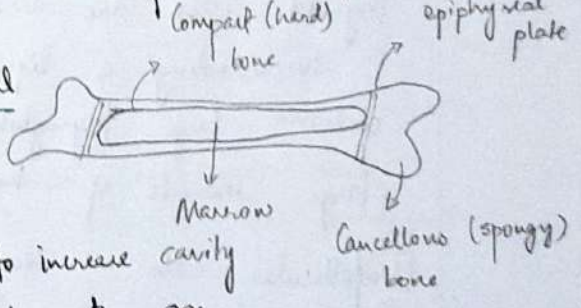
GH also enhances fat utilization for energy from adipocytes – 'ketogenic' effect.

GH decreases the use of carbohydrates.

GH also stimulates secretion of insulin-like growth factor (IGF) in liver and other tissues. Increases lipolysis, protein synthesis & amino acid uptake & decreases glucose use

Somatostatin (secreted by hypothalamus – GHIH) inhibits secretion of GH through -ve feedback loop.

Long bones grow due to epiphyseal plate – they produce cells by mitosis which then ossify.



IGF acts on epiphyseal plate to increase cavity bone growth. As people reach the age of maturity, estradiol inhibits growth by sealing epi plate.

Osteoblasts are cells that deposit new bone on surface of older bone. Simultaneously, osteoclasts digest / dissolve bone. GH strongly stimulates osteoblasts.

GH exerts a lot of its effects through intermediates called 'Somatomedins' or IGF, produced by liver

Pygmies have a congenital inability to synthesize somatomedin C. They have normal level of GH, but no IGF

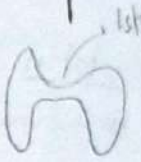
High level of IGF can inhibit pituitary

Regulation of GH secreting cell
The cell has GPCRs for GHRH and somatostatin
It regulates transcription factors

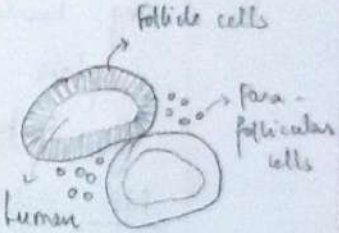
Acromegaly - tumor in GH cells after adolescence (epi disks are sealed) makes the bones become thicker and soft tissues continue to grow.

Thyroid Gland

It sits on the trachea in the throat. It's about 20g and very well vascularised from superior thyroid artery



Thyroid cells are arranged in follicles
Surrounding a liquid colloid core that contains large thyroglobulin protein. They store large amounts of hormone extracellularly.

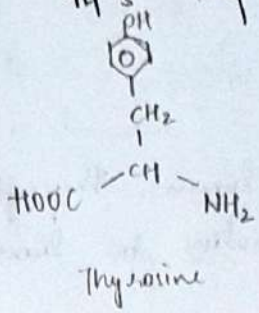


Parafollicular cells — secrete calcitonin.

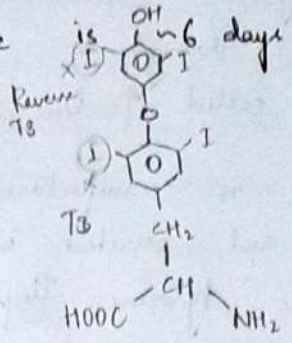
Tyrosine —(Iodinase)→ Monoiodotyrosine ↦ Diiodotyrosine + Monoiodotyrosine } → 3,5,3-triiodothyronine (T3)

& diiodotyrosine → tetraiodo thyronine (T4)

93% is T4 and 7% is T3, but when it has to activate, T4 loses one iodine and binds to receptor as T3.
⇒ T4 acts as reservoir & is in equilibrium with T3.
T4's half life is ~6 days, it's more stable.



Tyrosine

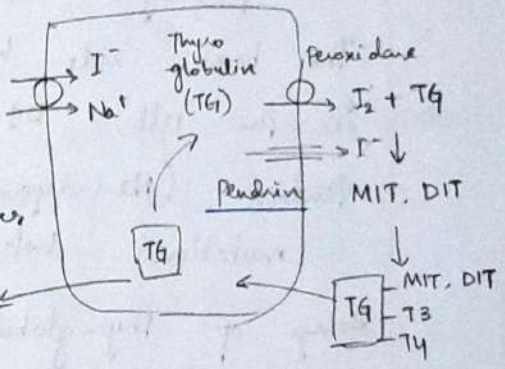


Iodide pump (Iodine trapping)

Iodide is absorbed into blood vs and thyroid selectively takes in iodide and uses it for synthesis.

Iodide trapping — I^- ions are selectively pumped from blood to the cell & into lumen.

It happens through Na^+-I^- symporter (NIS), which works due to conc. gradient of Na^+ across the membrane

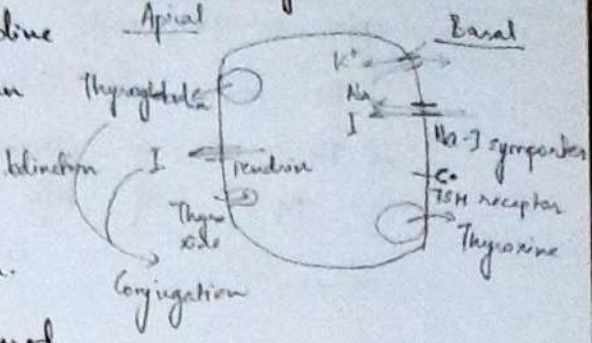


Pump can also transport thiocyanate, perchlorate and nitrate ions, which compete with I^- for transport

Peroxidase enzymes on apical side oxidise I^- to I or I_3^-, which can then combine with tyrosine

Lecture 18/4/22

Iodine is taken up from the blood through Na-I symporter. Conc of iodine in the cell is 30x more than blood. Iodine goes into the lumen of follicle through a protein channel called pendrin.



Steroid secreting cells have SER

Thyroglobulin protein is manufactured by Rough ER and secreted into lumen. Thyroglobulin is a homo-dimer tyrosine. Thyroglobulin in lumen is called colloid

Thyroid peroxidase (TPO) – protein on the apical side oxidises the iodine, so it can combine with tyrosine.

Mono & Diiodotyrosine molecules combine to form T3 & T4

The iodised globulin is endocytosed & there is proteolysis to form T3 & T4.

The basal side has TSH receptor, which is a GPCR.

Deiodination In the cell, D1 enzyme acts on T4 → T3

Pendrin (Na-independent chloride-iodide transporter) has some mutational hotspots – it can lead to hypothyroidism.

Storage of Thyroglobulin (TG)

Thyroid gland can store lots of TG. After a round of synthesis, a TG molecule has ~30 thyroxine molecules. So thyroid hormones enough for 2-3 months are stored in the gland. Effects of deficiency can take long to show up.

Release of T3 & T4

Thyroid hormones should be first cleaved from TG before they can be released into the blood

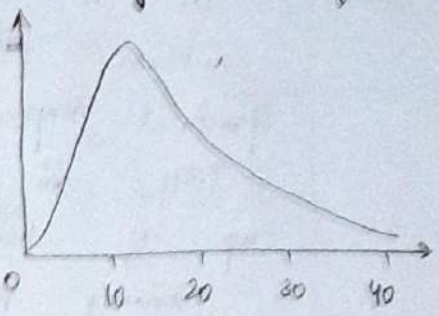
They are cleaved by proteases in the lysosome vesicle which fuses with endosome containing (TG + T3/T4)

TH moves in the blood after combining to thyroxine-binding globulin, which are plasma protein synthesized by liver. TH accounts for 99% of circulating thyroid hormone. T3 is physiologically active & has much greater affinity for receptor. TH is in dynamic equilibrium between bound and free states. When free, TH is converted to T3 and is more active

T3 half life : 1 day TH = 6.5 days.

Thyroid hormones have slow onset & long duration of action

When large quantity of thyroxine is injected, the BMR increases and reaches a peak 10 days after injection.



BMR is meant measured by O_2 consumption

Thyroid hormones increase cellular activity - increases growth
Increases BMR, rate of utilization of food for energy and growth rate in young people.
T4 increases transcription of large no. of genes

- TH also increase the no., size and activity of mitochondria - all enzymes involved in metabolism. TH stimulates all cells & increases the production of ATP
- Also increases ion exchange in cells
  Na^+-K^+-ATPase activity is increased → ↑ transport of Na^+ & K^+
  This is how BMR is increased
- Increases cardiac output → for O_2 needs and stimulates bone formation
- They promote heat production. Hypothyroidism leads to decreased cold tolerance. So TH is involved in thermoregulation

Effect of TH on amphibian metamorphosis
TH is essential for metamorphosis, which is a rapid metabolic process.

Mechanism of action
T3 interacts with thyroid hormone receptor, which binds to retinoid x receptor. Together, the thyroid hormone response element regulates the transcription and translation of certain proteins — which increases metabolic rate, promote growth, CNS development & cardiovascular activity

Regulation of TH secretion
TH is stimulated by TSH, released by cells of anterior pituitary

Structural importance.
TSH, along with LH, FSH and hCG, is made up of two peptide chains. α chain is common among them, whereas β chains are unique to each hormone. α chain is thought to be the effector part, whereas β chain provides specifity.

TSH receptor is a GPCR which activates production of cAMP and phospholipase C. Essentially, it stimulates everything — more pumps, more channels, everything.

TSH is regulated by thyrotropin-releasing hormone (TRH), secreted by hypothalamus. Its production is negatively regulated by T3, T4 conc. Its a tripeptide hormone

Exposure to cold increases TRH and TSH secretion

Hyperthyroidism - nervousness, hyperphagia, weight loss, heat intolerance, fine tremor & excess increase in BMR

Graves disease - an autoimmune disease where antibodies bind to TSH receptor and stimulate production of TH.

Goiter - iodide deficiency in mountainous regions causes endemic goiter

20/4

Lecture

Hormones of Adrenal Cortex

Adrenal glands are situated on top of kidney

Adrenal medulla is the main source of epinephrine and norepinephrine

Adrenal glands can be divided into 3 zones from outside to inside -

- Zona glomerulosa
- Zona fasciculata - cells arranged in radial columns
- Zona reticularis

They mainly secrete steroidal hormones. If we extract steroidal compounds from adrenal gland, we get 30-40 steroids, but only 6-7 are hormones because they're bioactive i.e. they can bind to receptors and trigger action. Others compounds are intermediary metabolites.

Based on the function of these hormones, they can be classified into mineralocorticoids and glucocorticoids.

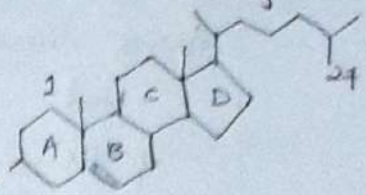
Some hormones show both mineralo and glucocorticoid activity. — Aldosterone mineralocorticoid activity is 3000 times that of cortisol

Cholesterol and fat is distributed by liver

Aldosterone

Mineralocorticoid secreted by zona glomerulosa. It conserves Na^+ ions in the body & also regulates K^+.

The starting material for most steroid hormones for is cholesterol which arrives in the form of low-density lipoproteins which can travel in blood and are easily taken up by endocytosis.



Cholesterol - C_{27} - steroid nucleus is made up of 4 rings.

First, cholesterol side chain is cleaved, and we get pregnenolone. From this, aldosterone, cortisol, testosterone and estradiol.

Aldosterone : strongest mineralocorticoid. It has aldehyde and ketone groups

Cortisol : v. important glucocorticoid

Zona glomerulosa - aldosterone

Zona fasciculata - mainly secretes corticols

Zona reticularis - they secrete steroid hormones that act like androgens, which exhibit same effect as that of testosterone

If secreted in excess, it can have masculinizing effects

Quantifying the effect of Cortisol

Cortisol increases glucose levels and has effect on protein and fat metabolism.

Set the effect of cortisol activity (lowering Na^+ & ↑ glucose) as 1. Aldosterone's mineralocorticoid activity is 3000.

Organic synthesis gave rise to various synthetic steroids

Eg: Dexamethasone has 30× better glucocorticoid activity than cortisol

Glucocorticoids also show anti-inflammatory effects So. dexamethasone was used during COVID

Adrenal cortical hormones are transported in blood bound to corticosteroid binding globulin (CBG) or transcortin. 95% of cortisol & 60% of aldosterone travel bound to CBG ⇒ this affects half life : 1.5 - 2 hrs for cortisol and 15 - 20 mins for aldosterone

Metabolism & excretion.

Steroid nucleus can't be broken down by mammals. So, enzymes change the side chain to make it unrecognizable to receptors. Conjugation increases water solubility, so it can pass through renal capillaries and get excreted. So, urine steroid levels can tell us about hormone imbalance.

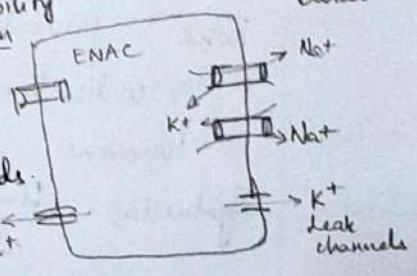
Physiology of mineralocorticoids

Aldosterone : principal mineralocorticoid. In its absence, there is progressive loss of Na^+ from kidney, which causes hyponatria - goes down to 120-140 mEq/ml

The ability to excrete K^+ is impaired if aldosterone decreases - causes hyperkalemia. Increased K^+ in blood result in partial depolarisation of all cells, leading to cardiac arrhythmia and weakness of muscles. K^+ level doubles from 4 mEq/L to 8-10 mEq/L.

Aldosterone mainly acts on principal cells of late DCT and CT. to increase Na^+ permeability

Epithelium Sodium channel (ENaC) helps in reabsorbing Na^+ from kidney, sweat glands, colon and salivary glands.



Aldosterone affects the expression of channels so that a gradient is established, and Na^+ is reabsorbed, whereas K^+ is excreted

ENaC - blocked by Afrin nativuatic peptide, which causes nativuresis & diuresis

Mechanism of action

Aldosterone enters the cell and binds to Mineralocorticoid receptor (MR) in cytoplasm. The combined molecule goes into nucleus, and changes gene transcription to increase no. of pumps and channels. (ENaC & Na-K-ATPase)

But its effect can be seen in 2 mins — too fast for genomic timescale, so it must have some direct effect

MR also has some affinity for cortisol. (There's 100x more cortisol than aldosterone). Much higher conc. of cortisol is inactivated into cortisone by 11β-hydroxysteroid dehydrogenase, which allows aldosterone to bind to MR.

The active component of liquorice (mulethi / jeshtamadh) inhibits 11β-HSD, so cortisol binds to MR. This increases Na^+ reabsorption, which in turn retains water and increases blood pressure. Genetic disorder can be lead to hypertension

If there's fall of BP. JGA cells are stimulated, angiotensin II is produced and they stimulate cells of Zona glomerulosa to produce aldosterone

ACTH & high K^+ levels are also good stimulants 21/4

Lecture

Physiology of Glucocorticoids

Zona fasciculata secretes glucocorticoids — cortisol, corticosterone and cortisone. Cortisol is the dominant hormone.

Synthesis: Liver synthesizes LDL, which is taken up by cells of zona fasciculata.

Cholesterol can be used immediately or stored as lipid droplet of cholesterol esters.

The cholesterol is taken up by mitochondria through steroid acute regulatory protein (StAR). It is then acted upon by cytochrome P450 scc, which catalyzes conversion of cholesterol → pregnenolone, which is then converted to progesterone, an intermediary metabolite in this cascade, but not excreted. Progesterone is converted to cortisone and cortisol, which are secreted into blood and carried to different parts through corticosteroid binding globulin (CBG) - 90% binding affinity ⇒ half life : 70 - 120 mins.

Excretion of cortisol

It's conjugated with a salt, so it's more soluble in water and unrecognizable to receptors so it can be excreted through urine

Receptors are present on skeletal muscle, adipose tissue, liver, some parts of brain, blood vessels etc

Unliganded glucocorticoid receptors (GRs) are present in cytoplasm, bound to heat shock protein (hsp).

Once cortisol binds to GRs, hsp's are released (glucocorticoid response element) and two bound GRs dimerize. This complex enters the nucleus and effects transcription patterns to cause some effects.

Muscle

↑ protein degradation
↓ protein synthesis
↓ glucose utilization
↓ sensitivity to insulin

Liver

↑ glycogen storage
↑ gluconeogenesis by
↑ activity of enzyme
↑ amount of enzyme

Adipose tissue

↑ lipolysis
↓ glucose utilization
↓ sensitivity to insulin

SAVE GLUCOSE!

So, mainly, cortisol is a glucose sparer, it increases gluconeogenesis by proteins and fats. by increasing enzymes and breakdown of proteins catalysing

It can increase gluconeogenesis by 6-10 x.

Cortisol depletes protein and decreases protein synthesis, but it increases protein in liver (for gluconeogenesis) and plasma. Enhances liver enzymes required for protein synthesis

Protein is broken down mainly in skeletal muscles and lymph nodes. & other body parts long-term high levels of cortisol makes the person physically weak and makes immune system very weak.

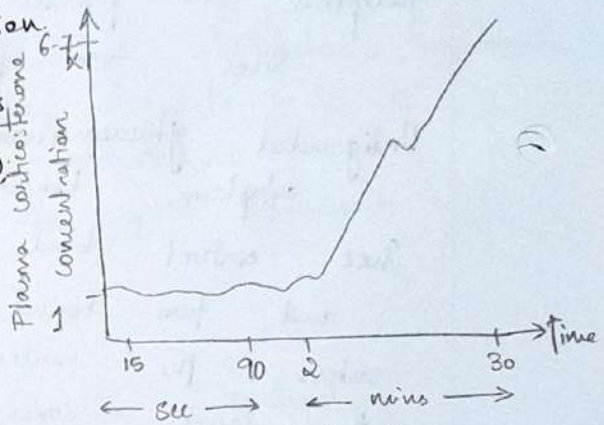
Cortisol also increases conc. of free fatty acids n fats.

During development, cortisol also plays an important role in maturation of lungs and secretion of surfactant.

Cortisol is important in resisting stress and inflammation

Almost any type of stress (trauma, infection, extreme heat or cold, restraining) increases secretion of ACTH. followed by increased cortisol secretion.

When there is stress, hypothalamus releases corticotropin releasing H (CRH), which increases ACTH secretion, which acts on Zona fasciculata to secrete more cortisol



Hypothalamus - pituitary - Adrenal (HPA) axis plays a role in modulating immune system

Hans Selye observed that when there is exposure to stress, there is a characteristic pattern —

1. increase in size of adrenal gland (stimulation of HPA axis)
2. involution of thymus
3. decrease in size of lymphoid organs.

★ Short-term stress response : stimulation of sympathetic NS which – increases heart rate, BP
glucogenesis (liver)
dilation of bronchioles
changes in blood flow pattern
increase metabolic rate
} due to epinephrine and norepinephrine released by adrenal medulla.

★ Prolonged stress response : hypothalamus (CRH) → Anterior pituitary (ACTH) → Adrenal cortex (Cortisol) which –
- converts proteins & fats to glucose for energy
- Suppression of immune system
- ↑ glucose in blood

Inflammation is a localised physical condition where the tissue is red, hot, swollen and painful. The inflamed part releases chemicals & blood vessels become more permeable – which causes swelling
Here, free cortisol levels are higher, because there's partial degradation of CBG by enzyme elastase (secreted by mononuclear leukocytes). High cortisol levels help in managing inflamation. ⇒ anti-inflammatory effects
Cortisol stabilizes lysosomes in proximal cells, so it prevents apoptosis.
Decreases permeability of capillaries, migration of WBCs, lymphocyte
Action of cortisol on immune cell division & release of IL1
Nuclear factor KB (NF-KB) is a transcription factor that stimulates inflammatory response. Cortisol induces formation of inhibitor of nuclear factor that binds to NF-KB
- Reduce lymphocyte count in periphery by redistributing cells
- Inhibits Ig synthesis & apoptosis

Regulation
CRH (Hypothalamus) → ACTH (Pituitary) → Cortisol (Adrenal cortex)

Lecture - 25th April

Adrenal Medulla - cells called chromaffin cells

Innervated by neurons from thoracolumbar spinal cord, whose axons pass through which synapses in the paravertebral sympathetic ganglia to form splanchnic nerves

Principal secretory products - epinephrine & NE [catecholamines]

→ Overview of ANS

Parasympathetic : Craniosacral

Preganglionic } Acetylcholine
Post ganglionic }

Sympathetic : Thoracolumbar centers
Preganglion - ACh
Post-ganglion - Norepinephrine

Spinal cord ——(ACh)——> Adrenal medulla ——> Epinephrine (80%) NE (20%)

- Adrenal medulla - specialised sympathetic ganglion whose preganglionic fibers emerge from thoracic spinal cord, without synapsing at ganglion.

AM has nicotinic ACh receptors

- Medullary hormones affect every tissue of the body
- Adrenal medulla not necessary for survival

* Substantia nigra has pathway enzymes only till formation of dopamine. Postganglionic fibers can secrete till NE

→ Biosynthesis

Hydroxylation of tyrosine ——(tyrosine hydroxylase)——> dihydroxyphenylalanine (DOPA) is the RDS.

Activity of tyr. hydroxylase is stimulated by phosphorylation, and inhibited by catecholamines (product inhibition)

Secretion is closely regulated

Tyrosine → DOPA → Dopamine →(1) Norepinephrine →(2) Epinephrine

Only adrenal medulla secretes epinephrine (arises from neuroectoderm).

① Dopamine β-hydroxylase

② Phenylethanolamine N-methyl transferase

Enzyme ① that catalyses dopamine → NE resides within secretory granules.

Dopamine is pumped into the granules by an energy-dependent stereospecific process. For post-ganglionic SNS axons and some adrenal medulla cells, synthesis is complete after NE production, it remains in granules until needed.

NE has to re-enter cytosol and get methylated for formation of epinephrine

After synthesis, epinephrine is also stored in chromaffin granules. (to prevent oxidation)

- Enzyme ② : PNMT that converts NE → E is partly stimulated by glucocorticoids, and arrangement of capillaries in adrenal gland increases amt of cortical exposed to medulla
- Glucocorticoids may determine the ratio of NE : E

Half-life of medullary hormones : NE – 15 secs
Epi – 10 secs

90% of catecholamines are removed in a single passage through most capillary beds. Clearance from blood requires uptake by both neuronal & non-neural tissues.

Excess NE and Epi taken up are degraded in neuronal cytosol by monoamine oxidase (MAO)

→ Physiological Actions

Act on almost all tissues & equip us for fight or flight

Effects of medullary hormones is seen in seconds – ideal for rapid short-term adjustments demanded by a changing environment.

Cortical hormones kick in 30 mins later, maintaining and amplifying the effects of medullary hormones

100 B

fight or flight response

Body responds to fear or extreme stress with a massive, coordinated activation of SNS & adrenal medulla.

Body responds by –

- ↑ heart rate, cardiac output, BP
- Redistribution of blood flow, away from viscera to skeletal muscle
- ↑ ventilation, dilation of airways
- ↓ GI tract activity
- ↑ blood glucose conc.

Adrenergic Receptors – α & β (each divided into 1, 2)

- NE mainly excites α receptors, and β to smaller extent
  Epinephrine excites both α & β about equally
- Relative effects of NE & Epi on organs is decided by types of receptors found on the organs

function –

α	β
Vasoconstriction	β1 – Cardioacceleration
Iris dilation	Increased myocardial strength
Intestinal relaxation & sphincter contraction	Lipolysis
Pilomotor contraction	β2 – Vasodilation
Bladder sphincter contraction	Intestinal, uterus, bladder wall relaxation
	Bronchodilation
	Calorigenesis, Glycogenolysis

Pancreas – 1-2 million islets of Langerhans – α, β & δ cells

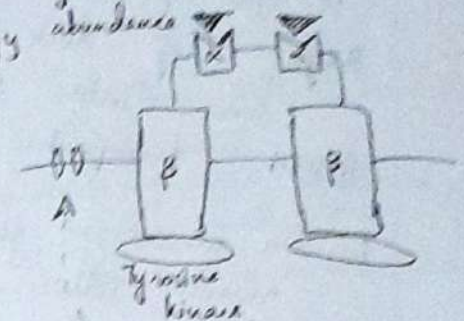
α (10%) – Insulin & Amylin δ (10%) – Somatostatin

β (80%) – Glucagon

Lecture 27/4

Insulin (51 aa long) [Banting & Best – 1922] A, B chains

Almost all except cells in the body have receptors to insulin, associated with energy abundance



Insulin receptor is a tetramer of 2 α and 2 β subunits.

α subunits are extracellular, and β units have tyrosine kinase, which when activate autophosphorylate receptor and trigger other things –

1. Increase glucose transporters
2. protein and fat synthesis
3. Growth and gene expression

Also activates enzymes, including a group called Insulin Receptor substrates

Time scales – happens in minutes

1) Increased uptake of glucose by all cells in the body } seconds
2) Membrane becomes more permeable to amino a., K^+, PO_4^{3-} }
3) Change activity levels of intracellular metabolic enzymes } 10-E mins
4) Rate of translation & transcription is also affected. } hours – days

Glucose Transporters – 4 types

They are integral membrane protein. They transport glucose and other related hexoses

GLUT1 – expressed widely in fetal tissue & in adults, in erythrocytes endothelial cell of barrier tissues (blood brain barrier). Its constitutively expressed.

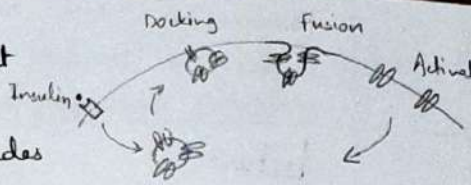
GLUT2 – bidirectional transporter that allows glucose to travel back & forth. Expressed in renal tubular cells, liver cells, pancreatic β cells

GLUT3 – expressed mostly in neurons and placenta

GLUT4 – Found in adipose tissue & striated muscle – they can be induced to be expressed on the membrane

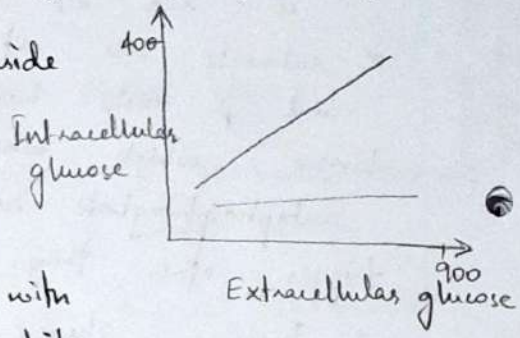
Circulates in blood unbound. Insulin is synthesized as proinsulin that is cleaved to produce insulin which is cleaved to produce insulin. Degraded in liver by insulinase

Mechanism of GLUT4 insertion



- In absence of insulin, GLUT4 are present in vesicles inside the cells.
- When insulin binds, signaling cascades are elicited that translocate GLUT4 vesicles to the plasma membrane.
- There, they dock & fuse. They allow more glucose to come into the cell
- GLUT4 transporters are constantly recycling through the cell

Insulin increases glucose conc. inside muscle cells



* High carbohydrate meal

Levels of insulin peaks along with the blood glucose levels, while glucagon levels decline

* High protein meal

Here, amino acid levels increase, while blood glucose levels remain more or less the same

But, insulin and glucagon — both levels rise, which helps in converting amino acid to glucose and its subsequent use by cells.

→ Insulin promotes liver uptake, storage and use of glucose

↳ causes most (60%) of glucose to be stored as glycogen in the liver. In between meals, glucagon levels rise and liver glycogen is split back into glucose for use.

28/4

Lecture

Mechanism of increasing glucose uptake

1. Insulin inactivates liver phosphorylase which splits liver glycogen → glucose
2. Causes enhanced uptake of glucose by liver cells. It does this by increasing activity of glucokinase
3. Increases activity of enzymes that promote glycogen synthesis

Glucose is released from the liver between meals

- After a meal, blood glucose starts to decrease ⇒ insulin decreases
- Lack of insulin reverses all the effects listed earlier,
- Increase of glycogen activates phosphorylase in liver which splits glycogen into glucose phosphate
- Glucose phosphatase (inhibited by insulin) now causes phosphate radical to separate from glucose, allowing glucose to diffuse into blood.

Control of blood glucose — antagonistic effects of insulin and glucagon maintain blood glucose levels.

If levels fall below 50 mg/100 ml, symptoms of hypoglycemic shock develop, characterized by fainting, seizures & even coma. Diabetes patients are vulnerable to it

Glucose transporters in the brain

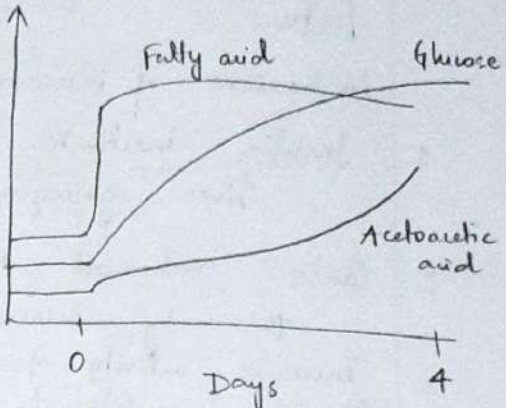
Capillaries in the brain are continuous and covered by feet processes of astrocytes. Epithelial cells and astrocytes both have constitutively expressed Glut 1 transporter, and neurons have Glut 3. So glucose conc. of CSF is maintained b/w 45 - 80 mg/100 ml.

- Insulin promotes conversion of excess glucose into fatty acids

When glucose entering liver is more than what can be converted to glycogen, insulin promotes conversion of glucose to fatty acids

Fatty acids are packaged as triglycerides in low-density-lipoproteins which transport them to adipose tissue to be stored as fat.

Experiment : Pancreatectomy

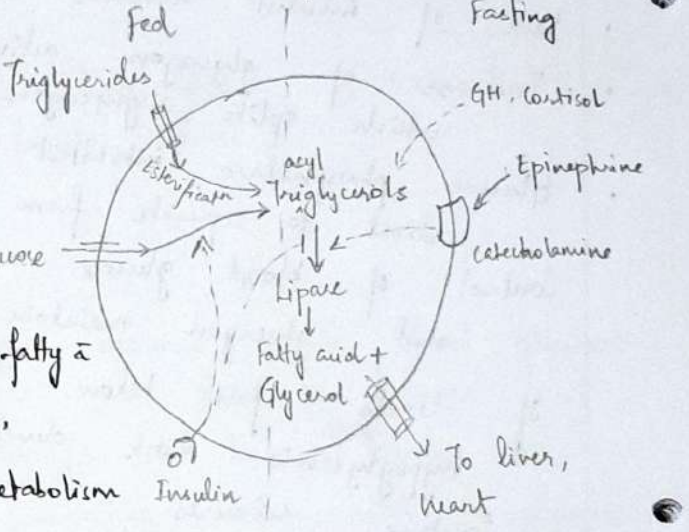


Insulin's effects on fat metabolism are also important in the long run. This can cause atherosclerosis - deposition of fat on capillaries, leading to heart attack or stroke

conc. in blood

Change in metabolism also causes neuropathy, retinopathy & kidney problems in the longer run.

Energy metabolism in adipocyte during fasting and fed state



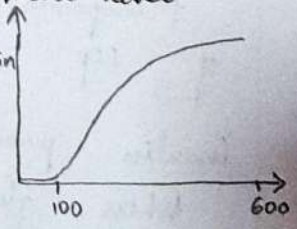
Insulin deficiency causes lipolysis & release of free fatty ā

Insulin affects the 'switch' between carbs & lipid metabolism

→ Insulin promotes protein synthesis and storage by stimulating transport of aā into cells, and translation rate, which creates more protein.

Over a long period, insulin also increases gene transcription, inhibits catabolism of proteins and decreases the rate of gluconeogenesis in the liver (conserves amino acids).

→ Insulin secretion is regulated by blood glucose level



- ↑ glucose, aā, fatty acids, glucagon, Ach in blood stimulate β cell
- Growth hormone & cortisol - stimulate β cell
- Somatostatin, NE, epi - inhibit β cells

* because K^+ ~~channels~~ ions accumulate inside

Lecture

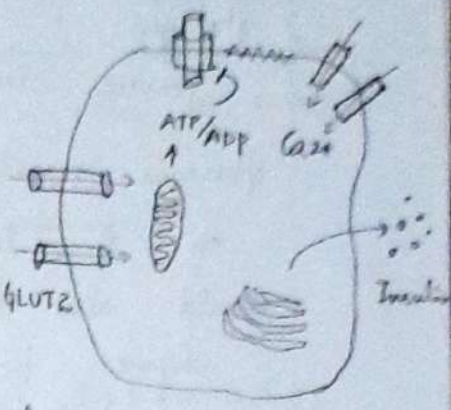
Mechanism of insulin secretion in response to glucose and glibenclamide

At high glucose, the ATP : ADP ratio increases in the β cells of pancreas

↑high ATP level block K^+ channel, which depolarizes the membrane*

Depolarization causes Ca^{2+} channels to open, and Ca^{2+} ions flow in.

This triggers insulin secretion in blood



Insulin excess

Maintaining blood glucose range is very important.

When blood glucose levels fall, insulin secretion is inhibited. Glucagon & epinephrine reverse the fall in blood glucose levels.

Glucagon

Secreted by α cells of Islets of Langerhans in pancreas

It increases blood sugar level : 1 mg / kg can increase blood sugar level by 25%. Its a hyperglycemic hormone, acts antgonistically to insulin

It's made of 29 amino acids.

Effects on glucose metabolism

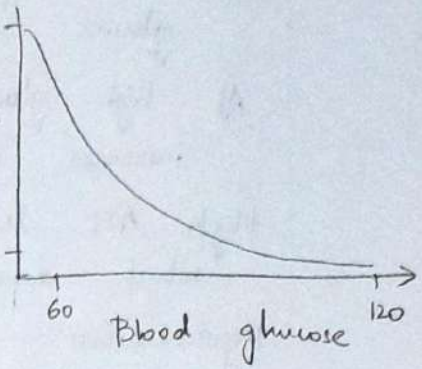
- breakdown of liver glycogen (glycogenolysis)
- increased gluconeogenesis in the liver by increasing rate of amino acid uptake by liver cells, and then conversion to glucose.

This is done by activating enzymes for amino acid transport and metabolism.

Both insulin & glucagon have $T_{1/2}$ of about 5-6 mins.

Glucagon is typically G-PCR associated

Glucagon is also regulated by glucose levels in the blood



Glucagon mainly only acts on the liver, whereas insulin would also act on muscle & adipose tissue

Ionic control of glucagon secretion.

At low glucose level, in the α cell, the ATP:ADP ratio will be cell. Here, low ratio induces some K^+ channel activity (different K^+ channel), which causes moderate depolarization, which opens Na^+ & Ca^{2+} channels such that glucagon is released into the blood.

partly open

P/Q type Ca^{2+} channel

At high glucose level, high ATP:ADP ratio, there's NO K^+ channel activity (fully closed). This causes strong depolarization, which ~~opens~~ inactivates Na^+ channel → low P/Q type Ca^{2+} activity ⇒ no glucagon release

Diabetes Mellitus (DM)

Syndrome of impaired carbohydrate, fat & protein metabolism caused by lack of insulin secretion or decreased sensitivity of tissues.

1) Type 1 - Insulin dependent - IDDM - caused by lack of secretion due to congenital or autoimmune diseases

2) Type 2 - Non-insulin dependent - NDDM - caused by decreased sensitivity of target tissues to the metabolic effect of insulin. In both cases, blood glucose level ↑s, cell utilization of glucose ↓ but of protein, fat ↑

Type 1

Caused by injury to β cells by viral infections or autoimmune disorders, though heredity decides the susceptibility

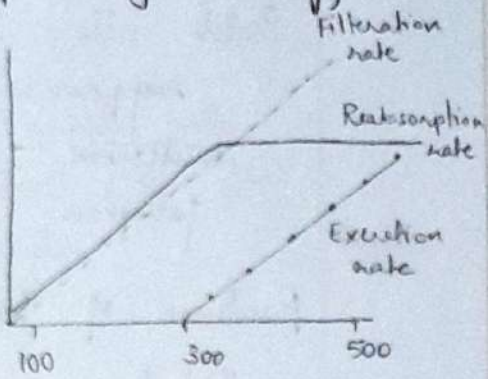
Usual onset occurs at 14 years → juvenile diabetes mellitus.

3 principal effects can develop within days or weeks —

1) Increased blood glucose
2) Increased utilization of fats for energy
3) Depletion of proteins

Increased blood glucose levels causes —

- loss of glucose in the urine (upto 100g in a day)
- can cause cellular dehydration
- tissue injury to blood vessels which increases risk of heart attack, stroke, kidney disease, retinopathy and gangrene



- also damages other tissues — causes peripheral neuropathy, impaired reflexes, bladder control, decreased sensation in extremities and other symptoms of peripheral nerve damage
- hypertension, abnormal fat metabolism, renal injury, atherosclerosis

Type II : Resistance to metabolic effects of insulin (90% of cases)

Increasing no. of Type II cases at early age is related to increasing prevalence of obesity

Insulin resistance - reduces glucose uptake (muscle & fat cells)
reduced glycogen synthesis & storage (liver)
↳ it's a disruption in insulin signaling cascade → GLUT not inserted

Hyperglycemia : consistent blood sugar level of 300+
Glycosuria : excretion of glucose in the urine
Polyuria : frequent urination :: high levels of urine is produced
Polydipsia : excessive drinking
Causes depletion of body's proteins → rapid weight loss despite polyphagia

= Glucose tolerance test (used to diagnose diabetes)
= hyperinsulinemia (used to diagnose insulinoma)

Lecture 1/5/2022

Hormonal control of Reproduction in Male

Sex determination : XY - male

It occurs due to sex determining gene (SRY gene) in the Y chromosome, which produces Testes determining factor (TDF). Its expression causes development of primary sex cords & other male phenotype; they also develop / reshape hypothalamus & pituitary.

This happens during 11th - 13th week.

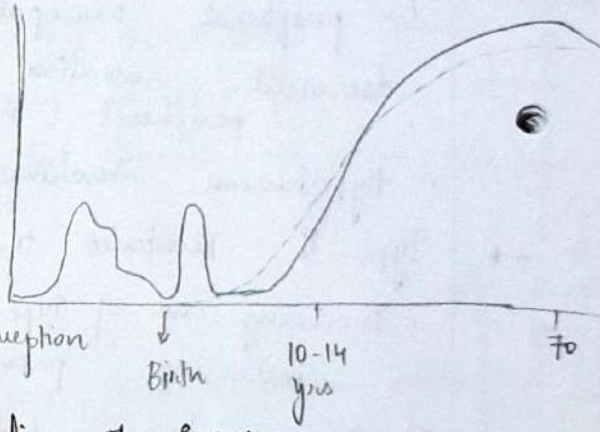
Leidig cells of tester secrete testosterone

Sertoli cells secrete anti-mullerian hormone, which suppresses the expression of female phenotype, mullerian ducts which later develop into fallopian tube etc.

Funtions of testosterone during fetal development.

Testosterone is secreted from around 8th - 10th week of fetus.

This production is stimulated by human Chorionic Gonadotropin when the male is a fetus.



After 10 - 13 yrs of age, testosterone production increases rapidly and helps in production of sperm

If a female fetus is injected with excess testosterone, it causes development of male sexual organs even though the fetus is female.

Structure of Testes

Seminiferous tubules → Rete testis → Epididymus → Vas deferens

→ Seminiferous tubules

There is intratubular compartment and peritubular compartment (where leydig cells exist).

In the intratubular compartment there are —

1. Spermatogonia (stem cells)
2. Primary & Secondary spermatocyte
3. Spermatid (23 chr - haploid)
4. Spermatozoan (with tail)

Peritubular myoid cells are smooth muscle cells which surround the tubules & contract so that sperms are moved along the tubules.

Blood - Testis Barrier

Adjacent sertoli cells are joined together by tight junction. Their basal side processes over spermatogonia, & at all stages, spermatocytes get their nutrition from Sertoli cells. The tight junctions form blood-testis barrier. Beyond the barrier, there's no blood, lymph or nerve.

The spermatogonia are outside this barrier. The barrier creates a compartment with certain features, which is optimal for development of sperms.

Steroids can cross this barrier with ease.

Fluid within the lumen of testes is different than that of plasma — it contains lesser protein & glucose, but rich in androgen, estrogen, K^+ ion, inositol & aspartic acid

Intratesticular level of testosterone maybe 100 fold than that of blood. Barrier also prevents antigenic product of testes from entering into the blood.

Sertoli cells have FSH receptors & they also respond to testosterone from Leydig cells.

Sertoli cells are also called Nurse cells. They can also act as phagocytes, consuming residual cytoplasm during spermatogenesis.

Sertoli cells also secrete Inhibin which exerts -ve feedback on FSH. They also secrete fluid with Androgen Binding protein (ABP) which binds to testosterone & keeps it readily available in the lumen.

Spermatogonium gives rise to 512 sperms over 64 days.

Leydig cells

They mainly secrete testosterone in response to LH. They're also called interstitial cells.

Mechanism of Testosterone production

LDL from Liver → Cholesterol → Pregnenolone → Progesterone $\xrightarrow{2 \text{ steps}}$ Testosterone + SHBG → Estradiol (less) / dihydrotestosterone (more)

5/5/22

Lecture

Relationship b/w Leydig & Sertoli cells

LH stimulates Leydig cells to produce testosterone; which goes into Sertoli cells and bind to ABP.

Sertoli cells are stimulated by FSH

Transport of testosterone — 50% is bound to albumin, 45% to SHBG and 5% is free.

dihydrotestosterone ↳ more ↓ like T3 - T4

Estradiol hormone is also present in males
It is important for nursing spermatocytes in seminiferous tubules. It also affects bones
Testosterone → Estradiol in liver & Sertoli cells

Mechanism of action of Testosterone
It stimulates production of proteins virtually everywhere in the body, but more specifically on the prostate gland. mRNA expression change can be observed immediately (30 mins)

Testosterone $\xrightarrow{5\alpha\text{-reductase}}$ Dihydro testosterone (DHT)

DHT replaces Heat shock proteins and binds to Androgen receptor. DHT-AR dimerise, get phosphorylated and change the gene expression level of prostate cells through PSA (Prostate Specific Antigen)
This leads to increased rate of protein production.

PSA is a glycoprotein enzyme made by prostate gland
High PSA levels maybe indicative of prostate cancer, prostatitis or enlarged prostate gland
PSA levels are normally variable, but prostate cancer/ enlargement (generally common in 60+ yrs) causes higher than normal PSA levels.

Functions of Testosterone :- on liver : ↑LDL ↓HDL
- Formation of male phenotype in the fetus & helps in development of male sex organ
- Feedback inhibition of gonadotropin secretion
- Larynx hardening — RBCs more → ⇒ Anabolic hormone
- Skeleton strengthens; & muscle mass : abdominal visceral fat increases
- Sperm production and prodⁿ of secondary sexual characters

Baldness : Testosterone promotes body hair and decreases growth of hair on head. If a female has more androgens (from zona reticularis), she might also become bald.

Testosterone has other important effects on 2° sexual characters.

It increasing increases metabolic rate & helps build muscle. So, similar anabolic steroids are used as performance enhancing drugs in various forms.

Excretion of Testosterone

It is converted to more soluble & inactive form & excreted by via kidney or, bile.

CNS - (mainly hypothalamus, pituitary & limbic system) has receptors for testosterone. Testosterone has several effects on CNS and influences behaviour - eg. aggressiveness.

Gonadotropin Releasing thormone (GnRH) released from hypothalamus triggers the release of LH & FSH from pituitary. (10 amino acid long)

The rhythmicity of release of GnRH is itself a signal for either LH or FSH cells to respond. (freq + quantity)

Was initially called LHRH

Hypophysectomy leads to atrophy of leydig cells, inhibition of spermatogenesis and steroidogenesis.

Ernest Knobil et al demonstrated that pulsatile GnRH is required for gonadotropin secretion. They used continuous infusion in a primate model.

LH, FSH, TSH & hCG have some α unit, and different β units.