How the body works PHR1031 - Book 1

STOPGAP

HOW THE BODY WORKS 1

Biology Refresher

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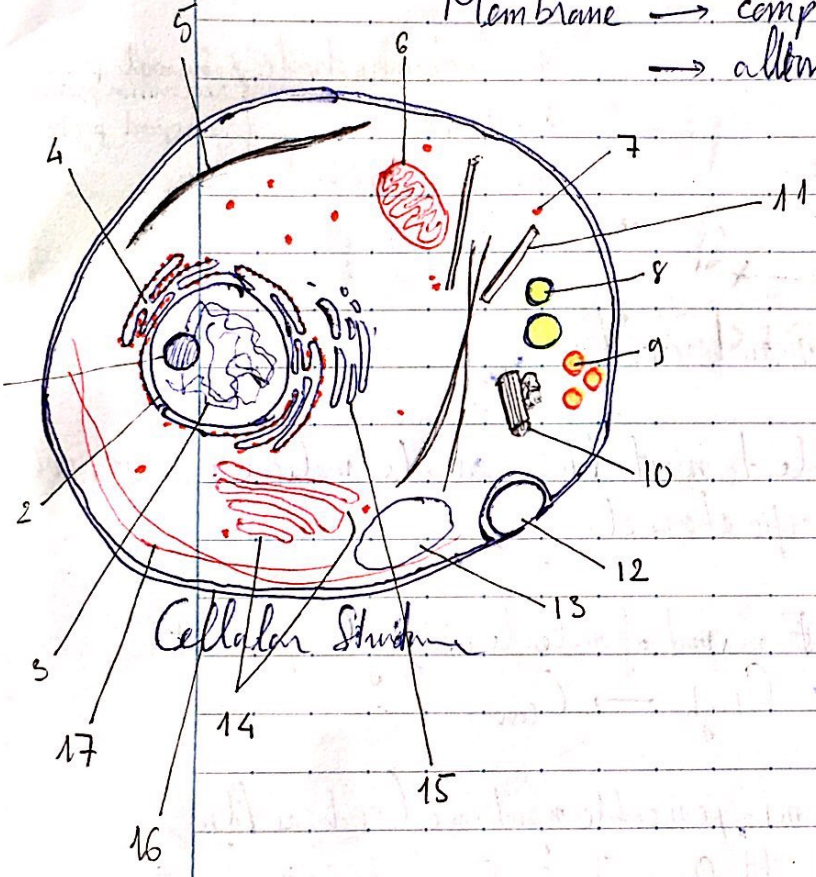
1) The cell

- Prokaryote / prokaryotic cell : w/o organelles
- Eukaryote / eukaryotic cell : w/ organeles + membrane

These organeles carry diff. & diverse function
Membrane → compartment - like structure
→ allow organeles to facilitate reactions & proc

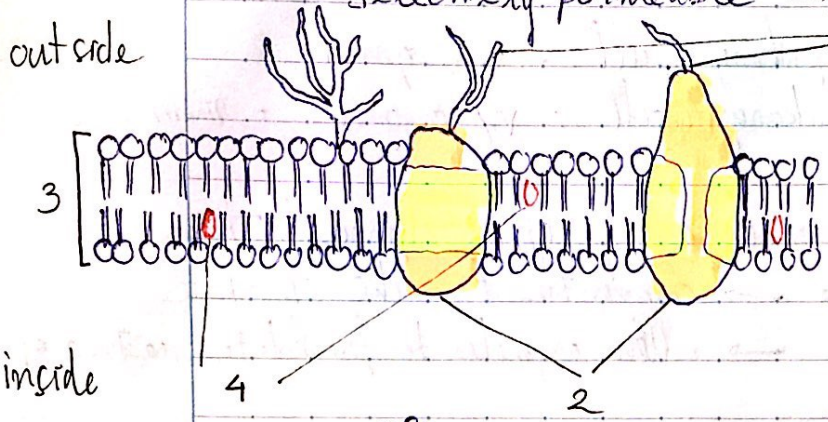


Cellular Structure

1. Nucleolus
2. Nucleus
3. Chromatin
4. Rough endoplasmic reticulum
5. Intermediate filament
6. Mitochondria
7. Ribosome
8. Peroxisome
9. Lysosome
10. Centrosome
11. Microtubule
12. Secretory vesicle
13. Vacuole
14. Golgi vesicle / apparatus
15. Smooth endoplasmic reticulum
16. Plasma membrane
17. Mino filament

All organeles submerged in Cytoplasm

All cells are surrounded by "Plasma membrane" (Plm.)
- Selectively permeable → allow ⇐ prevent.



Cell membrane

hydrophobic zone } protein
hydrophylic "

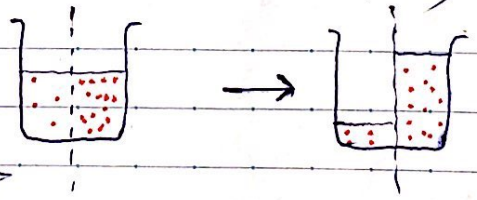
1. Carbonhydrate { channel protein / recognition protein / transport protein
2. Protein
3. Phospholipid bilayer
4. Cholesterol

Molecules crossing membranes

- Plm → impermeable to most H_2O-soluble molecules, ion, polar
  ⟷ need specific channel.

- Diffusion: PASSIVE movement of molecules along C gradient
  $C_{high} \rightarrow C_{low}$

- Osmosis: Across semi-permeable membrane (such as Plm)
  Change of H_2O



Controlled by <u>tonicity</u>

- Isotonic solution: $C_{sol} = C_{cell}$
- Hypotonic " : $C_{sol} < C_{cell}$
- Hypertonic " : $C_{sol} > C_{cell}$

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- Many ways to pass thru membrane

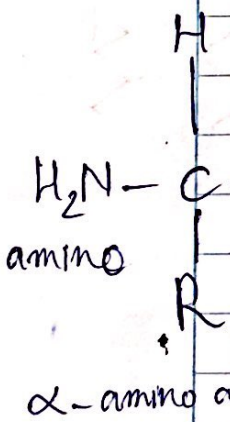
- Simple diff. : uncharge patricle move from $C_{high} \rightarrow C_{low}$
- Facilitated diff. : thru protein channels from $C_{low} \rightarrow C_{high}$
- Active transpt. thru protein + ATP from $C_{low} \rightarrow C_{high}$
- Endocytosis : substances thru membrane go inside (3 types)
- Exocytosis : vesicle fuse with membrane

2) Biomolecules

4 main types of bromeleeules : carbonhydrates, lipids, proterns, nucleic acids

3) Protein

Most common organic constituent.



- Link together create peptide bonds
  → polypeptides
- Are synthesised in rebosomes (located freely in cytoplas
  if we inside cell
  " (on rough endoplasmic reticulm) if we outside cell
- Can be hydrolysed by boiling with Proteases (enzymes breakdown protein)

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* 2 Classes of proteins
  - Fibrous protein : long & narrow strands, insoluble, play structural roles in cell
  - Globular proteins : compact & round shape, soluble, play functional roles in cell

* Different roles of proteins
  - Structure : Support body tissue
  - Hormones : Regulation
  - Immunity : Fight
  - Transport :
  - Movement : Muscle
  - Enzymes : ↗ reaction speed.

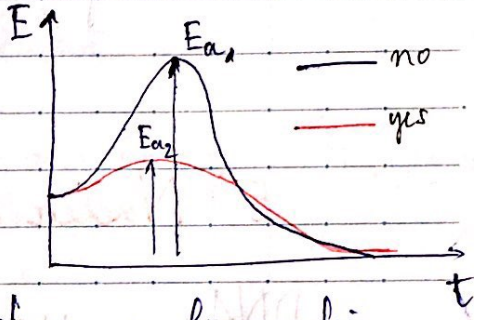
* Protein structure levels.
  - Primary (1°) : chain of aa o-o-o-o-o-o
  - Secondary (2°) : α-helix & β-sheet
  - Tertiary (3°) : 3-D
  - Quaternary (4°) : ≥ 2 chains of aa

* Enzymes
  - Biological catalyst
  - Highly specific protein → 1 enzyme for 1 reaction

- Have an active site (cavity) → attachment for reactants
  create enzyme – substrate complex

- Works by reducing activation energy
- Sensitive to pH & t°

- Denaturation happens when pH & t° is at non-optimal point
  → change enzyme structure



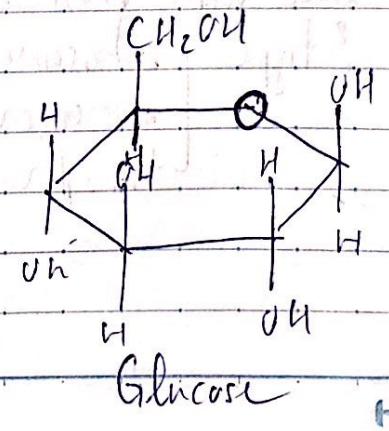
- Enzyme inhibition
  - Competitive : binding to active site
  - Non-competitive : binding to non-active site
    but change shape → no longer active

4) Carbonhydrate

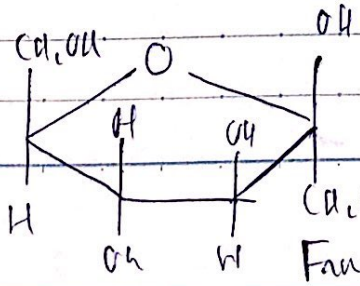
Roles : – source of chem E
– E reserves
– form structural component (eg: membrane)
– part of DNA & RNA
– combine w/ other biomolecules

Monosaccharides

– Simple sugar



Glucose



Fructose

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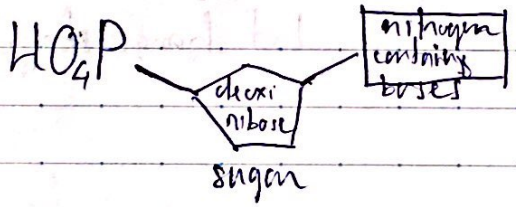
Disaccharides :
- 2 Monosac bmol together by glycoside linkage

Polysaccharides.
- Starch : amylose + amylopectin (2:8)
- Cellulose : amylose
- Glycogen : dạng dự trữ glucose storage in human liver

5) Nucleic acid

DNA: 

purine A G (large)
pyrimidine T ~~X~~ C (small)

Complimentary base paring A = T
G ≡ ~~X~~ C

1 pair = 0,34 nm = 3,4 Å
d = 2 nm

RNA
- Same with DNA but w/ ribose sugar & U
- 3 type { ribosomal
messenger
transfer

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6) Lipid

- Insoluble in H_2O ; soluble in other non-polar solva
- 3 ~~types~~ groups

• Triglycerides : fat & oil = 3 fatty acid + glycerol

C – saturated fatty acid
C – monosaturated "
C – polyunsaturated "

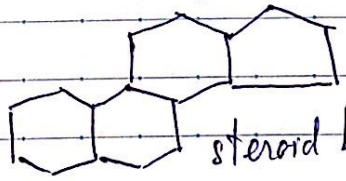
• Phospholipid : replace 1 acid chain with (PO_3^{2-}) grou

⟶ { fatty acid tails
phosphate head

C – fatty acid } hydrophobic tails
C – fatty acid
C – PO_3 – R } hydrophilic head

these campounds are marked as amphipathic
which means they have both polar & non-polar regio

• Steroid:



steroid backbone

Week 1 27/2/2017

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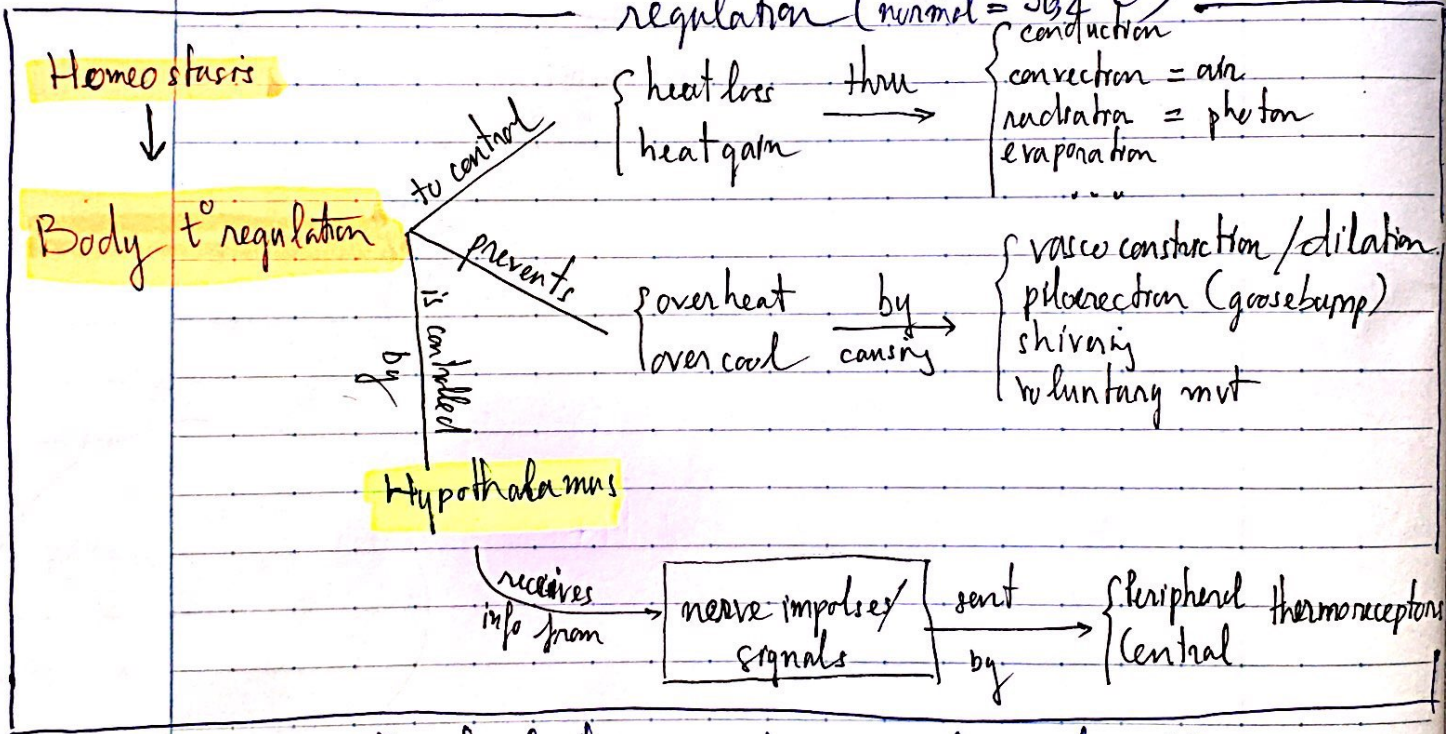
I) Homeostasis

- The ability to retain internal environment despite the changes of external environment.

Eg: Blood sugar, body t°, Na K in blood

- This week is only about body t°

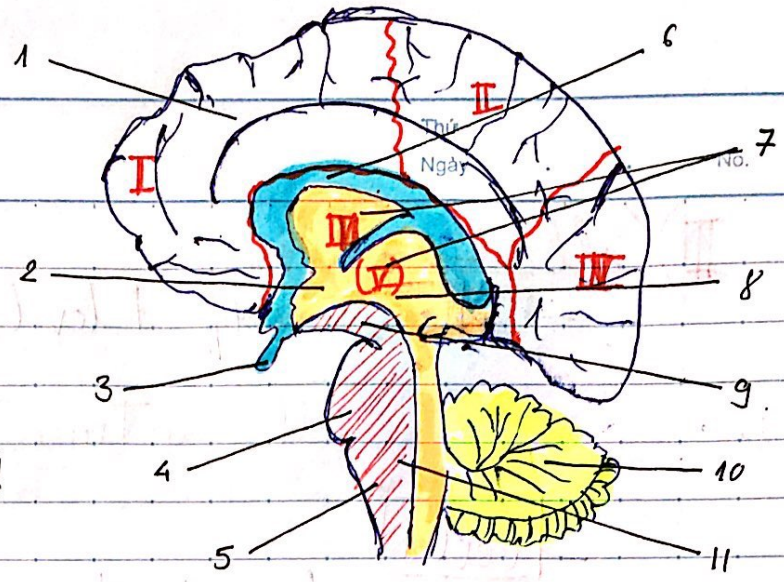
- Graph: the importance of homeostasis in body temp. regulation (normal = 36,4 °C)



- Peripheral thermoreceptors monitor skin t°
  Central " core t°

- Hypothalamus = a part of brain contain small number of nuclei w/ variety of functions. This part mostly links w/ hormones discretion, which regulates homeostasis process { blood pressure, heart rate, body t°, ...

- The brain:



1. Cerebrum
2. Hypothalamus
3. Pituitary Gland
4. Pons
5. Medulla
6. Corpus callosum
7. Ventrical
8. Thalamus
9. Midbrain
10. Cerebellum
11. Brain stem

* Brain cortex = outside layer of brain containing gray matter.

Brain lobes:

I Frontal lobe
II Parietal "
III Temporal "
IV Occipital "
V Limbic "

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II) Cell → System

– There are different level in human organisation:

Cell → Tissue → Organ → System

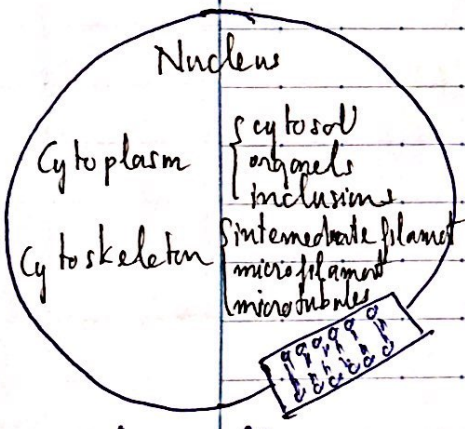
– Cells

- Basic living subunit = smallest unit able to carry function of life
- Differ in size, shape & function (shape & size are optimised for function)

Eg: Nerve cell :
Smooth muscle cell :
Red blood cell :

- Cell structure : contains { nucleus, cytoskeleton, cytoplasm } enclosed by membrane

* Cyto- = cell



The cell

+ Nucleus : a 2-membrane spherical structure contain DNA

+ Cytoskeleton : providing shape, structure, support, internal organisation & transport, mvt

+ Cytoplasm : { Cytosol = fluid contain nutrition; Inclusion = non-soluble substances; Organelles = compartment w/ specialised func

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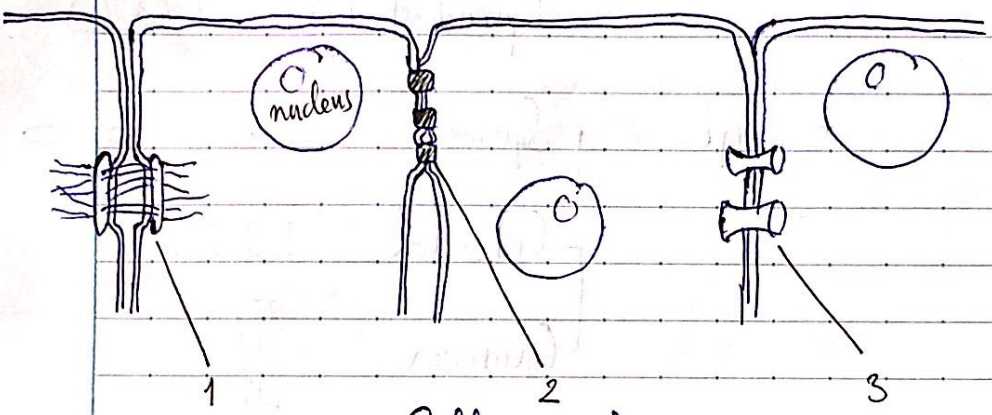
Tissue Group of cell w/ similar structure & function
These cells are held by special connection

→ **Cell junctions** : anchor cells or provide a gateway for cellular exchange



Cell junctions

1. Anchoring junctions : protein attachment between 2 cell (animal)
   - desmosome : cell - cell
   - ~~cytoskeleton~~
   - hemidesmosome : cell - extracellular matrix
   → provide mechanical stability
2. Tight junctions : tightly stitched seams between cells (animal)
   prevent materials passing between cells
   → found in digestive system

3. Communicating junctions : a passageway for transmission of chemical or signal
   - Gap junction : a tunnel between animal cell by a protein call **connexin**
   - Plasmodesmata : in plants → no care

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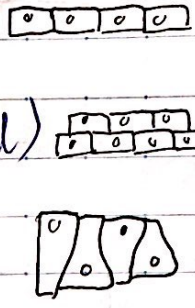
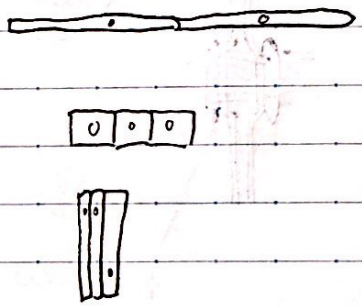
* Tissue classification

- Epithelial tissue:

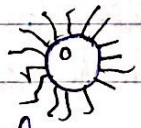
- Responsible for protection, absorption & discretion
- Classified in 3 main categories:
  - + Cell layers
    - simple (1)
    - stratified (several)
    - pseudo-stratified



  - + Shape
    - Squamous
    - Cuboidal
    - Columnar



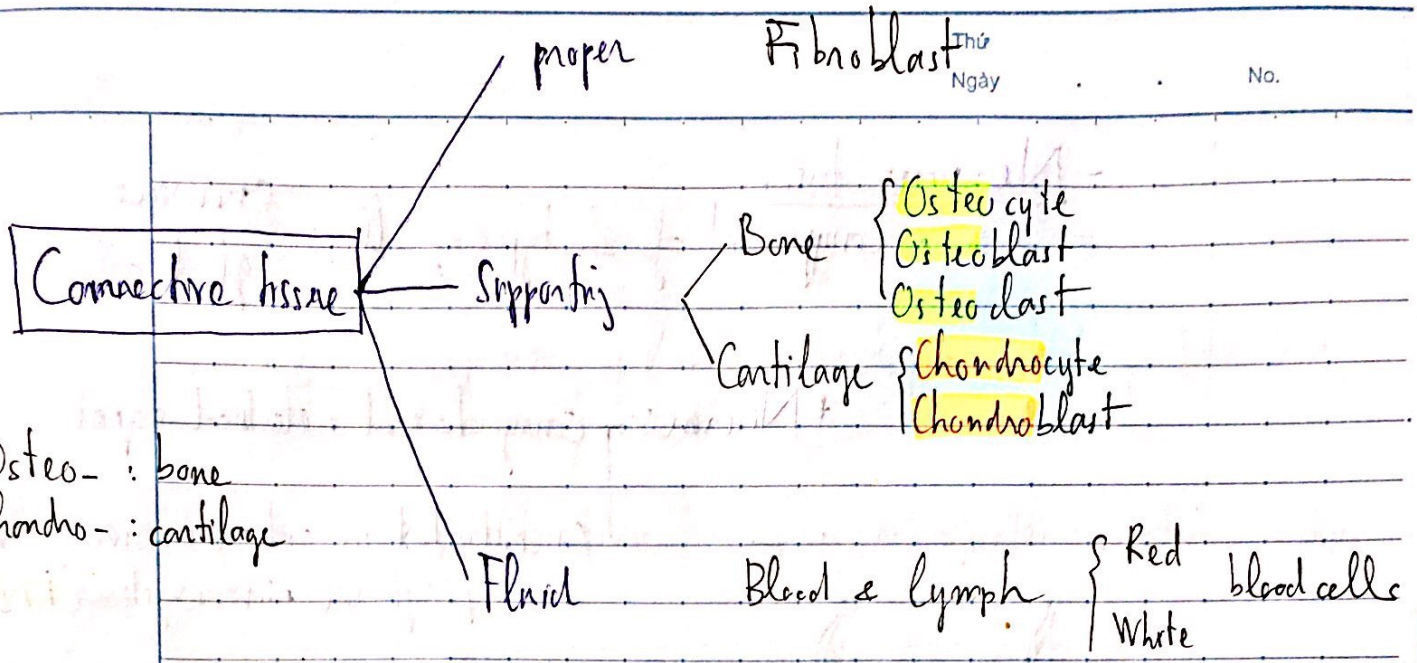
  - + Presence of cilia & keratin
    - cilia → fur, comb → lung
    - keratin → protect from damage → skin



- Connective tissue:

- 3 main types:
  - connective tissue proper
  - supporting connective tissue
  - fluid connective tissue

* -cyte : a mature cell
- phage : bacteria
- blast : immature tissue



* Osteo- : bone
Chondro- : cartilage

- Are made up of 3 components { collagen, elastic fiber, ground substances

- Muscle tissue

- Generally movement purpose
- Will learn more in week 7
- 3 types:
  - + Skeletal — movement of skeleton; voluntary control; striated in appearance
  - + Smooth — mvt of hollow organ (intestine...); involuntary
  - + Cardiac — mvt of the heart; properties between skeletal & smooth

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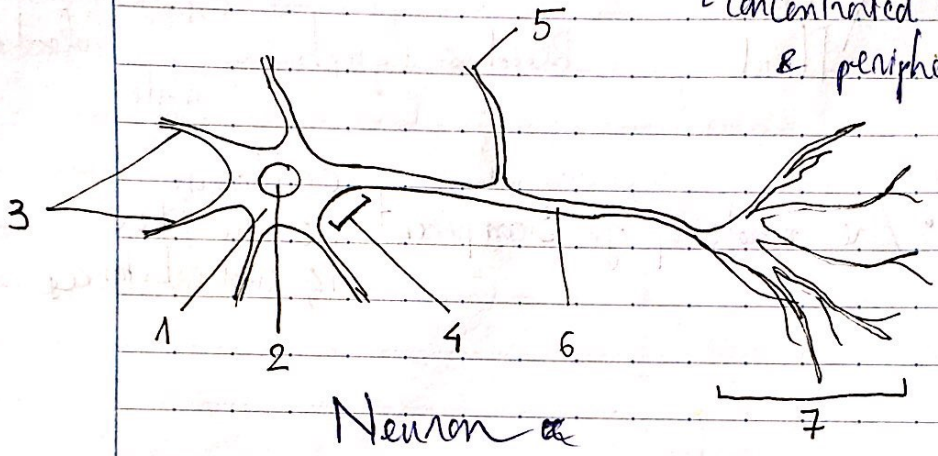
- Nervous tissue

- composed of 2 types of cells: { neurons / glial cells

+ Neurons → carry chemical & electrical signal
→ concentrated in central nervous system & peripheral nervous system (PNS)



Neuron

1. cell body
2. nucleus
3. Dendrites
4. Initial segment
5. Axon collateral
6. Axon
7. Axon terminal

+ Glial cells → support cell → supporting neurons
→ Eg. astrocytes; Schwann cells
oligodendrocytes.

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Organ & Organ system

- Organ = composition of ≥ 2 tissue types which perform ≥ 1 common functions

(CNS)

Eg.: skin (barrier) ; liver (detoxification); stomach (digestion)

- Organ system = interdependent organs working together

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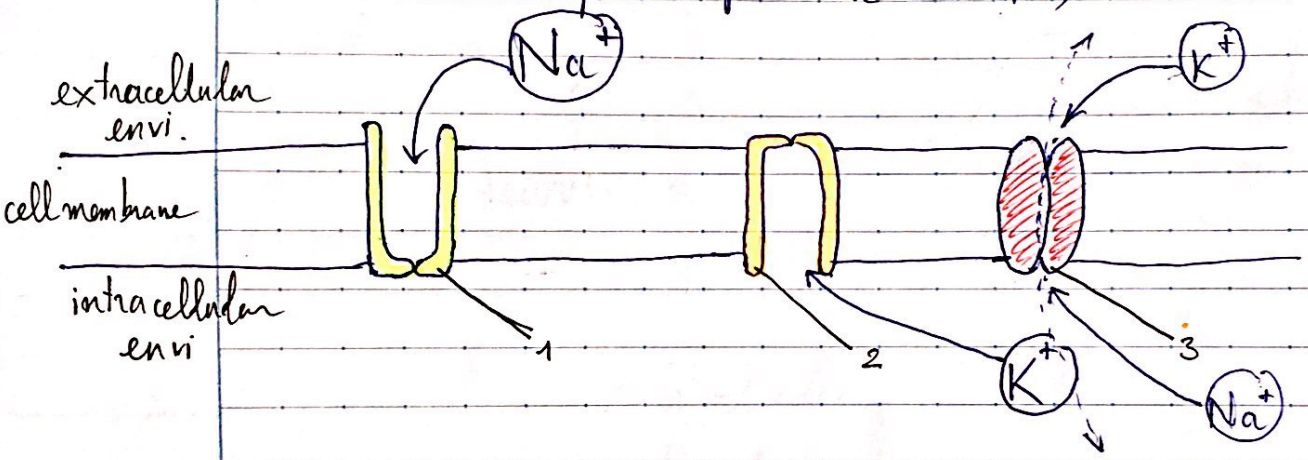
III) Cell membrane

- Vital in cellular exchange (nutrition, ion, molecules)
- Structure (Review Refresh)
  - → selectively permeable
    - only small, uncharge, hydrophobic can pass the membrane directly
    - everything else must go pass a protein channel.

- Nerve & muscle tissues are excitable via electrical signal
  - → that's why ~~the~~ cell membrane is important
  - → responsible for muscle contraction, ...



1. Na^+ channel
2. K^+ channel
3. Na^+/K^+ pump: maintain concentration gradient to prevent diffusion

- Proteins can be in 1 of 3 states ← open, closed, inactive
- Concentration of ions:

Ion \ Envi	Extracellular	Intracellular
K^+	5	← 150
Na^+	140-160	→ 10-15
Cl^-	100	→ 10
Ca^{2+}	1	→ 0,001

→ { K^+ has potential to go out of the cell; other ions ... to go inside.

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- NaK pumps: { $3Na^+$ out
$2K^+$ in

→ [Maintain concentration gradient
Require ATP
Uneven distribution of ions → electric charge between 2 side of membrane

Explain (?): Given that ~~or~~ the sum of every charged particle is 0

→ { Intra = 0 (if diffusion happened)
Extra = 0

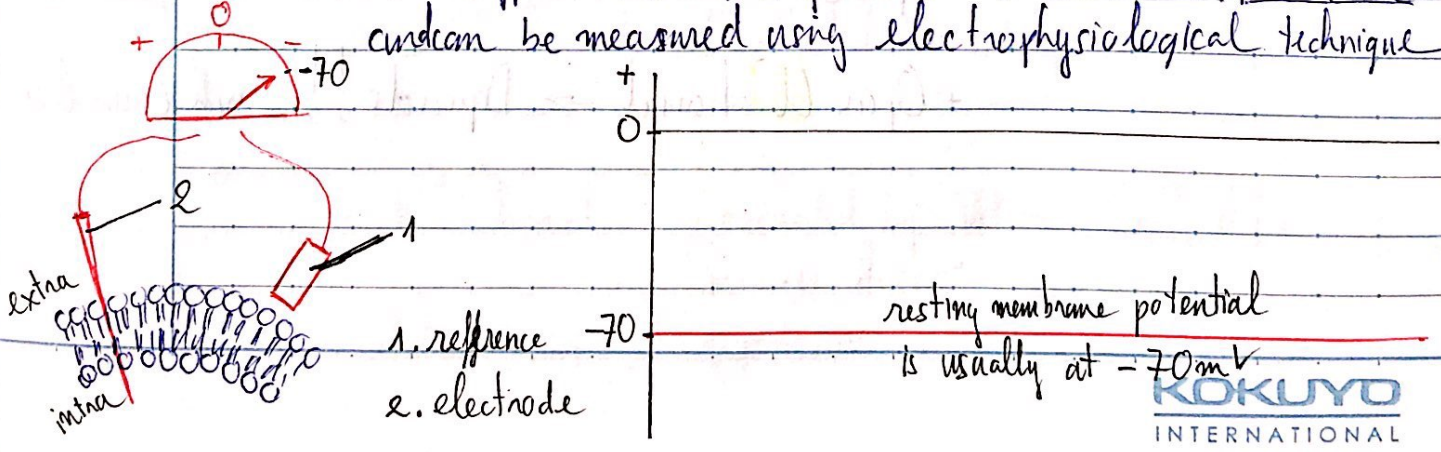
NaK pump { $3Na^+$ out
$2K^+$ in → positive charged particle would mainly be out side → inside the cell will be more negative (in relation to out side, not negative particle charge)

extra	0	0	intra	extra	+	−	intra
$10Na^+$			$10Na^+$	$17Na^+$			$3Na^+$
$10K^+$			$10K^+$	$8K^+$			$12K^+$

(not exactly calculated, only for reference)

The uneven distribution of ions → difference of voltage

- This difference in voltage is called membrane potential can can be measured using electrophysiological technique



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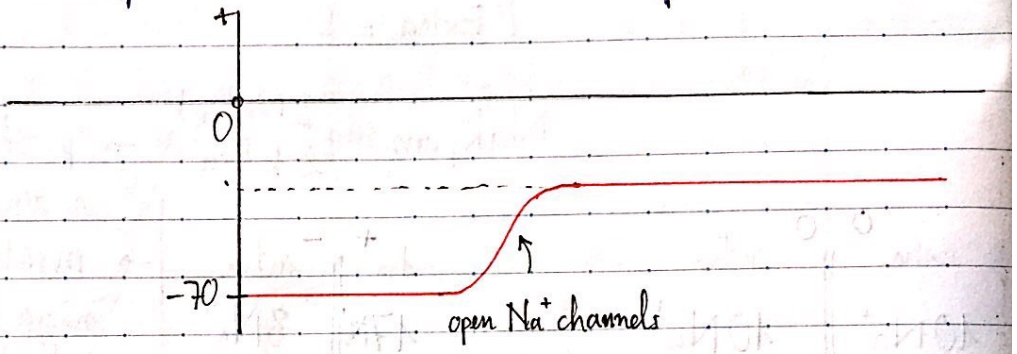
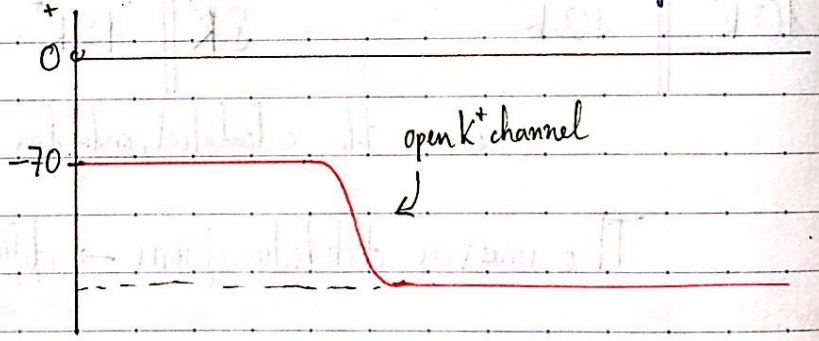
- Polarisation:
  + Depolarisation: make membrane potential less (-)
  + Repolarisation: make " return resting state
  + Hyperpolarisation: make " more (-)

Eg.:
+ Open Na^+ channels → Na^+ influx → Depolarise



+ Open K^+ channels → ~~K^+~~ flows out → Hyperpolarise



+ Open Ca^{2+} channels → same as Na^+ → Depolarise

+ Open Cl^- channel → Depends !!. (will learn later)

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- Calculating the membrane potential:

- Goldman - Hodgkin - Katz equation:

$$V_m = \frac{RT}{F} \log\left(\frac{pK.[K]_{out} + pNa[Na]_{out} + pCl[Cl]_{out}}{pK.[K]_{in} + pNa[Na]_{in} + pCl[Cl]_{out}}\right)$$

V_m = membrane potential (mV)

$R = 8.314 \frac{J}{K.mole}$

T = Kevin. t°

$F = 96500 \frac{C}{mol}$

pK; pNa; pCl = membrane permeability

$[\ ]_{out}$ = concentration outside

$[\ ]_{in}$ = " inside

- Equilibrium potential: membrane potential regarding 1 ion

- Nernst equation

$$E_{ion} = \frac{RT}{F} \log\left(\frac{[K^+]_{out}}{[K^+]_{in}}\right)$$

- Roles of each channel:
  - + Na^+ channels { activated by Voltage
    { nerve
    { depolarise
  - + Ca^{2+} channels { activated by Voltage, IP3, Ca^{2+}
    { nerve, smooth muscle
    { depolarise
  - + K^+ channels { activated by Voltage, Ca^{2+}, ATP
    { neave, heart
    { repolarise, hyperpolarise

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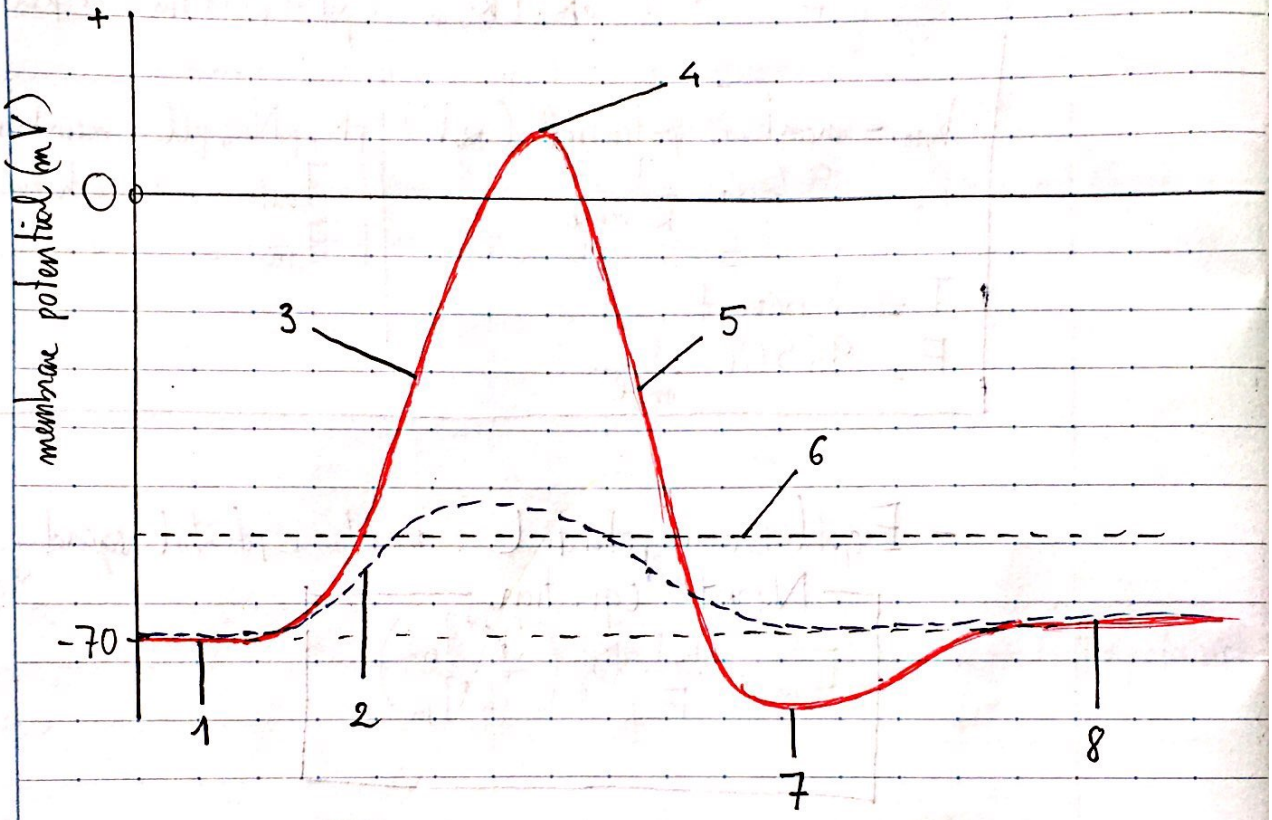
- Action potential : a reversal of membrane potential as a result of a change in membrane permeability

Resting → Depolarise → Repolarise → After-hyperpolarise → Resting



1. resting membrane potential
2 stimulus
3 depolarisation / Na^+ influx
4 peak
5. repolarisation / K^+ outflux
6 threshold.
7 after-hyperpolarisation / K^+ outflux
8 resting "

Action potential

- Characteristic of Action potential
  - All or none → one overcome threshold will continue
  - Identical
  - No ↓ in strength
  - There are refratory period (delay)

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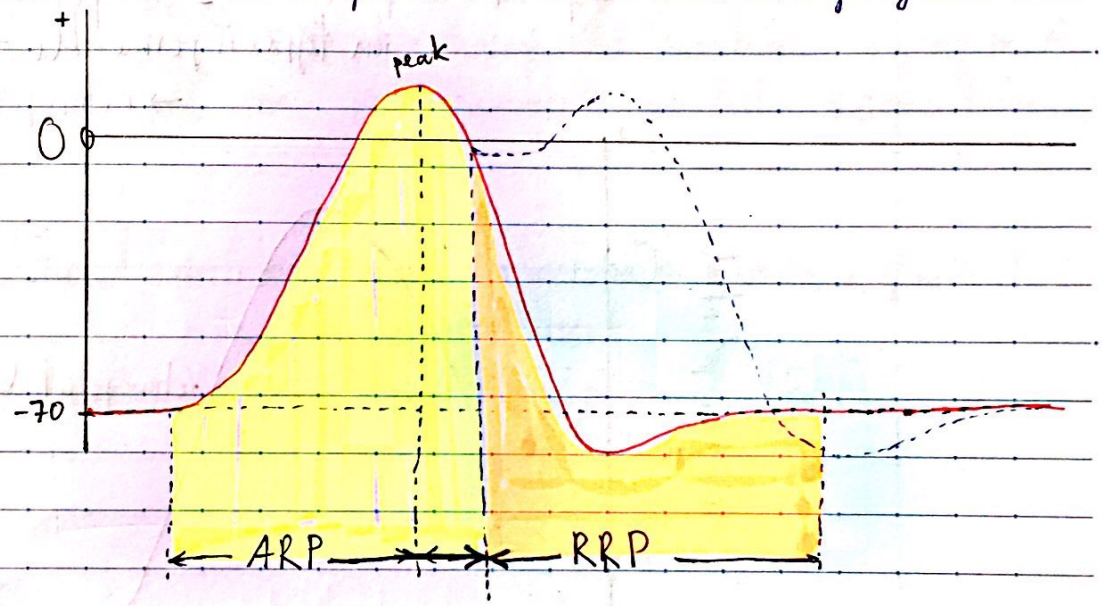
- Refractory period: the time during 1 action potential that cannot occur another action potential
2 types: absolute & relative refractory period.

+ Absolute refractory period (ARP): can't have another action potential no matter how strong the stimulus is

+ Relative refractory period (RRP): can't have another action potential unless there is a strong enough stimulus



- In this graph: when action potential starts, Na^+ influx happens, all Na^+ channels open → cannot have more Na^+ to flow in
→ cannot have another action potential

when the peak has ended, Na^+ channels will be inactive state (or closed) → if there is a strong enough stimulus
→ can reactivate the Na^+ channels to have another action potential

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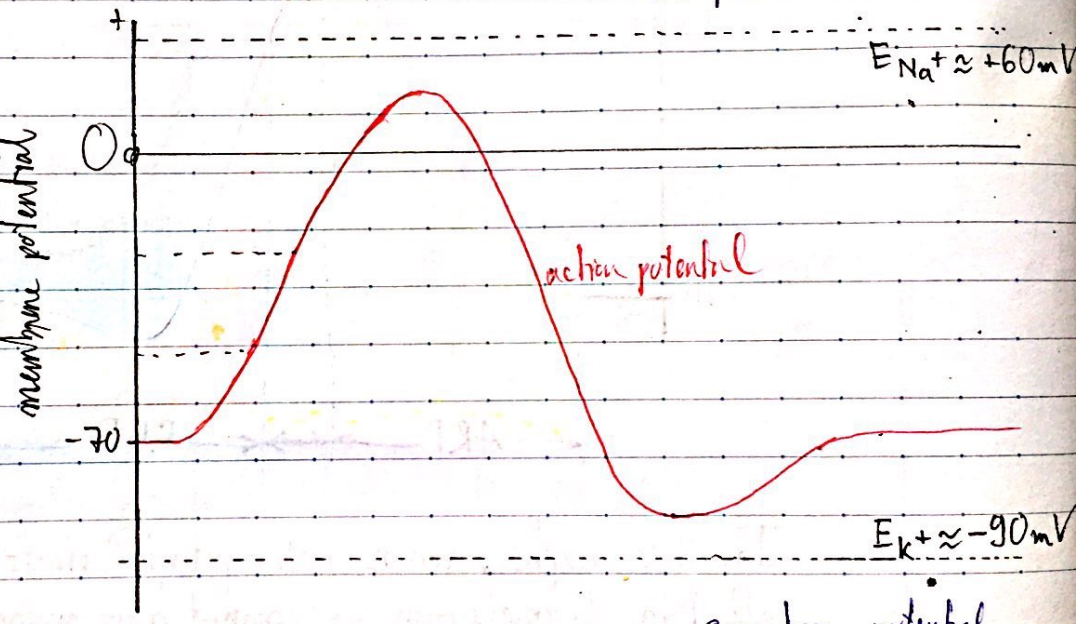
- Relationship between { membrane potential / action potential / equilibrium potential (for Na^+ & K^+)

+ Membrane potential = the difference of voltage between the inner and outer cell membrane
+ Action potential = the change of membrane permeability → change of ion distribution → change in membrane potential
+ Equilibrium potential = the potential if only one ion ~~type~~ is permeable → the limit → action potential cannot excess



Relationship between { membrane potential / action potential / equilibrium potential }

* Explain equilibrium potential (of 1 ion)
- Use a compound call KX (K = potassium ; X = sth else) that ~~some~~ is soluble and can create ions

$$KX \xrightarrow{H_2O} K^+ + X^-$$

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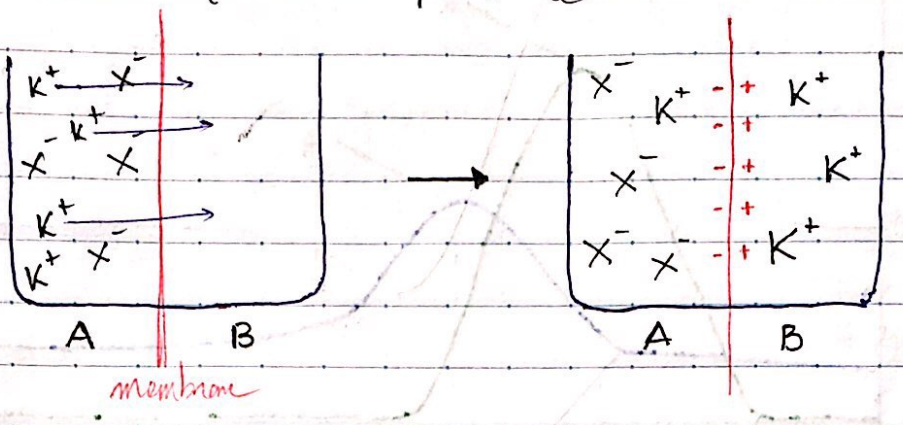
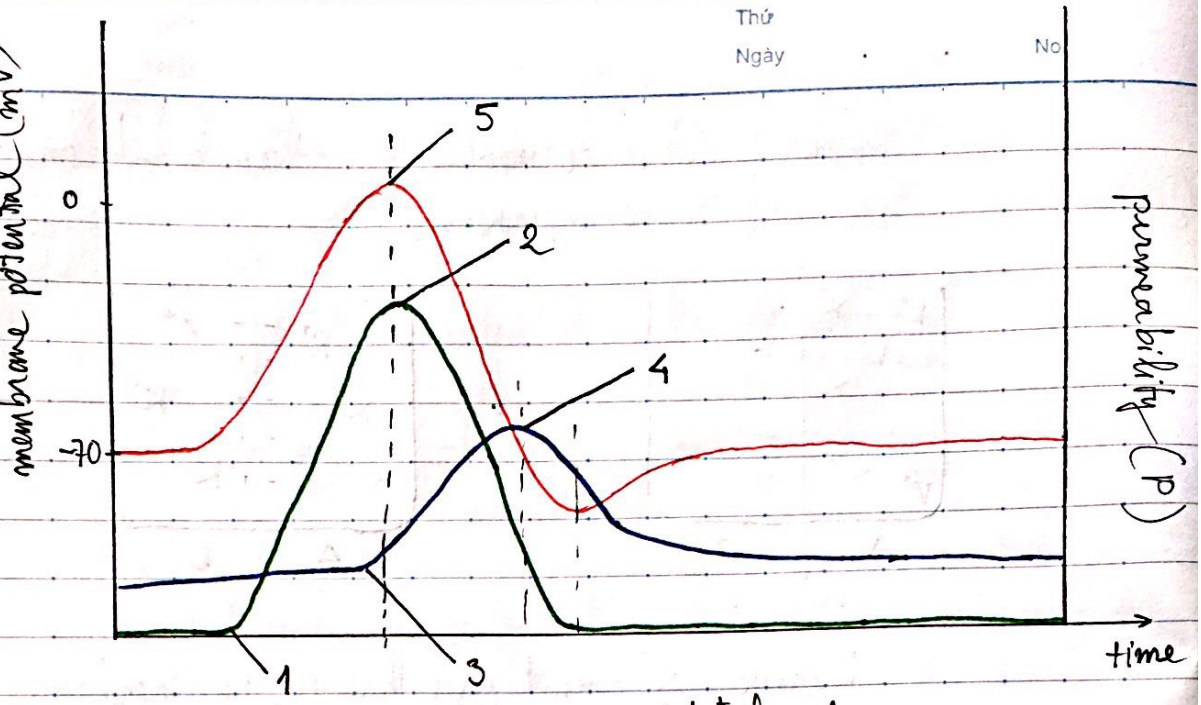
and { K^+ is permeable than membrane
X^- is impermeable



- Because X^- cannot pass through the membrane → stay in A
  K^+ can pass through → follow the concentration gradient
  → uneven distribution of ion

- When equilibrium occur → record the voltage of both A & B with B is reference point
  → We get equilibrium potential (E_{K^+})

- Relationships between { action potential
  membrane permeability
  + The state of Na^+/K^+ channels determine action potential (as said in Polarisation)
  + These phases can be described in following graph

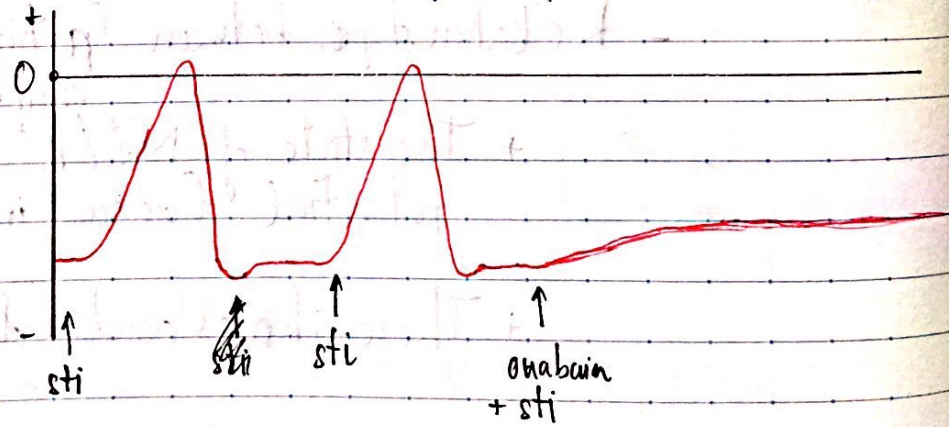


— action potential
— K^+ permeability
— Na^+ permeability

1. Na^+ channels open
2. Na^+ channels close
3. K^+ channels open
4. K^+ channels close
5. peak action potential

– Scenarios:

+ Ouabain blocks NaKpumps:



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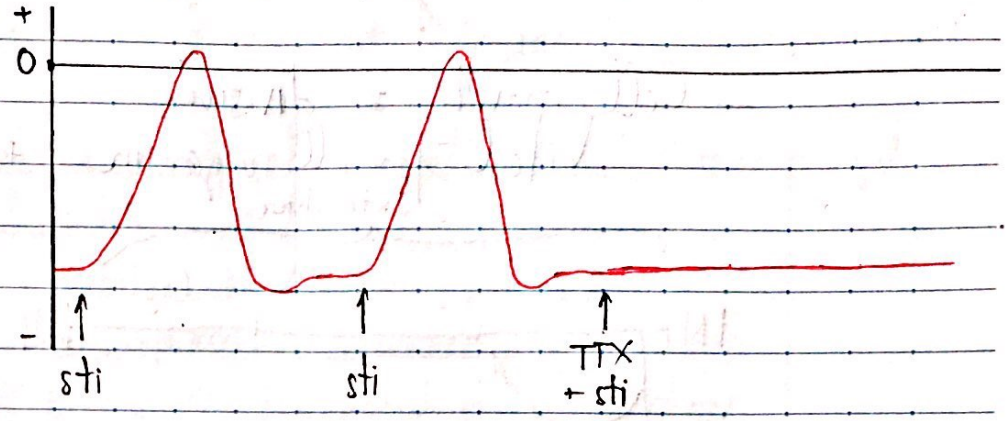
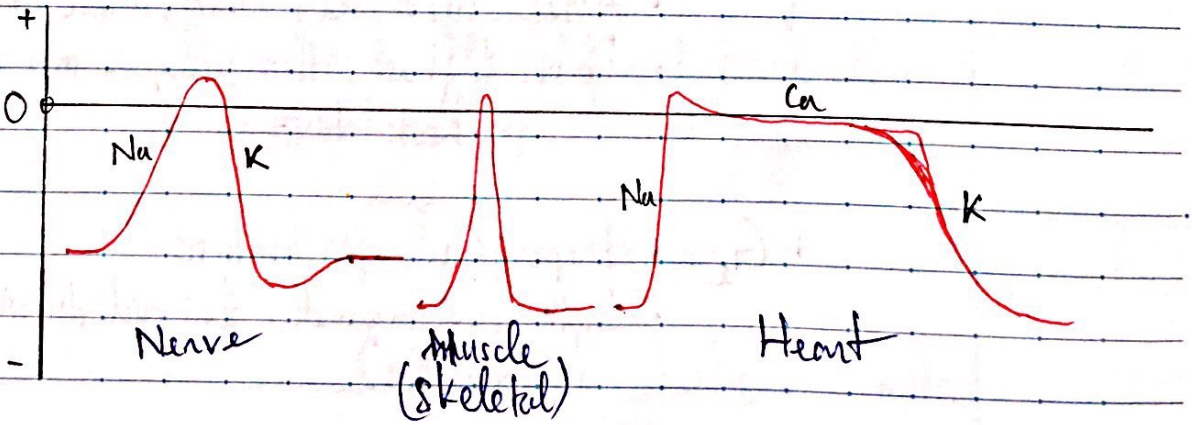
+ Tetrodotoxin (TTX) blocks Na^+ channels.



- Osmolarity & Tonicity
  + Osmolarity: Concentration of all solute particles (penetrating & non-penetrating)
  + Tonicity: Concentration of non-penetrating solute particles
    → determine the effect of solution on the cell
    - hypotonic
    - hypertonic
    - isotonic

- Different types of action potential: throughout different tissues, cells



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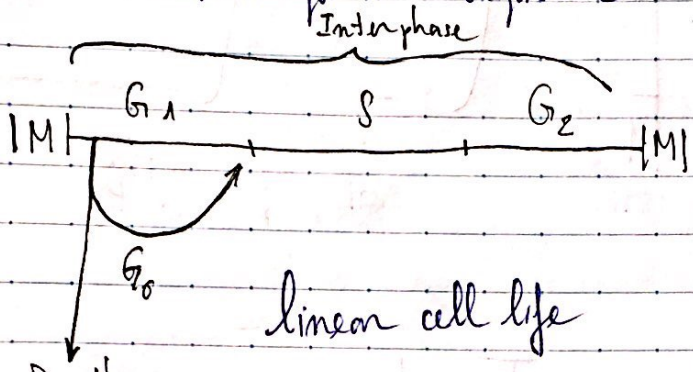
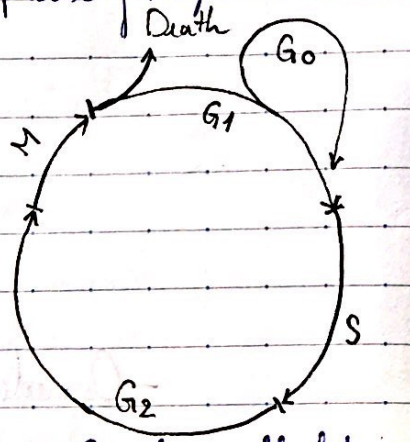
IV) Cell cycle – Cell fate

– Cell growth & division
Vital for all organism + is precisely regulated.



linear cell life



Circular cell life

– Role of each phase:

+ G_1 : • RNA & protein synthesis → cell growth
• At the end of G_1, the cell has accomplished most of of its growth
• Synthesise organelles for fully functioning
• In diploid (2n) state, but not yet duplicate DNA

+ S : • DNA duplication
• After synthesising DNA, double amount of DNA
• Past S phase, the cell goes into a "quality control" point
→ check DNA

+ G_2 : • Preparation for mitosis
• Synthesise organelles that aid division (centrosomes, microtubules)

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+ G_0 : • Resting cells
• Eg: starvation, tissue undergeneration → leave the cycle and rest
• Most of these resting cells are able to re-enter cycle

+ M : • Mitosis
• 4 subphases: prophase
prometaphase / metaphase
anaphase
telophase

– Cell cycle is molecularly regulated by enzymes / protein
→ to ensure { faithful replication
cell growth
mitotic phase

These regulation factor is important as if it is mutated → cancer

Early model (yeast & frog egg) → 2 distinct processes in controlling cell cycle.

The yeast model
– Generate mutant cells (by radiation or chemical)
↔ different cell phenotypes


wild type


elongation mutant


wee mutant

these mutants are called cell-division-cycle (cdc) mutants

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- The elongation mutant spent too much time in G_2
  wee mutant " little " G_2

- Suggestion: some key proteins in controlling cell cycle have been mutated & no longer functioning
  → incorrect transition to M phase

* This is a type of sequential checking: a step must be done before another occurs
→ Checkpoint:
- In G_1: analyse internal & external environment before DNA syn & division
- In G_2: DNA check & repair
- In metaphase: chromosomes positions check

A protein called cyclin-dependent protein kinase (CDK) are known to trigger major events of cell cycle
⇒ Domino theory

The frog embryo model
- The egg move directly and rapidly from S phase to M phase with nonrecognisable G phase

- Chemicals can stimulate an unfertilised frog egg to divide w/ periodic contraction

- Both nucleus-removed and nucleus-containing cells contract at same period → no checkpoint require, but enzyme associated w/ maintaining timing
⇒ Clock theory

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Stem cells

- Cells that can reproduce (renew) themselves and generate more specialised cells
They are pluripotent (or totipotent), which means they can reprodu indefinitely and have capacity to specialise cell

- Embryonic stem cells are pluripotent and can differentiate into any type of cell

- Induced pluripotent stem cell can be created from any cell

⇒ Stem cells are essential for tissue repairing with specialised cells cannot divide anymore.

- In most tissue, there are stem cell niches. The asymmetrical position of the niches (polen) that allow stemcells to divide asymmetrically. There are 2 type of asymmetries:

  + Environmental asymmetry: Because of the effect of hormones, nearby cell, etc., the cells receive the signal inviting differentiation

  + Divisional asymmetry: Due to the polarity during cell division (unbalance niches, ...), 2 daughter cells are not identical.

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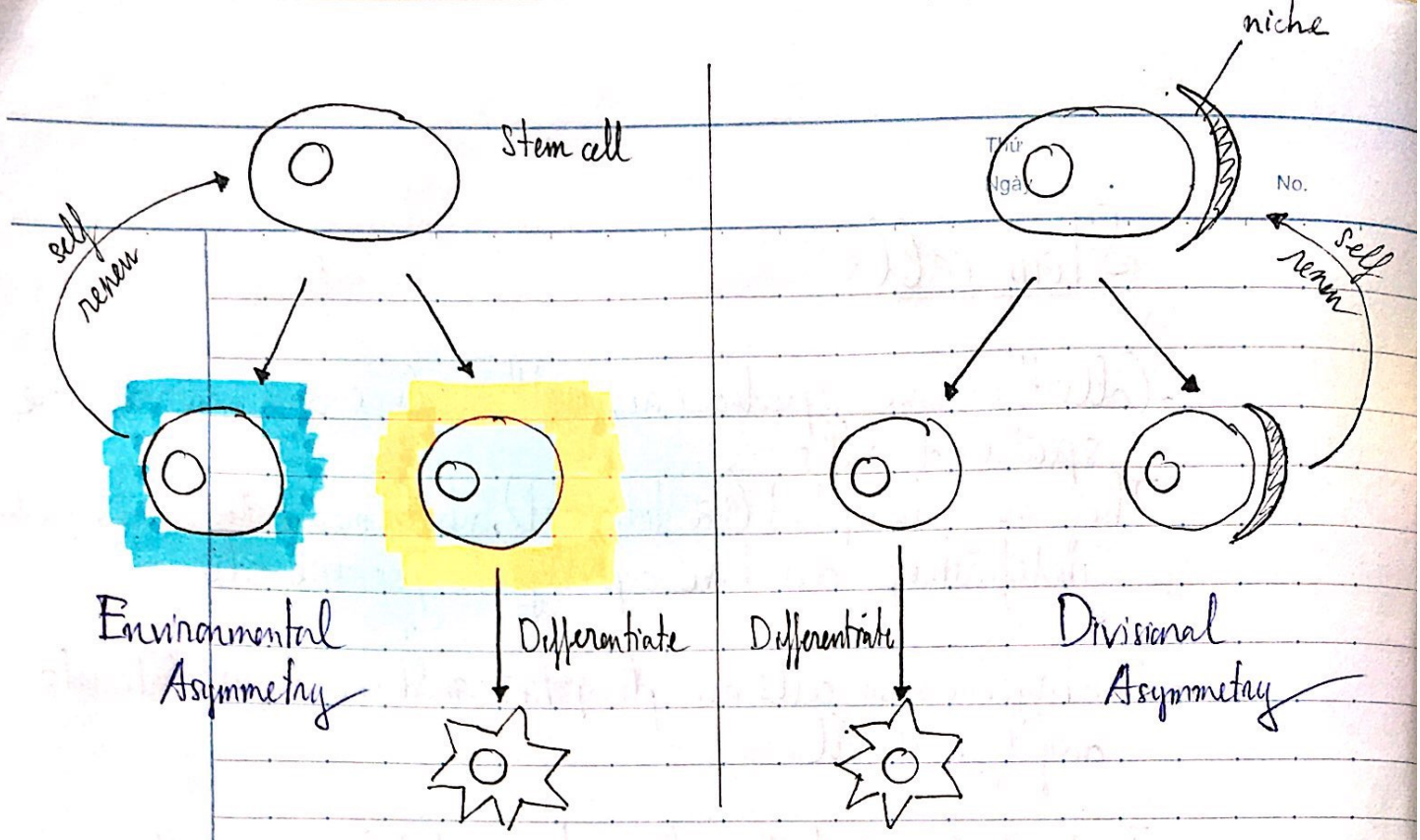
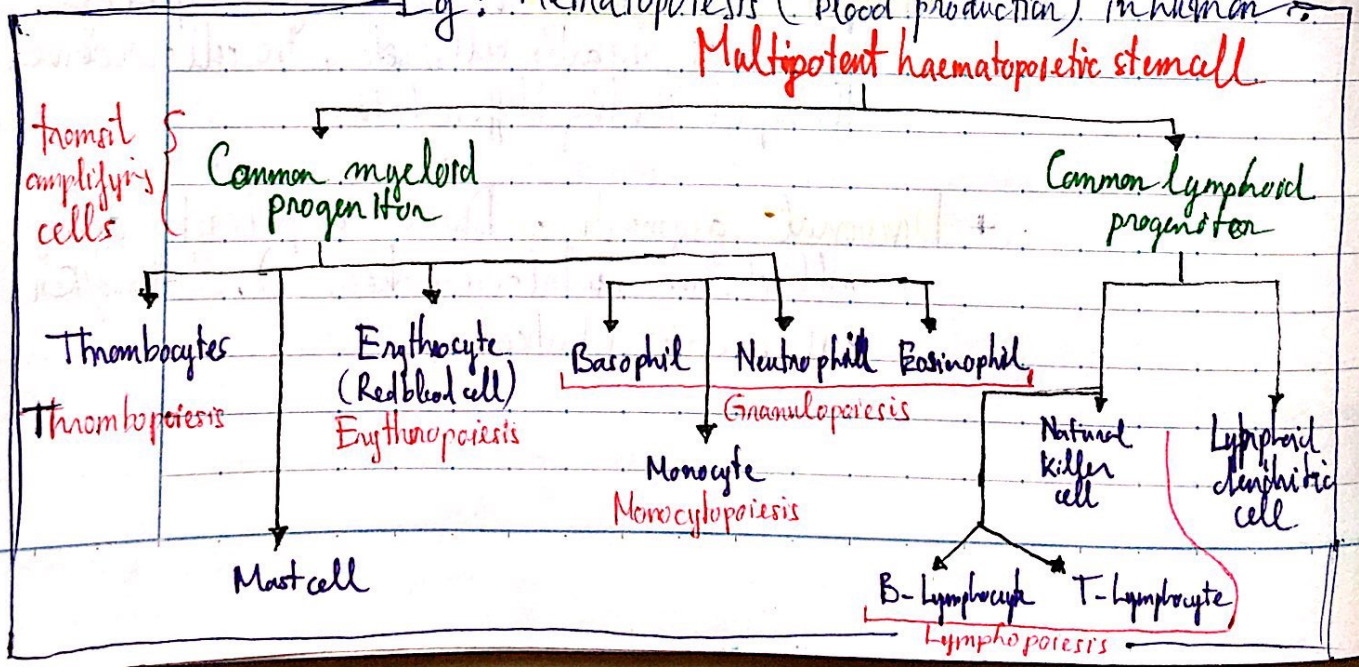


Cell lineage

- Actual stem cells rarely divide since they are often in G_0 phase
  - → Other cells divide more quickly, called transit amplifying cells, and the daughters of these transit cells will differentiated

Eg: Hematopoiesis (blood production) in human:



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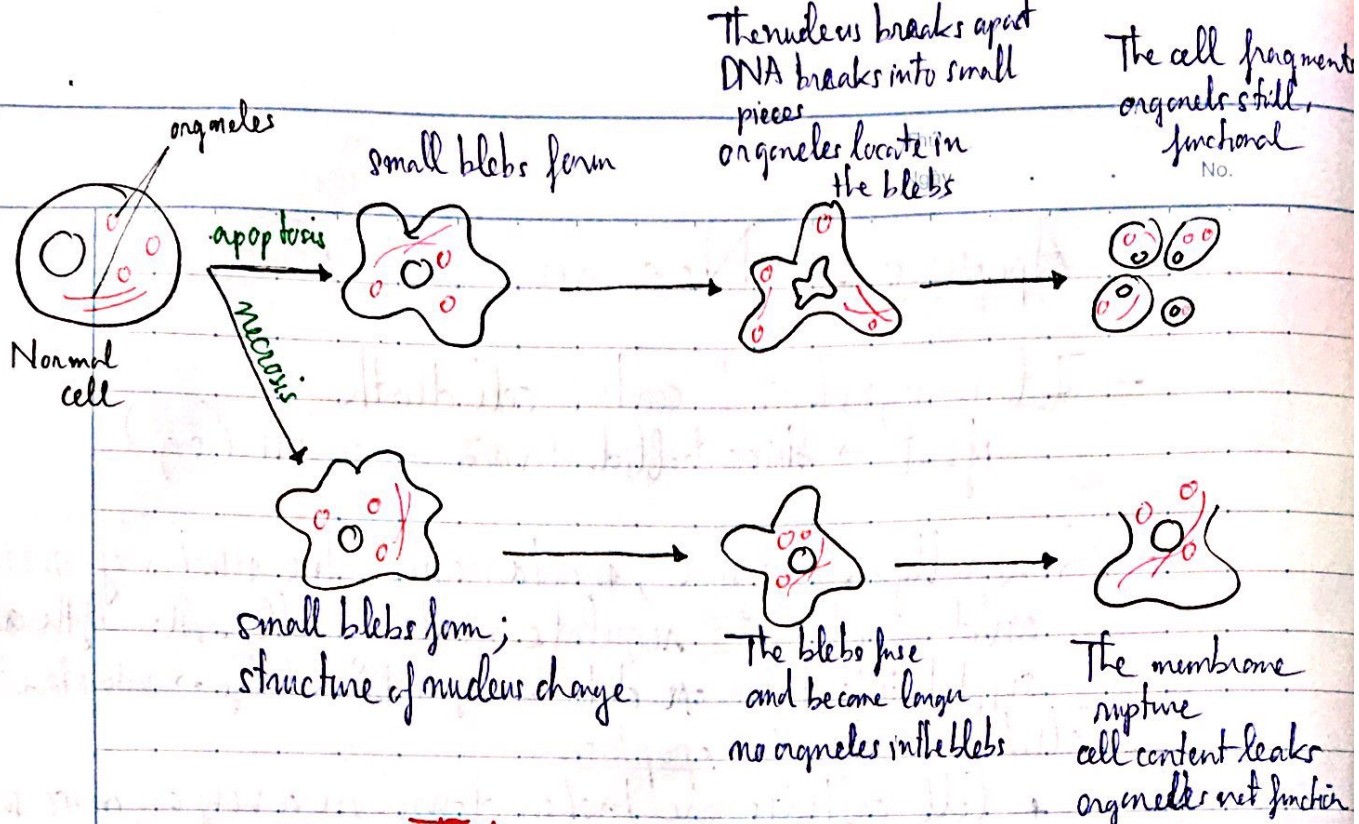
Apoptosis - Necrosis

- It is important to control cell death
  if not → uncontrolled division → cancer (eg.)

- Generally, in tissue, maintenance the number of mitosis and apoptosis to regulate number of cell. Also if the cell no longer supplied with nutrition or detect a major DNA damage → reduce to eliminate

- Cellular change in <u>apoptosis</u>:
  + Cell contents are broken down in a very organise way → no leakage → difficult to detect
  + Begins with membrane convolution, chromosomes compaction, cytoplasm condensation.
  + As the cell start to shrink, nuclear envelope destroyed, membrane enclose particles → cell fragments
  + These fragments are engulfed by phagocytic cells (cells that eat other cells or bacteria, particles)

- Cellular change in <u>necrosis</u>
  + Opposite to apoptosis, necrosis is often messy and toxic for other nearby cells.
  + Many causes of necrosis: O_2 deprivation, virus, damage (eg.)
  + Begin with cell swelling, chromatin being digested, plasma & organelle membrane being disrupted, ER vacualised
  + Then organeles break down completely and the cell spill its content into the extracellular environment, trigger the immune system → inflamation



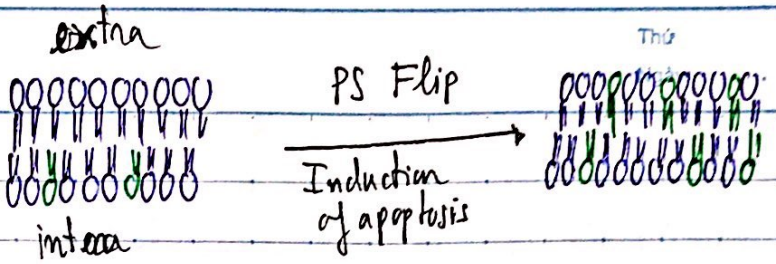
Pathway of a cell's life

- Remember: Unlike "sending out a signal" like necrosis, apoptosis do not send any signal, only release apoptotic bodies & "engulfment protein" to induce phagocytic cells to engulf and break them down ≠ immune response

- Within apoptotic cell, the mitochondria became more permeable & secrete a small protein call "cytochrome c" (important in forming a signaling complex to initiate the programmed degradation of cellular protein by activate a proteases (enzymes that break down peptides) called "caspases" (cysteine-aspartic proteases)

- Another change in apoptotic cell involves the loss of plasma membrane lipid bilayer asymmetry as the glycerophospholipid phosphatidylserine (PS) is now distribute on both side of the membrane

- Cellular DNA is digested by endonuclease (enzymes degrade DNA)
  → Cell content return to original biomolecules, recycled by phagocytes



C. Elegans model

- The model is used to understand the regulation of apoptosis and the specific protein related to it, by studying mutant both forward & reverse genetics
- Worms were irradiated → { wild type; mutants with cell death abnormalities (CED mutants)
- CED mutant either { producing too many cells ← not enough apoptosis; producing too few cells ← too much apoptosis
  ⇒ { same due to the degrading enzymes; same to regulatory component; same to adapter protein (that linked the action of regulator to degradative enzymes)

	Regulator	Adapter	Effector	
C. Elegans	CED-9	→ CED-4	→ CED-3	→ Death
Human equivalent	Bcl-2	→ Apaf-1	→ Casp 9	→ Casp 3 → Death

*Explain: (from right to left, C. Elegans):
- CED-3 is the degradative enzyme, pull the trigger of apoptosis
- CED-4 activate CED-3
- CED-9 bind to CED-4 to prevent activation
- Other enzyme called EGL-1 is transcriptionally activated in respon to death signal, catalyse the release of CED-4 from CED-9

Week 2 6/3/2017

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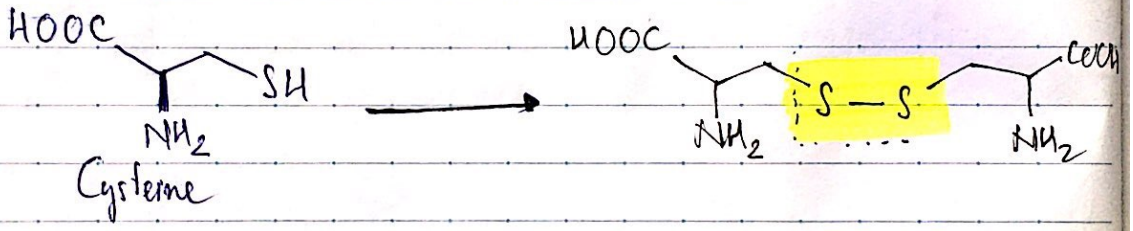
I) Protein – Structure & Function

- Protein conformation: is the spatial arrangement of atom in a protein → every conformation can be achieved without breaking the covalent bond is call possible conformation

- The function of protein depends greatly on it conformation

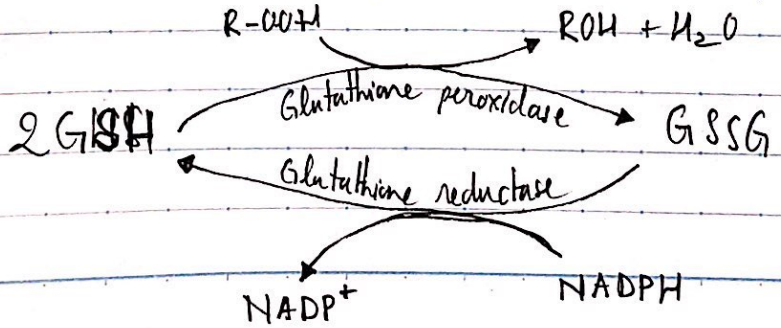
S–S bonds in proteins

- The disulphide (S–S) bonds are covalent bonds that form between the functional R group of Cysteine (Cys) residue and form part of primary structure of protein

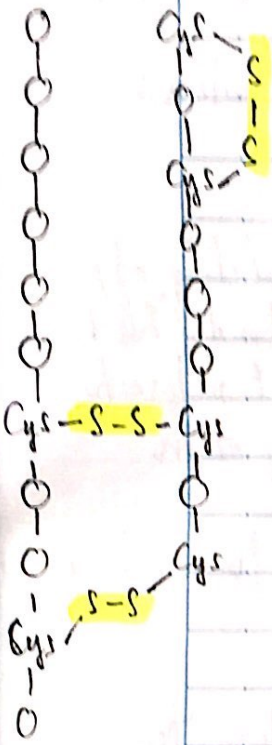


- Eg: Glutathione (GSH) is a tripeptide (γ-Glu-Cys-Gly) and is an example of the S–S reactive nature.

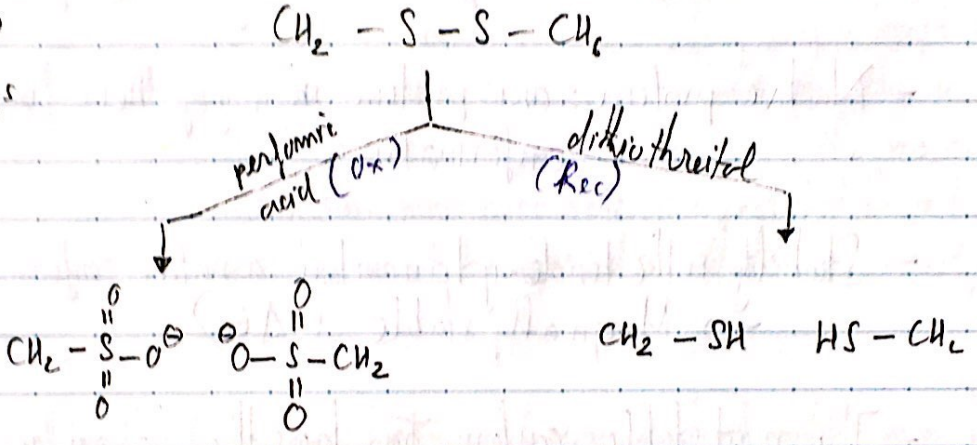
This compound presents in all cell since it is a redox buffer (keep -SH reduced and Iron in Fe^{2+} state) and also remove peroxide toxic



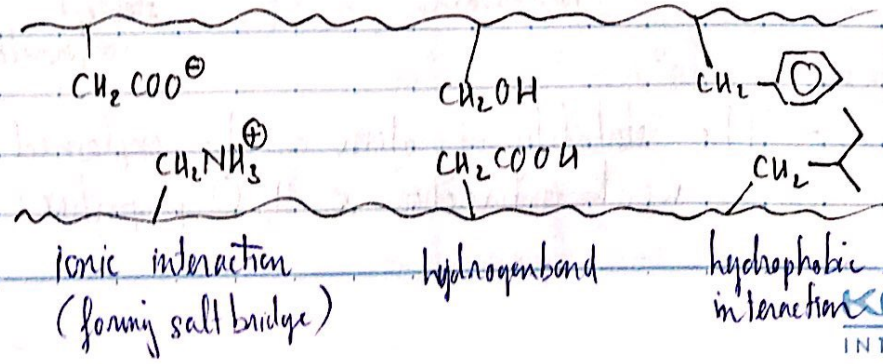
Two enzymes are involved in this process:
- Glutathione peroxidase uses GHS & peroxide as substrates
- Glutathione reductase uses nucleotide co-enzyme NADPH and GSSG as substrates



- Disulphide bonds are a mechanism for sequencing polipeptide chain since they interfeae with the other chain
  → breakdown by many ways.



Weak interactions in 2° & 3° protein structures
- Weak interactions are hydrogen bonds, ionic interaction, hydrophobic interaction.
- These non-covalent bonds also are fundamental in enzyme mechanism, antibody function & receptor-ligand interactions



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- Hydrogen bond can occur between [separate peptide bond / functional group in R

- These interactions affect 3° structure of proteins.

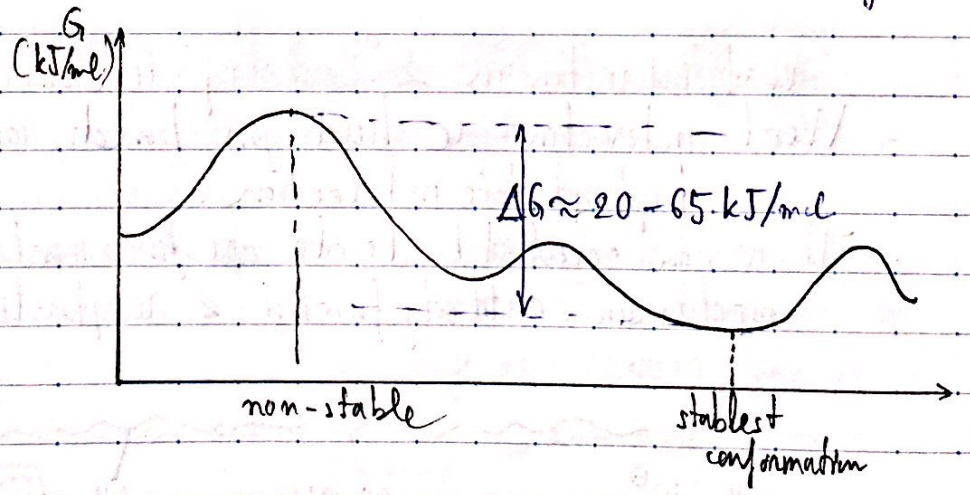
Protein stability

- Weak interactions are responsible for the stability of protein. Even though it is harder to break a covalent bond (200 kJ/mol) than weak interaction (≈ 4-30 kJ/mol), because weak interaction are so numerous → predominantly stabilise protein.

- Native protein: any protein in any of their functional, folded conformations.

- Stability is the tendency to maintain a native conformation
  ⟹ Marginally stable (ΔG)

- The most stable conformation has the lowest free energy (G)



- The stability of protein can be explained in terms of weak interaction & H_2O properties:

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+ As mentiom, weak interactions one the main factor that stabilise protein structure → the one w/ maximum number of weak interaction will have lowest Gibbs free E. (G)

+ Protein stability also depends on Entropy. Even if protein is folded by many weak interaction, because the proteins can also form hydrogen bonds with H_2O → there would be no much difference between the folded and unfolded conformation (due to the increase entropy when reacting with H_2O). However, there are hydrophobic residue inside the protein structure, if these interact with H_2O, they will interupt the hydrogen bonds between H_2O - H_2O, leading to the rearrangement in H_2O → decrease S. Therefore, the maximum weak interaction must cooperate the fact that those hydrophobic residue must be buried inside the folded protein.

- Each protein has been designed to function in a particular environment. Human body can be considered a mild environment, with some exceptions. Extreme conditions could result in changes of protein structure, therefore maybe function. This is called Denaturation. These conditions, such as pH, heat, physic, urea, detergent and organic solvent, affect the weak interactions of protein (primarily hydrogen bonds)

Eg: • Heat: If ↑°/ gradually, the protein will remain intact until and abrupt loss of structure

• pH: The change of pH will alter the net charge and disrupt some hydrogen bonds.

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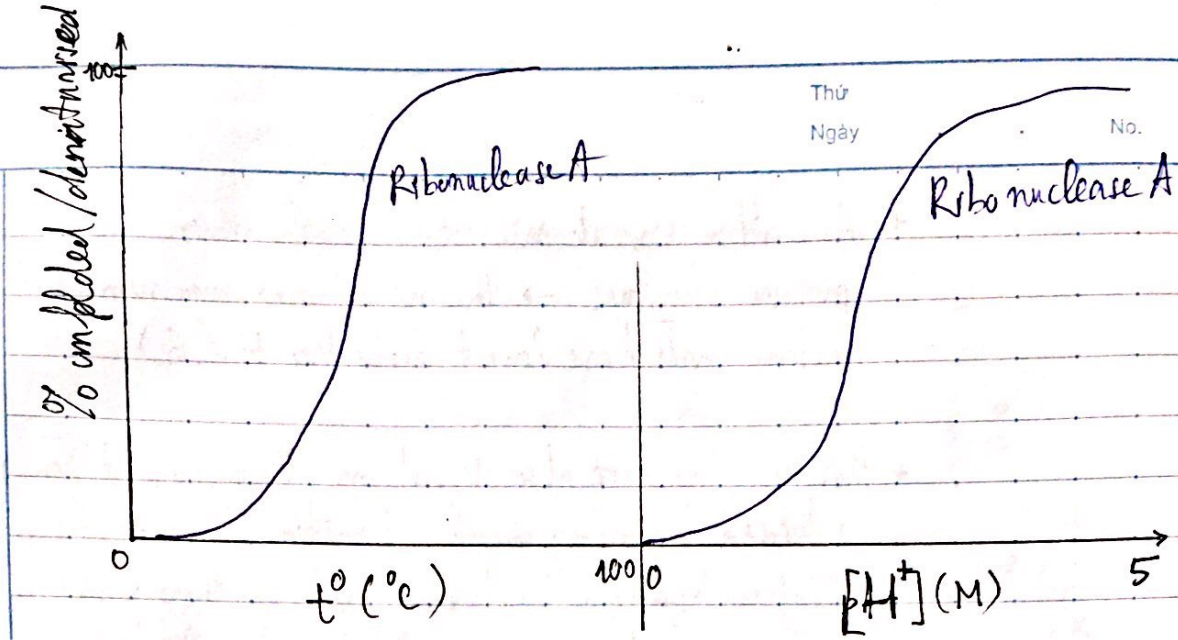
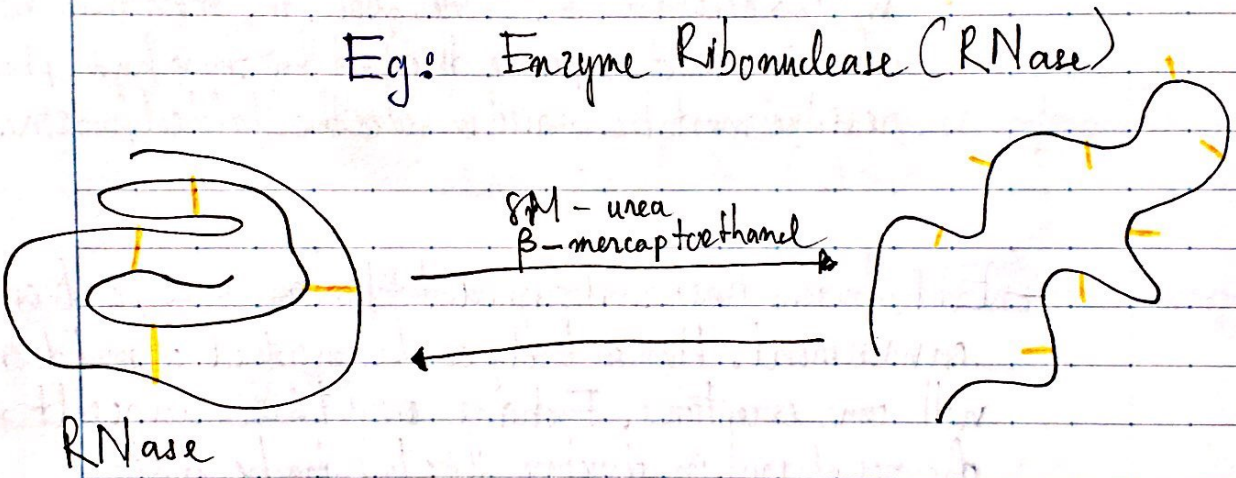


- The 3° structure of globular protein is determined by its aa sequence → denaturised protein can regain its native conformation. This is called Renaturation.

Eg: Enzyme Ribonuclease (RNase)



- The urea disrupt the hydrophobic interaction
- The β-mercaptoethanol is a reducing reagent, cut the S-S bond, create Cys residues
- After the urea & reducing reagent are removed, the random chain of aa refold with high accuracy rate (the same positions of 4 S-S bonds)
- Even though this protein can do this, but this only apply for the minority. Others may need assistances (molecular chaperone)

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pH & net charge of polypeptides

- Human body is a mild condition, where pH overall = 7, $t° = 36°C$
  However, there are still some varieties:
  - pH in stomach ≈ 1 - 2
  - pH small intestine ≈ 8
  - pH ~~white~~ blood ≈ 7.4

- Proteins can change their function due to the change of pH
  pH affects the net charge of aa chains.

- Using Hasselbach-Henderson equation to calculate the net charge of amino acid.
  - $pK_1 = -\log(K_{-COOH\ term})$
  - $pK_2 = -\log(K_{-NH_2\ term})$
  - $pK_i = -\log(K_R)$

The pH value at which aa contains no net charge is called isoelectric point (pI)

- Derivation from Hasselbach-Henderson equation

$$pK_a = pK_a + \log\frac{[A^-]}{[HA]}$$

$$Q^- = \frac{(-1)}{1 + 10^{-(pH - pK_a)}} \quad ; \quad Q^+ = \frac{(1)}{1 + 10^{+(pH - pK_a)}}$$

$$Q_{mole} = \sum Q^+ + \sum Q^-$$

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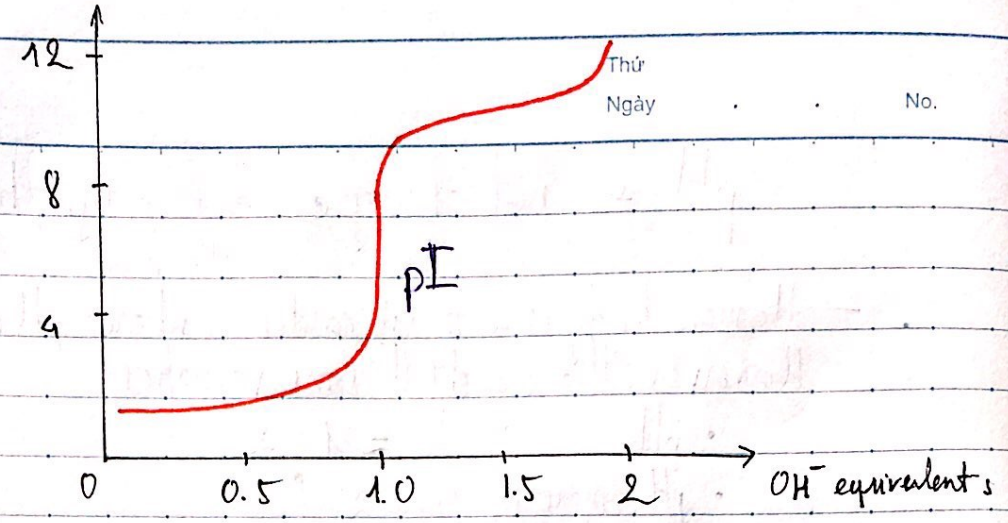

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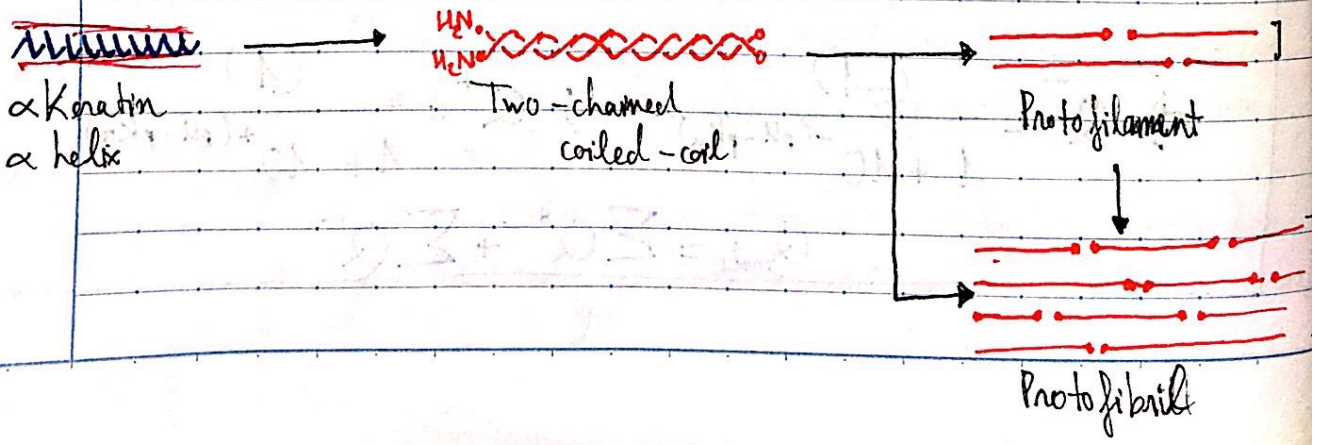
Structural Proteins

Keratin

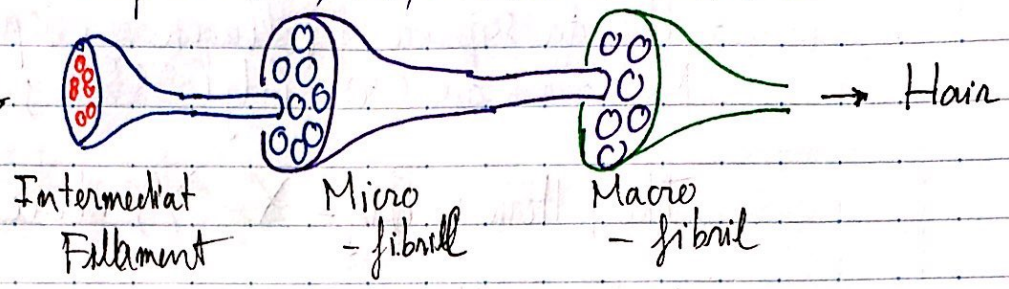
- Keratin is a simple structural protein with coiled-coils that interact to form tetramers that assemble in filament or bundles to eventually forms hair & nail. Other keratins are responsible for nails formation

- α-Keratins are a part of a broader family called intermediate filament (IF) protein (all IF proteins have the structural function and share the structural feature)

- α-Keratin is a right handed α helix. 2 strands of α-keratin with amino termini at same end, wrap each other to form a supertwisted coiled-coil → very strong. This coil is left handed.



- The surface of the coil are made up with hydrophobic aa residues, their R groups mesh together in a regular interlocking pattern
  → High in Ala, Val, Leu, Ile, Met, Phe



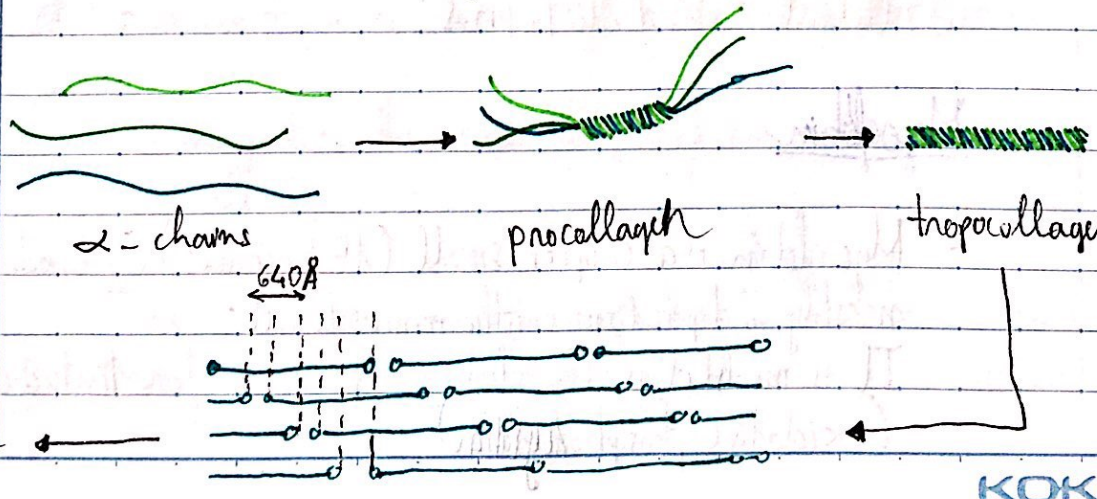
- Usually, covalent bonds don't exist between 2 polypeptide chains. However in Keratin, the strength is enhanced by S-S bonds

Collagen

- There are many type of collagen. Like α-Keratin, collagen is used to increase strength.

- Collagen helix is quite distinct from the α helix
  → call it **α-chain**

- Collagen is also a coiled-coil, but different 3° & 4° structure: it is a trimer of 3 α-chains supertwisted about each other, and this is right handed.



- Collagen are secrete into extracellular matrix or interstitial space where they serve vital structural role

- The aa sequence of collagen is a repeating tripeptide pattern. Most common aa are: Gly (35%); Pro (21%); Ala (11%)

The pattern is Gly – X – Y, where Y often is Proline

Proline & Hydroxyproline allow very tight turn to occur in the aa chain that only Gly can fit into

Hydroxyproline formation depends on Vitamin C (ascorbic ac

- The role of collagen can be studied thru Inherited genetic mutation as the mutation results in defects in aa chain of collagen. Those who suffer from these defects are said to have Ehlers – Danlos syndrome, characterised by very elastic skin

Globular Proteins

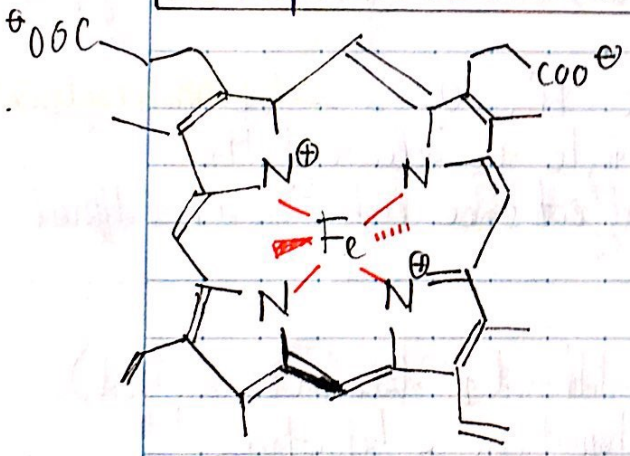
Myoglobin

- Myoglobin is a compact, small (153 residues) O_2 binding protein, mostly and predominantly in muscle cells
It is involved in O_2 storage & transport for mitochondrial oxidat (oxidative phosphorylation)

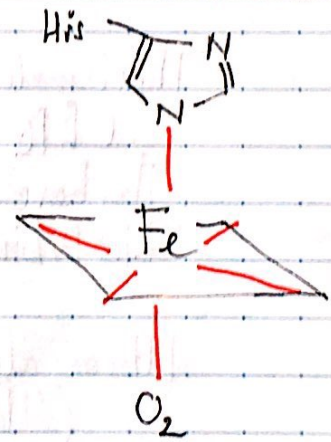
- Myoglobin is a conjugated protein, containing as prosthetic haem.

* Conjugated protein: protein contains additional group (prosthetic group) that are essential for its function. These group can link to aa by covalent bonds with R group.

Class of prosthetic protein	Prosthetic group
Lipoprotein	Lipid
Glycoprotein	Carbonhydrate
Phosphoprotein	Phosphate group
Haemoglobin	Haem (Iron porphyrin)
Flavoprotein	Flavin nucleotides
Metalloprotein	Iron, Zn, Ca, Cu, Molybdenum.



The organic structure (protoporphyrin) binds an iron atom in Fe^{2+} state.



One perpendicular is bond with a N atom in His R group

- In this pocket, the accessibility to haem group is limited and restricted.
→ only O_2

The iron in the haem group from Fe^{2+} will be oxidised rapidly to Fe^{3+}, which won't bind O_2

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Haemoglobin

- Heamoglobin is a tetramer (2α ; 2β subunits)
Although the aa sequence is different from Myoglobin, each chain has 3° structure similar to Myoglobin

- Hb has 4° and the different subunit interact with each other, affect the way it binds to O_2 (and CO_2).

The binding of O_2 & Hb is ~~has~~ example for positive - cooperativ
where 1 O_2 binds to Hb, it is easier for another O_2 to bind.

- Hb is also a allosteric protein, which has additional binding site for other molecules, thus alter the conformation of protein

These molecules can be H^+, CO_2 & 2-3 Bisphosphoglycerate (BPG) which promote O_2 release of Hb
They have additional effect since each ligand has different site to bind to.

Hb can also bind to additional modulators (in blood)
(Additional info: homotropic & heterotropic)
- The amount of CO_2 is also related to amount of H^+ (Bohr effect)

The Bohr effect

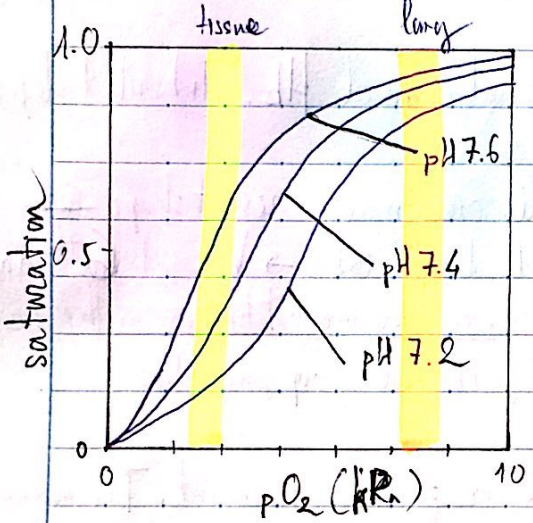
- The pH & CO_2 concentration on the binding and release O_2 by Hb is called the Bohr effect

- Hb transport about 40% H^+ (in total amount), ≈ 17% CO_2
(the remaining H^+ is absorbed by HCO_3^- buffer
CO_2 as dissolved HCO_3^- & CO_2)

- The binding of CO_2 & H^+ >< the binding of O_2 :
  - Low pH & high $[CO_2]$: affinity for O_2 ↓ → O_2 is released to tissues
  - High pH & low $[CO_2]$: ↑ → Hb binds O_2 in lung

$$HHb^+ + O_2 \rightleftharpoons HbO_2 + H^+$$

$$CO_2 + H_2O \underset{\text{carbonic anhydrase}}{\rightleftharpoons} HCO_3^- + H^+ \text{ (tissue)}$$



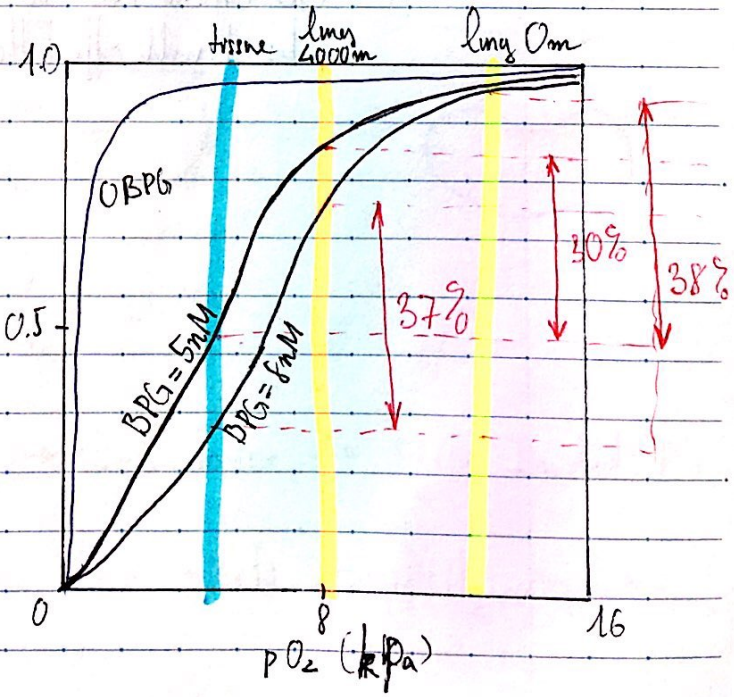
At tissue, mitochondria proceeds respiration
→ release CO_2 → $[H^+]$ ↑ → pH ↓
→ release O_2

At lung, exped. CO_2 → pH ↑ → bind O_2

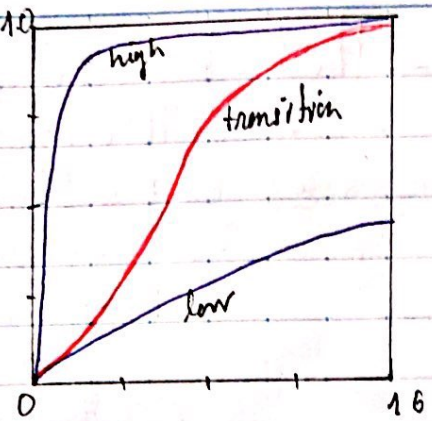
BPG on Hb-O_2 :

BPG decreases the affinity of Hb to O_2

- At sea level, low BPG = 5mM
  → O_2 release in tissue ≈ 38%
- At 4000m, low BPG = 5mM
  → O_2 release in tissue ≈ 30%
- At 4000m, ↗ BPG = 8mM
  → O_2 release in tissue ≈ 37%



In summary, the best way Hb binds and releases is follow the hybrid state of high affinity and low affinity (a sigmoid curve)
Bind good at lung
Release good at tissue



Hb disease

- Haemoglobinopathies are abnormal Hb. Inherited defect in Hb can lead to diseases.
  Eg: sickle cell anemia, cresent shape erythrocyte are presented. due to Glu → Val at 6th aa.
  this is a non-conservative substitution as the aa have different functional group properties

- Thalassemias, either α or β chain is absent. The amount of absent will affect the severity

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II) Enzymes & Co-enzymes

Ligands & enzymes

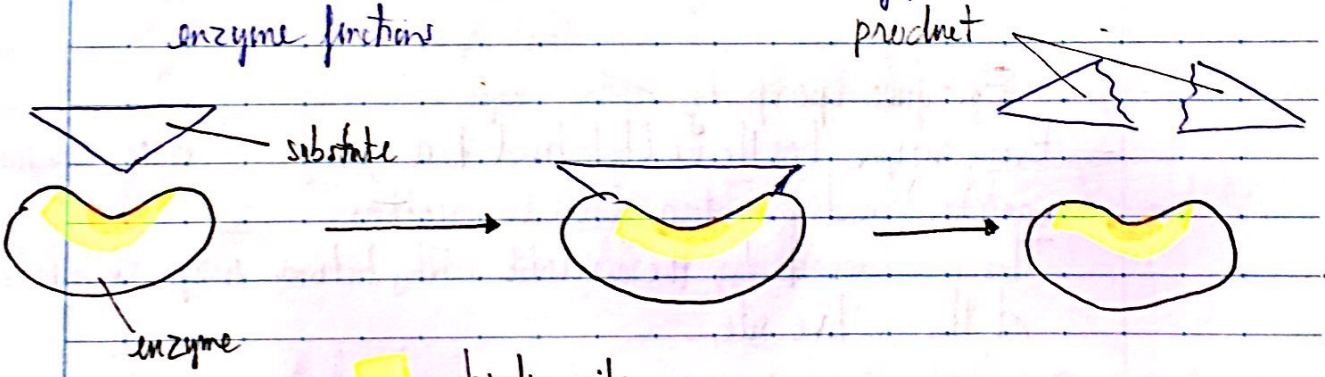
- Ligands are molecules that can bind reversibly to macromolecules. The specific sites that ligands bind to are binding site.

Receptors & antibodies are example of protein that bind to specific ligands (can be any kind of molecule) via non-covalent or weak interaction

- Enzymes are protein that catalyse changes to the ligand (substrate) by weak interaction.

The binding of substrates or inhibitors to enzyme is an example of receptor-ligand binding

Enzymes are generally monomeric or 4° structure, act as biological catalysts under mild condition. All structural levels of protein are essential to enzyme function



$$\text{Enzym}(E) + \text{Substrate}(S) \rightarrow E\text{-}S \text{ complex} \rightarrow E + \text{Product}(P)$$

There are 5 main features: Reaction rate, specificity, regulation

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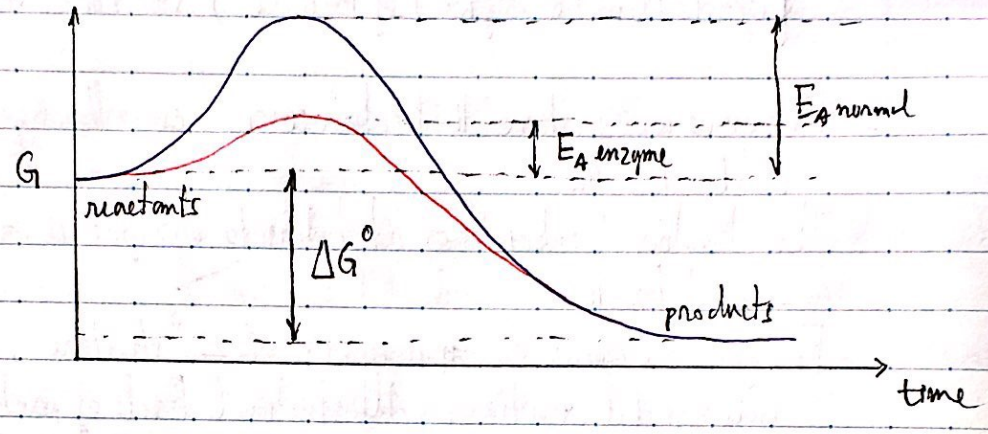
Enzyme reaction rate

- Enzymes have high reaction rate when enzymes can boost reaction $10^5 \rightarrow 10^{17}$ time faster than non catalysed reaction.
When bind to E to form ES complex, the E_A is lowered.

- Enzymes do not change the equilibrium, just speed up the process of reaching equilibrium by lowering E_A



Enzyme specificity

- Every enzyme has the ability to bind to a specific substrate (or some varieties) and promote a particular reaction.
This is achieved by the reversible binding between enzymes & substrates at the active site.

- The 3 dimensional structure of enzyme allow and restrict the substrate

- The aa residues in the active site are responsible for facilitating reactions

- Enzymes are classified by the reaction they catalyse. Most enzymes' name will end with -ase (not works for many member of zymogen)

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+ Oxidoreductase : transfer e (hydride ion or H^+)
+ Transferase : transfer functional group
+ Hydrolase : hydrolysis reaction
+ Lyase : cleavage of group to form double bonds
or addition of group to double bond
+ Isomerase : transfer group within molecule → isomer
+ Ligase : bond formation by condensation + ATP cleavage
+ Kinase : transfer PO_4^- to specific substrate

Enzyme regulation

Very important since enzymes should be ready so that their catalytic capacity is modulated to response to changes in cellular envi

- pH & t°: like protein

- Enzyme concentration: the amount of Enzyme is influent by m RNA degradation and the actual enzyme degradation
Rate of enzyme synthesis can be controlled by transcriptional activity

- Substrates - Products concentration: Enzymes don't change K_{eq} and ΔG°
→ follow the rules of equilibrium

- Tissue & cellular location: Some enzyme can only be active in a particular environment (extreme)

Iso enzymes (Isozymes)

- Enzymes with different structure catalyse a same reaction
Often found in different tissue (or organelle)

Eg: the different isozymes of creatin kinase e

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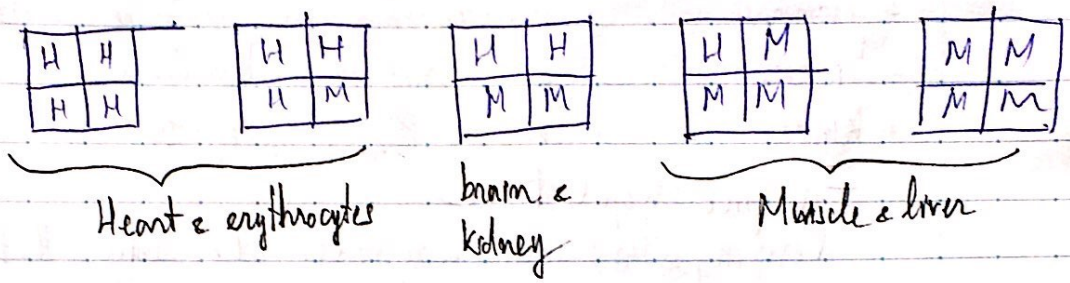
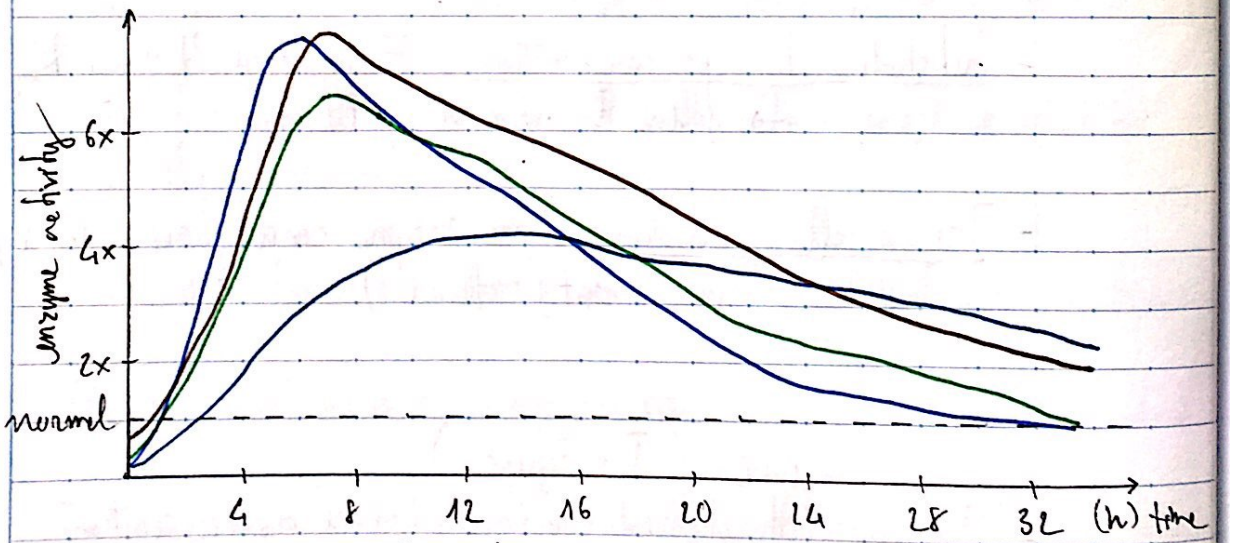
~~Lactate~~ lactate dehydrogenase (LDH)

- LDH is a conjugated enzyme that is a tetramer found in both skeletal & cardiac muscle. There are 2 types of subunit: a heart predominant (H) and skeletal muscle (M)



- Advantage: • customised enzyme for specific reaction and environment
  • meet the metabolic needs of particular tissues

- Very useful in diagnosis for tissue damage
  Eg: LDH, creatine kinase can be used to diagnose heart attack (myocardio infraction)



- Myocardiac infraction is the term for the heart attack by the blockage of Cholesterol and the artery suddenly cracks.

- When the heart muscle is damage, the cells die because of necrosis
  → burst and the cytoplasms (containing enzymes) leak out
  → Enzymes concentration ↗ abruptly, and degrade slowly.

- Additional: Patient are given aspirin to reduce the pain
  Aspirin act as a competitive inhibitor and the binding w/ receptors are irreversible.

Regulation of enzymes by covalent modulation

Irreversible covalent modulation

- Zymogens are eg. of irreversible covalent modulation of enzyme function
  Zymogens in inactive form, can be cleaved by other enzymes, proteases, to become active.

  Eg: - Digestive enzyme (trypsinogen) is converted to trypsin in small intestine
  - Pepsinogen → Pepsin in stomach

  - Enzymes involved in "Blood clotting cascade".

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Reversible covalent modulation

- Happens when a small molecule binds to the enzyme via a process catalysed by another enzyme. Mostly encounter: phosphate group. Other group: acetyl, thiol, hydroxyl, glycan, lipid.

- Kinase will add a PO_4^{3-} to a specific aa w/ an alcohol side chain in it; phosphotase can remove PO_4^{-}.
The change in protein conformation is due to the change in the charge that the PO_4^{3-} binds to.

Regulation of enzymes by non-covalent modulation

Cofactors & Coenzymes

- They are prosthetic group that are essential for enzyme function. Even though mostly are non-covalent, some time covalent bonds also involved

  - Cofactors: Metal ion (K^+; Zn^{2+}; Ca^{2+}; Fe^{2+}) that take place in catalysis
  - Coenzymes: Organic cofactors. They cooperate with enzyme by bringing specific atoms or functional groups.
    Often, coenzymes are derived from vitamin
    (Body can also generate metabolic coenzymes)

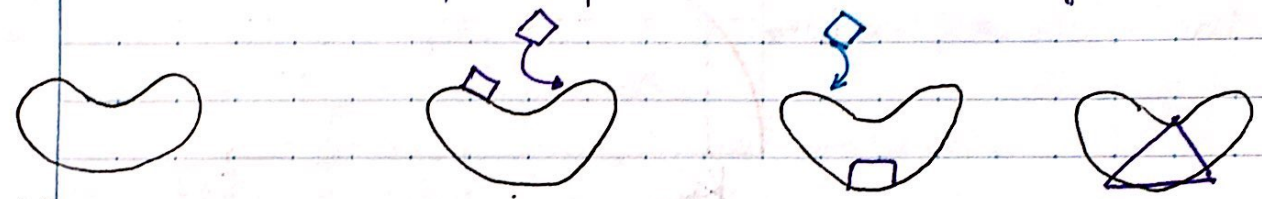
- Coenzymes often contain nucleotide group, such as nicotinamide adenine dinucleotide (NAD^+) involved in dehydrogenase reaction, carrying hydride ion (H^-)

Other coenzymes carry acetyl & acyl group (coenzyme A), CO_2 (biotin), amino (pyridoxal phosphate), one-C groups (tetrahydrofolate) & PO_4^{3-} (ATP & other nucleotides)

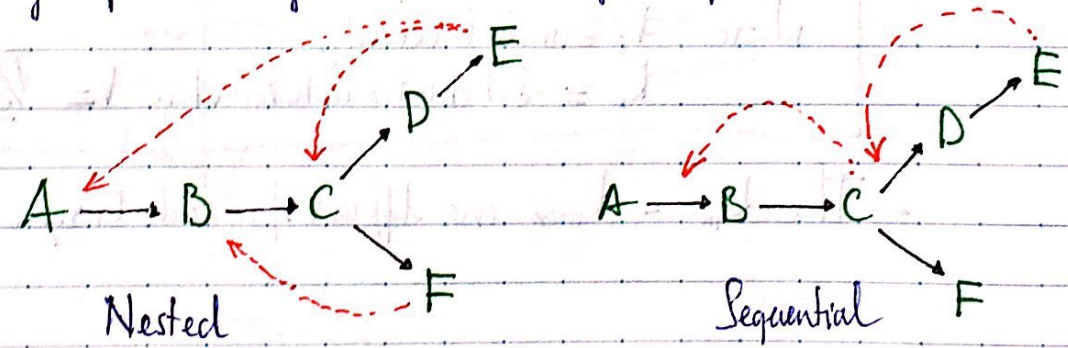
- Vitamins are precursors of several enzyme
  → Absence of any vitamin leads to characteristic deficency disease.

Allosteric modulation

- Allosteric enzymes are modulated by a non-covalent binding of a ligend to an alternative site (allosteric site.)
  ⟶ Changes in shape and alter the activity



- Allosteric modulation is very common and can regulate metabolic pathways
  Eg: a product may inhibit the enzyme before that.



- Allosteric enzymes are often oligomeric (have few repeating unit)

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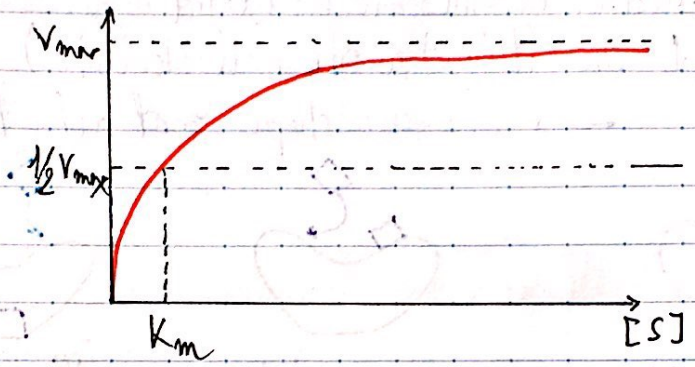
Basic Enzyme kinetics

- This deals with the rate (speed) of enzyme catalysed reactions
  Enzyme velocity refer to the rate of the reaction

- Initial velocity (V_0) is the fastest rate of an enzyme
- The Michaelis - Menten graph:



Michaelis - Menten equation

$$V_0 = \frac{V_{max} \cdot [S]}{K_m + [S]}$$

where V_0 = initial velocity,
K_m = Substrate concentration when $V_0 = \frac{1}{2} V_{max}$

- The K_m & V_{max} are different for each Enzyme & substrate

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Enzyme inhibitors & drugs

Reversible inhibitors

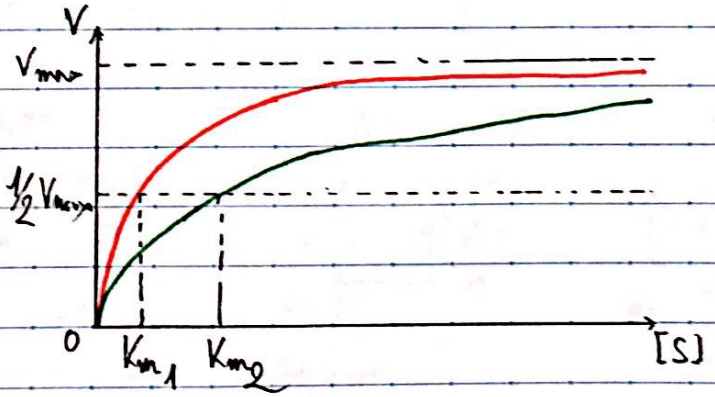
- Bind to enzyme by weak interaction and can be dissociated from the enzyme ⟶ follow Michaelis-Menten kinetic as substrate

Competitive inhibitors

- Act as a false substrate, bind to the active site
The inhibitor resemble the native substrate and form weak interaction w/ enzyme ⟶ favorable
By adding main substrate, the reaction ⟶ normal.

⇒ Competitive inhibitors ↗ K_m but don't change V_{max}

Eg: • Treat methanol ingestion by ethanol
• Ibuprofen



Irreversible inhibitors

- Bind to enzyme by covalent bonds at or near active site
aa w/ -OH or -SH are particularly vulnerable

Eg: Aspirin permantly block cyclooxygenase in prostaglandin synthesis.

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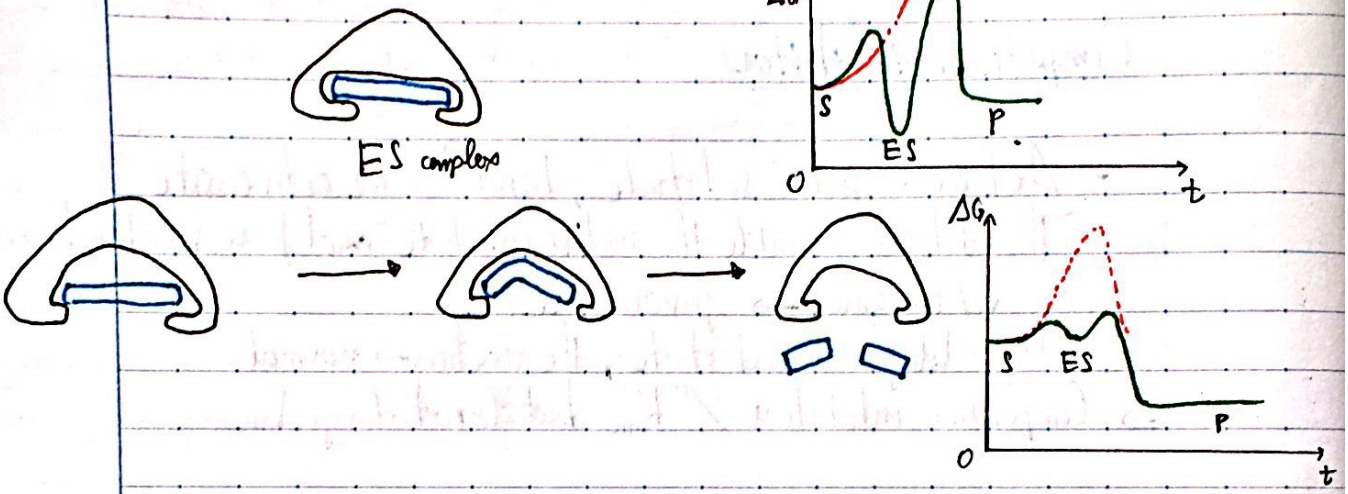
Active site ε complementary to substrat vs transition state

- If the active site of enzyme bind perfectly w/ substrate, it will stay there firmly since it is in the stable state.

- In fact, the active site will encourage the formation of the substrate into transition state → lower E_A.



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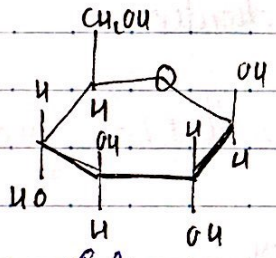
III) Complex Carbonhydrates

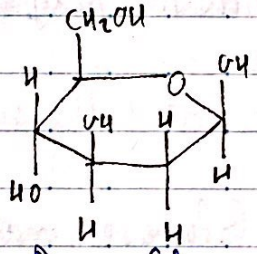
- Sugar & starch are a major part of human's diet. Oxidation of Carbonhydrates is the central energy-yielding pathway in all cells in bodies

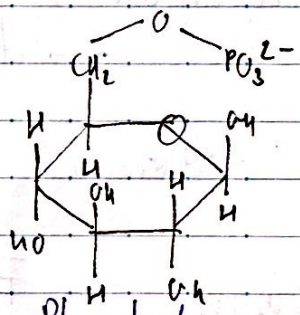
- Carbonhydrate is the most abundant biomolecules on earth
  - Structural support in plants, bacteria, insects
  - Supporting connective tissue, lubrication of skeletal joints & cell adhesion

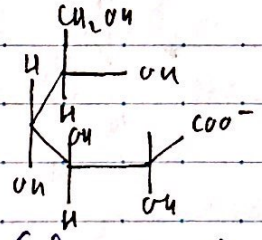
Introduction

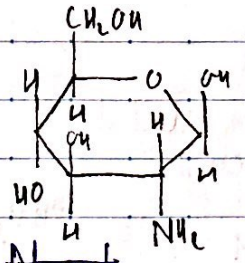
- Glucose and some derivatives:

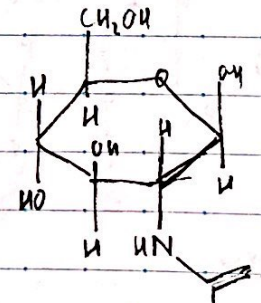

Glucose

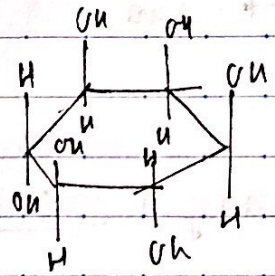

Deoxy-Glucose

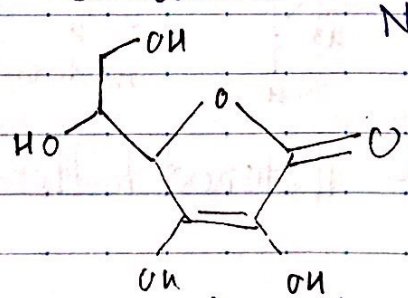

Phosphoglucose


Gluconic acid

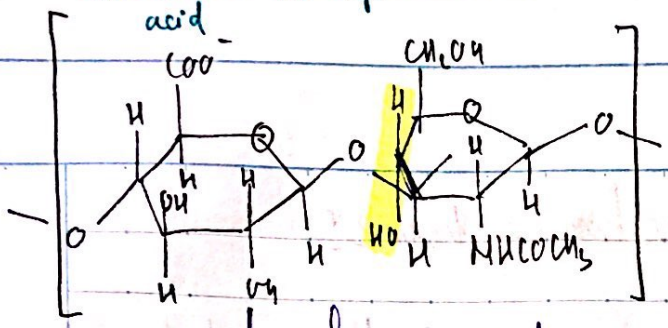

Glucosamine


N-acetyl-glucosamine


mositol

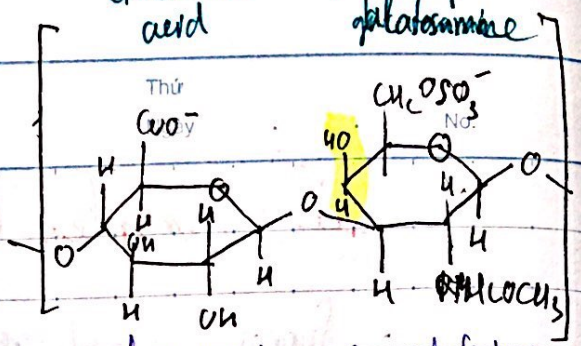

ascorbic acid
(vitamin C)

Glucuronic acid — N-Acetyl Glucosamine



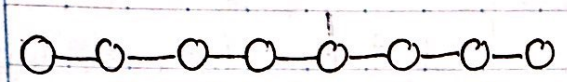
hyaluronic acid

Glucuronic acid — N-Acetyl galactosamine



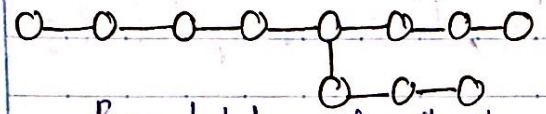
chondroitin-6-sulphate

- Similar derivatives can be generated of other monosaccharides.

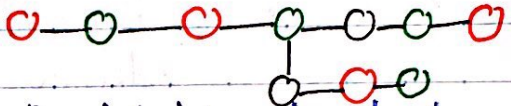


Unbranched homopolysaccharides

Unbranched heteropolysaccharides



Branched homopolysaccharides



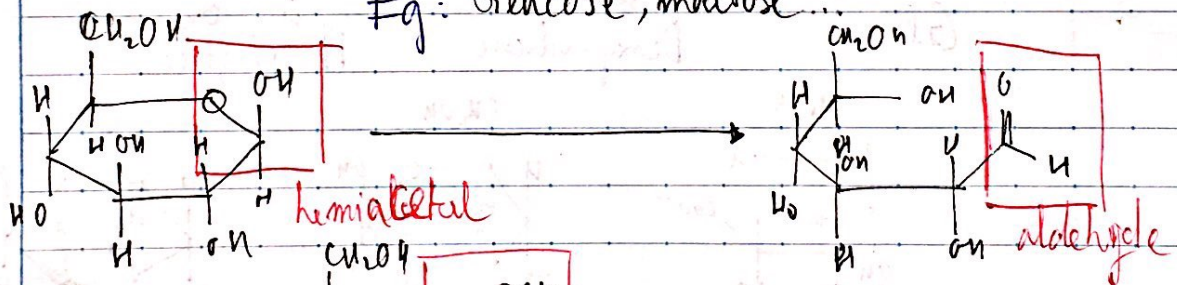
Branched heteropolysaccharides

- Sucomplex → 1 way to order it is to identify reducing end
→ direction in polysaccharides

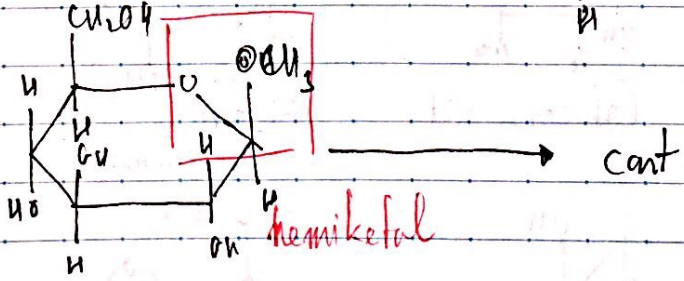
Reducing end is the part of the sugar that has a reducing property

Eg: Glucose, maltose...

reducing



non-reducing



- The C that is next to the O in the ring is anomeric C

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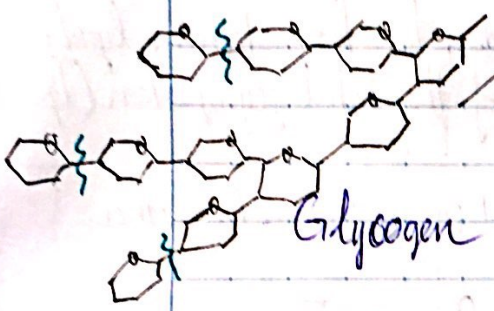
Carbohydrate macromolecular structure

- Branched glucose homopolymers → used to store glucose
The major homopolysaccharide in the body is **Glycogen**

Amylopectin has the similar structure but w/ fewer branches



Glycogen

- Non-reducing ends will be cut off by digestive enzymes

- Glycogen breakdown is the response to low sugar blood levels.
The key enzyme activated is **Glycogen Phosphorylase** that catalyses glycogen breakdown at non-reducing ends. This enzyme is present in liver & muscle cells → Liver is important in blood glucose homeostasis

- Glycogen is synthesised in liver when sugar in blood is high. **Glycogen Synthase** is the key enzyme in extending the polymer

Usually, glycogen links to a core protein or glycogenin at the center of the molecule
More specific, when link to glycogenin, link to Tyr in glycogenin

- Adding reducing ends is a good idea because the energy source is more accessible.

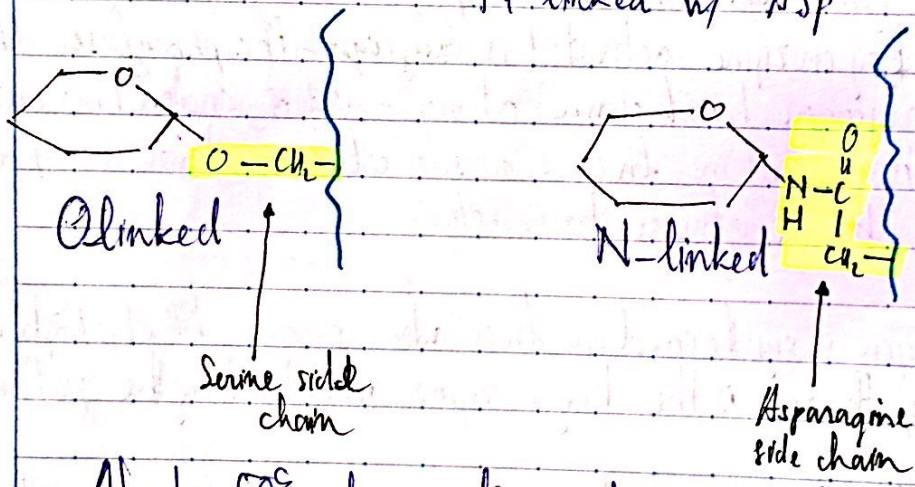
Complex carbohydrates

Very common. Usually contain an Oligosaccharide or Polysaccharide and another bio molecule forming glycoconjugates.

Many are heteropolysaccharides

Glycoproteins & Glycolipids

- Glycan units add a hydrophillic dimention to proteins or lipids.
  Glycan may account for 1-70% of the total glycoprotein (lipid) mass
- Glycoprotein may have several different sugar joined by either α or β linkage.
  The glycan is either O-linked w/ Ser or Thr residues
  N-linked w/ Asp



- About 50% of mammalian proteins are glycoprotein
  Eg: Antibodies

- Not all glycoproteins are secreted as glycolysation is important in directing protein to there cellular compartment
  Eg: Most proteins in lysosome are glycosylated

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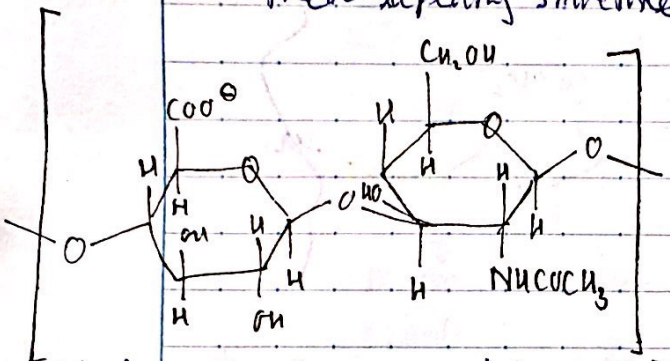
Ngày . . No.

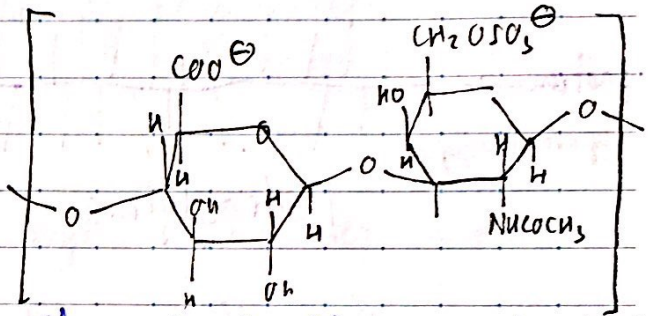
Glycosaminoglycan

- Found in ECM and play a vital role in maintaining H_2O. They are heteropolysaccharide consisting unbranched repeating negatively charged disaccharide units containing amino group.

- Glycosaminoglycans are stretched out because of the (-) charged in their repeating structure



Hyaluronic acid – repeating heteromer of β-glucuronic acid linked by β1-3 to N-acetylglucosamine. ~5000



Chondroitin 6-sulphate – pretty much same with Hyaluronic acid but w/ OSO_3^- at C_6, have shorter chain 15-60

- Sulphated glycosaminoglycans include chondroitin sulphate; Keratan sulphate; heparin sulphate (closely related to heparin which is even more sulphated)
  - Chondroitin : Glucuronic + N-acetylglucosamine (β1-3)
  - Keratan : Galactose + N-acetylglucosamine (β1-3)
  - Heparan : Many.

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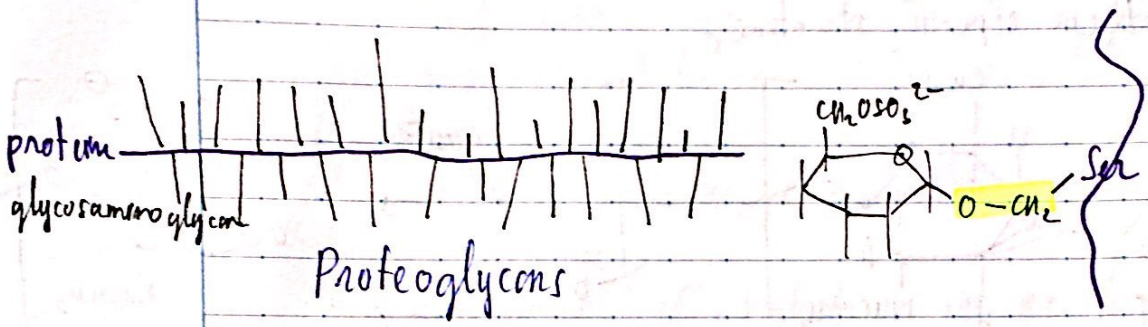
Proteoglycans

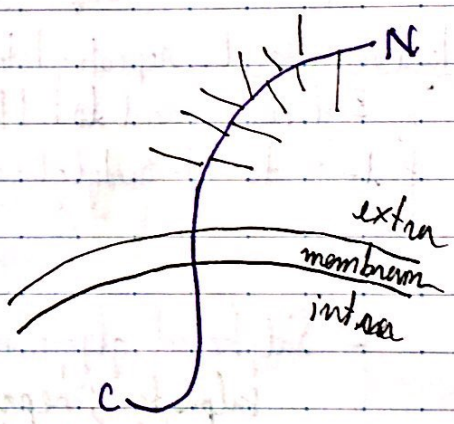
- Mostly occur in ECM and connective tissues
  Have vital role in cell dev & extracellular communication

- They are hybrid macromolecules: glycosaminoglycan + protein core by glycosidic covalent bond (usually O-linked) at a Ser residue

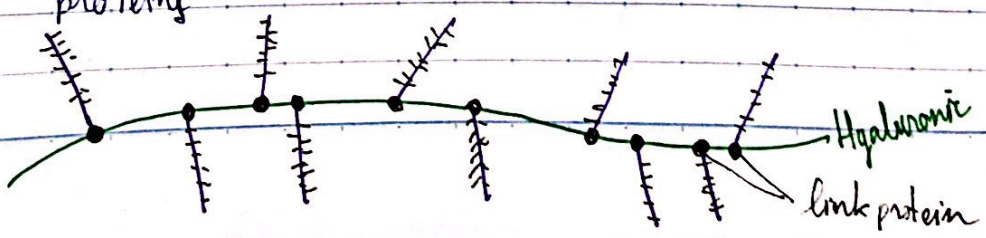


Proteoglycans

- Proteoglycan can also directly attach to the plasma membrane
  - Syndecans are membrane bound proteoglycans w/ a single ~~transd~~ trans-membrane
  - Glypicans are extracellular protein attached to the membrane by a lipid anchor



- Proteoglycans can come together and form aggregates that interact w/ other component in the ECM
  The proteoglycans attach to the backbone by ~~protein~~ link proteins



Extracellular matrix

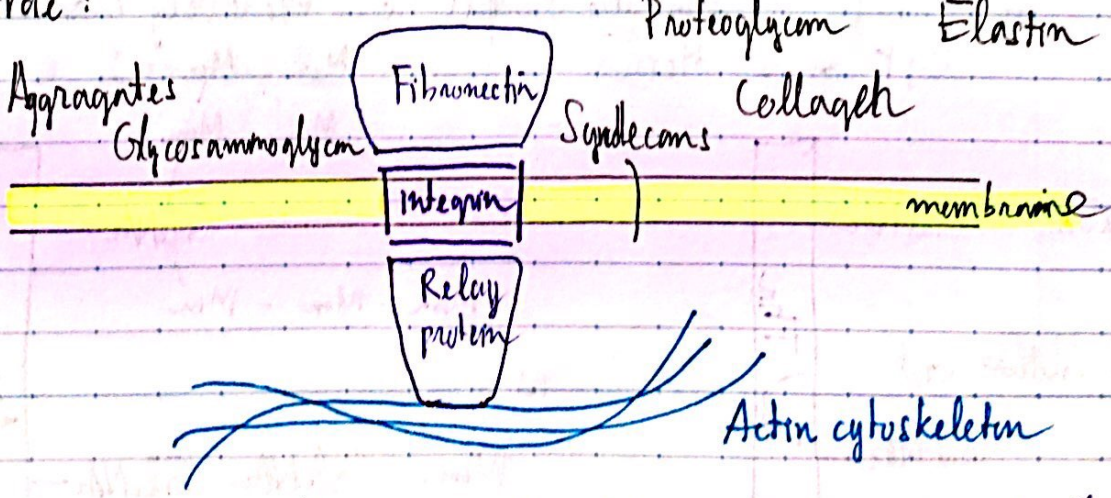
- Is the space between cells, within tissue and the basement membrane (which is a specialised compact form of ECM that is present in every tissue where it is in direct contact with endothelium & epithelium → form a boundary of the tissue)

- Extremely important. The content of ECM is mainly secreted from nearby cells. It:
  - Provide a scaffold to hold the cells in tissue together
  - Hormone and other molecules' pathway to infiltrate interaction

- Main components are protein & proteoglycans. Each tissue has a unique ECM environment

Cells adhere to the ECM via specialised plasma membrane bound protein receptors called **Integrins**. Integrins also react w/ cytoplasmic skeleton within the cell
→ There is a direct route of molecular communication between extracell and intracell. This can also assist in cell migration within tissue (important in normal dev of body)

Outside:



The ECM interact with proteins like fibronectin to communicate, that binds to integrin, which binds to relay protein that interact with actin cytoskeleton.

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Proteins in ECM

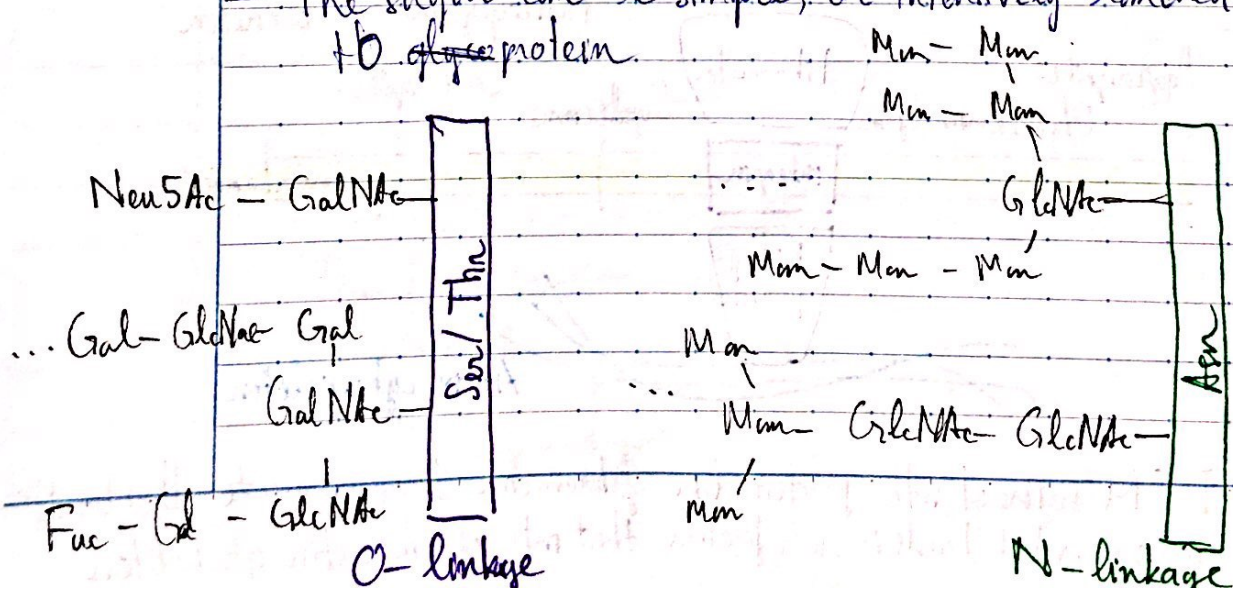
- Collagen is the major component of ECM
- Fibronectin is the protein specialized in cell adhesion & migration
- Elastin is a protein which give the elasticity to the tissue

The sugar code

- Carbonhydrates can be used to exchange info
  Many ways that the chain can be linked to glycoprotein (lipid)
  → the difference in the glycan and the linkage form the basis of the sugar code

- This is important since most proteins being exported are glycoprotein. The specific oligosaccharide chains encode info to allow cells to traffic proteins to the targets, interact w/ other cells, undergo appropriate der & tissue differentiation, and even recognise protein age

- The sugar can be simple, or intensively branched attached to ~~glyco~~protein.



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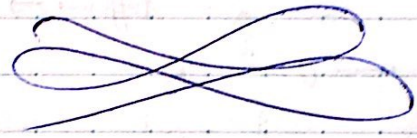
- Lectins are protein that read the sugar code.
  Have strong & highly specific binding to specific sugars attached to glycoprotein (lipids)
  Eg: Concanavalin A binds to Mannose-α1-OCH_3

  • Disease involves influenza virus protein hemagglutinin binds to oligosaccharide Neu5Ac(α2-6)Gal(β1-4)Glc
  Neu5Ac can be found at many plasma glycoprotein
  → hemagglutinin lectin assists the entry of the influenza virus into target cells.



- The sugar code & adhesion by integrin can be formed in inflammation

  + On leukocytes membrane there are { sugar code
    integrin (low affinity)
  + Chemokine control the movement of leukocyte
  + The sugar chain & integrin (high affinity) binds to E-selectin & P-selectin
  + Leukocytes migrate through endothelial → ECM

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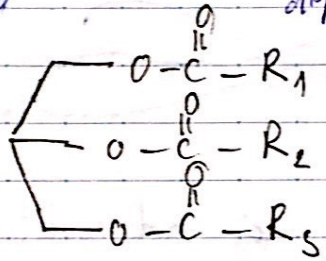
IV) Lipids & membrane

Classes of lipids

Triacylglycerols (TAGs)

- TAGs contain 3 fatty acids ester linked to glycerol backbone
  TAGs are the main storage form of lipids in animal
  TAGs form a water insoluble fat store in our body where they are stored in adipocytes
  - If 3 fatty acids are the same → simple TAG
  - " different → mixed TAG

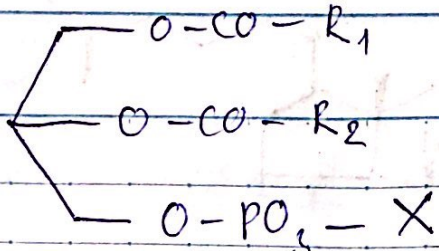


Glycerophospholipids

- Glycerophospholipids are derivatives of phosphatidic acid as they have the phosphatidate backbone
  ↔ All phospholipids contain a phosphoric acid residue

- All glycerophospholipids contain a polar group at C #3 & 2 fatty acids at C #1 and 2 → amphipathic

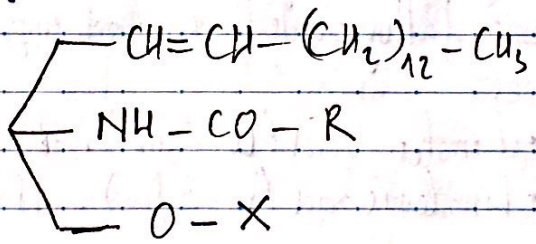
- Form a major component of membrane but also found in other structures



X can be -H, - choline (phosphatidylcholine), - serine (phosphatidylserine), - ethanolamine (phosphatidylethanolamine) -inositol (phosphatidylinositol)

Sphingolipids

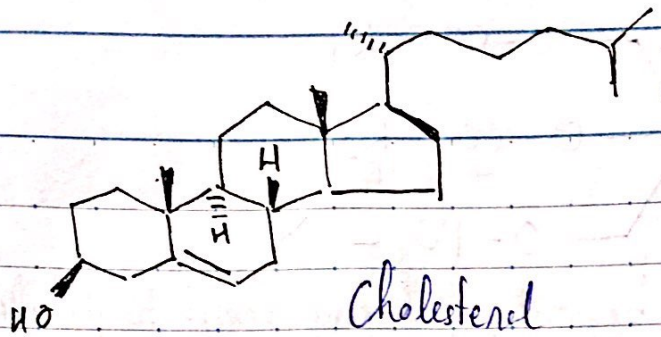
- Also found in plasma membrane, play an important role in forming myelin in nerve cells.
- Are derivatives of sphingosine (a long chain of alcohol)
- Overall appearance similar to glycerophospholipids. However, they have only 1 fatty acid at C#2



X can be -H (ceramide), - phosphocholine, - phosphoethanolamine, - glucose, - glucosamine or other complex carbohydrate

Sterols

- Important component of plasma membrane
  Some are vitamins & hormone
  Sterols are actualy derivatives of isoprene



Cholesterol

- Cholesterol does have a polar head & non-polar tail.

Lipid structure links to function

Essential fatty acid

- Mammalian hepatocytes cannot make fatty acid w/ double bonds past Δ^9 → essential for human diet
  These essential are ω-3 & ω-6 family fatty acid
  Member of these fatty acid can be made into a variety of highly unsaturate fatty acids that support important physiological & dev processes
  - Linoleic acid (ω-6 fam): $18:2(\Delta^{9;12})$
  - Linolenic acid (ω-3 fam): $18:3(\Delta^{9;12;15})$

- Linoleic acid is the precursor for eicosanoids that comprise prostaglandins; leukotrienes; thromboxanes
  Eicosanoid exert control over many bodily system (inflammation, immunity, nerve messenger)

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Triacylglycerol – storage forms of lipids

- Advantage of using fat = energy store:
  - C atoms of fat are highly reduced → potential energy thru fatty acid oxidation
  - Per gram, TAGs nearly twice energy as carbohydrate
  - TAGs are hydrophobic → lightweight (no H_2O associated)
  - TAGs insulate against the cold.

Eg: Palmitate 16:0 & Glucose

Even though Palmitate contain more C, it produces more energy per C than glucose does since the C in acid is fully reduce → more potential energy

Storage of fat in adipocytes

- Adipocytes (so called fat cells) are the storage site of TAGs.
  Fat droplets occur in cytoplasm of adipocytes.
  These droplets have a core of TAGs and Sterol esters surrounded by a monolayer of phospholipids; then further coated with a group of proteins, known as perilipins.

- There is another way to store fat → waxes
  Waxes are non-polar esters of long chain saturated & unsaturated fatty acids & long chain alcohol
  Secreted by skin glands

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Enzymes that degrade fat

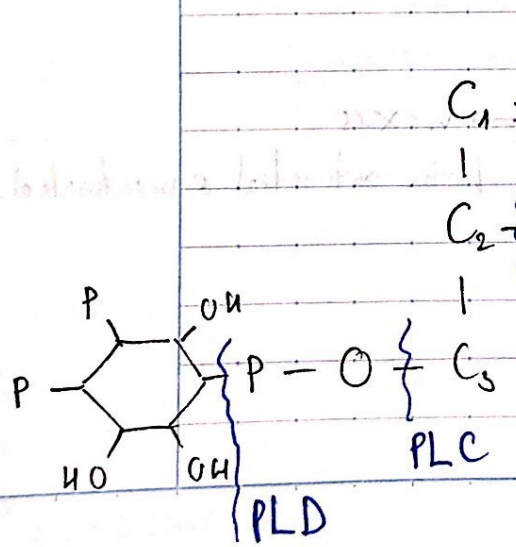
Lipases

- Are the enzymes catalyse hydrolysis reaction of TAGs
  Found in digestive tract, where they are actually release from the pancreas
  Also found in adipocytes & steroid synthesising cells

Phospholipases

- Are found throughout the body & all cells contain membranes
  Phospholipases = important in maintaining the membrane components and transmitting signal processes
- Are enzymes that catalyse selective removal of fatty acid
  - PLA_1 : fatty acid at C#1
  - PLA_2 : fatty acid at C#2
  - PLC : convert glycerophospholipids into diacylglycerols
  - PLD : convert glycerophospholipids into phosphatidates

Eg: Cleaving Phosphatidyl inositol biphosphate (PIP2) a minor but important in plasma membrane



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Lipid vitamins

- All vitamins are derived from isoprene.

- Lipid vitamins require bile salt (salt from steroid acid, such as cholic acid) to be absorbed
  → Patients w/ malabsorption will lack vitamin
  → Best taken with a fatty meal

- Lipid vitamin is not excreted by kidney, sometime accumulate to a toxic level in rich-fat structure (such as fat cells)

- Lipid vitamins are A, D, E & K
  - Vitamin A: derived from β-carotene, create retinol & retinal
  - Vitamin D: derived from cholesterol, under UV light
  - Vitamin E: natural antioxidant
  - Vitamin K: lipid quinone, required for synthesis of blood clotting fr

Steroid hormones

- Are all from cholesterol → 2 classes
  - Corticosteroid: made in adrenal gland (or kidney)
  - Sex steroid: made in the gonads (ovaries or testes) or the placen

- Once secreted from cell, travel thru blood usually attached with a steroid bindi protein.
When reach target cell, will diffuse into the cytoplasm thru membrane and bind with steroid receptor protein (nuclear receptor)

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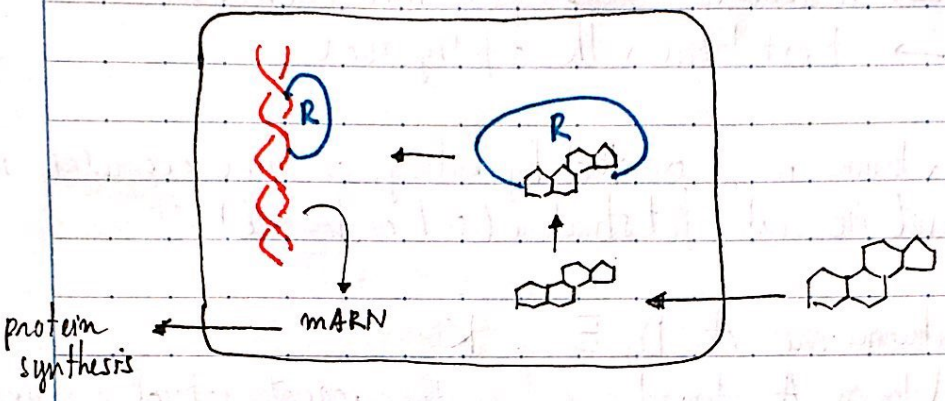
The steroid receptor can be found in the cytoplasm or nucleus.

- Binding to the receptor form a receptor-ligand complex that acts as a transcription factor (bind to a specific region of DNA in the gene promoter, alter gene transcription ↔ amount of mRNA)



Eg:- Cortisol from adrenal cortex, act on glucocorticoid receptors. Activated glucocorticoid receptor inhibits the gene transcription for the enzyme cyclooxygenase → anti-inflammatory effect

- Activated vitamin D (1,25-hydroxyl vitamin D_3)

Membrane

- Concist ≈30% phospholipids ; ≈ 20% cholesterol ; ≈ 50% protein & ≈ 10% carbonhydrate as glycoprotein (lipid)
(however the ration can be varied)

- The phospholipid component { glycerophospholipids
phosphosphingolipids
sphingolipids
cholesterol

- The proteins are either integral, peripheral or lipid anchored; mostly play as receptors, relay proteins or channels

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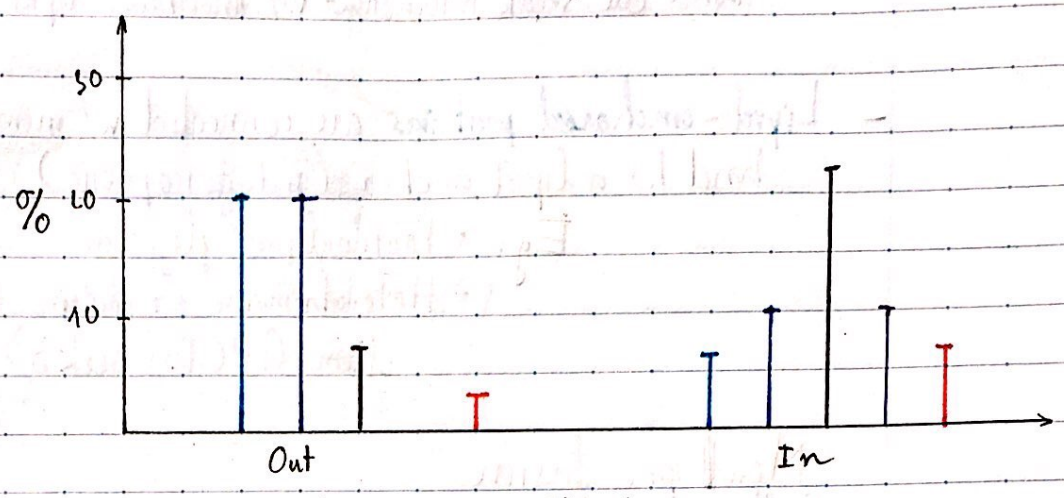
- The protein is not symmetrically distributed.



- Sphingomyelin
- Phosphatidylcholine
- Phosphatidylethanolamine
- Phosphatidylserine
- Phosphatidylinositol

Membrane proteins

- Not only plasma, but also organelles membrane

- **Integral proteins** contain hydrophobic regions embedded in the membrane, highly associated w/ membrane and also refer to as transmembrane protein or intrinsic membrain proteins

  Many integral proteins are receptors:
  - Channel link receptors (Ligand gated ion channel)
  - G protein coupled receptors (GPCRs)
  - Enzyme linked receptors

  Other integral proteins include ion channels, specific enzymes, carrier proteins and transporters (GLUT transporter that move Glc into the cell) or membrane fusion involved (SNARE protein)

- Peripheral proteins associate w/ membrane one l face by non-covalent bond ora weak interactions w/ membrane lipids or integral proteins

- Lipid-anchored proteins are connected w/ membrane by covalent bond to a lipid anchor (such as isoprene)
  Eg: • Proteoglycan glypican
  • Heterotrimeric G protein that relay signal from GPCRs (Week 3)

Membrane fusion

- Both lipid & protein component can undergo lateral diffusion around the bilayer thou they occur in
  Lipids can undergo transbilayer (flip flop) diffusion that reflect the balance of cell.

- Membrane fusion is important in exocytosis, endocytosis, budding of vesicles from the ER and Golgi complex, cell divisions, conceiving

Lipoprotein & lipid transportation

- Lipid transport around body = important since disruption leads to chronic condition such as hypercholesteremia (↑ blood cholesterol)

- Fatty acids are carried in the blood attached to the serum protein albumin
  TAGs & cholesterol are also moved around in lipoproteins

- Lipoprotein = aggregates of lipids & proteins
  4 types: • Chylomicron
  • Very low density lipoprotein (VLDL)
  • Low density lipoprotein (LDL)
  • High density lipoprotein (HDL)

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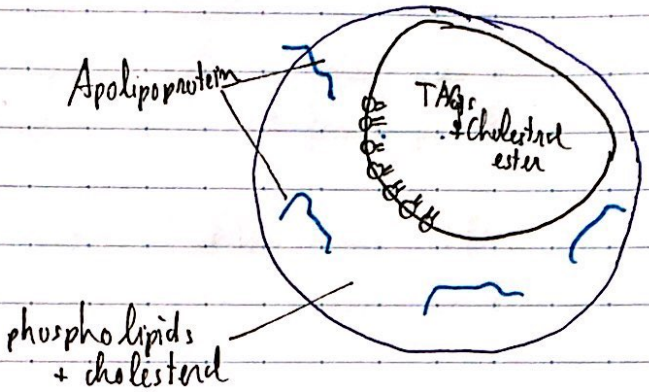
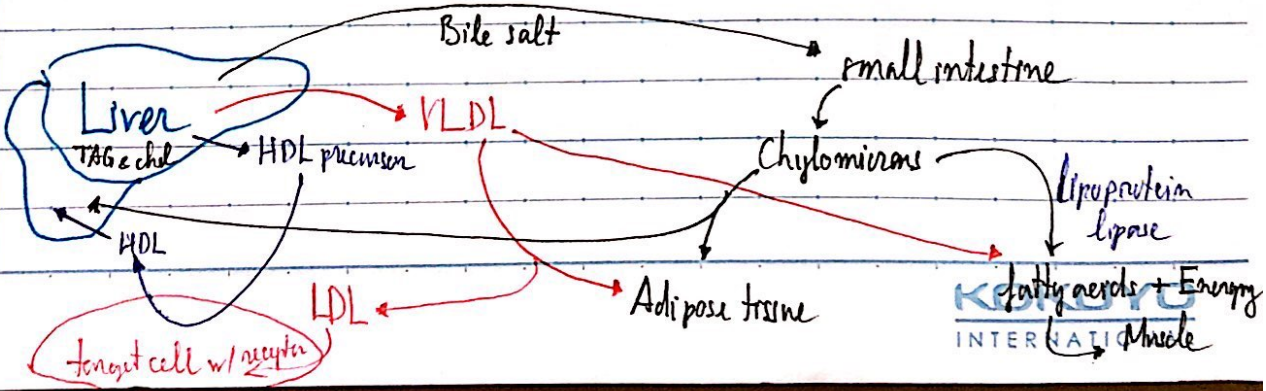
They all have some similar structure w/ TAGs and cholesterol ester buried inside & phospholipids, cholesterol & protein on the surface



Lipoprotein	TAGs	Chol. ester	Chole.	Phospholi.	Protein
Chylomicron	85	3	1	9	2
VLDL	50	12	7	18	10
LDL	10	37	8	20	23
HDL	4	15	2	24	55

- Dietary lipid is transported by chylomicrons that leave the small intestine to tissues. TAG & chole. synthesised in liver delivered by VLDL to other tissues. Lipoprotein lipase in the capillaries convert TAGs to free fatty acid delivered to tissues

HDLs (rich in chol.) → cell w/ LDL receptors that recognise protein on lipoprotein
DHLs return chol. to liver



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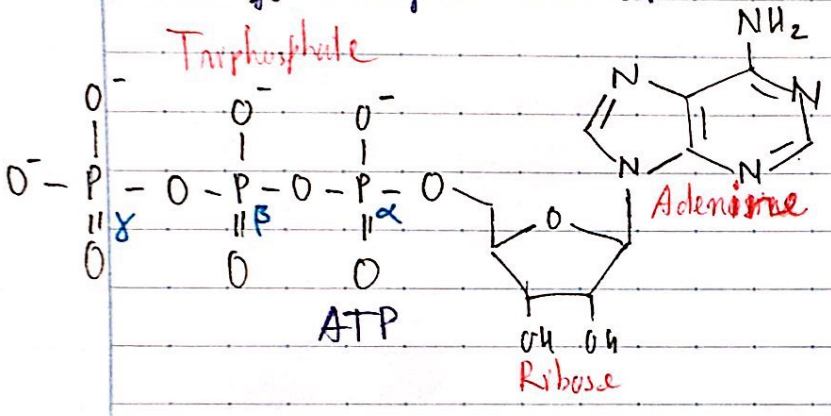
I) Energy metabolism

ATP – Energy source

- All cells need energy in the form of ATP to maintain function.

Nucleoside triphosphates (NTPs) such as ATP have high energy of "hydrolysis" which is used to provide chemical energy for enzyme reactions.



Cleavage of phosphonic anhydride bonds contribute to ATP's high E of hydroly

- Sometimes the γPi is cleaved and sometime both γ and β Pi to yield pyrophosphate (PPi)

- An enzyme, pyrophosphatase, present in all cells will cleave PPi to Pi to release further Energy.

It is thought that ATP is used because Adenosine has better contact point w/ many enzymes than other bases.

$$ATP \xrightarrow{H_2O} ADP + P_i \qquad \Delta G = -33\ kJ/mol$$

$$ATP \xrightarrow{H_2O} AMP + PP_i \xrightarrow{H_2O} P_i \qquad \Delta G = -66\ kJ/mol$$

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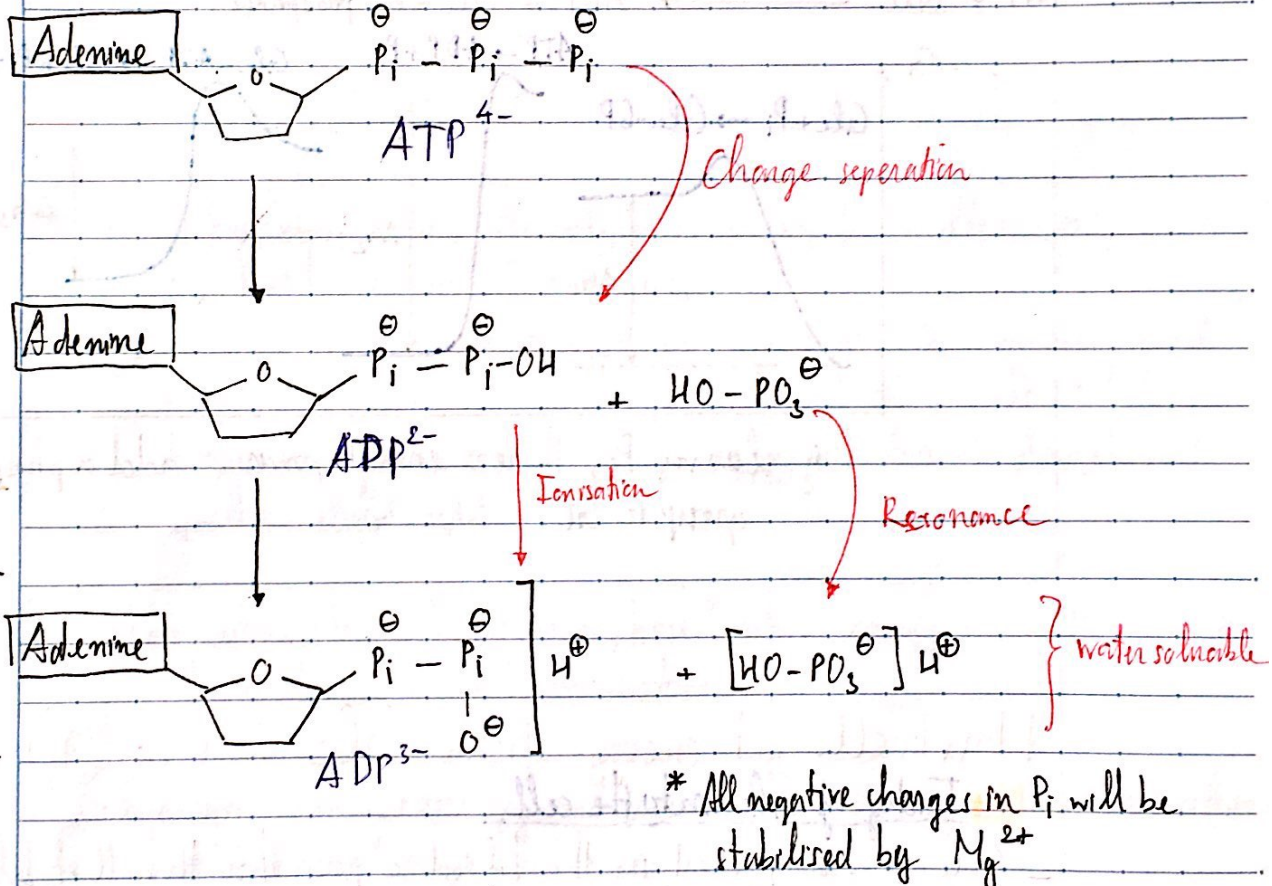
Energy from hydrolysis

- Phosphorylated compounds (such as ATP) ~~acetyl CoA~~ and thioester (such as Acetyl CoA) have large negative ΔG of hydrolysis due to more stable products:
  - The bond strain on reactants due to eletrostatic repulsion more relie
  - Stabilised by ionisation
  - Stabilised isomerisation
  - stabilised resonance
  - Water solubilisation ~~ca~~ ↗ hydration



* All negative charges in P_i will be stabilised by Mg^{2+}

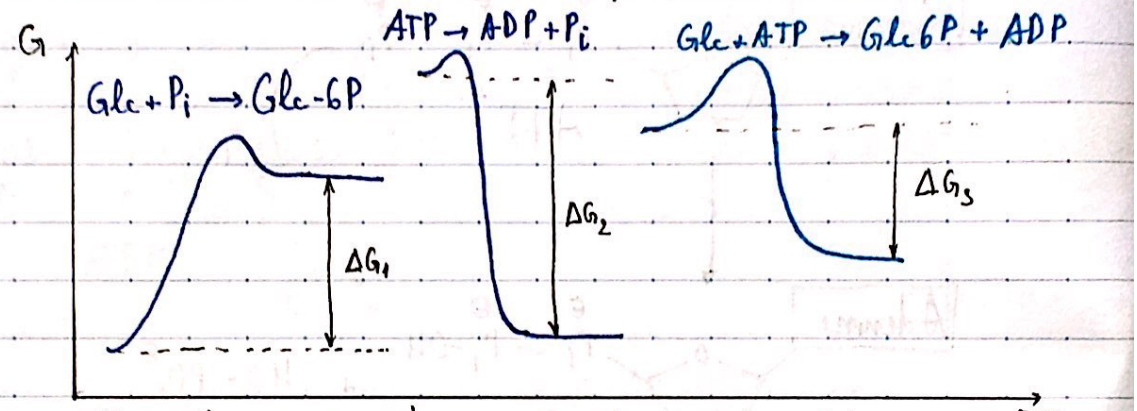
How Energy in ATP hydrolysis to do smthing

The enzymes can undergo coupled reactions to harvest energy from hydrolys of ATP and use the energy to catalyse the production of second produc

In bisubstrate reaction, catalysed by hexokinase (or glucokinase) ATP & Glc are both substrates.

The enzyme hexokinase use the energy produce by the cleavage and transfer of the γ P_i from ATP to allow the formation of phosphorylated glc molecules. This process is called energy coup

$$ATP + Glc \xrightarrow{\text{hexokinase}} ADP + Glc\text{-}6\text{-}phosphate$$



By cleaving P_i, there is enough power to add a phosphate group to Glc

How do cells get energy from Glc ? (Part 1)

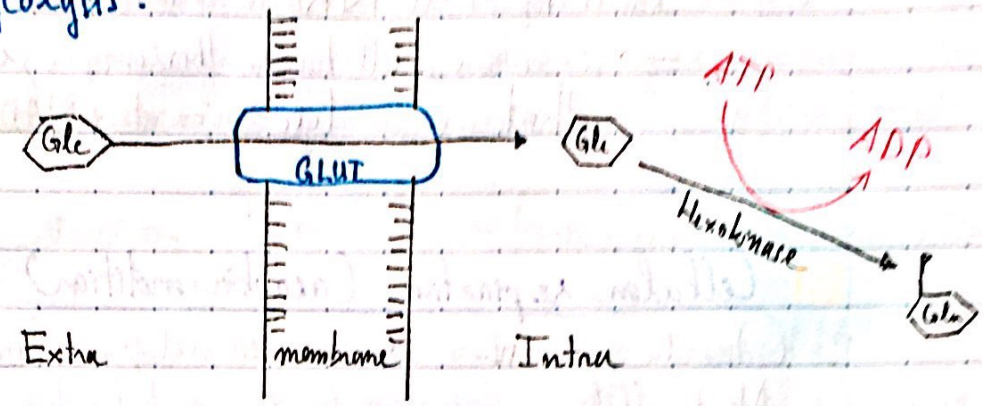
Entry of Glc into the cell

- Glc is transported in the blood & pass thru the wall of blood capillaries to enter tissue.

All cells contain glc transporters (GLUTs) that move glc into cell, (sometimes out side). There are 12 types of GLUTs and they have differential expressions.

Glc also passes the blood brain barrier as it also has a GLUT

- Once inside the cell, Glc immediately phosphorylated by hexokinase (or glucokinase in liver). This is the 1st step in metabolic pathway glycolysis.



Glycolysis

- Sweet breaking process. Glycolysis is an eg for multienzyme pathway that happens in all living cells.
All enzymes are found in the cytoplasm where glycolysis occurs. Each enzyme catalyses a small change in the substrate; with 1st step begins with hexokinase, then rearrange to fru-6-phosphate and further phosphorylated.

These initial steps is "preparation phase", where energy is invested to make the molecules easier to breakdown

- Glycolysis produces energy and generates precursor and substrate for other metabolic pathways.
  - Substrates for Glycolysis: Glc, ADP, phosphate & NAD^+
  - Product for Glycolysis: pyruvate, ATP, NADH

Glc can be also taken from glycogen at non-reducing ends.

- This process yeild { 2 ATP (4 but minus 2 for prep)
  2 NADH + 2 NADH (pyruvate → acetyl CoA)

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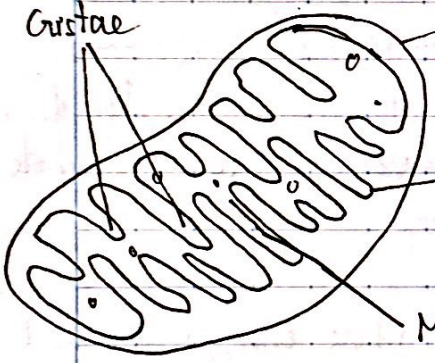
- Glycolysis may not require O_2. Under anaerobic condition, glycolysis generates pyruvate and NADH and some ATP. However, it will stop as all NAD in reduced form.
  → To continue, cells have another enzyme, lactate dehydrogenase, that can catalyse pyruvate + NADH ↔ lactate + NAD^+

Cellular respiration (aerobic condition)

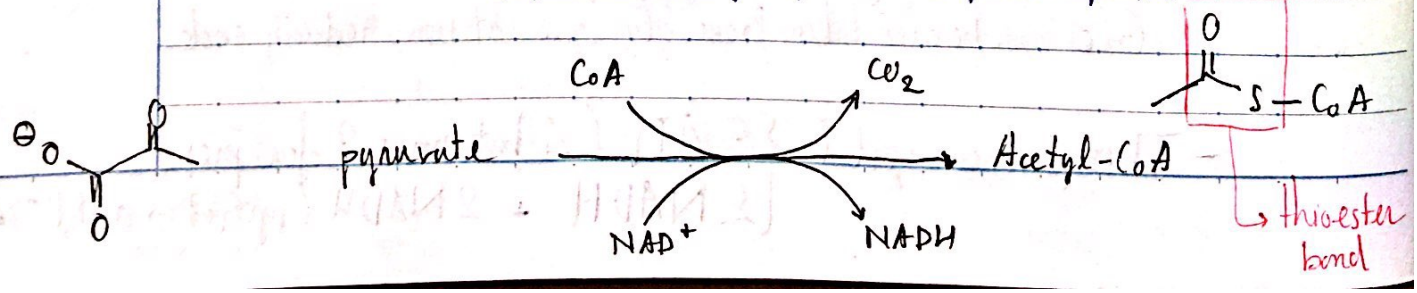
- Catabolic process where e are removed from nutrient molecules to O_2
  Most cellular energy is produced in mitochondria

- Under aerobic condition → more ATP
  O_2 is essential & ultimately accept e to form H_2O
  All events occur in the mitochondria, where most ATP come from



+ Outer mito. membrane is permeable to most small molecules & ions
+ Inner mito. membrane is impermeable & contains various transporter and e chain protein complexes

- First, pyruvate into mito. via a transporter called mitochondrial pyruvate carrier
  Once in mito., pyruvate converted to acetyl-CoA catalysed by pyruvate dehydrogenase ~~enzyme complexes~~



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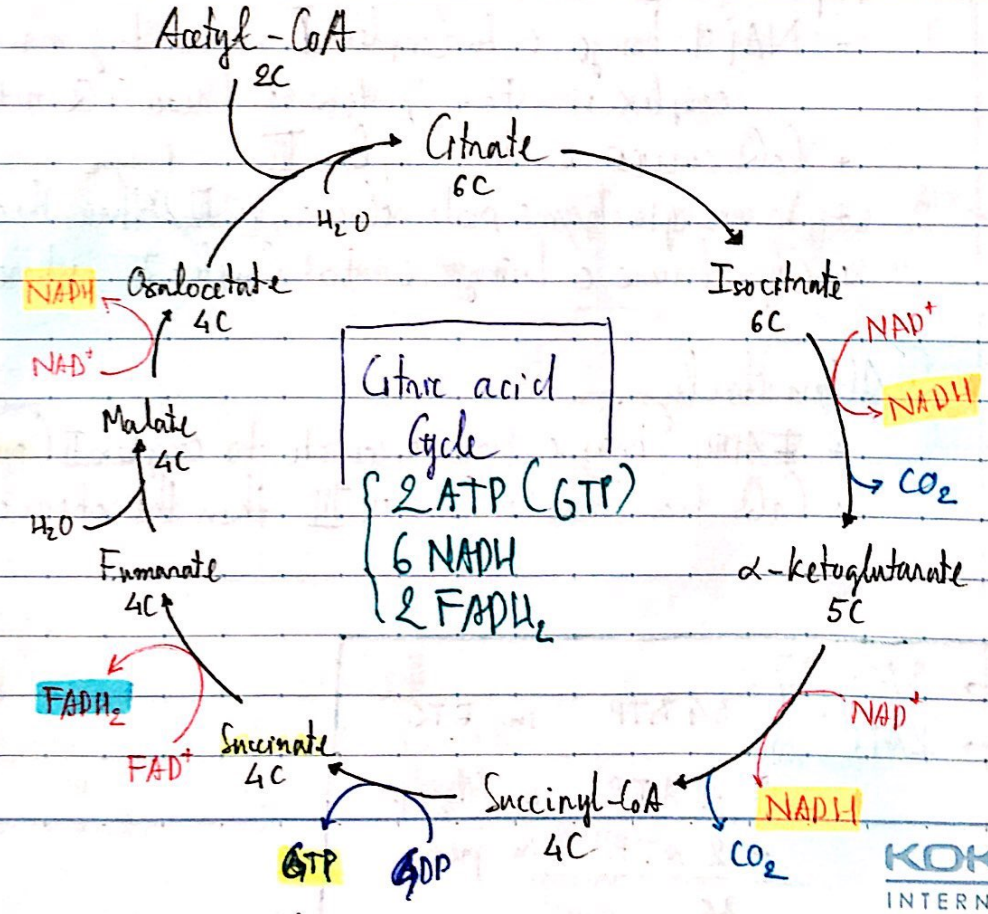
Citric acid cycle (Kreb)

- Involved enzymes found in mito. matrix. These enzymes operate in a cyclic pathway where the acetyl group of the incoming substrate acetyl-CoA is covalently linked to Oxaloacetate to form citrate.

Further reactions will eventually re form Oxaloacetate and release CO_2.

Major products of the cycle are reduced coenzymes NADH & flavin adenine dinucleotide ($FADH_2$) and guasonine triphosphate (GTP) which can be equal to ATP

The purpose of Kreb cycle is to produce reducing power in forms of NADH & $FADH_2$ for e. transport chain.



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How do cells get energy from Glc ? (Part 2)

Electron transport chain (ETC)

- ETC is made up of 4 major integral membrane protein complex in the inner mito. membrane
  With in the ETC there are e carriers that transport e within the complex or between complexes.
  Electron carrier:
  - Ubiquinone (Coenzyme Q)
  - Fe - S protein associated w/ flavoprotein ~~cytochrome~~
  - Cytochromes (which are small protein w/ heam group)

- The order of complexes that e passed thru was revealed by various experiments.
  → The order of carriers that deliver e to O_2
- Steps of ETC:
  + NADH brings e to Complex I, where they move thru the complex via Fe - S protein and reach CoQ in the inner membrane
  + CoQ carries e to Complex III
  + Various cytochrome protein (in complex III) transfer e thru the complex
  + Cytochrome c brings e to Complex IV, where O_2 get e

Alternatively:
+ $FADH_2$ brings e from succinate to complex II (succinate dehydrogenase)
+ CoQ transfer e to Complex III then the chain continue

NADH → 3ATP	34 ATP	in ETC
$FADH_2$ → 2ATP	+ 4 ATP	in Glycolysis
	- 2 ATP	in prep
	36	

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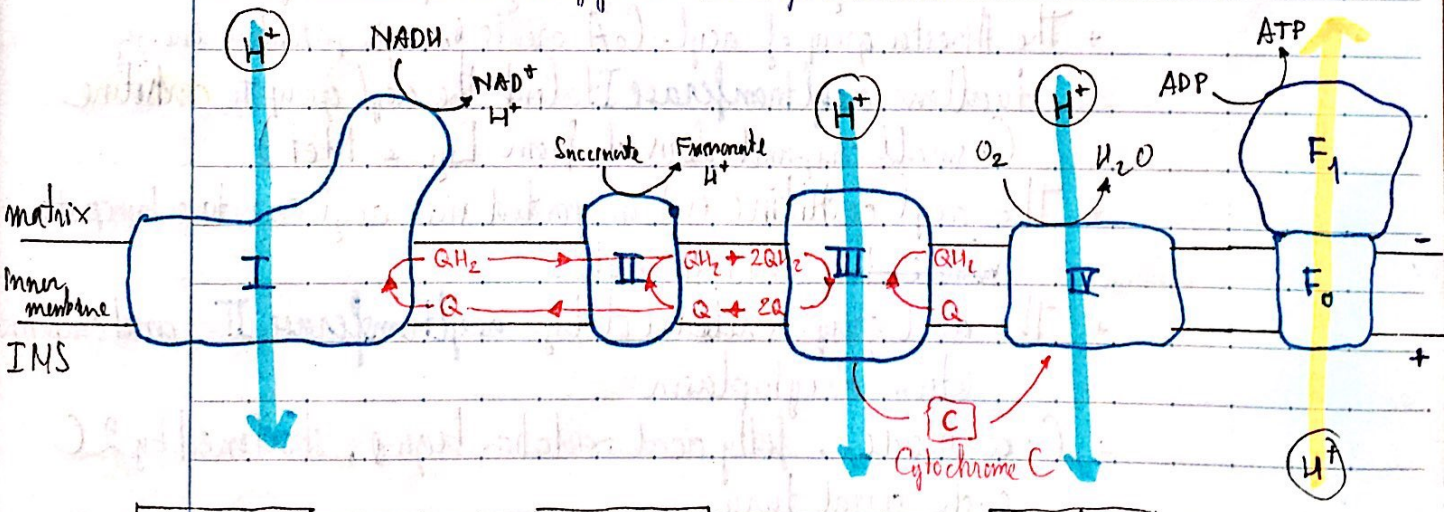
ATP synthesis by oxidative phospholycation

- Most of e creates lots of potential energy that can be use to make ATP
Because the last e acceptor is O & phospholysation.
→ oxidative phospholysation

- Enzyme catalyse ATP formation is a multisunit membrane bound protein complex w/ 2 subunit: F_0 & F_1
  - F_0 : integral membrane protein, sensitive to antibiotic oligomycin (That why it is called F_0)
  - F_1 : peripheral membrane protein facing the matrix, catalyse the formation of ATP

- Observation:
  - e transfer to O_2 is coupled w/ ATP synthesis
  - Require intact inner membrane to maintain $[H^+]$ gradient
  - While F_0 allows H^+ to flow back to the matrix, F_1 harvests the energy and catalyse reactions.



Complex I
NADH-ubiquinone oxidoreductase
NADH dehydrogenase

Complex II
Succinate-ubiquinone oxidoreductase
Succinate dehydrogenase

Complex III
Cytochrome bc_1 complex

Complex IV
Cytochrom c Oxidase

Complex V
F_1F_0 ATP synthase

How do cells get energy from fatty acids?

Fatty acids enter into cells

- Fatty acids are released from TAGs in adipocytes by reaction of lipases
- Fatty acids are imported into cells by fatty acid transfer protein

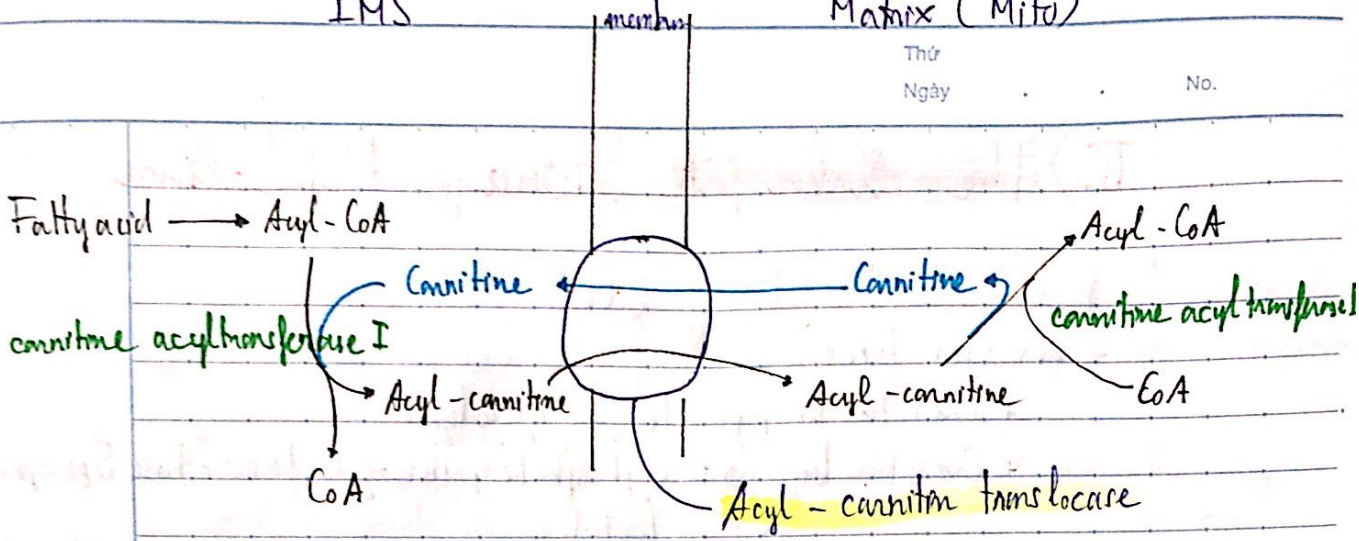
Fatty acid oxidation

- Fatty acid oxidation (β oxidation) happens in mito. of all tissues and is a spiral pathway

Fatty acid (16:0) + 8 CoA + 7 NAD^+ + 7 FAD

⟶ 8 acetyl-CoA + 7 NADH + 7 $FADH_2$ + H^+

- Entry of fatty acid into mito. is limited and involved shuttle transporter
  - + Fatty acid is activated in cytoplasm, covalently linked to CoA, forming an acyl-CoA (catalyzed by acyl-CoA synthase)
  - + The thioester group of acyl-CoA create enough potential energy to allow acyltransferase I to link the acyl group to carnitine (a small compound derived from Lys & Met)
  - + The acyl carnitine is transported via acyl carnitine transporter into the mito.
  - + The acyl group is released by acyltransferase II, and carnitine return to cytoplasm
  - + Once inside, fatty acid oxidation begins, shortened by 2C each spiral turn.
  - + NADH & $FADH_2$ are released and enter the ETC
    Acetyl-CoA is also produced goes to Kreb's cycle.



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II) ~~The cellular fate~~ Storage Metabolism

The cellular fates of Glc

- 4 major fates:
  + Oxidation to pyruvate by glycolysis
  + Oxidation by pentose phosphate pathway to form ribose 5phosphate → nucleotides
  + Form storage compound, such as glycogen
  + Synthesis of complex polysaccharides

All pathway start w/ the 1st step: phosphorylation by hexokinase to form Glucose-6-Phosphate

Glycolysis + Glycogen metabolism = most important

Glycogen metabolism

- Glycogen = homopolysaccharide of Glucose, stored in granules found in cytoplasm of liver & muscle cells

Excess sugar will be stored as glycogen as glycogen { liver: 10% of its weigh; muscle: 1% }

- Liver glycogen = vital in maintaining sugar blood since liver can cut the phosphate group → release free Glc into blood
- Muscle glycogen = source of Glc-6-phosphate for energy

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How does glycogen structure influence its role in metabolism?

- Very large (w/ α1-4 links & α1-6 branches), present in liver & muscle
  Tightly packed Glc surround a central core protein called **glycogenin**

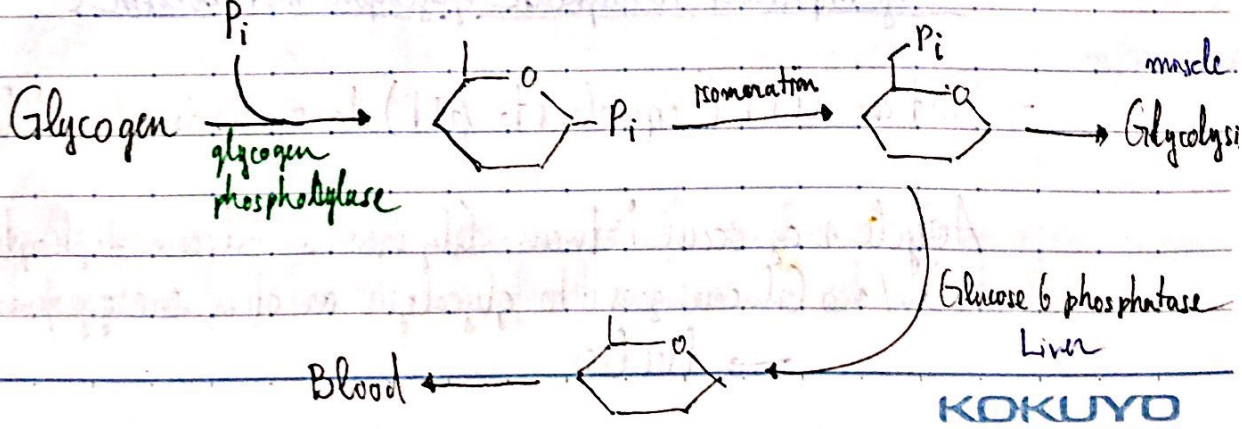
- Add & remove the non-reducing ends. Since there are so many non-reducing ends → activated **glycogen phosphorylase** enzymes can release lots of Glc at once

  Alternatively, glycogen synthesis can also be so fast when cellular Glc at high level, as **glycogen synthase** also works at non-reducing ends

Glycogen breakdown (Glycogenolysis) (liver, muscle)

- Key enzyme: **glycogen phospholylase**, catalyses reaction that remove a Glc residue from glycogen, also phosphorylates at C#1
  This enzyme's activity is strongly regulated.

- Glc-1-phosphate undergo isomeration to form Glu-6-phosphate
  - In muscle, kept as Glc-6-phosphate for glycolysis
  - In liver, Phosphate group is removed → free Glc because liver cells express enzyme **glc-6-phosphatase**



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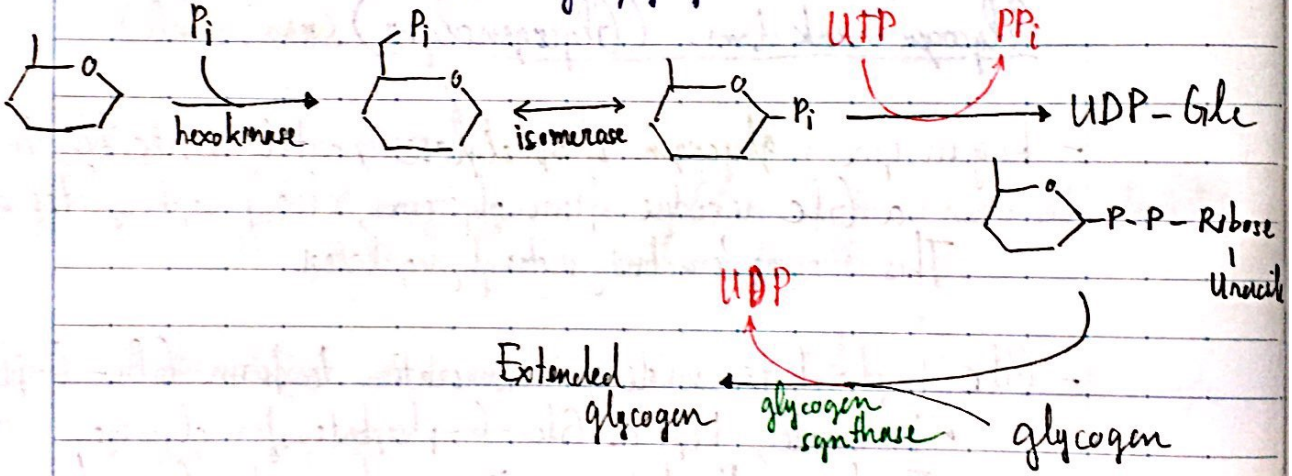
Glycogen synthesis (gliyogenesis) (liver, muscle)

- Key enzyme: glycogen synthase
- Glycogenesis is expensive: need energy to overcome E_A
  → activated Glc molecules
  → phosphorylated by hexokinase

Glucose-6-phosphate later activated to form a sugar nucleotide called UDP-Glucose (contain high energy phospho-anhydride bond)

UDP-Glc is the substrate of glycogen synthase
→ extending glycogen



Why important to regulate glycogen metabolism?

- Cost an UTP (equivalent to ATP) to synthesise 1 more link in glycogen

A cycle may occur between Glycogen & Glucose 1-phosphate
w/ no Glucose goes into glycolysis or other energy generating pathway
→ Useless

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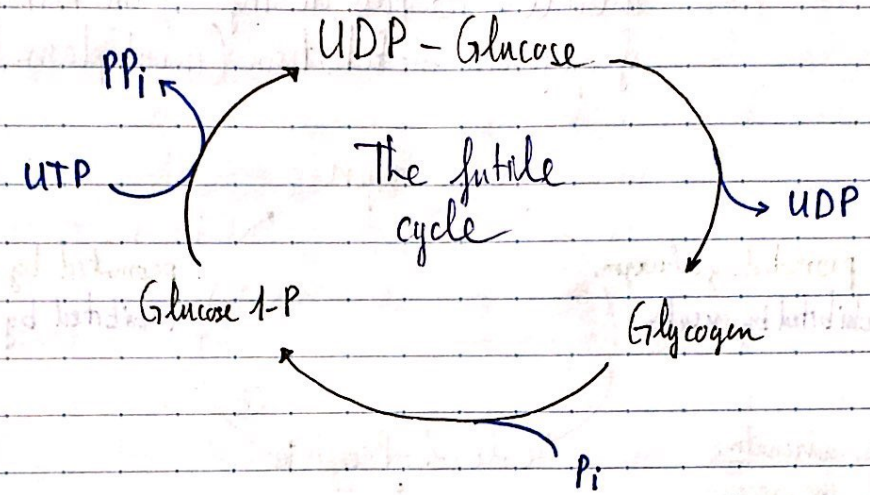
⇒ There should be some way to avoid this cycle
- Store when too much (glycogenesis)
- Break when need (glycogenolysis)



Regulation of glycogen metabolism

How?

- By hormonal signal, reflect blood sugar level & need of glucose of body.
- This is an eg. of co-ordinated regulation, involving insulin & glucagon

Both hormones are small protein, released from the pancreas and travel in blood

- Glucagon is from the α cells } of the islets of Langerhans in pancreas
  Insulin if from the β cells }

[Receptors for glucagon are found on the surface of liver cells
[Receptors for insulin are found on liver, muscle & fat cells

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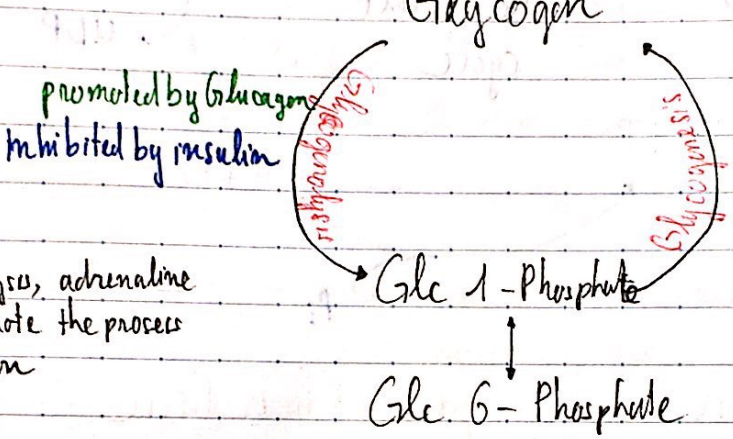
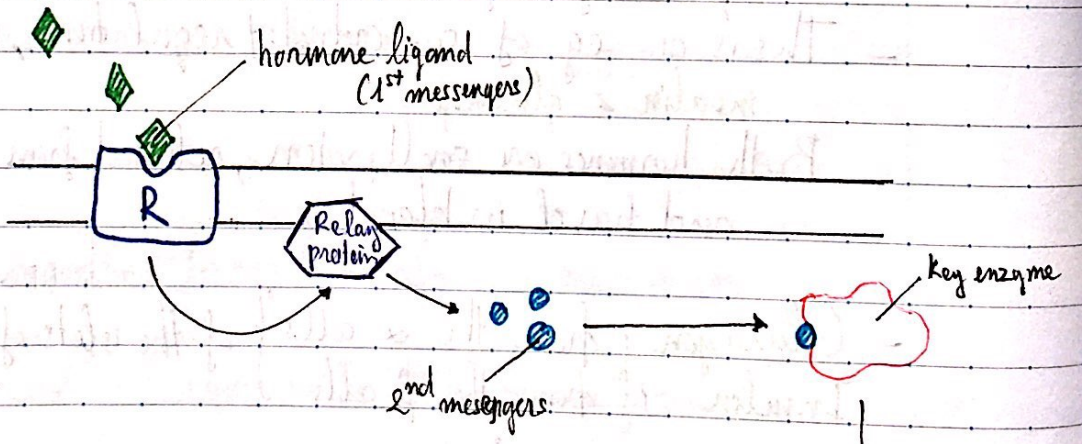
- These receptors are protein w/ spanning domain
When the receptors are activated by hormones binding to them
→ allosteric change that trigger a signal flow inside the cell to pass on info from hormone to keyenzyme of glycogen metabolism (in cytoplasm)



* In glycogenolysis, adrenaline can also promote the process as Glucagon

- The process of transferring info from outside to the cell is very important (to direct to specific path-way) and can be regulated from ion, molecules to protein



Hormone binding to receptor leads to conformation change → Physiological changes
→ signal for relay protein to produce small molecules (such as cyclic AMP) as 2nd messengers
→ 2nd messengers will bind to other proteins → change

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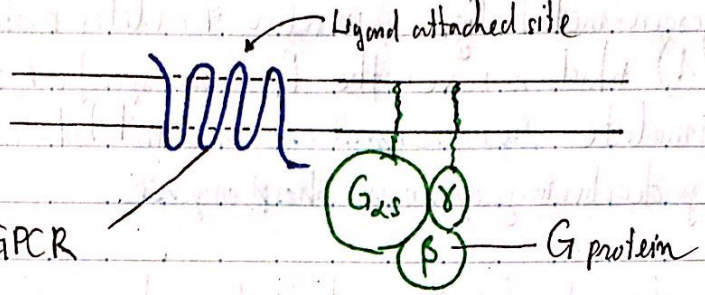
* The glucagon receptor is a member of G protein-coupled receptors (GPCR couple to the heterotrimeric G_s protein family.

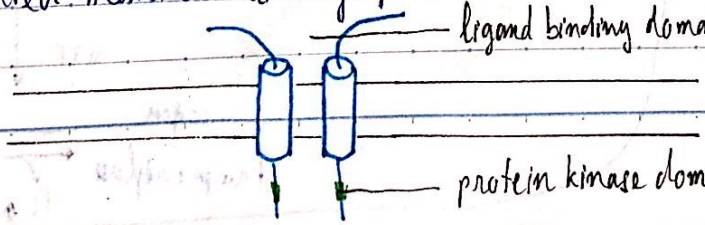
Typical GPCRs have 7 transmembrane spanning region, associated w/ peripheral G protein that bind w/ GTP when activated.



G_s protein stimulates an integral membrane called adenylatecyclase
→ Increased cellular cyclic AMP (cAMP)
→ cAMP in turn activates another enzyme, protein kinase A (PKA)
→ PKA in turn phosphorylates enzymes involved in glycogenesis (which reverses the function of those enzymes: active to inactive)

- Glucagon receptor are found in liver cells
However, both liver & muscle cells express β adrenergic receptors so that adrenaline can also stimulate glycogenolysis thru same signal path way

* The insulin receptors is a member of Tyrosine specific protein-Kinase Receptors (TKRs, a receptor enzyme), contain external insulin binding domain, a transmembrane spanning domain and internal enzyme domain (in cytoplasm)
Activated member usually form a dimer

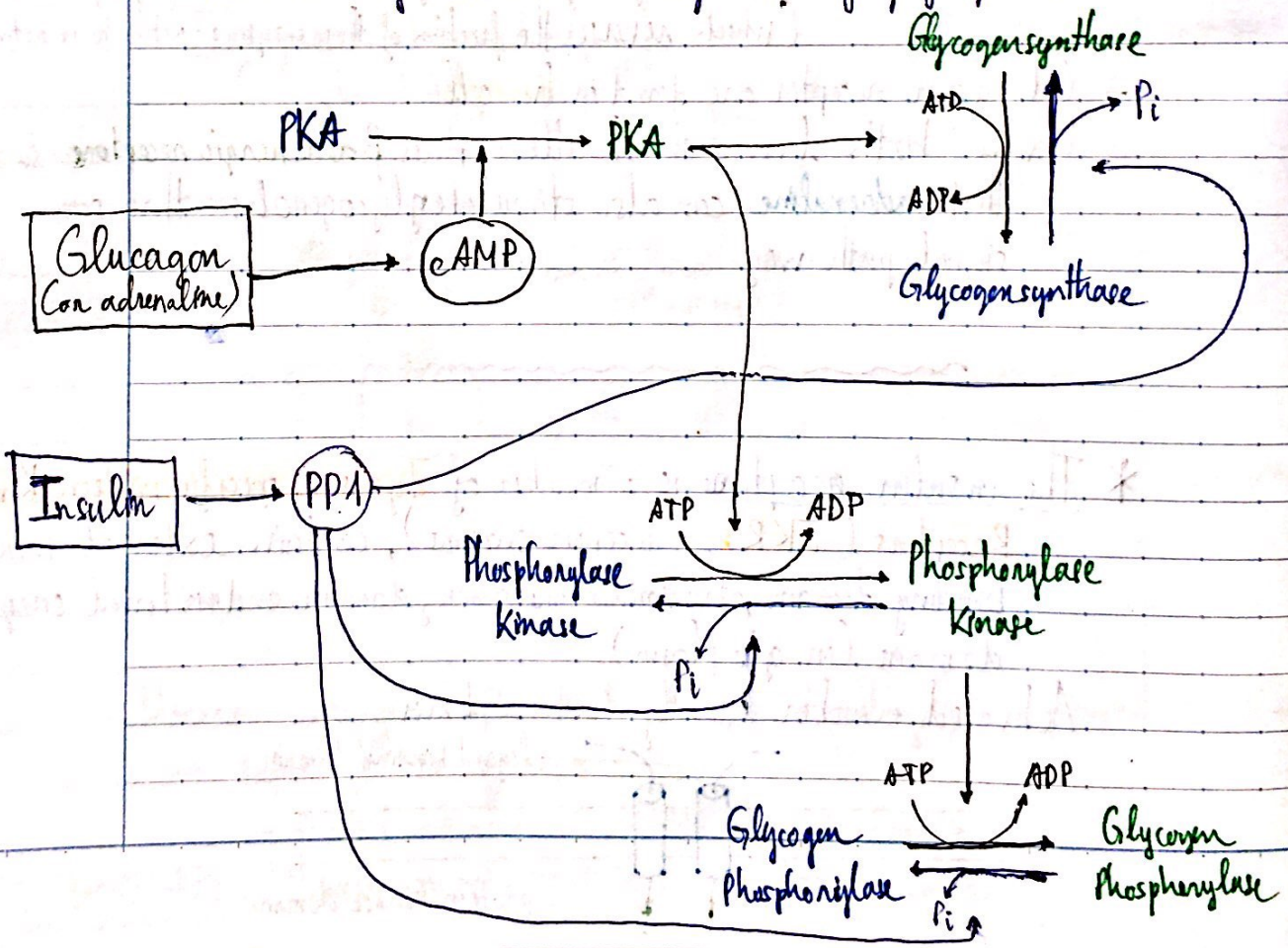


- After insulin bind to receptor, kinase enzyme is activated and phosphorylates the insulin receptor substrate (IRS) which is a protein complex in cytoplasm that directs many intracell signal cascade.

- In glycogen metabolism, insulin stimulates protein phosphatase 1 (PP1) which removes the Pi from specific enzymes and so stimulate glycogen synthase and inhibits glycogenolysis by deactivating glycogen phosphorylase.

Insuline also stimulate the mvt of glucose transporters (GLUT4)
→ increases glucose uptake

- Overview of coordinated regulation of glycogen metabolism



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—— Insulin path way — inactivated enzymes
—— Glucagon path way — inactivated enzymes

Lipid storage

Just like glycogen metabolism → 3 hormones: insulin, glucagon, adrenaline

Fatty acid synthesis (liver)

- Mostly occur in liver, involved the condensation of 2-C unit in the form of acetyl-CoA
Fatty acid synthesis is catalysed by fatty acid synthase complex in the cytoplasm, using NADPH as reductant.

- Citrate from mito. thru the acetyl group shuttle involving the citrate transport system.
Acetyl-CoA is then converted to malonate & used as a starting point for fatty acid synthesis

Insulin promote } the fatty acid synthesis
Glucagon inhibits }

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Metabolism of TAGs & Lipogenesis

- Lypolysis = hydrolysis of stored TAGs

In fat cell, TAGs hydrolysis is catalysed by **hormone sensitive lipase**

- Adrenaline, adrenocorticotropic hormone & growth hormone activate hormone sensitive lipase.
- These hormone increase cAMP levels to stimulate PKA phosphorylation

- Insulin inhibits hormone sensitive lipase by dephosphorylation

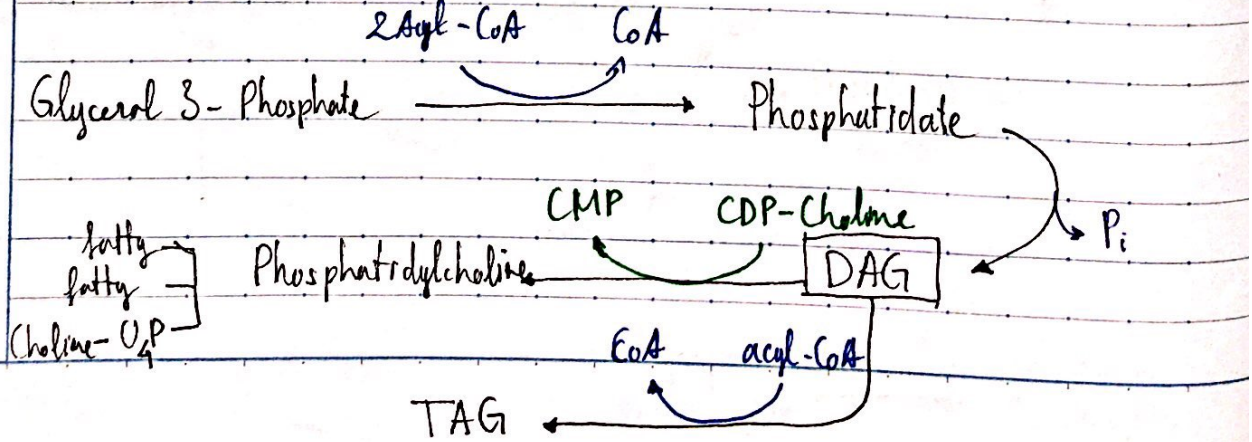
$$TAG \xrightarrow{\text{hormone sensitive lipase}} \text{Glycerol} + 3 \text{ fatty acids}$$

- Synthesis of TAG & phospholipids is similar to each other and the body will form one or the other based on its needs.

Fatty acids are stored in TAGs in fat cells but TAGs can be made in other cells, then transport in lipoproteins

hepatocyte
adipocyte

- Before synthesising of TAG, there are several prep steps:
  - Production of acetyl-CoA from Glc or aa
  - Synthesis of fatty acids
  - Formation of Glycerol phosphate to form the backbone.



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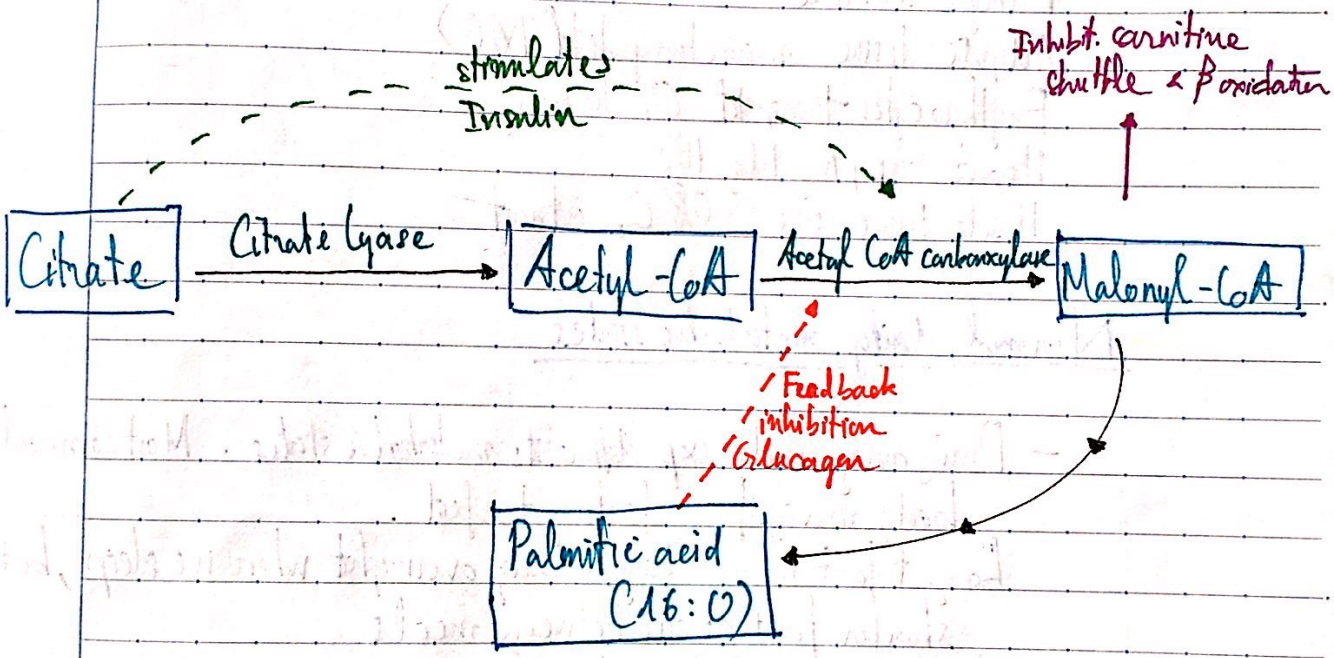
- Nitrogen containing phospholipids are made from diacylglycerol (DAG)
  Other phospholipids are made from phosphatidate.

How lipid & carbonhydrate metabolism linked?

- The degradation product is Acetyl-CoA → Kreb
- Regulated by hormones: insulin, glucagon & adrenaline
- Reciprocal relationship between
- Energy used to synthesise lipids is from carbonhydrate metabolism.



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III) Integrated metabolism

Body organ & tissue function & cooperation

chém gió =))

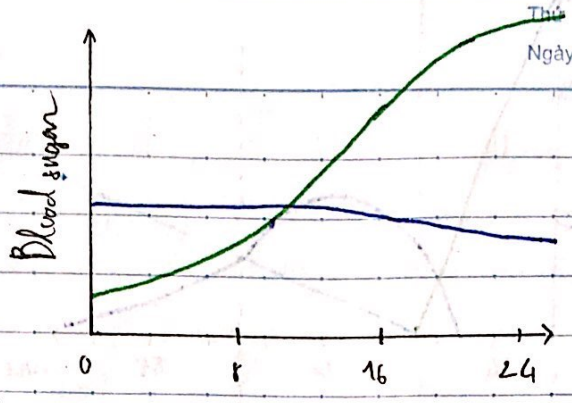
- The brain in charge & depends on glucose as its incoming substrate to generate ATP
- Food absorbed in intestine ; lipid via chylomicrons to lymph system before entering the blood stream ; glucose & amino acids directly to the liver by hepatic portal vein
- Liver = metabolism service, maintain blood glucose & fast & aa
- Kidney = excrete
- Adipose tissue maintaining fed (TAG)
- Erythrocytes transport O_2 to body.
- Heart pumping blood
- Muscle tissue use 50% O_2 at rest

Normal daily metabolic states

- During a day, body exp different metabolic states. Most commonly body swing from fasting to fed.
- Largest fast in a day usually overnight when we sleep, but shorter fast occur between meals
- The fed state starts after the meal
- Some will do exercise ⟶ exercise state.

Importante of blood glucose homeostasis

- Different situations, different pathway will be operating to maintain blood glucose levels are constant (~5mmol/L in blood to supply brain & erythrocyte)



Blood glucose remain constant after 2 4hrs after meal before slightly declining. Fatty acid level rises simultaneously

- Blood glc maintained by the liver and regulated by pancreatic hormones, such as glucagon & insulin (or adrenalin & glucocorticoids)

- Intake glucose ~~[illegible]~~ absorbed in the intestine are released by liver will eventually enters the blood stream
  Glucose from liver initially from glycogen, but if the fasting period is longer, liver can synthesise glucose thru a process called gluconeogenesis

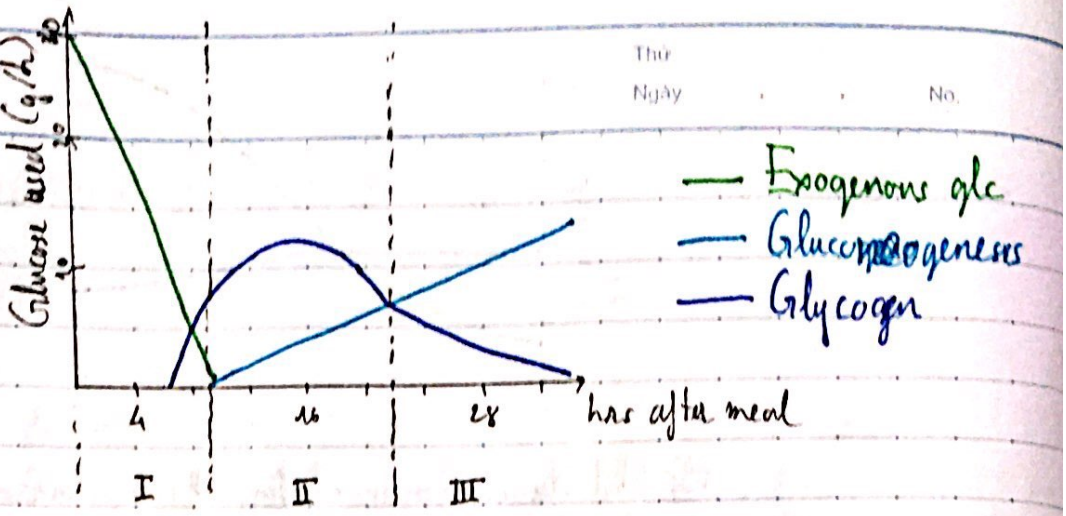
Gluconeogenesis

- Formation of Glc from non-carbohydrate precursor (eg alanine, pyruvate)
  Occur in the cytosol of liver & kidney
  Important in glucose homeostasis

- It uses 7 reversible step of glycolysis. & include 3 bypass steps.
  These bypass steps occurs at the irreversible enzyme steps in glycolysis

  The bypass enzyme are expressed in liver (and less in kidney) → limited to these organs

- The final bypass steps is catalysed by Glucose 6-phosphatase to form glucose (same in glycogenolysis)



- Phase I: Glucose mostly from meal
- Phase II: Glucose from glycogen as the exogenous glucose levels decline
- Phase III: Glucose from gluconeogenesis as glycogen levels fall.

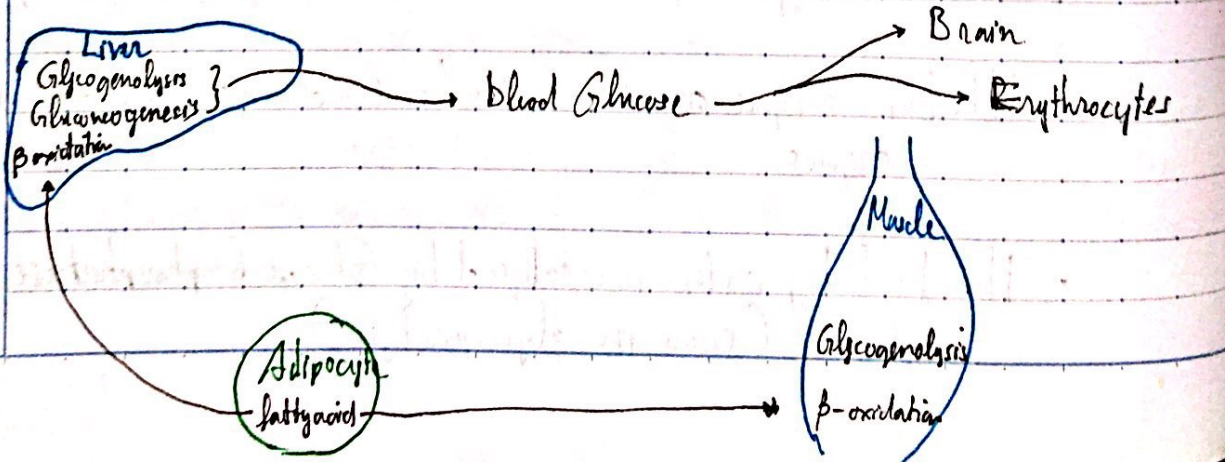
Metabolic states

Fasting state

- During overnight fast → paramount for body to maintain Glc lvl by activating glycogenolysis and gluconeogenesis (in liver)

Adipocyte also contribute to maintaining Glc lvl by releasing fatty acid that are carried (by attaching to albumin) to liver & muscle
Glycogenolysis happens in the liver, creates Glc for all tissue but mostly used by erythrocytes & brain

- Different pathways are regulated by some changes of blood hormone lvl



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Fed state

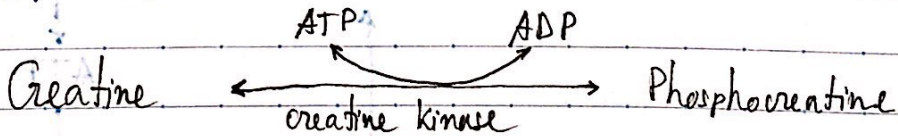
- After meal → Glc ↗ → signal the pancreas to excrete hormones to alter the pathway.

Most notably: every nutrition is directly delivered to the liver via the portal vein

Exercise state

- Demand rapid adaptation, begins w/ signal from brain to muscle
  Glucose arises in liver & muscle from glycogen
  Fatty acids are oxidise (can account in 50% of O_2 consumption)

- Muscle contain important resource: creatine (derived from Arg & Gly), can be reversibly phosphorylated to form phosphocreatine by enzyme creatine kinase:



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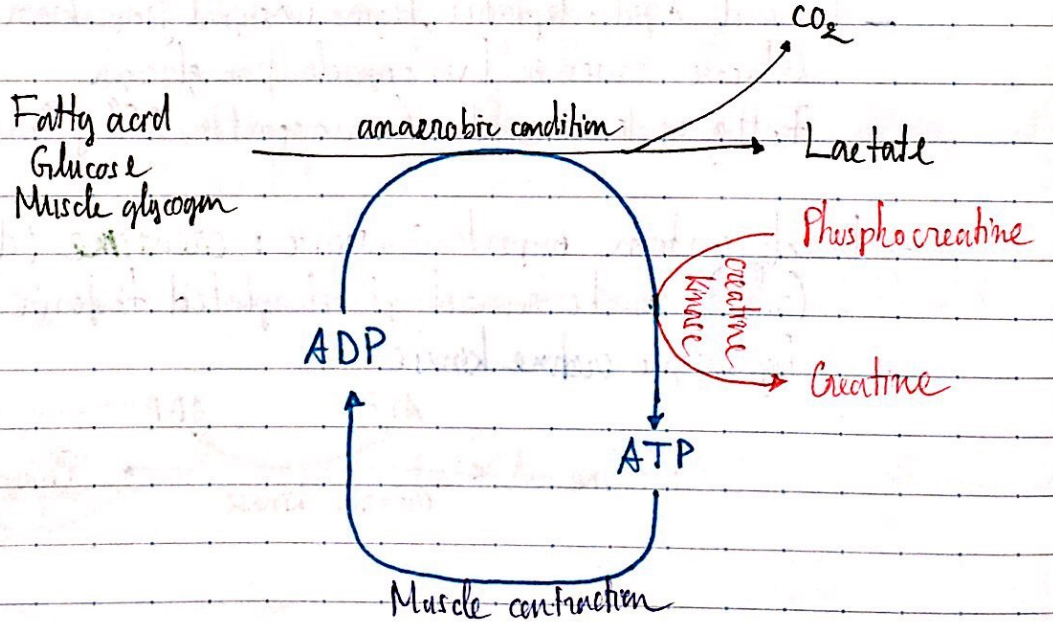
- In the cell with Ca^{2+} also increase to stimulate muscle contraction and also activate phosphorylase kinase (which activates glycogen phosphorylase)

Additionally, anticipation to exercise release adrenaline, promote glycogenolysis thru is receptor couple G_s protein to activate adenylate cyclase and ↗ cAMP, activate PKA

Anaerobic exercise

- Need ATP in short period (faster than diffusion of substrate (O_2) into the muscle from blood)
  → Energy comes from muscle glycogen and path way is anaerobic glycolysis → last production is lactate

Muscle also contain a small amount of phosphocreatine which can be dephosphorylated to form ATP



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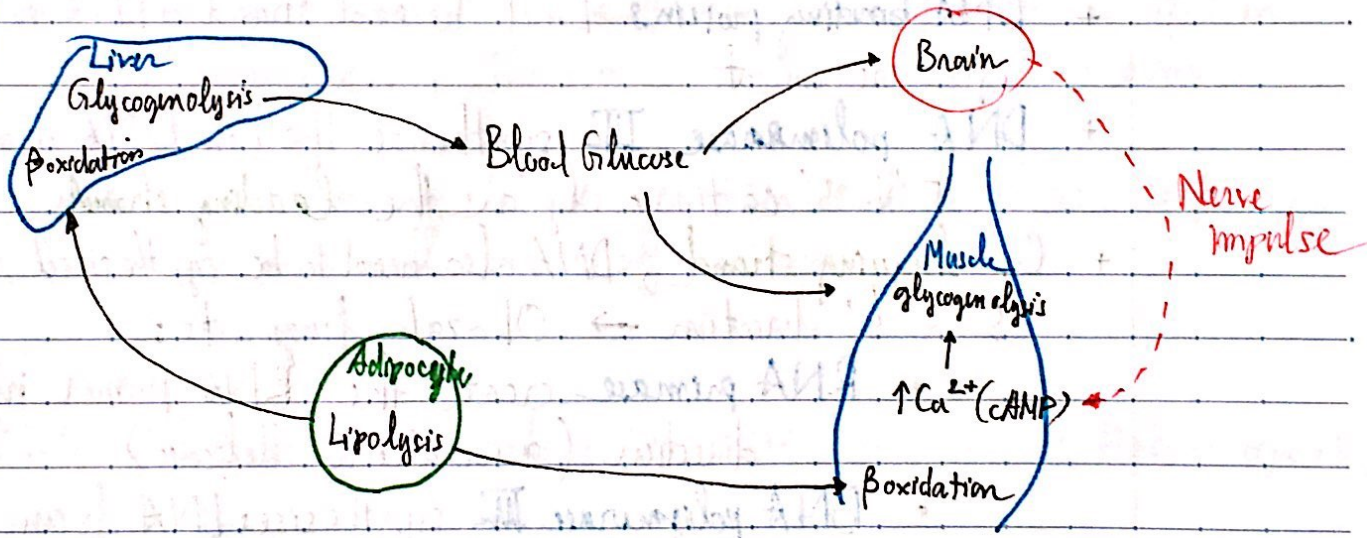
Aerobic exercise

- Can be sustain for long periods.
  → Fuels can be oxidised completely

Glycogen is used primarily to generate blood glucose
Fatty acids are used as energy source by liver & muscle cell.

- Coordinated changes in circulation occur : deliver O_2 & substrates, remove CO_2 & products.
  These changes are activated by sympathetic nervous system and adrenal to divert blood flow to the muscles

- During prolonged exercise, growth hormone & cortisol also rise to accompany increased adrenaline (& glucagon) and decreased insulin.



IV) DNA in clinic

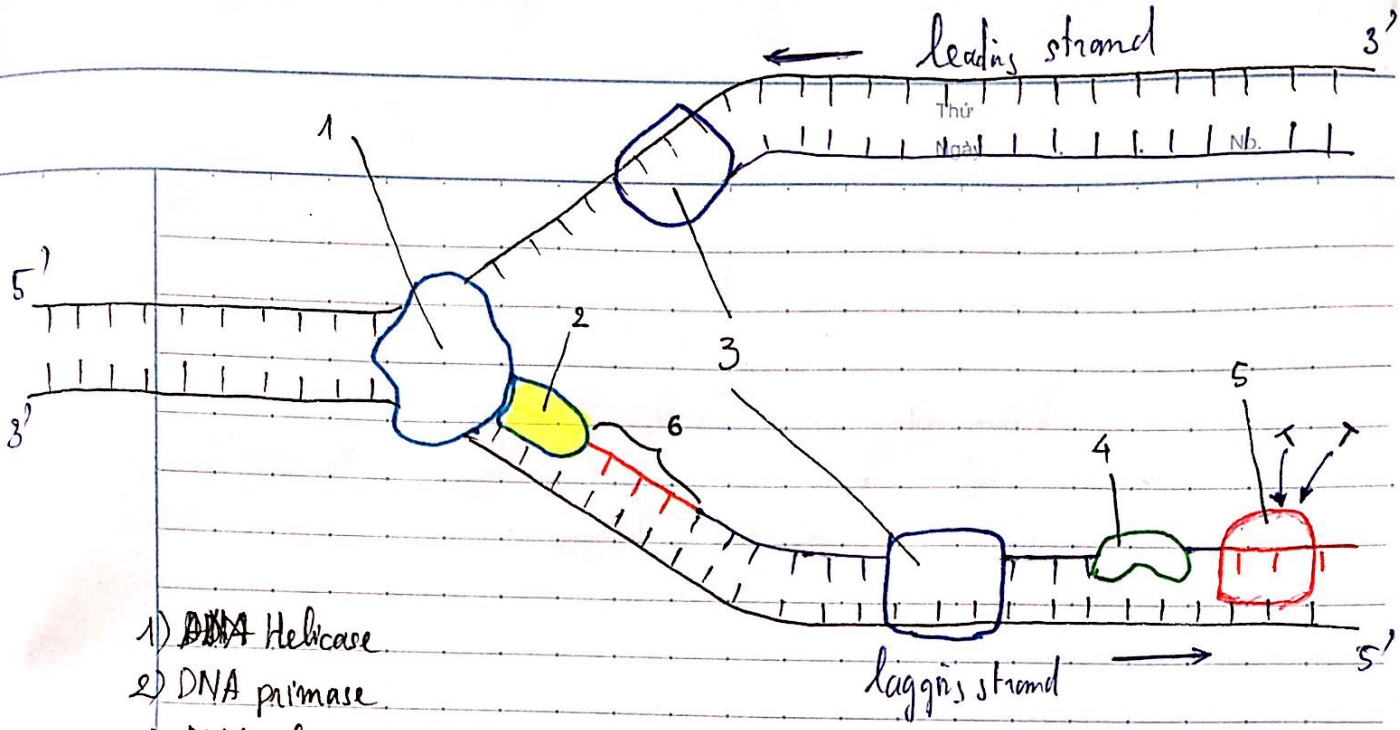
DNA Replication

- Synthesis of 2 identical daughter DNA and identical to the parent DNA
- Occur during S phase
- Occur w/ high fidelity as the interest of the organism to produce very accurate template
- Start at the origin of replication
- Both strands are the templates

New DNA is always synthesised in 5' to 3' (on template 3'→5')

Mechanisme of DNA ~~dyn~~ Replication

+ Helicase seperate 2 strands of DNA
+ DNA binding proteins bind to each strand of DNA to keep them from reconnect
+ DNA polimerase III synthesise the new DNA strand in 5' to 3' continuously on the leading strand
+ On lagging strand, DNA also need to be synthesised in the 5'-3' direction → Okazaki fragments:
  - RNA primase create the RNA primer in 3'-5' direction (associates w/ Helicase)
  - DNA polymerase III synthesises DNA from the primer in 5'→3' direction
  - DNA polymerase I replaces the RNA Primer
  - DNA ligase links the Okazaki fragment



1) ~~DNA~~ Helicase
2) DNA primase
3) DNA polymerase III
4) DNA ligase
5) DNA polymerase I
6) Primer

DNA polymerase cannot synthesize new strand from scratch, first on the template → There must be something first → primer.

Also on the leading strand → after each synthesis, the primase at the end will be cut off → aging.

Note: Topoisomerase relaxes the DNA strand before Helicase seperates

Week 4 20/3/2017

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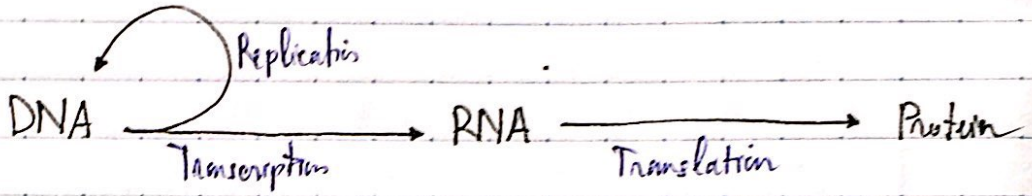
I) Transcription

Targetting transcription in the pharmacy

- Transcription – process of copying sequence information from 1 strand of DNA to an RNA.
  Occurs in the nucleus, involving the activity of proteins including transcription factor and RNA polymerase



Mechanism of RNA transcription

Initiation

+ Start w/ a proteins called transcription factors bind to DNA by recognising specific sequences of DNA called transcription factor binding site. This sequences located at the Promoter region of the gene.
  - Basal transcription factor binds to the promoter region of the gen
  - Then transcription factors bind
  - RNA Polymerase binds, then the process can be trigger

Elongation

+ Elongation phase: Once transcription is initiated, DNA double helix unwinds and ARN polymerase read the template strand, adding nucleotide in 5' → 3' direction
  The DNA rewinds after being transcribed
  In eukaryotes, typically 22 – 25 nm/s

Termination

+ Termination: terminator sequences located at the end of the gene (near non-coding sequences)
  RNA reach the sequences and stop, disconnect to DNA

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Transcription is strictly regulated

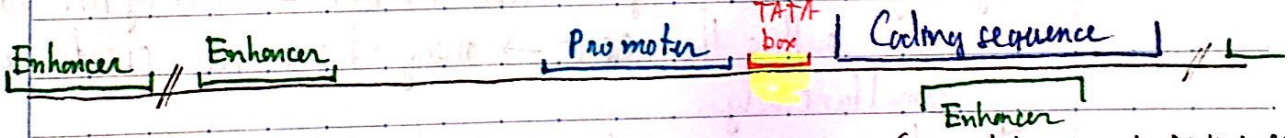
- Tightly control to ensure right genes are turned on at right moment

• Sometimes a product is always required → may be turned on constitutively
  Eg: Housekeeping genes that encode proteins for essential cell function

• Most of the time, specialised genes can be turned on & off to ensure the amount of product is appropriate
  Eg: When ppl get sick, the body secretes a small protein called cytokine to ignite the immune system (no longer available when healthy)

Transcription factors & promoter region

- transcription starts in the promoter region
- The promoter region contains specific sequences for transcription factor to bind to



- TATA box: binding site for TATA binding protein (unwinds & seperate DNA strands)
- Enhancer: sequence that can be bound by transcription factors to increase the chance of transcription will occur

Each transcription factor will bind to a unique sequence, known as 'consensus sequence' for that factor. The assembled factors may activate or repress transcription
In addition, basal factors and coactivators are not enough to drive transcription but create the anchor point for other factors & RNA pol

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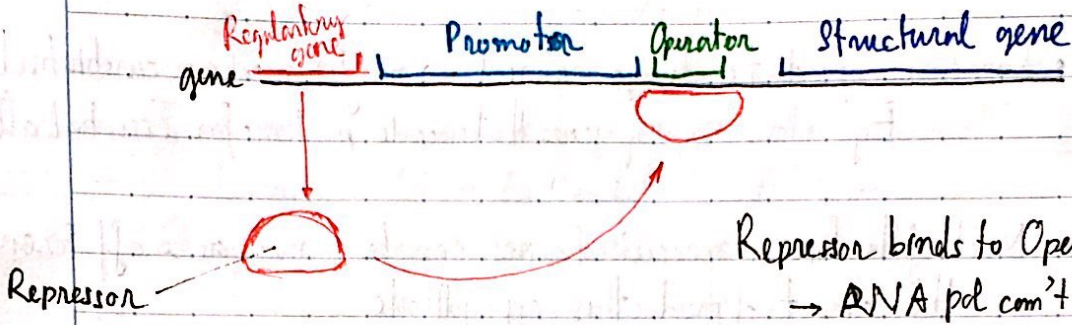
Eg: Lac operon is an eg of repressed transcription

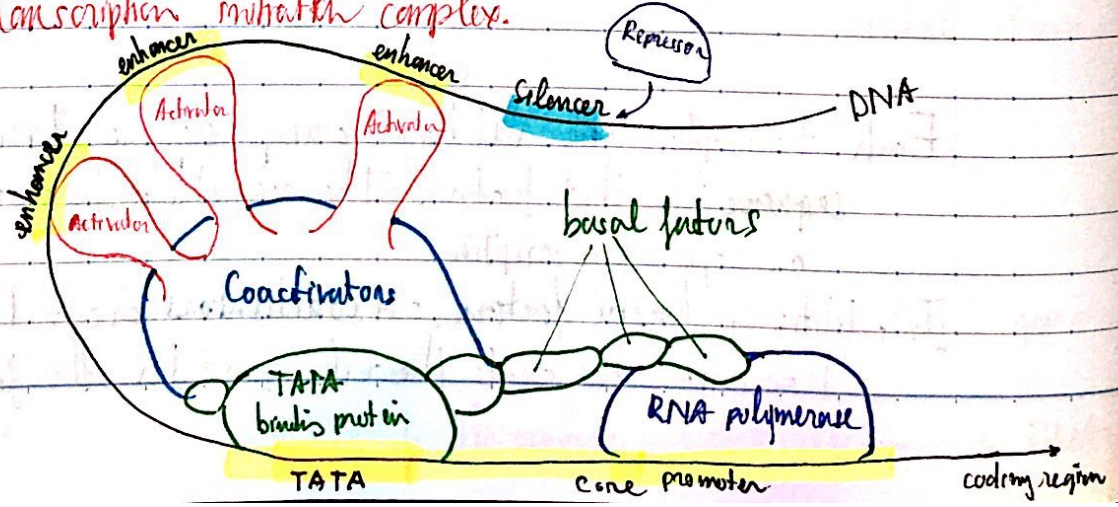


- RNA read DNA strand by identifying the template strand: the template contain anti-codon, and RNA Pol will bring the complementary nu to pair with the template

- Only 1 strand is the template, and RNA is synthesized 5'-3', just like DNA replication

- If only 1 RNA is synthesised at a time → lots of time to complete and suffice the needs → many transcription events occur simultaneously.
The frequency dependson signals (both ex & internal)

Transcription initiation complex.



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- Activators: regulatory proteins bind to DNA at enhancer sequences. When DNA folds → enhancer is brought into proximity w/ transcription complex, the activators interact w/ the complex to ↗ rate of transcription.

- Repressors: regulatory proteins bind to silencer sequences, prevent the binding of activators → ↘ rate of transcription.

- Basal factor: transcription factors, in response to co-activators, position RNA Pol at the start of a protein-coding sequence, then release RNA Pol to transcribe.

- Co-activator: transcription factors transmit signal from activators to basal.

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II) Translation

- The process of transform information sequences to protein (polypeptide) from mRNA

Translation takes place in 3 steps

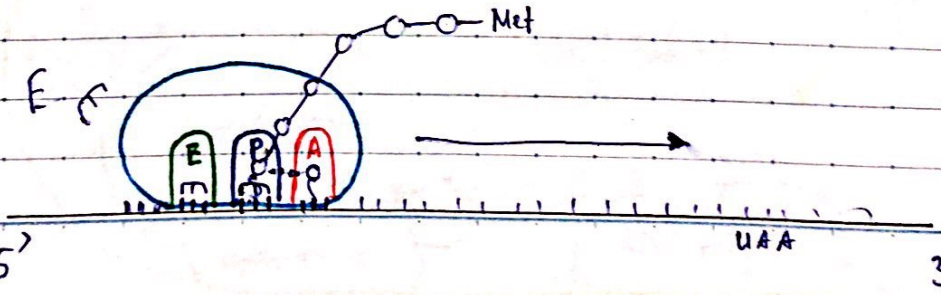
- Before protein is synthesized, mRNA move out of the nucleus to the rough ER

- 3 stages:
  - Initiation: ribosome assembly, mRNA and initiation factors (protein) ressemble to form initiation complex
    This requires 5' cap sequence, GTPs initiation factors
    The 5' cap is a heavily modified 5' guanine nu that mark the initiating AUG (Shine-Dalgarno box)
  - Elongation: aa are added as the ribosome moves along the mRNA
    Require aminoacyl-tRNA, elongation factors & GTP

    Met goes in Peptidyl site (P), 2nd aa goes in Amino site (A), then form peptide bond

    Empty 1st tRNA move to E site
    This process is energy intensive (GTP → GDP)

  - Termination: Stop when reach stop codon (UAA, UAG, UGA)
    Ribosome disassembles



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The genetic code

- A gene is the sequence of nucleotide contains info necessary to code for 1 poly peptide chain

The sequence of nu in DNA forms the Genetic code

- Genetic code is **degenerate**
- Genetic code is **redundant**
- Genetic code is **universal**
- The 3rd position in each codon is less specific

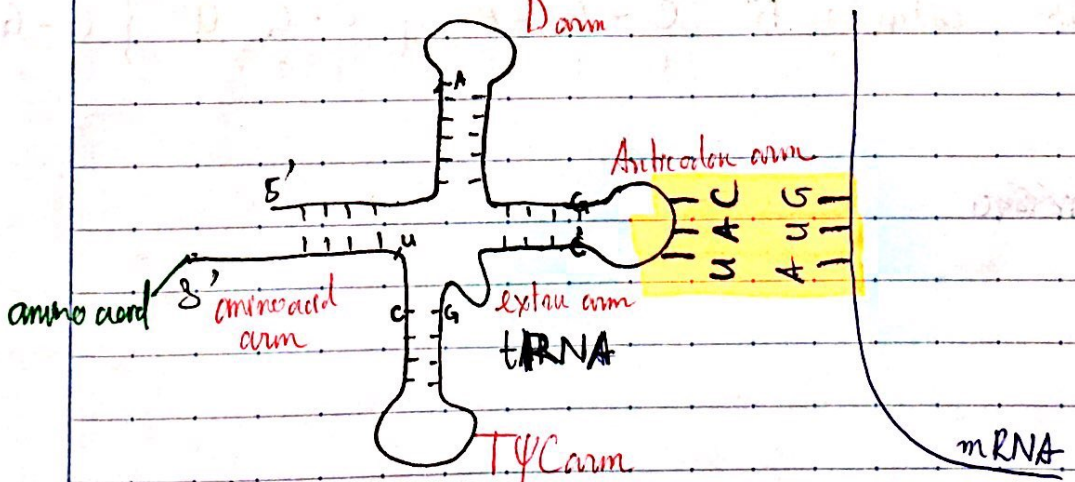
tRNA & amino acyl tRNA synthetase

- tRNA are small RNA molecules that deliver specific aa to the ribosomes.

The tRNA anticodon will interact with mRNA codon.

- Aminoacyl tRNA synthetase catalyses the binding of aa to tRNA
  → "Activated" tRNA

There is only 1 synthetase for each aminoacid, and they have very accurate proof reading mechanism (error only occur every $10^4 - 10^5$ reactions)



Amino acyl tRNA

The wobble base

- Need explanation for the number of tRNA in relation to number of aa ? (45 tRNA for 61 aa)
  → Wobble base

- Inosine (I) is a modified nu that is often found in 5' tRNA position
  This nu allows non-Watson-Crick base pairing with the 3' base in mRNA codon

⟹ Explain { Redundancy
N° tRNA ≤ N° aa

- As can propably see, the first 2 nu in the codon usually determine the specific aa, while the 3rd is not as important.
  → can be changed.

		3	2	1		3	2	1		3	2	1	
tRNA anticodon:	3'	G	C	I		G	C	I		G	C	I	5'
mRNA codon:	5'	C	G	A		C	G	U		C	G	C	3'
		1	2	3		1	2	3		1	2	3	

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III) Immunology

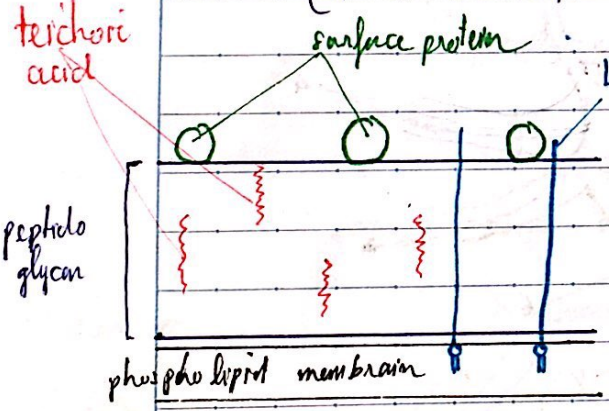
How body can recognise a pathogen

- From the vid : bacterias have a protein surface call M protein
  ⇒ This is an eg for Pathogen associated molecular pattern (PAMP)

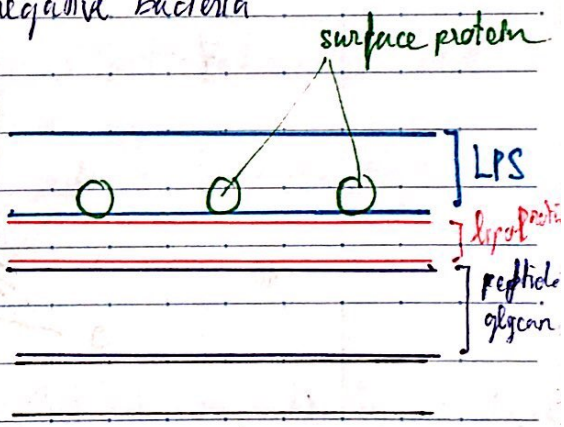
The immune cells recognise PAMP thru Pattern recognition receptors (PRR)

- The interaction between PRRs and PAMPs is non-specific
  ⇒ PRRs can also recognise PAMPs from another type of bacteria

- Other PAMPs that are present in bacterias are lipopolysaccharide (LPS) on surface of Gram-negative bacteria



Gram (+) bacteria



Gram (-) bacteria

Where do immune cells develop

- Immune cells arise from bone marrow, which differentiate in central lymphoid organs : thymus & bone marrow

Immune cells migrate via bloodstream or lymphatic system

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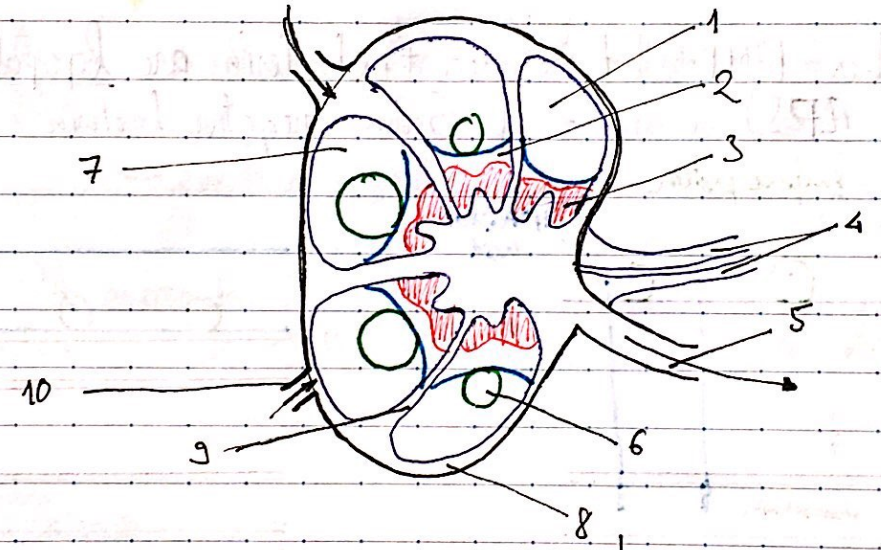
to lymphoid organs including lymphnode, spleen, lymphoid tissues associated w/ mucosa (gut + tonsils, peyer's patches, appendix)

- Lymphoid tissues = center of immune response, where all immune cells interact w/ pathogens

Lymphatic vessels drain the fluid that have collected from the extracellular space to the lymph node

Pathogen including the virion & PAMPs will be carried to the lymph node, interact w/ B cells (may also w/ denchitic cells, macrophages & T cells)



1. Primary lymphoid follicle (mostly B cells)
2. Paracortical area (mostly T cells)
3. Medullary cord (macrophages & plasma cells)
4. Atery vein
5. Efferent lymphatic vessels
6. Germinal center
7. Secondary lymphoid follicle
8. Marginal sinus
9. Cortical sinus
10. Afferent lymphatic vessels

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Specificity in immune response

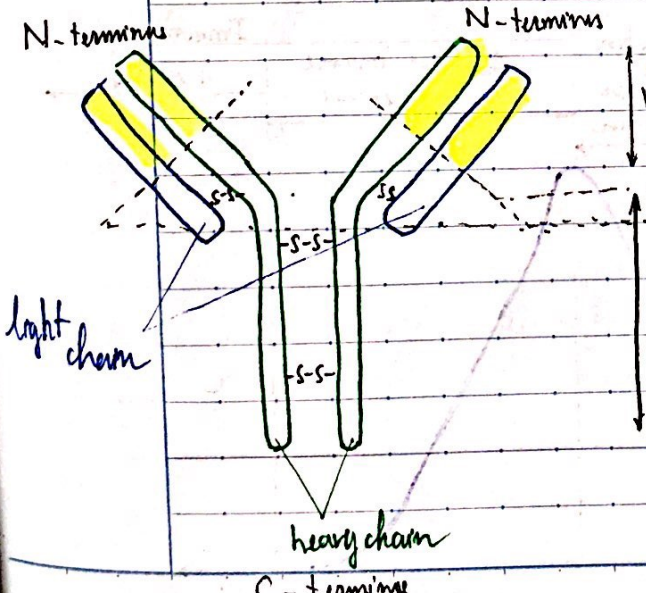
- The PAMP follow the lymphatic vessel to the lymph node and activate one particular B cell, which later divide to an army of effector cells called **plasma cells**

Plasma cells are protein factories, they have extensive ER which allows them to make a large amount of protein called **antibody** (this process is energy intesive → ppl feel sick)

- The B cells that divides after interacting w/ PAMP is the only B cell that can recognise the PAMP
The part of the PAMP that was recognised by the B cell is called **antigen**

The B cells produce soluble antibodies that also bind to PAMP

- Antibodies are small soluble ~~molecules~~ proteins, bind directly to antigen w/ high specificity and affinity



- Antibodies consists of 2 identical heavy chains & 2 identical light chains

- A flexible hinge allows the antibody to bind with the pathogen or the PAMP
  - The variable region gives specificity
  - The constant region interact w/ other components in the immune system

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- Antibody generally recognise a small region on a large molecule such as polysaccharide or protein.
The structure that recognised by antibody is called **epitope** or **antigenic determinant**

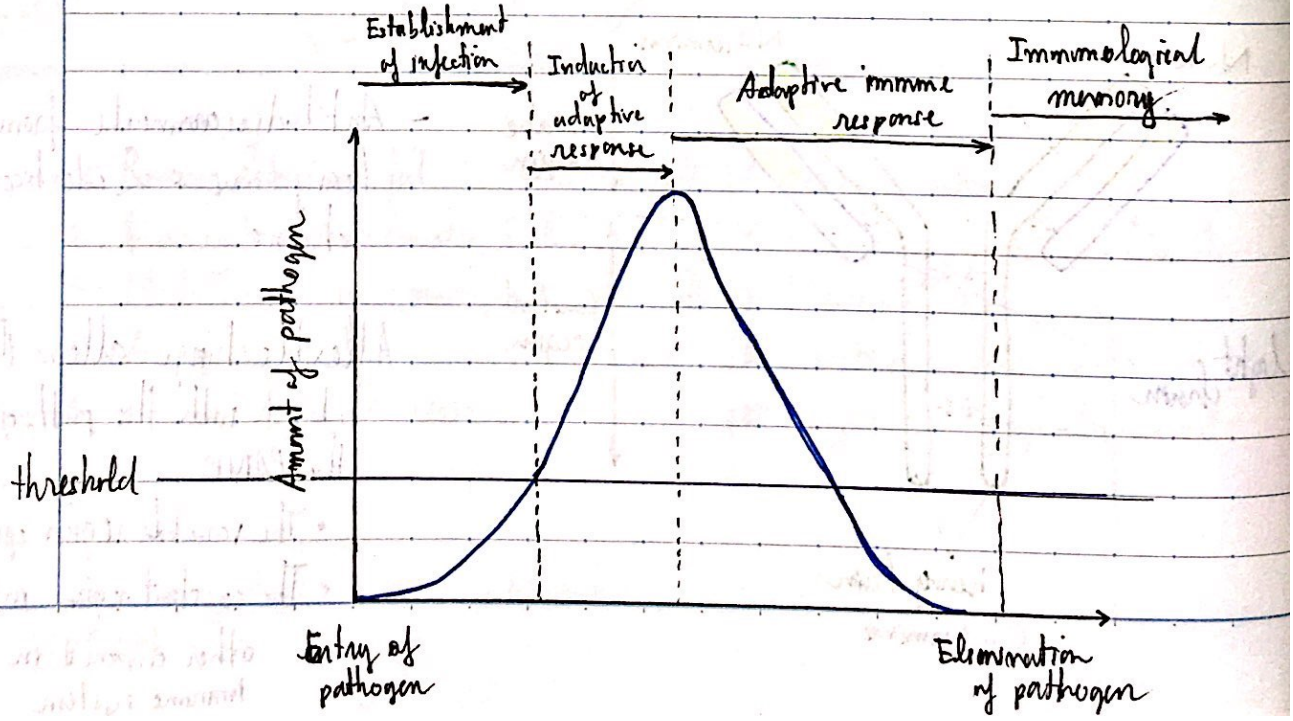
- Antibody doesn't kill the pathogen by itself, but signal a **phagocytic cell** to engulf the pathogen

When is an adaptive immune response activated?

- When the body 1st exposed to an antigen, the **non-specific innate immune response** is activated.

If the antigen overwhelms the innate immune response, the **highly-specific immune response** will be activated.

The trigger to activate the adaptive immune response is the amount of antigen: once the antigen passed the threshold, the B cell that recognise the antigen proliferated (4 days after exposure)



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Phagocytosis = non-specific cellular immune system

- The infected cells that have been flagged by antibodies will be eaten by ~~macrophage~~ phagocytes (non specific interaction)
  The phagocyte recognises that bacteria is a pathogen, but doesn't care which pathogen

- **Macrophages** and **Neutrophils** are main type of macrophages in the immune system.

Inflammation

- 3 essential roles:
  - Deliver additional effector molecules & cells to infected site
  - Induce local blood clotting
  - Promote tissue repair

- During inflammation, phagocytes are recruited to infected site by signal from infected cells, sent by **cytokines** (small proteins that affect behaviour of other cells) and **chemokines** (subset of cytokines that stimulate migration of cells)

Cytokines produced by macrophages at the site of infection cause dilation of the blood vessels and changes in **endothelial** cell walls ⟶ Mvt of neutrophils and monocytes out of the blood vessels and into infected tissue
Blood vessels become more permeable and plasma fluid leak to tissues

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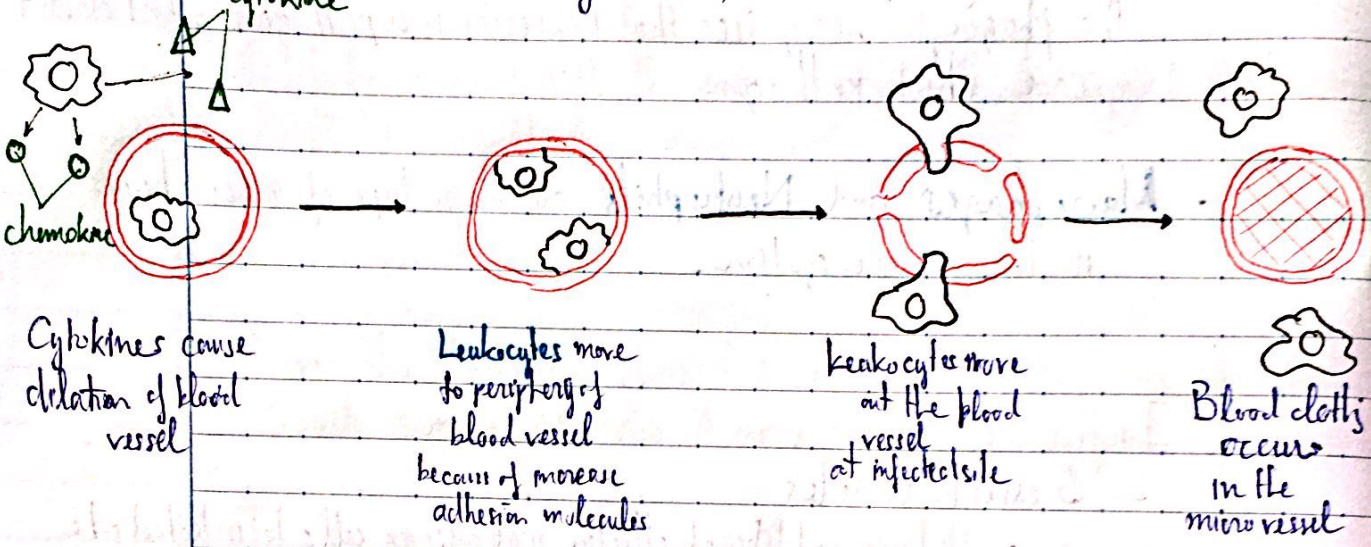
- Characteristic changes.
  - Key inflammatory cells : Macrophage & neutrophils
  - Cytokines are soluble proteins, important in inflammatory response
  - Characterised by : pain, redness, heat, swelling at site of infection



Different pathogen activate different immune cells

- When body is infected by a virus, virons will be detected by a type of immune cell called dendritic cell, a class of antigen presenting cell.
  They present the antigen to other immune cells that will kill infected cells.

- Cytotoxic T lymphocyte (CTL) plays important role in eliminating infected cells by releasing cytotoxic proteins into infected cells.

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Parasites & allergy

- When patient has allergy one parasite, eosinophils are activated, release granule components that are toxic to parasites, including eosinophils themselves

3 line of defences.

- 1st line:
  - Involving secretion of chemicals and body barrier.
  - Including intact skin, membrane
- 2nd line:
  - Innate immune response
  - Non-specific & non-adaptive
  - Inflammation, fever, blood clotting, phagocytosis
- 3rd line
  - Adaptive immune response
  - Specific & adaptive
  - 2 simultaneous responses [B cells recognise antigen → signal phagocytes
    T cells mediate immune response

    the 2 process is called respectively Humoral immunity & Cell-mediated immunity

Memory

- Once adaptive immune response is triggered, not all adaptive immune cells will be eliminated, remaining in the body and ready to become active if exposed to same pathogen again
  → Vaccination

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Week 5 27/3/2017

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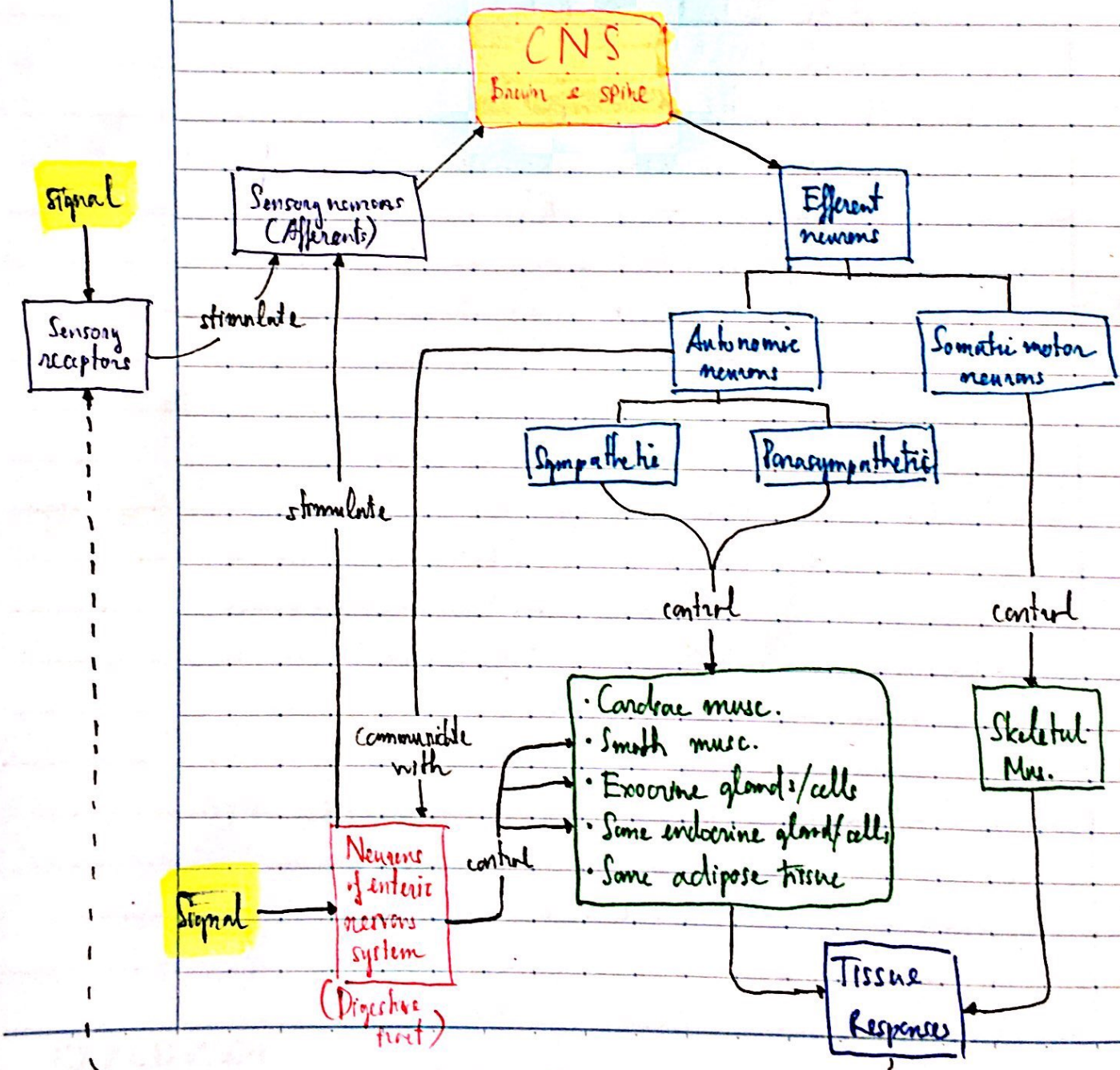
I) Nervous system

Organisation of the nervous system

- Nervous system = vital for cell comm. & control.

Divided into { Central Nervous System (CNS): brain & spinal cord
Peripheral Nervous System (PNS): neurons linked to spinal cord and not in the brain



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* The CNS integrates incoming info and determines a response
The incoming info. can be external (what happening around) or internal (what happening inside).

The CNS initiates activity: • Input may not necessary
• Output may not detectable

* The PNS [passes the info from CNS to the rest of the body
[pickup info from the body to the CNS
3 divisions of PNS
• Afferent neurons (info to CNS): Sensory neurons are a type of afferent neurons that monitor internal & external envi.
• Efferent neurons (info from CNS): Somatic (motor) neurons initiate skeletal muscle contraction. Autonomic neurons initiate smooth & cardiac muscle contraction
Autonomic neurons → 2 branches: { sympathetic / parasympathetic
• Enteric neurons: are 1 part of neurons system found entirely within the gut

Neuronal & Glial cells

- Nerous system = organisation of neurons + supporting tissue
- Components in neuronal structure:
+ Neurons (10-20%): specialised cells that transmit electrical signals and communicate their excitability via neurotransmitters (chemicals) across the gap (synapse). Human brain has 100 billion neurons & 100 trillions synapses.

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+ **Glial cells** : supporting cells, include Schwann cells, satellite cells, oligodendrocytes, astrocytes, microglia & ependymal cells. These cells provide appropriate environment for neuronal activity as neurons are vulnerable to damage

- **Schwann cells** and **Oligodendrocytes** : make the myelin that wraps around the axon of neurons and facilitates transmission of electrical activity

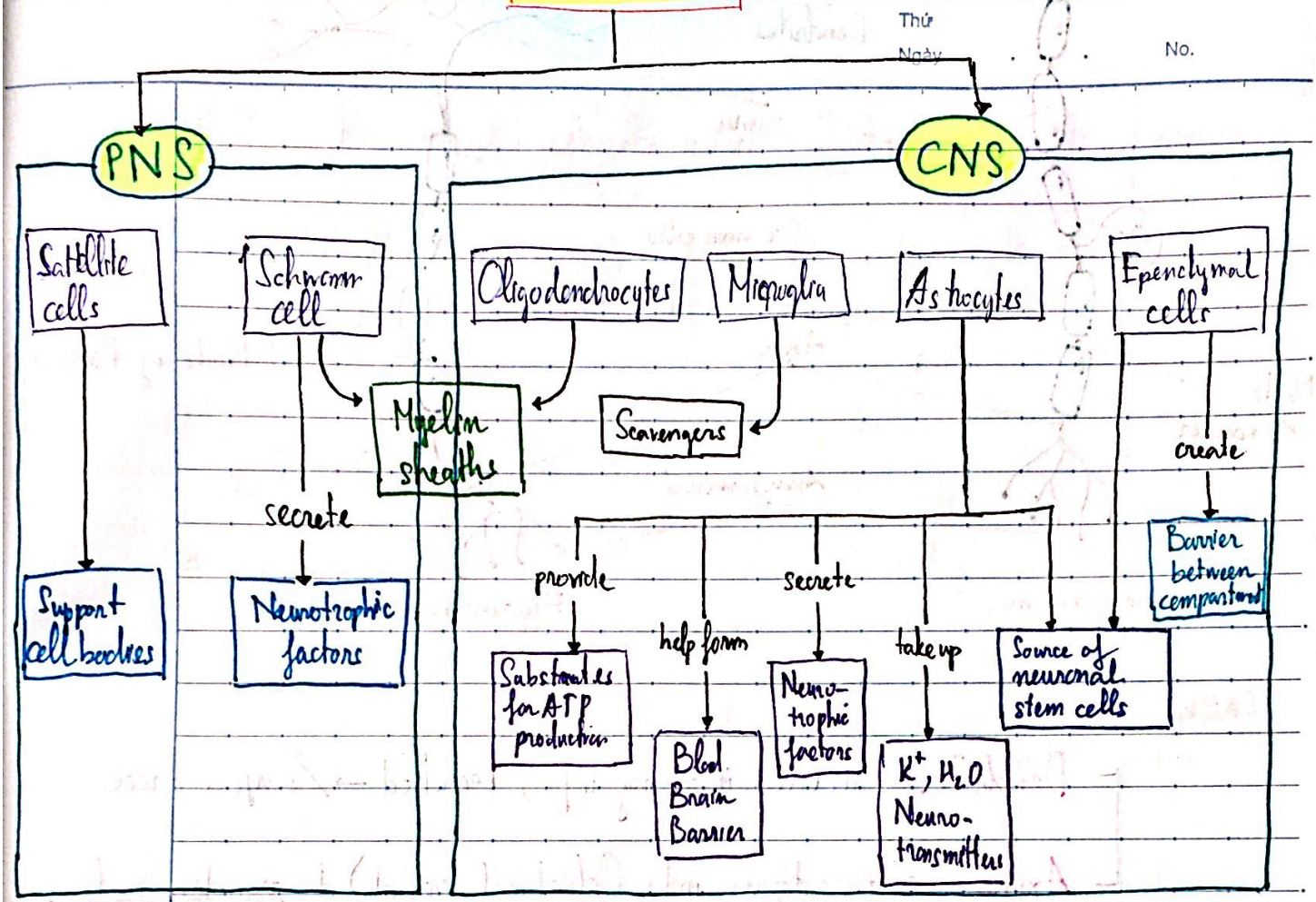
- **Astrocytes** : highly branched cell, help to form the blood-brain barrier (protecting the CNS); secrete neurotrophic factors that support the health & functioning of neurons; clean up neuronal envi. They are in contact w/ neurons & blood vessels → transmit nutrients between the 2.

- **Microglia** : specialised immune cell (act as CNS scavenger) when activated → remove invaders & damage cells Considered as 'macrophages of the brain'

- **Ependymal cells** : a type of epithelial cell, create selectively permeable barrier between compartments, they line the ventricles (fluid-filled spaces). Also a source of neuronal stem cells.

- **Satellite cells**

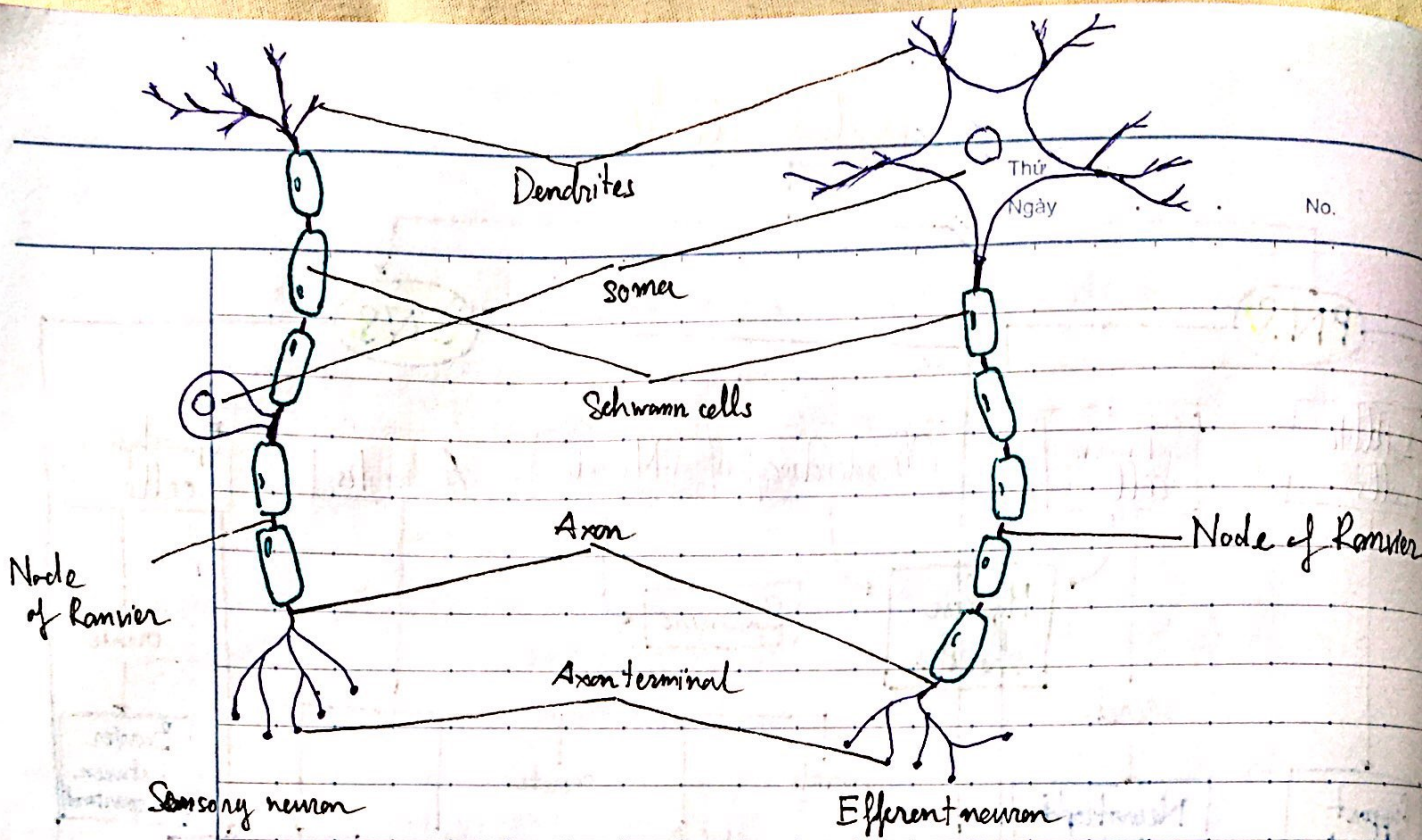
Glial cells



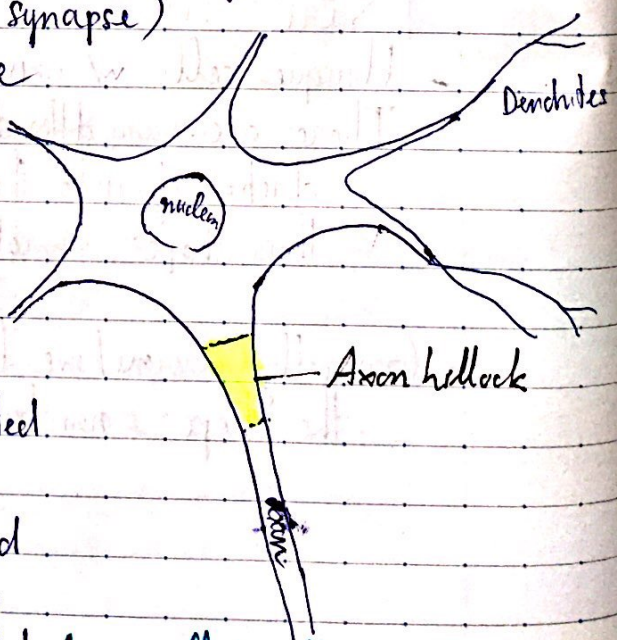
Neurons

- Unique cells w/ unusual shape & form (see week 1 - tissue)
  There are many different subtypes, and can be named according to the direction of info they carry (afferent, efferent, interneuron); or after their shapes, neurotransmitters or the brain areas.

- Generally, neurons have long processes extending from the cell body (soma)
  the shape & number of these processes varies on different types of neurons.



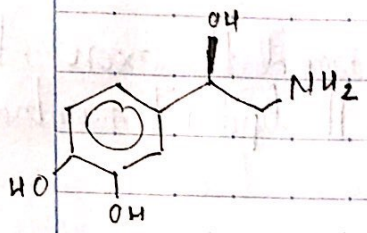
- **Dendrites**: receive incoming info, branched → ↗ surface area
- **Axons**: carry outgoing info (electrical signal) to axon terminal, whereby signal continue via the release of chemical messenger (neurotransmitter) that travel across the gap between cell
  - Another neron (synapse)
  - Another cell type



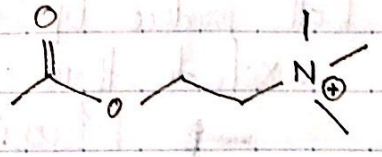
- The initial segment, or **axon hillock** is the point where action potential is initiated.

Sometimes the axon is branched (eg. Interneuron in CNS), the branches off the main axon is called **Axon collaterals**

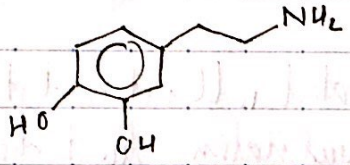
- Neurotransmitters are small molecules that are release from neurons.



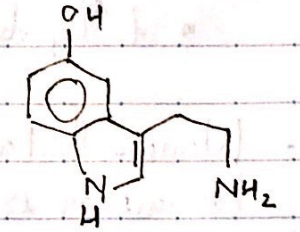
Noradrenaline (NA)



Acetylcholine (ACh)

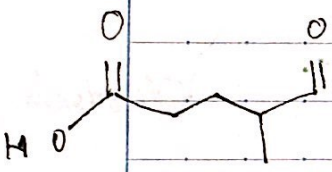


Dopamine (DA)

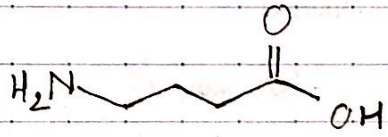


~~γ-amino butyric acid (GABA)~~

Serotonin (5-HT)



Glutamate



γ-amino butyric acid (GABA)

- Many other component of the neurons are typical for other cells, but more extensive in neurons.

  Eg.: • Expanded Rough ER since the neuron need the protein replacement continuously.

  • Extensive Microtubule network → maintain axon shape and mvt of cell component

- Many neurons have a myelin sheath around the axon → resistance of current leak.

The electrical signal that moves along the axon is called an action potential and the Na^+ & K^+ ion channels (required for propagation of action potential) are found in myelin-bare regions (Node of Ranvier)

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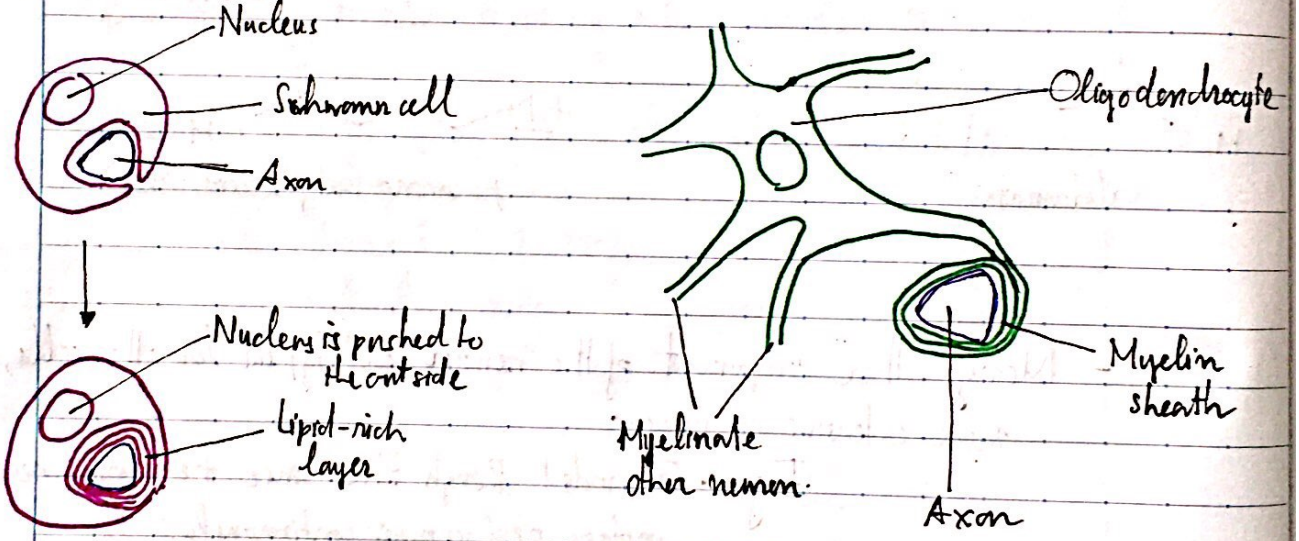
Schwann cells & Oligodendrocytes

- Both produce lipid-rich layer wrap around the axon, then exclude their cytoplasm, leaving the lipid rich membrane.
  → Myelination

  - 1 Schwann will cover 1 neuron (or 1 internode)
  - 1 Oligodendrocyte will cover 5 - 30 neurons

- Neurons that are not myelinated will not conduct as quickly
  Neurons can experience Demyelination due to diseases (eg. multiple sclerosis)



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II) Membrane excitability

How do neurons communicate w/ each other?

- 3 important components
  - Initiation in a neuron triggered by graded potentials or pacemaker
  - Action potential propagation
  - Synaptic transmittion

- Review membrane potential in Week 1

- The resting potential is determined mainly by $[K^+]$, and the cell is preameable to K^+, Na^+ & Cl^-

Ion	EC fluid (mM)	IC fluid (mM)	Potential (mV)
K^+	5	150	-90
Na^+	145	15	+60
Cl^-	108	10	-63

- These ions move thru membane via channel; the movement depends on concentration gradient.

- There are 3 main types of channeld:
  - Mechanically gated ion channel: response to physical forces
  - Chemically gated ion channel: response to chemicals
  - Voltage-gated ion channel: response to changes in voltage

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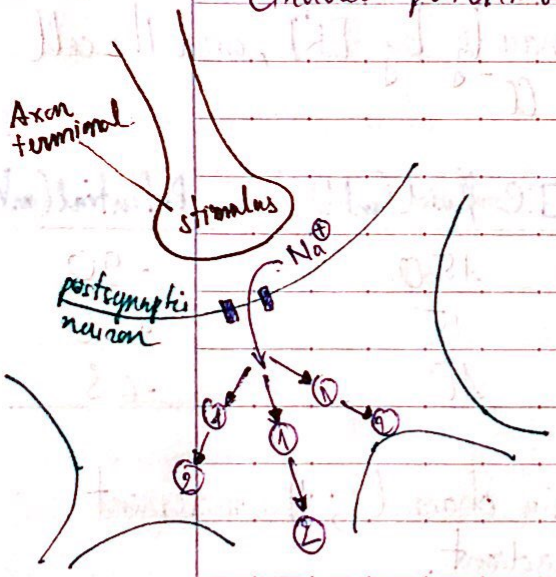
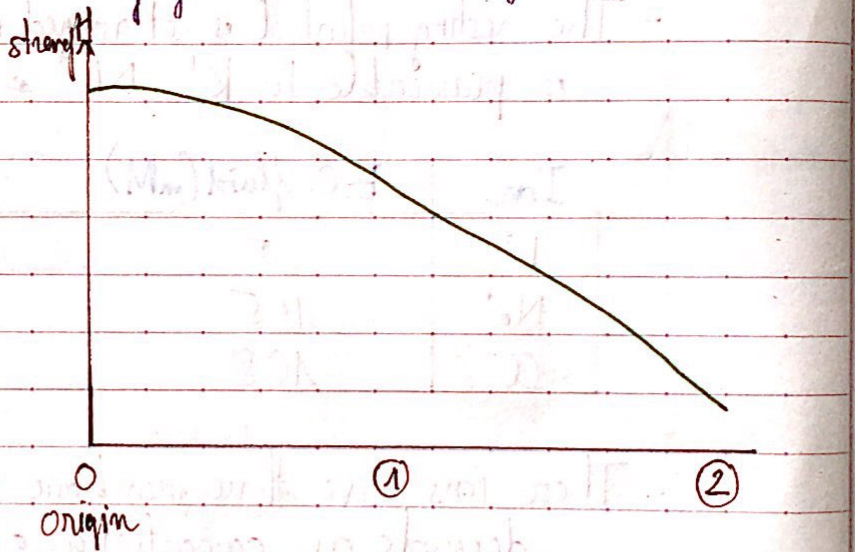
Graded potential

- Are signals that travel over a short distance and lose their strength as they travelling
  The magnitude can be varied → graded

- The potential can be positive or negative depends on the ions that enter and leave the cell (neuron) and the charge of the ion (K^+, Na^+, Ca^{2+}, Cl^-)

- Graded potentials usually follow a stimulus from the last neuron





- Graded potentials are generated by neurotransmitters acting on receptors which makes the cell more or less excitable by opening & closing channels

If graded potential is stray & positive → may trigger action potential (AP)

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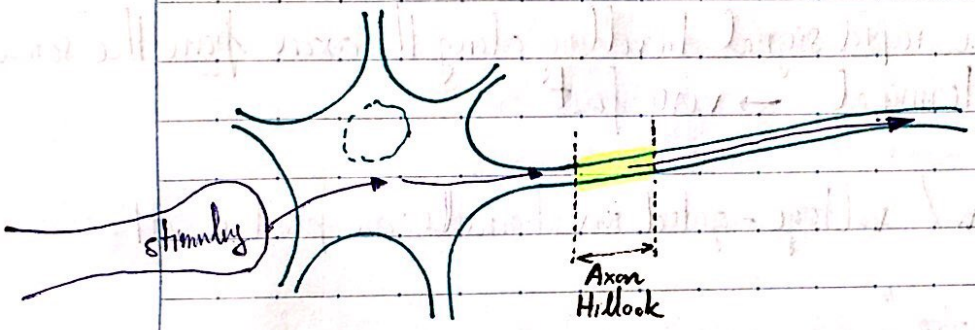
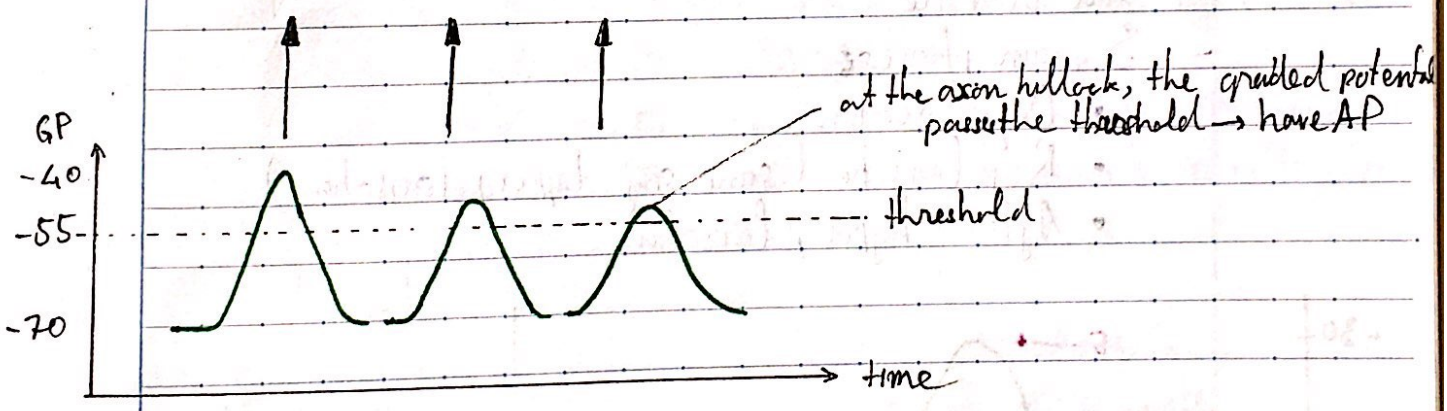
- Depolarising graded potential are excitatory → ↗ chance to occur AP → Excitatory postsynaptic potentials (EPSPs)
- Hyperpolarising graded potential are inhibitory → ↘ chance to occur AP → Inhibitory postsynaptic potentials (IPSPs)

– The graded potentials decrease in strength in relation to distance → when the graded potential reach the axon hillock (trigger zone), it must pass a threshold for AP to be produced (usually −55 mV)





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Action potential

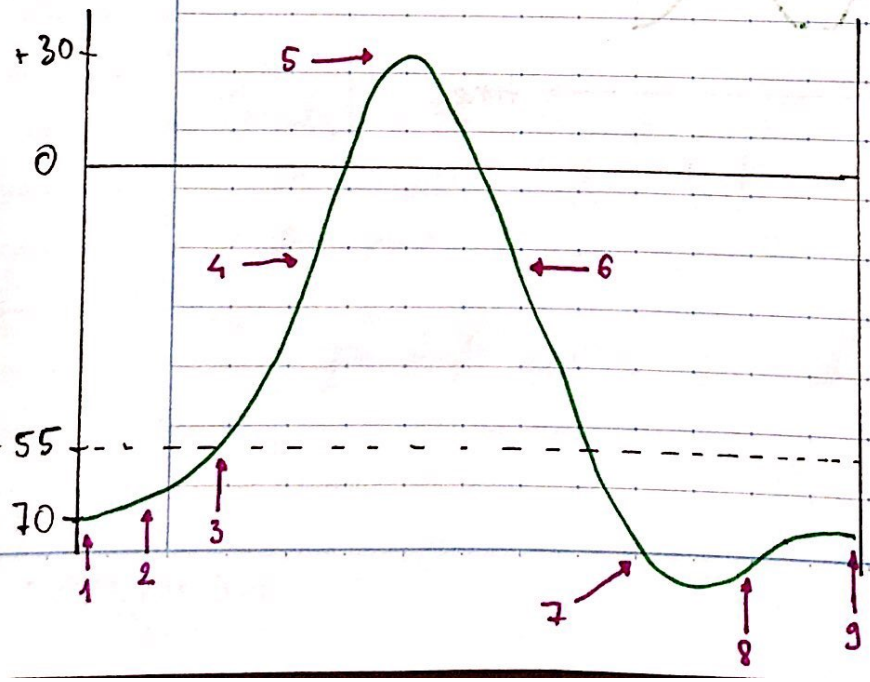
- AP is a large, uniform depolarisation capable of travelling long distances

Neuronal membrane have the ability to suddenly allow influx / outflux of Na^+ & K^+ via ion channels (voltage-gated)
These ion channels can detect the changes in voltage as an AP reaches them and turn open → propagation

- An AP is a rapid signal travelling along the axon from the soma to the terminal → very fast

Only cells w/ voltage-gated ion channels can produce APs.

- "All or none"
- 3 main phases
  - Depolarisation
  - Repolarisation (some say hyperpolarisation)
  - After-hyperpolarisation



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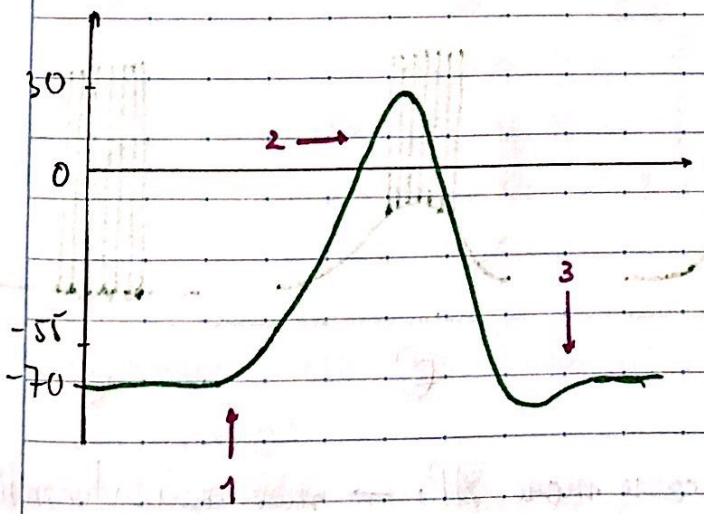
Steps of an AP:

1. Resting membrane potential
2. Depolarising stimulus (EPSP)
3. Membrane depolarise to threshold
   Na^+ gates open quickly → Na^+ influx
   K^+ gates open slowly
4. Rapid Na^+ → Depolarising
5. Na^+ channels close (inactivate)
   Slower K^+ channels open
6. K^+ out flux
7. K^+ channels still open; more K^+ leaving → Hyperpolarising
8. K^+ channels close
9. NaK pumps back to initial concentration gradient

Note that the Na^+ in 3 states, which are determined by 2 gates
- Close before an AP (activation gate)
- Open during an AP due to changes in voltage (positive)
- Close after an AP (inactivation gate) due to change in voltage (positive)



1. Activation gate
2. Inactivation gate
3. Na^+ channel get back to resting state → activation gate

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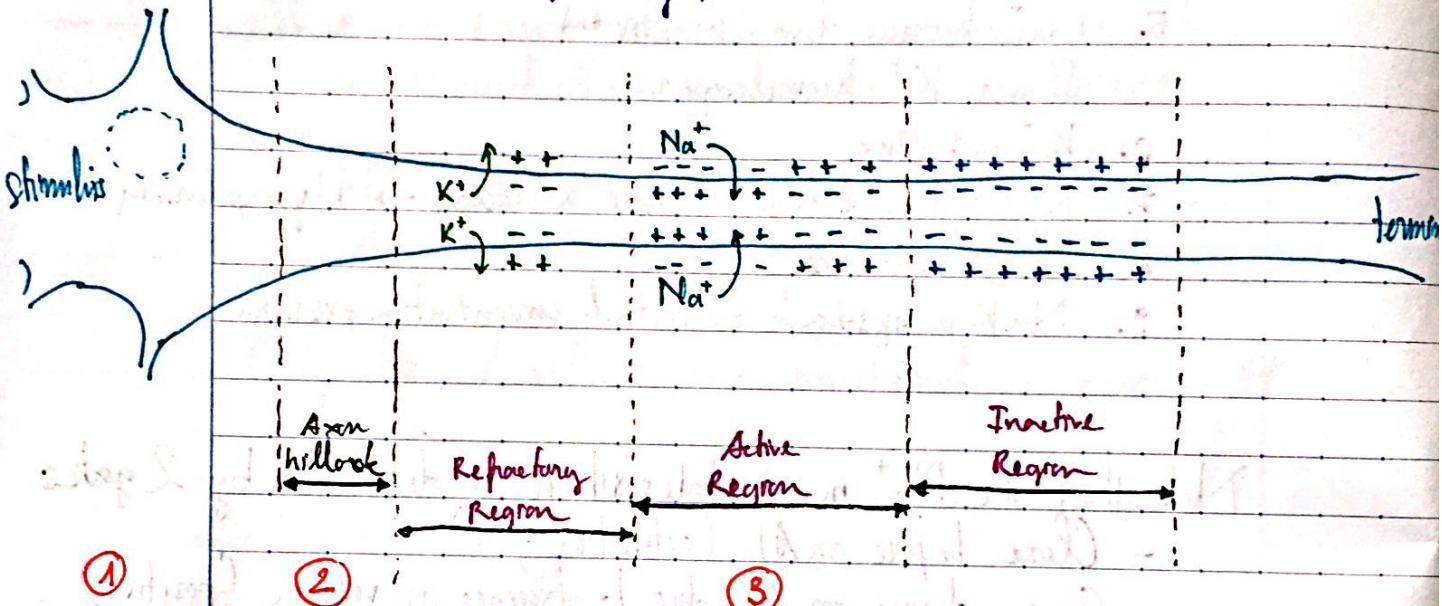
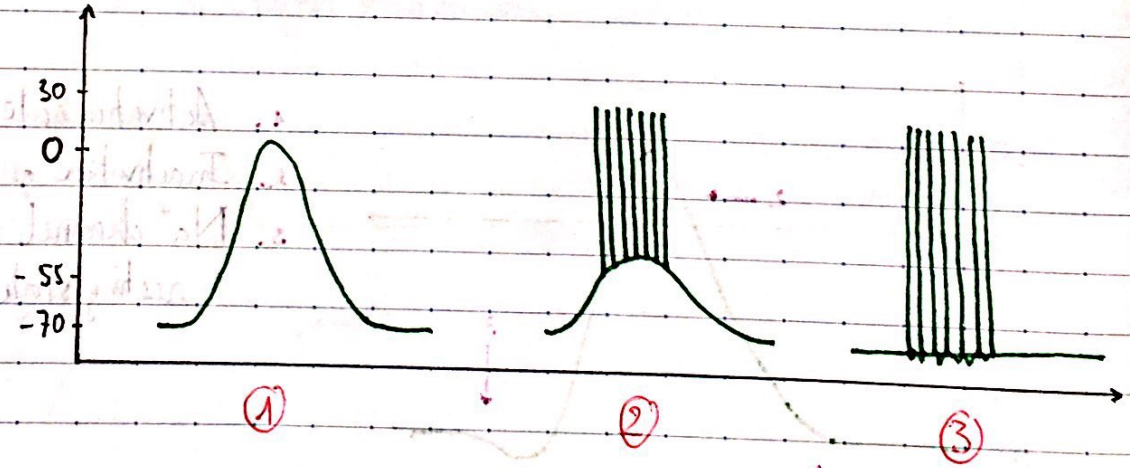
Action potential mvt in axon

- Beause the way of operating Na^+ & K^+ channel → 1 direction from the soma to axon terminals only.
Even though the later channels result in a positive change in voltage, the previous channel cannot regen due to refractory period.





- Stronger stimulus cause more AP's → more neurotransmitters

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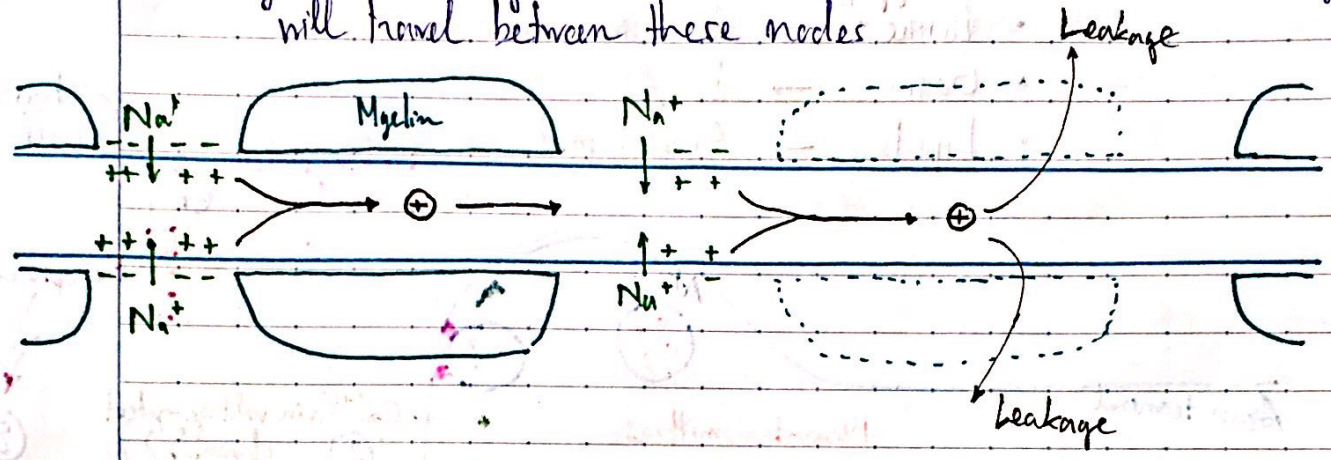
- The size & strength of APs is uniform as they travel along the axon. However the rate/speed can change.
  → Myelin.

Only the Nodes of Ranvier have Na^+ channel → The (+) charges will travel between these nodes.



How APs trigger release of neurotransmitters

- The cells don't directly contact
  → the gap between the axon terminal & target cell is called Synapse

- The neurotransmitters are released by Exocytosis.
  An AP trigger the voltage-gated Ca^{2+} channels
  → Ca^{2+} move into the axon terminal
  → Activate a series of protein (SNARE protein) which initiate the movt of vesicle to the membrane
  → release

- Chemical messengers (contained in vesicle) act upon different specific receptors
  There is variability in { receptors & receptor-mediated response / ligands }

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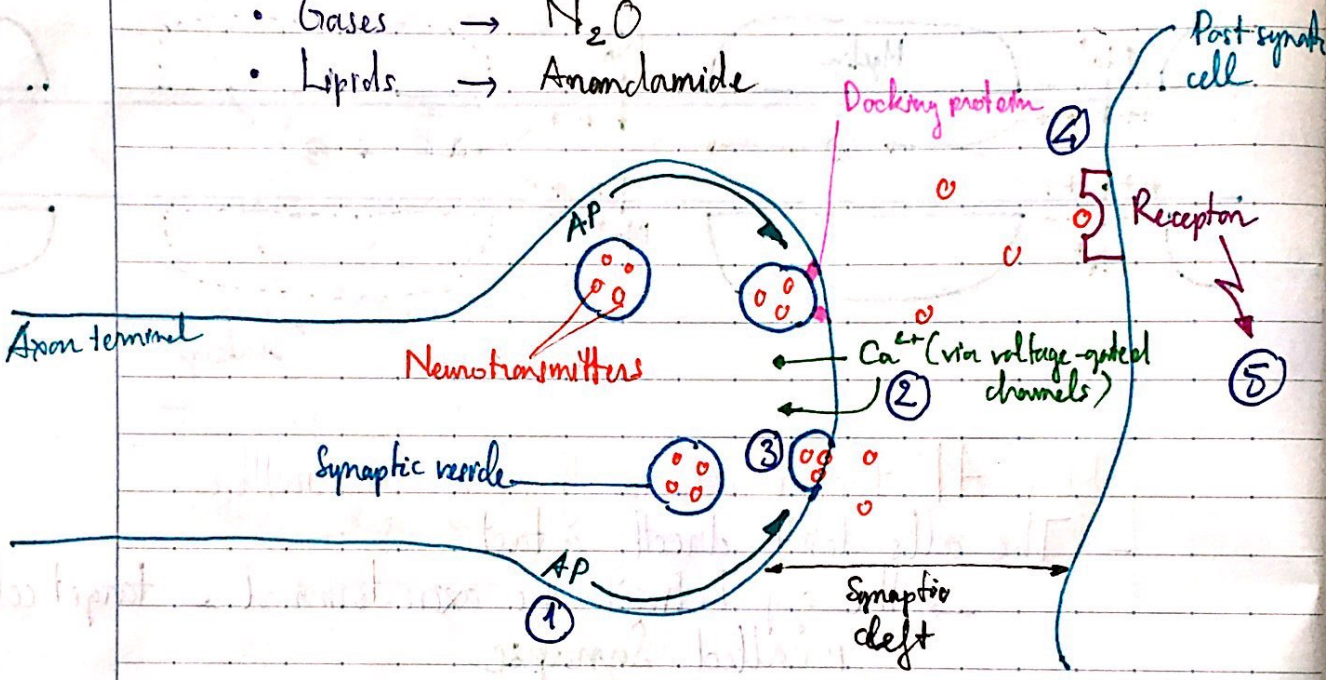
- The neurotransmitter can be:
  - AChO
  - Amino acids → Glutamate, anpartate, GABA, glycine
  - Amino acid derivatives → Dopamine, histamine, adrenaline
  - Polypeptides → Substance P, opioid
  - Purines → Adenosine, ATP
  - Gases → N_2O
  - Lipids → Anandamide



1. An AP depolarise axon terminal
2. Depolarisation open voltage-gated Ca^{2+} channels → Ca^{2+} enter the cell
3. Ca^{2+} trigger exocytosis
4. Neurotransmitters diffuse (across synaptic cleft) & bind w/ post-synaptic cell's receptors by weak interactions
5. Binding initiates response

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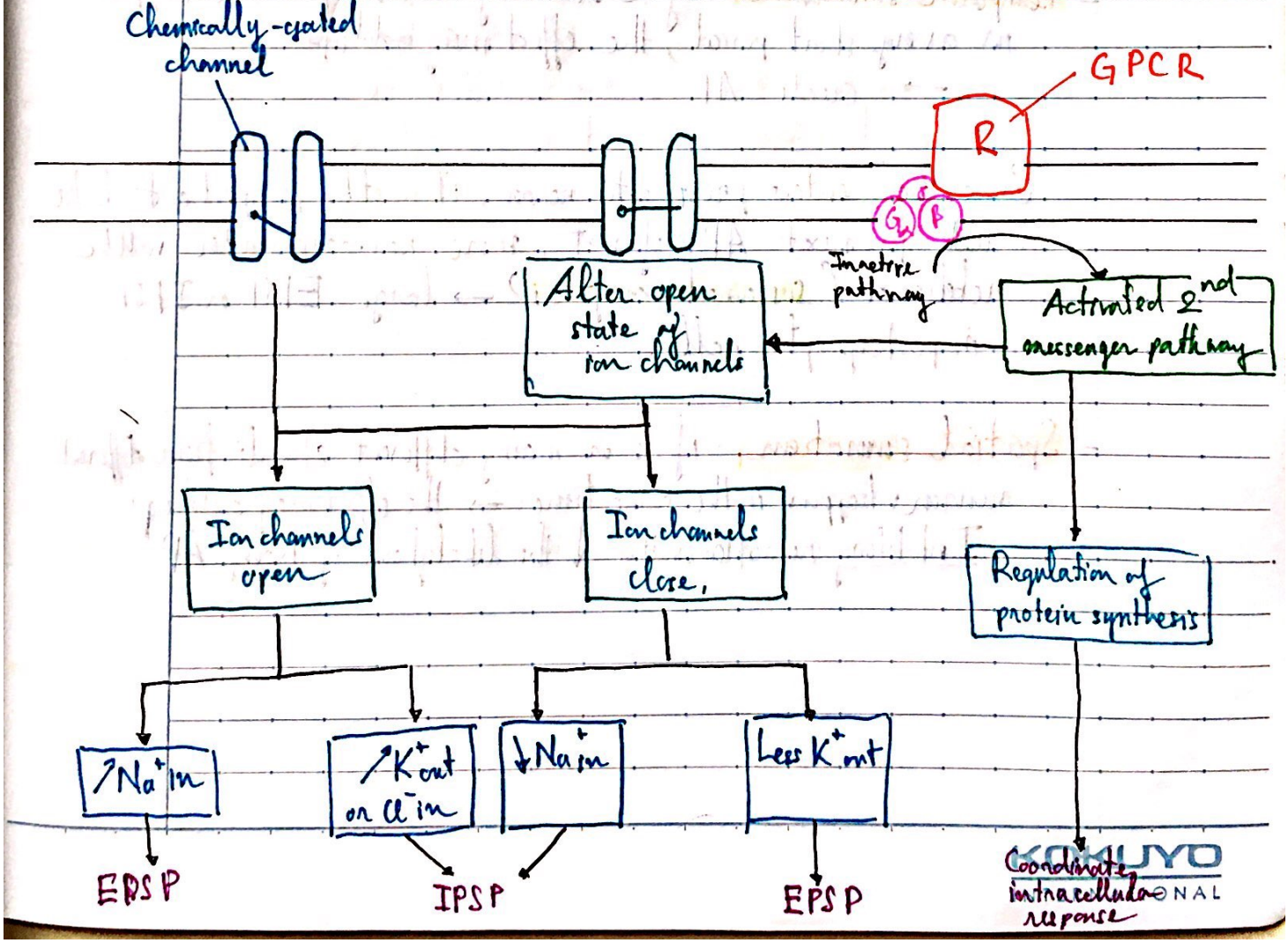
So how about after neurotransmitter release?

- The neurotransmitter – receptor binding is highly specific and the effects can be varied

- Many neurotransmitters create rapid, short responses by directly opening ion channels (Na^+/Cl^- in ; K^+ out) to cause graded potential. The more neurotransmitters bind to receptors, the effect may added up as more channels open, more EPSP → APs

- Some neurotransmitter create slow, long response by activating 2nd messenger systems, which relay signals from membrane to target molecules (in cytoplasm or nucleus) (Weeks)



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- Some eg. for neurotransmitters are Glutamate & GABA

- Glutamate = "Excitatory" neurotransmitter, important in learning & memo
  However, high amount can be toxic to neuron (excitotoxicity)
  & excess Glu transmission is thought to underlie seizures.
  Drugs that ↓ Glu transmission are used as anti-epileptics

- GABA = "Inhibitory" neurotransmitter, ↓ activity of neurons
  Drugs that ↑ GABA transmission cause drowziness, muscle relaxation, relieve anxiety...

- Temporal summation: if 2 or many Graded potential happen in a very short period, the effect may add up
  → create AP

Once Ca^{++} enters presynaptic neuron, it must be pumped out to be ready for next AP; if not, more neurotransmiter will be released (sustained exocytosis) → large EPSP or IPSP in postsynaptic cell.

- Spatial summation: if 2 or many different stimuli from different neurons happen in the same time → the effect may add up
  Inhibitory neurotransmitter ↓ the likelyhood of having AP

Thứ
Ngày . . No.

Cleaning up after neurotransmitter release

- After releasing, neurotransmitter must be broken down, recollected by neuron or remove from synapse via bloodstream or Glial cell.

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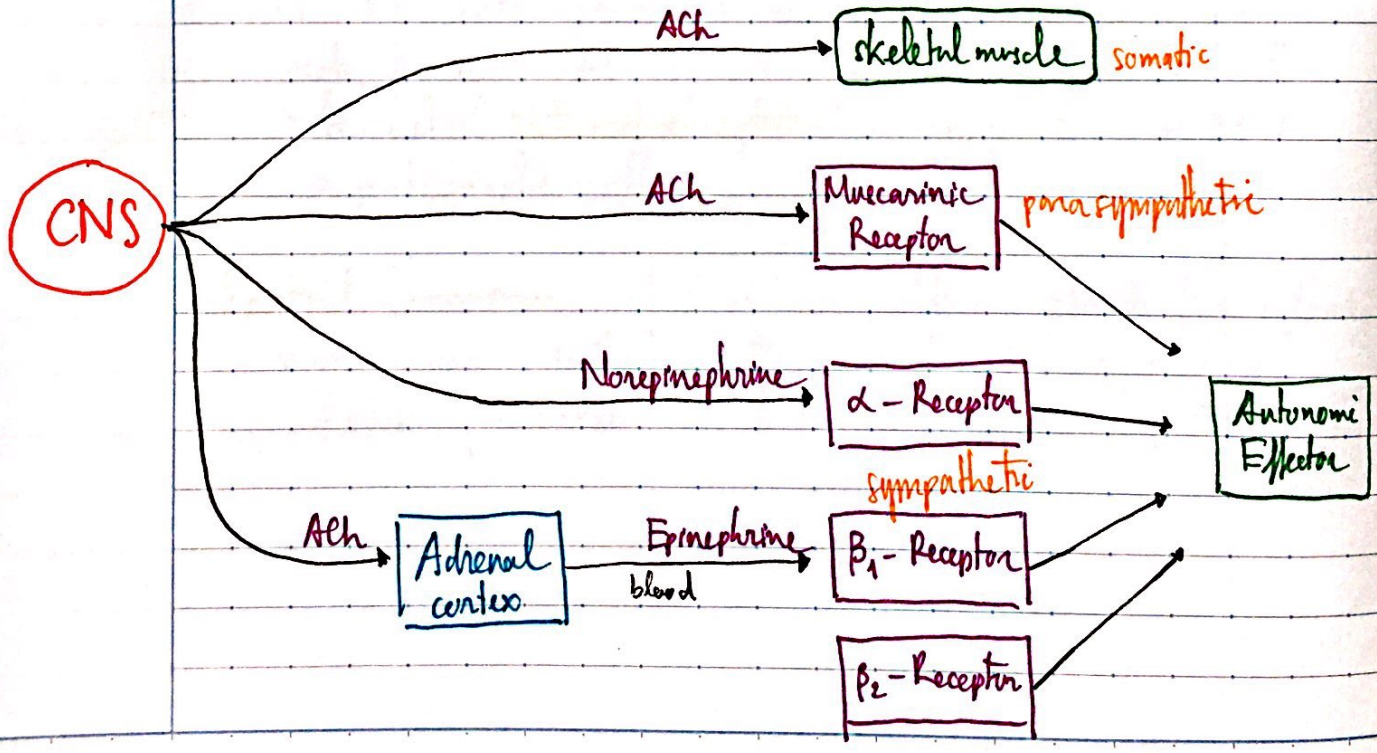
III) Peripheral nervous system (PNS)

Overview

- The PNS
  - obtains info about body & envi and send this to CNS
  - carries message from CNS to organs for response

- There are 3 major divisions:
  - Sensory ner. system: relay info to CNS about internal & external via afferent neurons
  - Somatic ner. system: AKA cerebrospinal ner. system, concerned w/ control of skeletal muscle
  - Autonomic ner. system: regulates smooth muscle & gland function (heart, blood vessels, gastrointestinal, genitals...)



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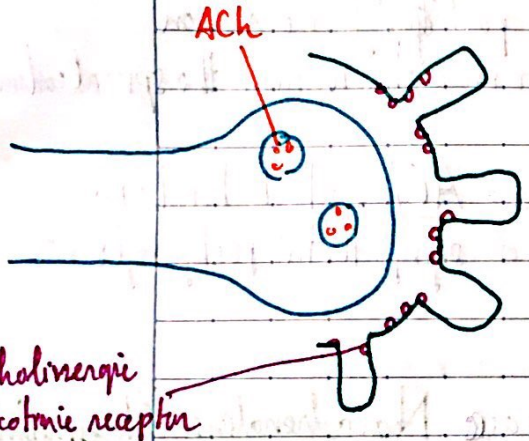
Somatic neurons

- Since the ~~motor~~ somatic motor pathway consist only 1 neuron from CNS → no neuron - neuron synapses (ganglia) outside CNS

The motoneuron synapses at skeletal muscle consist of axon terminal & motor end plate (region on skeletal muscle w/ ↑ no of receptors)



- In case of neuromuscular junction, receptors on skeletal muscle are always same type, called cholinergic nicotinic receptor since the neurotransmitter is AChe, and the receptors are ion channels.

- ACh acting on nicotinic receptors on the motor endplate always cause an AP → muscle contraction

Once ACh is released, it is broken down by an enzyme called Acetylcholinesterase (AChE) into acetyl & choline.

Autonomic nervous system

- Sympathetic ner. system: response to situation that the body needs to prepare (stress, fight). The sympathetic ner. system is activated, or when adrenaline (epinephrine) is released to circulatory system from adrenal medulla → response

- Parasympathetic ner. system: response to basic metabolic demands, undergo w/ maintenance & homeostasis

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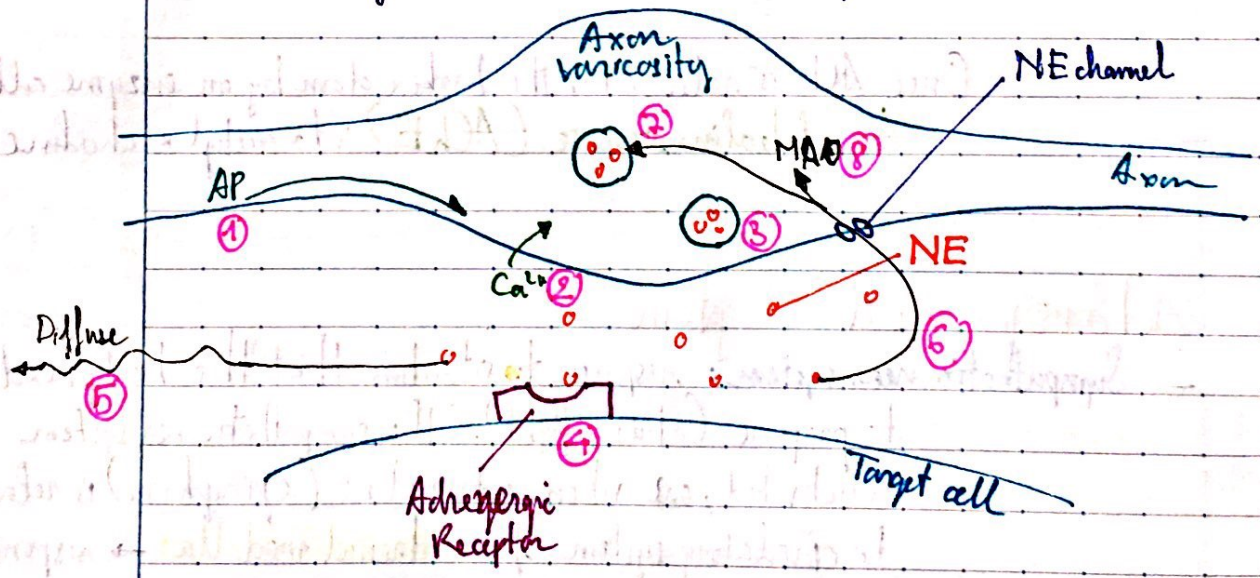
Sympathetic nervous system

- Respond to "fight or flight" situation
  Sympathetic neurons display continuous activity → regulation of heart, blood vessels and other organs is continual.

- Sympathetic neurons have { short preganglionic neuron / long postganglionic neuron
  → sympathetic ganglia often occur in cochain near the spinal column

- Sympathetic preganglionic always releases ACh, which binds to the cholinergic nicotinic receptors on sympathetic postganglionic neuron → excitatory event

Then the postganglionic neurons release Noradrenaline (Norepinephrine) which will bind to α or β-adrenergic receptors on target cell
(they are GPCR → 2nd messenger)



Thứ
Ngày . . No.

1. AP arrives at axon varicosity
2. Depolarisation opens Ca^{2+} channels
3. Ca^{2+} enters → promote exocytosis
4. NE binds to receptor → response
5. NE diffusion when release
6. NE is reabsorbed by neuron
7. NE can be taken back to vesicles
8. NE is metabolised by mito. (by monoamine oxidase)

- There are 2 subtypes of adrenoceptors α & β.
  And also subtypes of α & β: $\alpha 1$, $\alpha 2$; $\beta 1$, $\beta 2$

  Each type have each different function.

Parasympathetic nervous system

- Parasympathetic neurons have { long preganglionic neuron / short postganglionic neuron
  → parasympathetic ganglia often occur near the effector organ

- Parasympathetic preganglionic neurons always release ACh, excite the postganglionic neuron.

The postganglionic neurons also release Ach, binds to Muscarinic cholinergic receptors on target cells.

Thứ
Ngày . . No.

- Muscarinic receptors: GPCR → 2nd messenger.

They are expressed at many parasympathetic neuroeffector junction (heart, glands)
and some sympathetic neuroeffector junction (blood vessel, sweat)

There are 5 main types of Muscarinic receptor: M_1, M_2, M_3, M_4, M_5

Table of organ – system – receptor

Effector organ	Parasympathetic Response	Sympathetic Response	Receptor
Eye pupils	Constrict	Dilate	α
Salivary glands	Watery secretion	Mucous, enzyme	α ; β_2
Heart	Slow Rate	↗ rate & contraction	β_1
Blood vessels	—	Constrict, dilate	α β_2
Lung	Constrict	Dilate	β_2 (E only)
Digestive tract	↗ Motility & secretion	↘ "	α , β_2
Exocrine pancreas	↗ enzyme secretion	↘ "	α
Endocrine pancreas	↗ insulin secretion	↘ "	α
Adrenal medulla	—	Secrete catecholamines	—
Kidney	—	↗ renin secretion	β_1
Urinary bladder	Release	Retention	α , β_2
Fat tissue	—	Fat breakdown	β
Sweat glands	Sweating	Localized sweat	α
♂ ♀ sex organ	Erection	Ejaculate (♂)	α
Uterus	Depends on stage of cycle	"	α , β_2
Lymphoid tissue	—	Generally inhibitory	α , β_2

Thứ
Ngày . . No.

IV) Central nervous system (CNS)

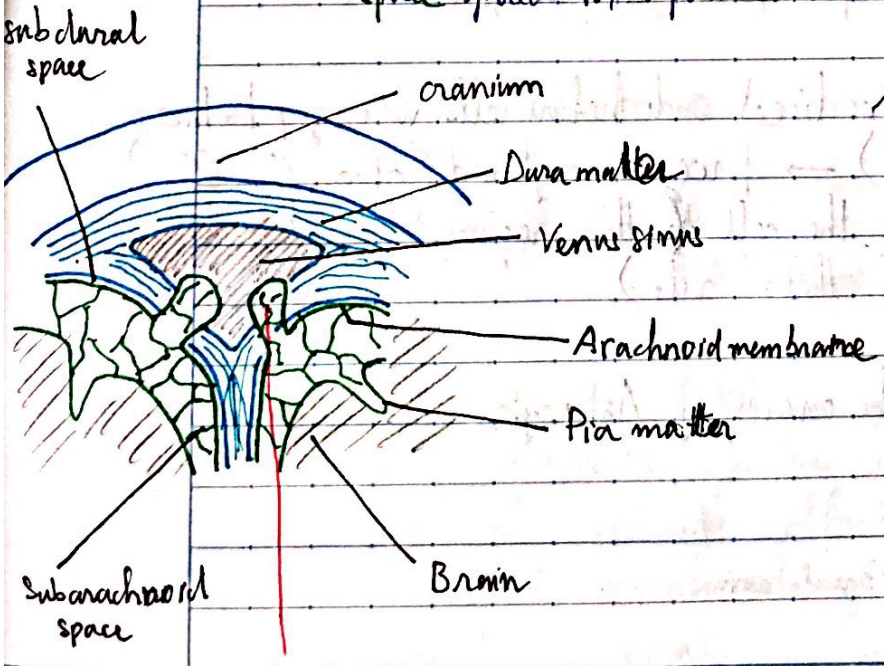
Processes protecting the CNS

- The CNS = brain + spinal cord + billions of neurons

Since neuron are irreplaceable → protection to CNS
- Brain is encased in skull (cranium)
- Spinal cord runs in a canal in the vertebral column
- Neurons of peripheral system branch out by passing thru the gap between sections in the vertebrae

- Underneath the skull are meningeal layers
  - Dura matter
  - Arachnoid membrane
  - Pia matter

These help to protect neuro tissue by prevent it bumping to the skull
Between the Arachnoid membrane & Pia matter is the Subarachnoid space filled w/ a fluid called Cerebrospinal fluid (CSF)



1 more important mechanism to protect the CNS is the blood brain barrier (BBB)

Thứ
Ngày . . No.

Flows of CSF

- The CSF is form from blood vessels, in parts of the ventricles called Choroid plexus. There, ependymal cells allow the flow of H_2O, some ion & nutrients from capillaries to form CSF.

Compared to plasma CFS { less albumin, K^+, HCO_3^-, Ca^{2+}, glucose
more H^+
same Na^+

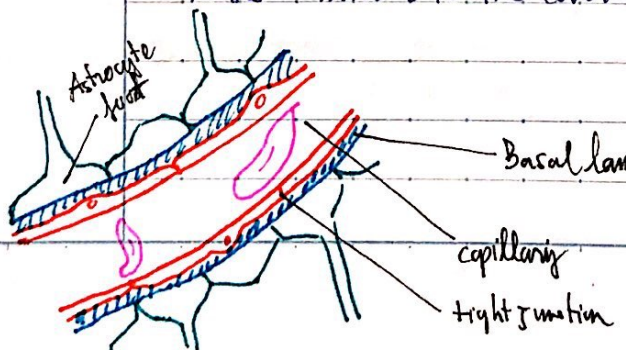
- Ventricles are essential holes in the brain, filled w/ CSF. Following formation in parts of ventricles, CSF from ventricles thru out subarachnoid space (where act as a cushion for CNS) then drain back into venous sinuses thru arachnoid villi, then to vein

The blood brain barrier

- The BBB isolate the CNS from potentially harmful particles in the blood, also from hormones & ion fluctuation

- Is composed by specialised endothelial cells w/ no gap between (tight junction) → force any compound (gluc, O_2, CO_2) to migrate thru the cell to other regions, to be inside the body → around the endothelial cells)

- A 2nd barrier is the covering of Astrocytes



Thứ
Ngày . . No.

- To minimise harm → extensive membrane transport system
  → control what, how fast substances enter the brain
  Substances must go through the endothelial cell
  → Large, charged molecules w/out specific channel will be excluded

Lipophilic substances enter brain rapidly, other via protein channels or transport proteins

Anatomy of the brain

4 major areas :
- Cerebrum
- Cerebellum
- Diencephalon
- Brain stem

The cerebrum

- 2 hemispheres, very convoluted w/ { fissures (deep grooves), sulci (shallow grooves), gyri (elevated folds) } to ↗ processing area.
- 2 major subdivisions { cerebral cortex (outer layer), subcortical regions (inner parts) }

- The cerebral cortex = 4 lobes w/ different function
  - Frontal: Motor, gustatory area ; motivation, cognition, personality
  - Parietal: auditory, olfactory
  - Temporal: somatic sensory
  - Occipital: visual

Thứ
Ngày . . No.

- The development of our fore brain (including cerebrum & some other area such as **thalamus** & **hypothalamus**)
  → ↗ reasoning & cognition

The cerebellum

- "Little" brain, essential for rapid processing sensory info to enable smooth, effortless motor control.

Fine-tune posture & balance: if a disturbance in posture or balance is detected → muscle contraction to recover

- The cerebellum constantly evaluates if motor mvt is working properly
  ⟶ **Feedback system**, where timing & controlling is required

- Subconscious movement.

Diencephalon

- Where **hypothalamus** is found. Hypothalamus = small brain region but important in sympathetic ner system (catecholamine release).
  Hypothalamus is also apart in homeostatic maintenance: regulates osmotic pressure, glu levels, hormones & t°
  The Hypothalamus secrete **neuro**hormones, control the release of other hormones.
  Also influence reproductive function, food intake, cardiac rhythms, behaviour & emotion (via limbic system) & cardiovascular (via medulla oblongata)

Thứ
Ngày . . No.

- The thalamus is also apart of Diencephalon, for processing info
  Considered as relay info station → middle of brain
  Most sensory info passes thru the thalamus goes to sensory cortex

Brain stem

- Links spinal cord w/ brain.

- Brainstem nuclei have many different functions, most vital for survival
  Control behaviour you not aware of
  Responses to stimuli are automatic & rapid.

- 3 sections:
  - **Midbrain**: auditory, visual, pupillary & eye mvts (↕)
    these are brain nuclei involved in arousal, attention,
    contain brain region that modulate pain
  - **Pons**: mastication (chewing), eye mvts (↔), muscle in facial expressi
    there are brain nuclei involved in arousal, attention,
    REM sleep
    contain brain region that process reflexes in blinking,
    lacrimation, salivation, equilibrium, auditory, bladder
    & respiratory pattern
  - **Medulla oblongata**: equilibrium, auditory, swallowing, coughing, vomiting
    salivation, tongue mvt & pain modulation
    important in respiration & cardiovascular control

Thứ
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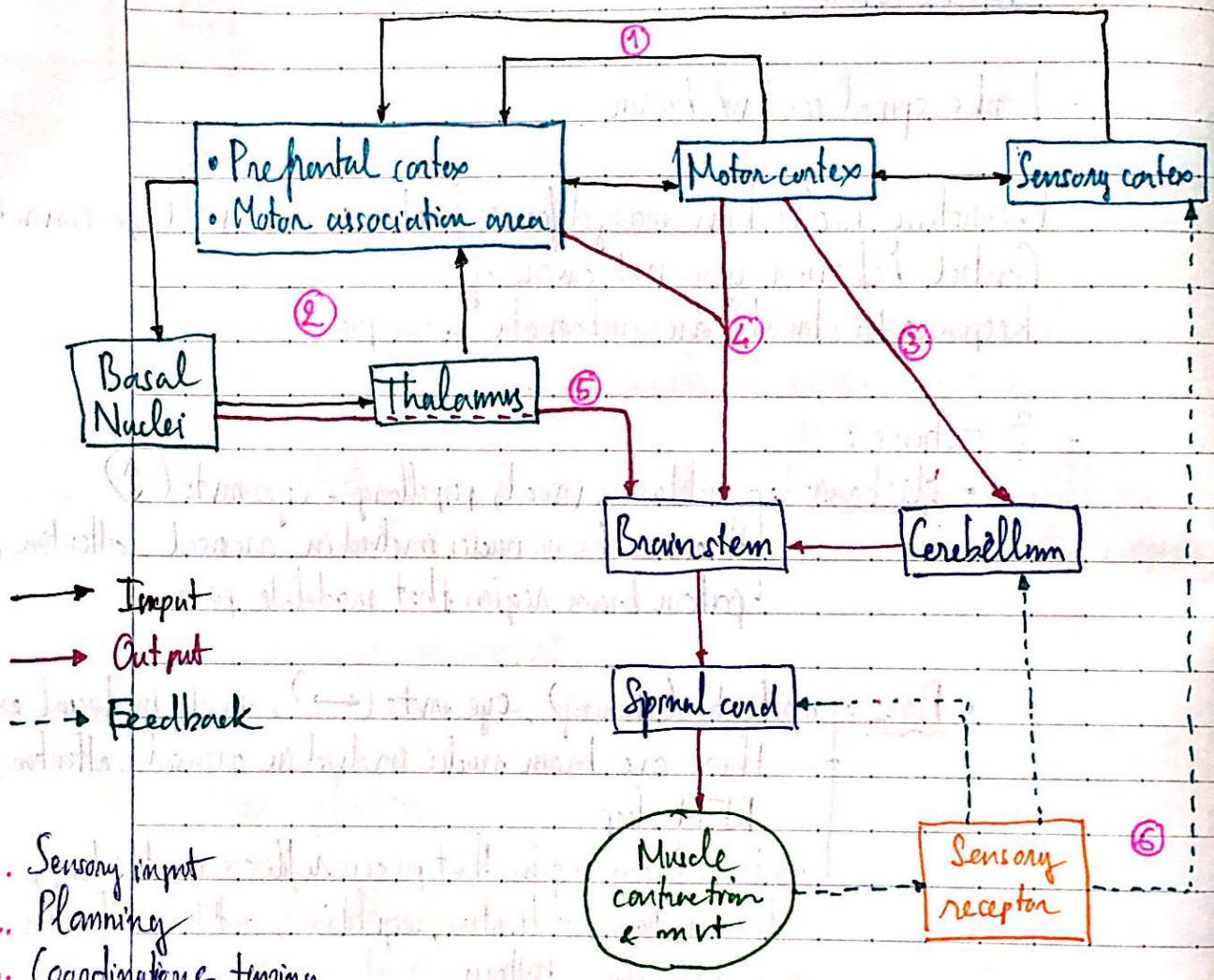
Parts of brain regarding function

Control of movement

- Planning & executing



1. Sensory input
2. Planning
3. Coordinate timing
4. Execution: corticospinal tract to skeletal muscle
5. Execution: extrapyramidal → posture, balance
6. Feedback

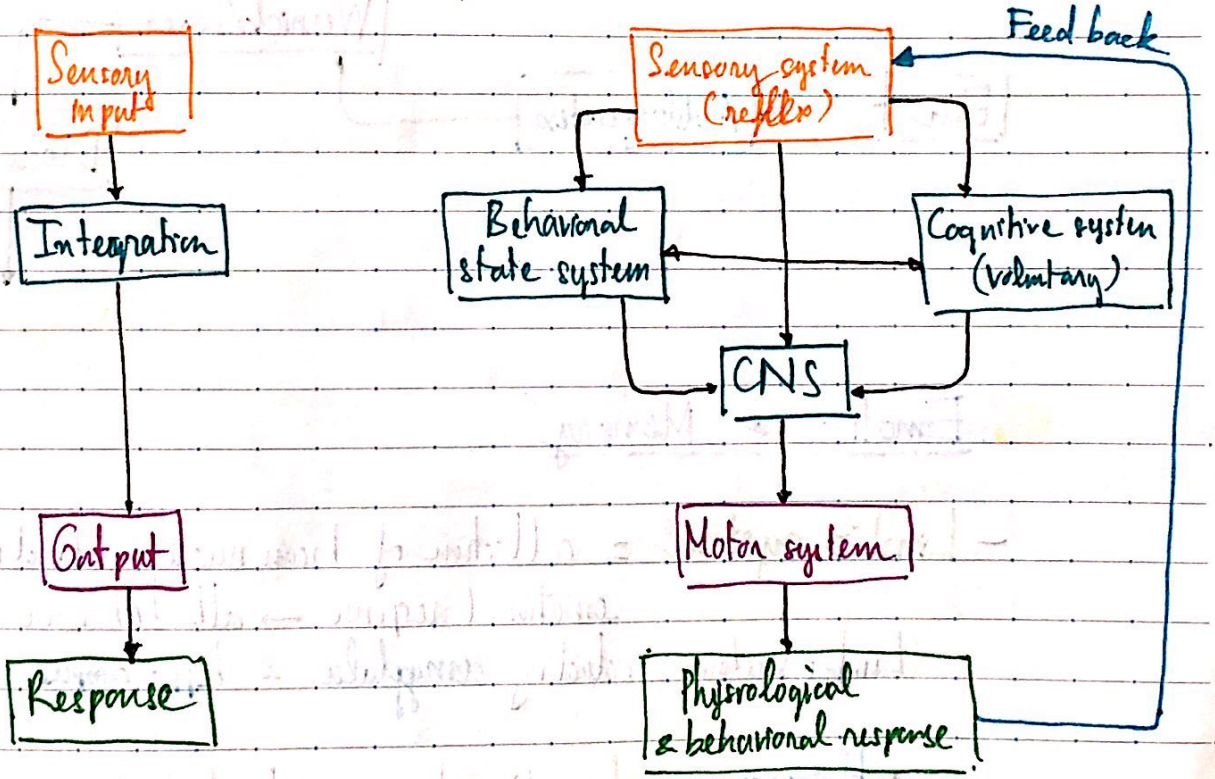
Thứ
Ngày . . No.

- Motor association area → plan complex mvt
  Basal ganglia → modulates motor plan, subconcious mvt
  ↳ inhibits unwanted mvt & facilitates desired mvt

- Voluntary mvt: Motor cortex takes changes to organise
  → brainstem → spinal cord → peripheral.

Involuntary mvt: No require processing in cerebral cortex, can be initiated directly from brain stem & spinal cord.

- The behavioral state & cognition can alter brain output.



Simple reflection: touching hot stuff and lifts the hand

Altering brain output: see acake but still don't eat because dinner is ready.

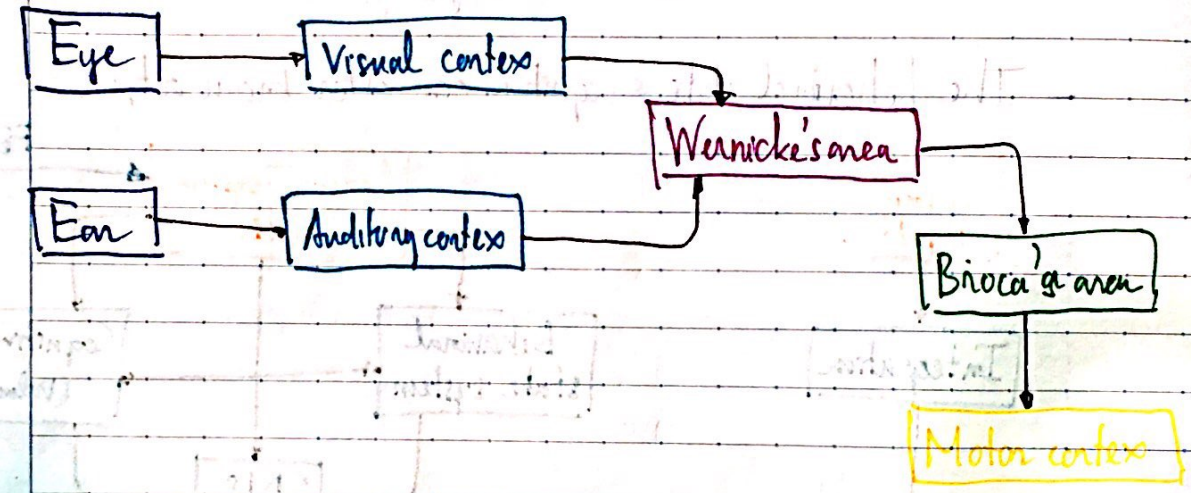
Thứ
Ngày . . No.

Language & Communication

- Several areas involved in specific language & comm task:

  - **Read**: eye → visual cortex → Wernicke's area → Broca's area → Motor cortex

  - **Hear**: ear → auditory cortex → Wernicke's area → Broca's area → Motor cortex



Emotion & Memory

- Limbic system = collection of brain nuclei involved in producing emotional response → alter behaviour
  Limbic system including **amygdala** & **hippocampus**

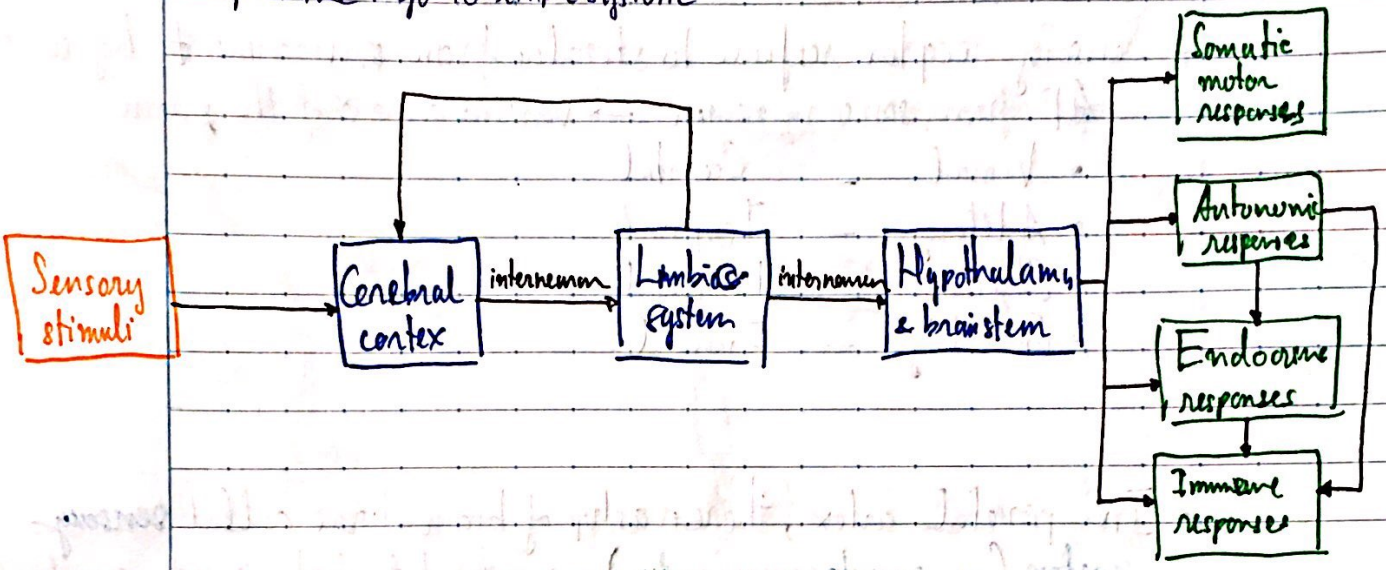
  - **Hippocampus**: formation, storage & retrival of info & memory

  - **Amygdala**: generate emotion base on previous emotions
    - stimulate → rage
    - damage → tame

Thứ
Ngày . . No.

- There are some parts of limbic system are important in reward
  → why some drug is addictive

- Emotion pathway is complex. Mainly associated w/ cerebral cortex, then pass the info to limbic system



- Limbic system also connects to the frontal cortex to create awareness of emotion & planning how to response
  → prolonged & intense emotion = memory

- When info enters CNS → short term, unless there is effort to remember
  - If info is long enough to do simple task → working memory (frontal cortex)
  - If info is consolidated → long term memory

Some memories are:
+ Reflexive (automatic) : riding bike
+ Declarative : studying

Week 6 3/4/2017

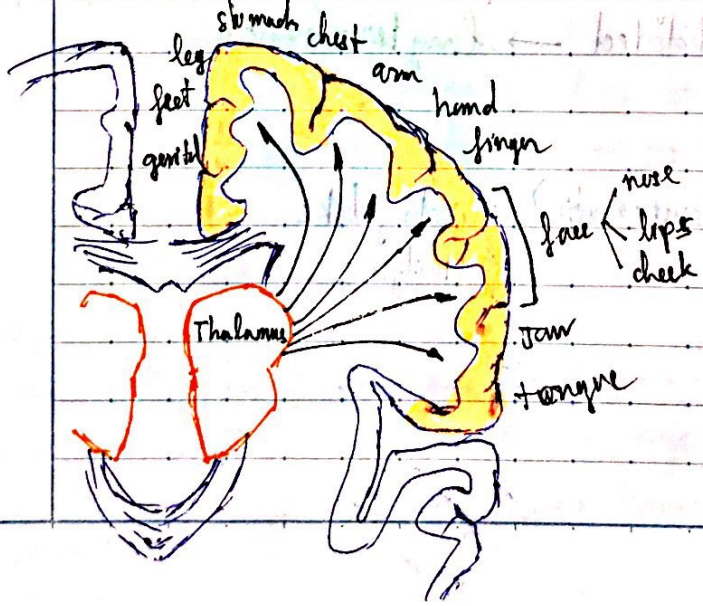
Thứ
Ngày . . No.

I) Sensory Nervous System (SNS)

Sensory pathway

- Sensory receptor response to stimulus from environment by sending AP from sensory neuron → various areas of the brain.
  - Visual — Occipital
  - Auditory — Temporal
  - Olfactory — Temporal
  - Gustatory — Frontal

- In parietal cortex, there is a strip of brain tissue called **sensory cortex** (or **somatosensory cortex**) → related to touch, joint, muscle position, pain, t° & itch.
  - Each part corresponds to a different part of the body
    - ↳ localisation of feel
  - Sensitive parts of the body will take up more space since more receptors are linked to that area

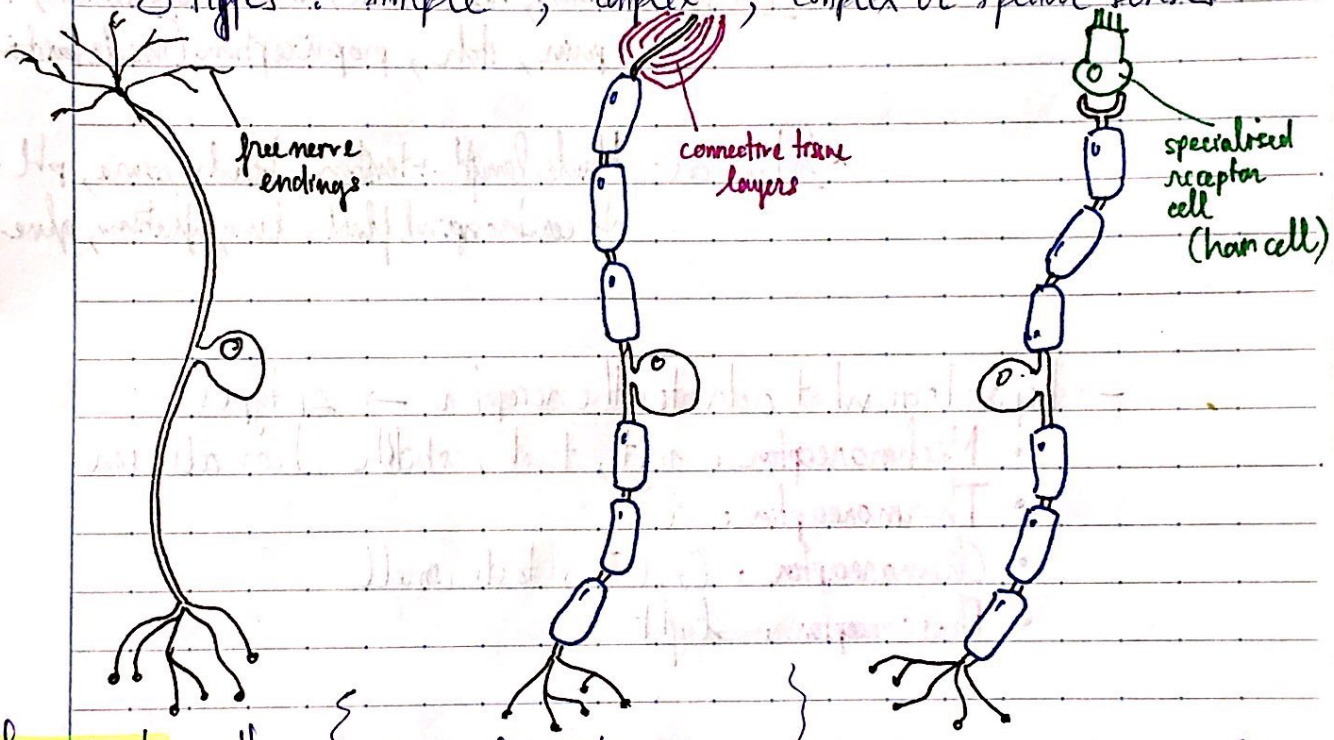


Thứ
Ngày . . No.

- PNS consists of { somatic, autonomic, sensory (SeNS)

SeNS has neurons that either have { sensory receptors at their ends / synapse w/ sensory cell + part of the brain involved in sensory perception.

- 3 types : simple , complex , complex or special senses



Simple receptor with free nerve endings & unmyelinated axon

Complex receptor w/ nerve ending enclosed in connective tissue capsules & myelinate axon

Specialised senses receptor is the cell that releases neurotransmitter onto sensory neuron → AP

- When activated, graded potential will occur and if large enough → AP
- A stimulus, often results in the influx of Na^+ → graded potential
  Info about intensity & extent only detected when it is processed by the sensory cortex ↔ some are processed subconsciously

Thứ
Ngày . . No.

- The cerebral cortex + brainstem + spinal cord = integration site

Depends on the importance of the stimulus, type → the body will adjust & respond without passing thru the sensory cortex

Eg:

- Concious: Vision, hear, taste, smell, equilibrium, touch, t°, pain, itch, proprioception (muscle position)
- Subconcious: Muscle length + tension, blood pressure, pH + O_2, pH cerebrospinal fluid, lung inflation, glucose, t°...

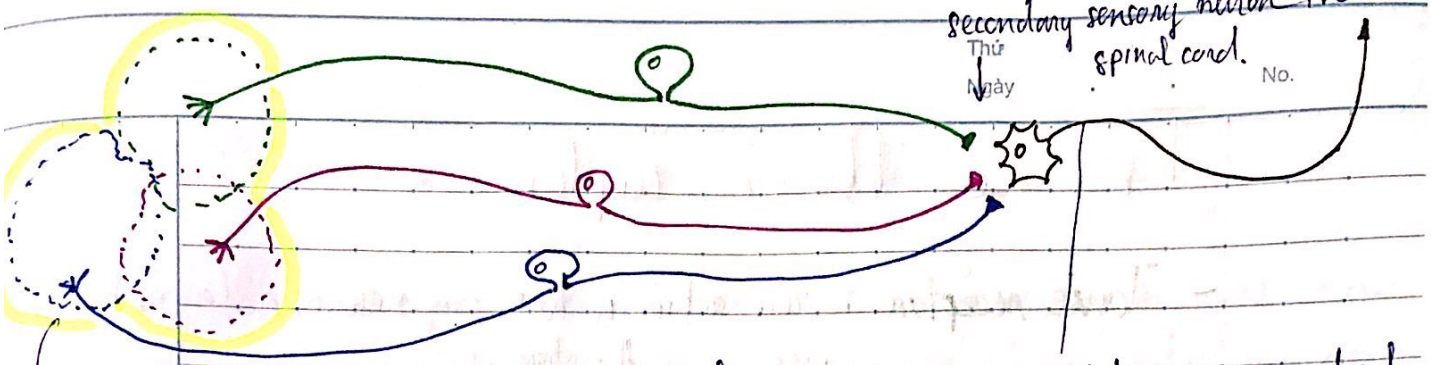
- Depends on what activates the receptor → 4 types
  - Mechanoreceptor: wrist, touch, stretch, hear cell, ear
  - Thermoreceptor: t°
  - Chemoreceptor: O_2, CO_2, taste, smell
  - Photoreceptor: light

Receptive field & sensory perception alteration

- A sensory unit = sensory neuron + receptor ending

A receptive field = portion of the body that 1 neuron can detect.

- Receptive fields can overlap to form a larger receptive field.



- Sensory perception can be altered by:
  - Sensory receptor mechanism
  - Sensory pathway mechanism
  - Genetic & environment
  - Reach consciousness
  - Damage, disease, disorder
  - Drugs

- Unless sensitive part of the body → larger perceptive field

- The duration of the stimulus is coded via slowly-adapting receptor, which consistently fire AP throughout the duration
However, other stimuli can activate rapidly-adapting receptor, which only fire AP when the condition changes

Thứ
Ngày . . No

Tonic & Phasic receptor

- Tonic receeptor: cause activation to sensory neuron as long as the presence of the stimulus
- Phasic receptor: not continue activating sensory neuron

Nociceptors & gate control theory of pain modulation

- Nociceptors are tonic receptors that send signal about pain. They can be thermo, chemo & mechano
- Activation of Nociceptor alerts the potential threat to health.
- Nociceptors can potentially respond to > 1 types of stimuli

Eg: Vanilloid family

- TRPV1 (transient receptor potential vanilloid 1) can be activated by capsaicin & heat
- TRPM8 (transient receptor potential melastatin 8) can be activated by menthol & cold

Both, if too much activation can cause pain

Pain fibers:

Fast	Slow
1st	2nd
sharp	Dull
Aδ fiber	C fiber
localized	poorly localized

Aβ fiber transmits signal from touch (not pain)

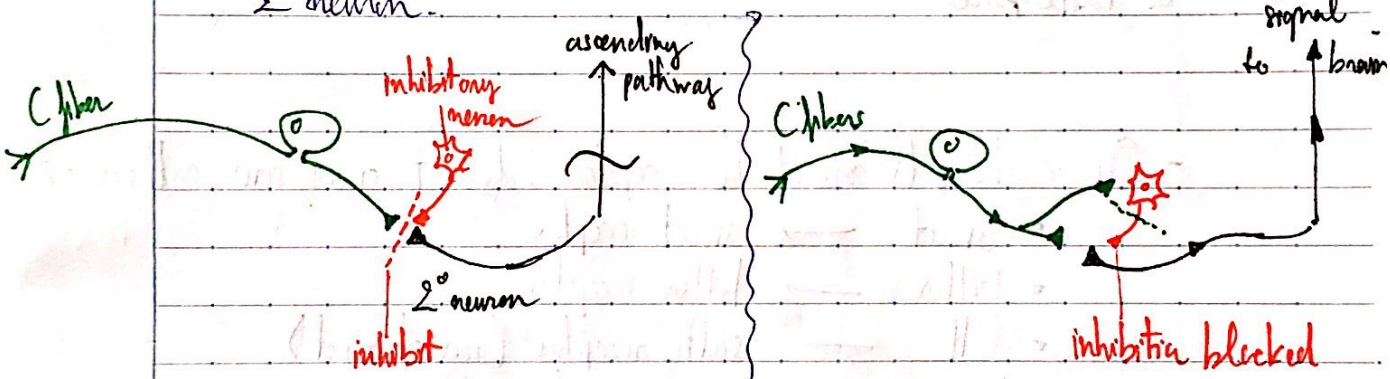
Thứ
Ngày . . No.

- TRPV1 & TRPM8 are ion channels → rapid acting.

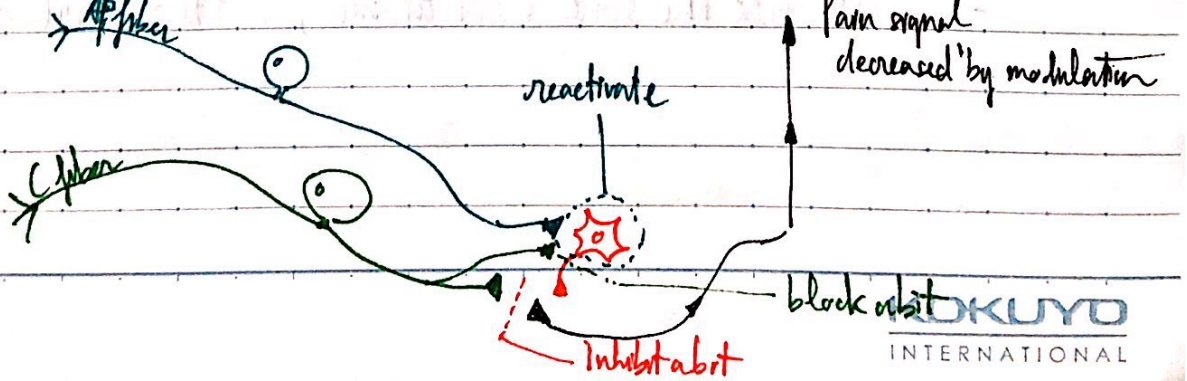
- After a receptor received a pain stimulus and sent a pain signal, nerve fibers called C fibers carry some pain info to spinal cord and eventually sensory cortex. But if the C fibers are only slightly stimulate → the info stop at spinal cord.

Other types, such as Aδ fibers can carry sharp & localised pain
C fiber .. carry dull & diffused pain

- Gate control theory: 1 interneuron in the spinal cord is tonically active to inhibit the info transmission from primary neuron to 2° neuron.



However, the effect may be more complicated. Another stimulus can decrease the pain signal. Eg: rubbing the heart area
→ Partial blocking



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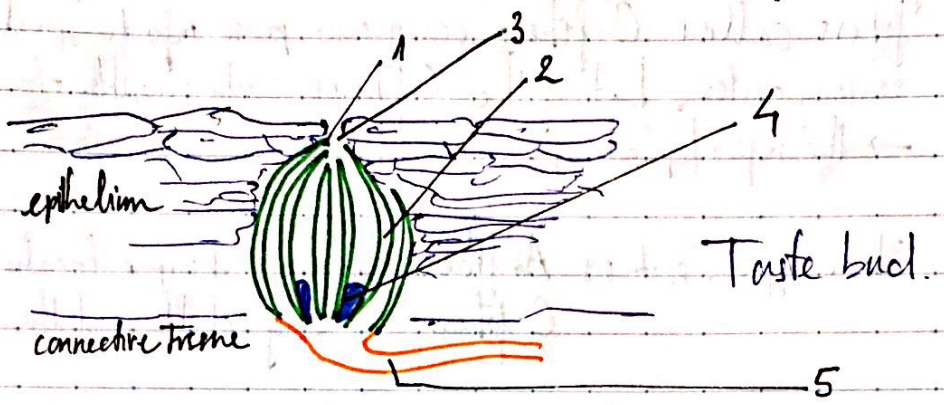
Ngày . . No.

Taste & smell

— Taste is sensed by chemoreceptors in **Taste buds** on tongue (each w/ 50-100 taste cells, replaced every 2 weeks)



1. Gustatory hair
2. Gustatory epithelial cells
3. Taste pore
4. Basal epithelial cells
5. Taste fiber

— On each cell are taste receptor, detect sweet, sour, saltiness & bitter

- Sweet → sweet receptor
- Bitter → bitter receptor
- Salt → salty receptor (ion channel)
- Amino acid → umami receptor
- Sour → taste cell responds to H^+

These taste receptors can be found elsewhere

— Smell has the same mechanism, but the stimuli are gaseous

Thứ
Ngày . . No.

II) Hearing & Balance

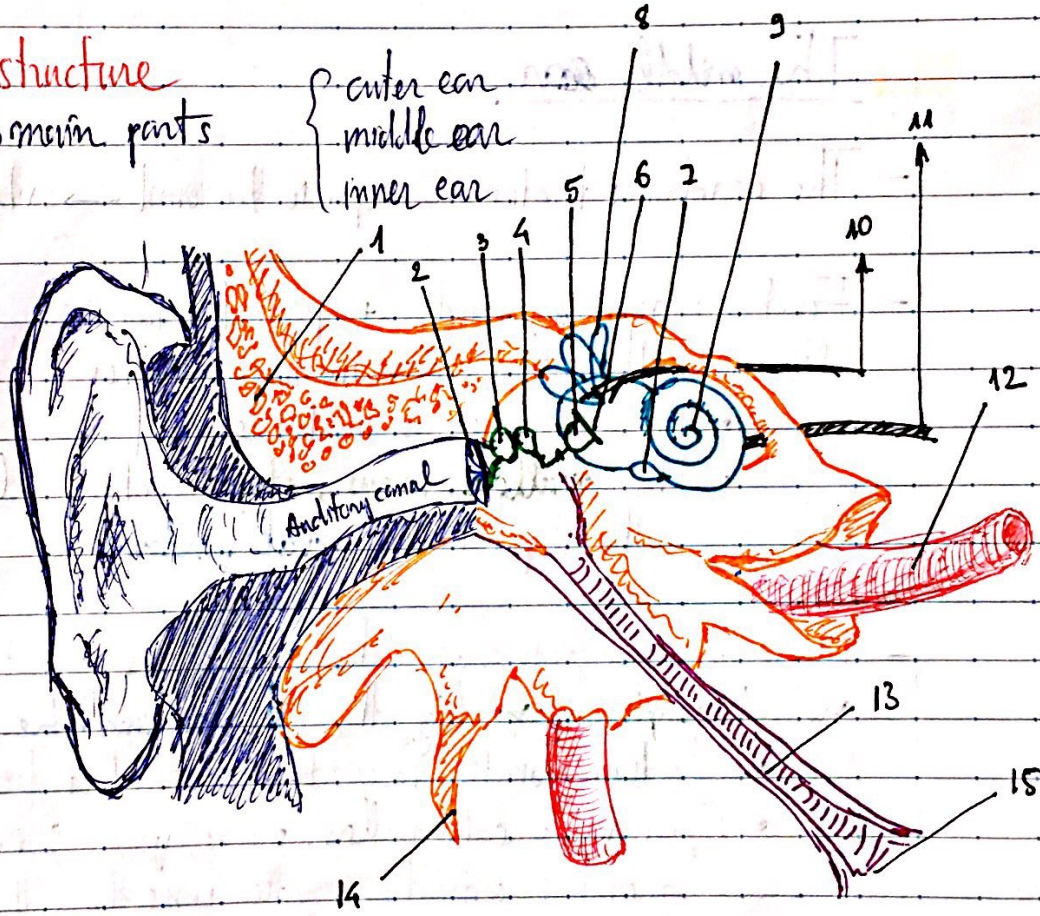
Sound

- Sound = vibration thru air
- 2 Characteristics: { loudness (0 → 80 dB)
  frequency (20Hz - 20kHz)

- Hearing loss is about 3dB / decade (>20yo)
  8dB / decade (<20yo)

Ear structure

- 3 main parts { outer ear
  middle ear
  inner ear



1. Temporal bone
2. Tympanic mem. (eardrum)
3. Malleus (Hammer)
4. Incus (anvil)
5. Stapes (stirrup)
6. Oval window
7. Round window
8. Semicircular canal
9. Cochlea
10. Vestibular nerve
11. Cochlear nerve
12. Internal carotid artery
13. Eustachian tube
14. Styloid bone
15. Nasopharynx

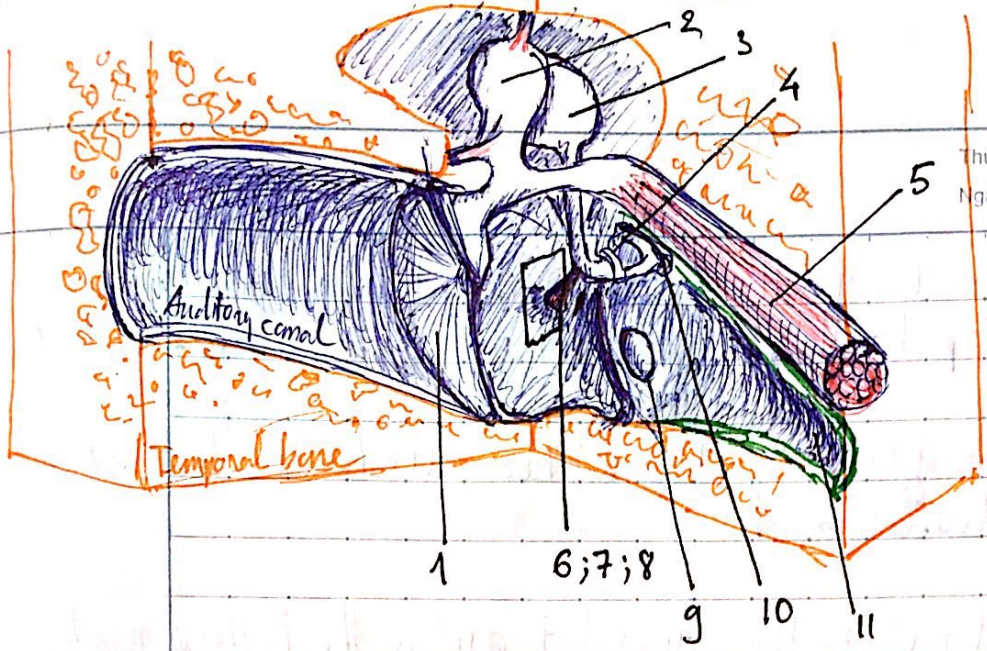
Thứ
Ngày . . No.

The outer ear

- 2 main function: channeling sound / protecting inner ear
- Sound is carried toward Tympanic membrane, which provides a source of amplified sound.
- The outer ear also secretes wax → prevent bacteria

The middle ear

- The eardrum vibrates in response to sound → vibration to mechanical E
- Function: transferring sound + protect inner ear
  However, the amplification in much greater:
  - The eardrum is much longer.
  - The malleus, incus, stapes act as a lever to push the stapes to the oval window.
- 1 more important feature of the middle ear is that it linked w/ Nasopharynx by the Eustachian tube
  - The tube usually closes to prevent dirt from nasal region
  - Open when eat, swallow, sneeze, yawn; because these activities contract a muscle runs along the tube called tensor tympani muscle → balance pressure
- The Eustachian tube could be blocked by mucus.



1. Tympanic membrane
2. Malleus
3. Incus
4. Stapes
5. Tensor tympani muscle
6. Tendon of stapius muscle
7. Stapius muscle
8. Pyramid
9. Round window
10. Oval window
11. Eustachian tube

- The tendon & stapius muscle play a role in responding to a loud noise. When in chronic loud noise condition, the stapius muscle contracts to move away from oval window → less sound transmission

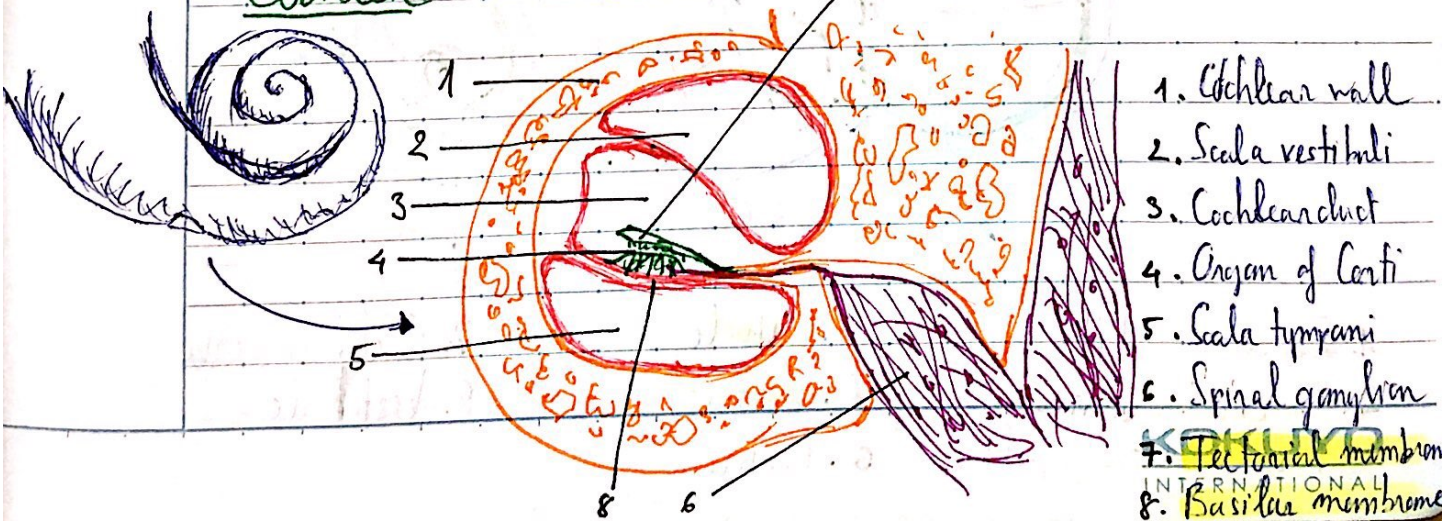
This can only be used for chronic loud sound, not sudden, since the muscle cannot contract that fast

The inner ear & hearing

- Filled w/ fluid, 2 main parts: { cochlea
  semicircular canals + otholith organ

which the otholith organ where hair cells & neuron are located to assist balance.

- **Cochlea** : snail-like structure

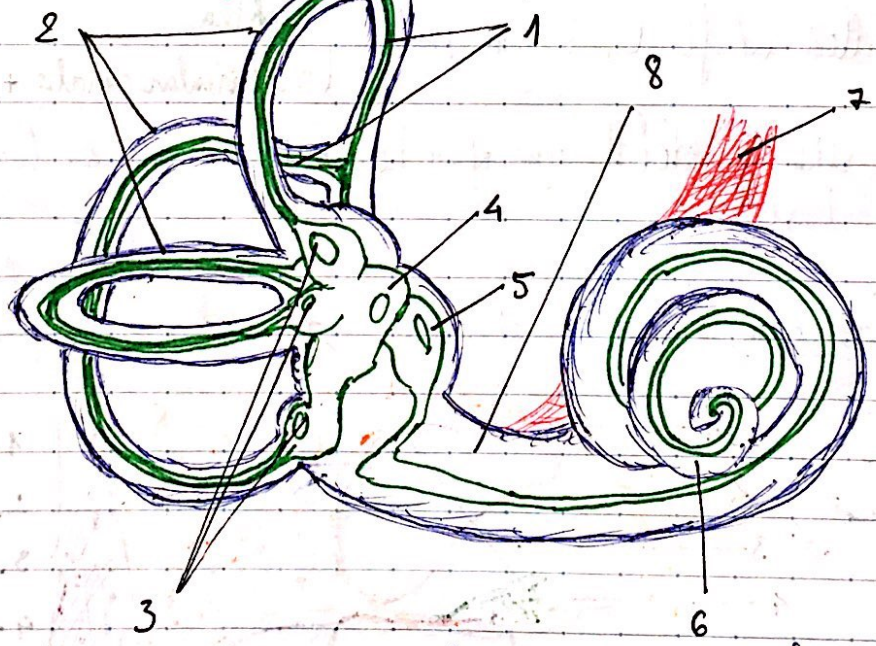


1. Cochlear wall
2. Scala vestibuli
3. Cochlear duct
4. Organ of Corti
5. Scala tympani
6. Spiral ganglion
7. Tectorial membrane
8. Basilar membrane

Thứ
Ngày
No.

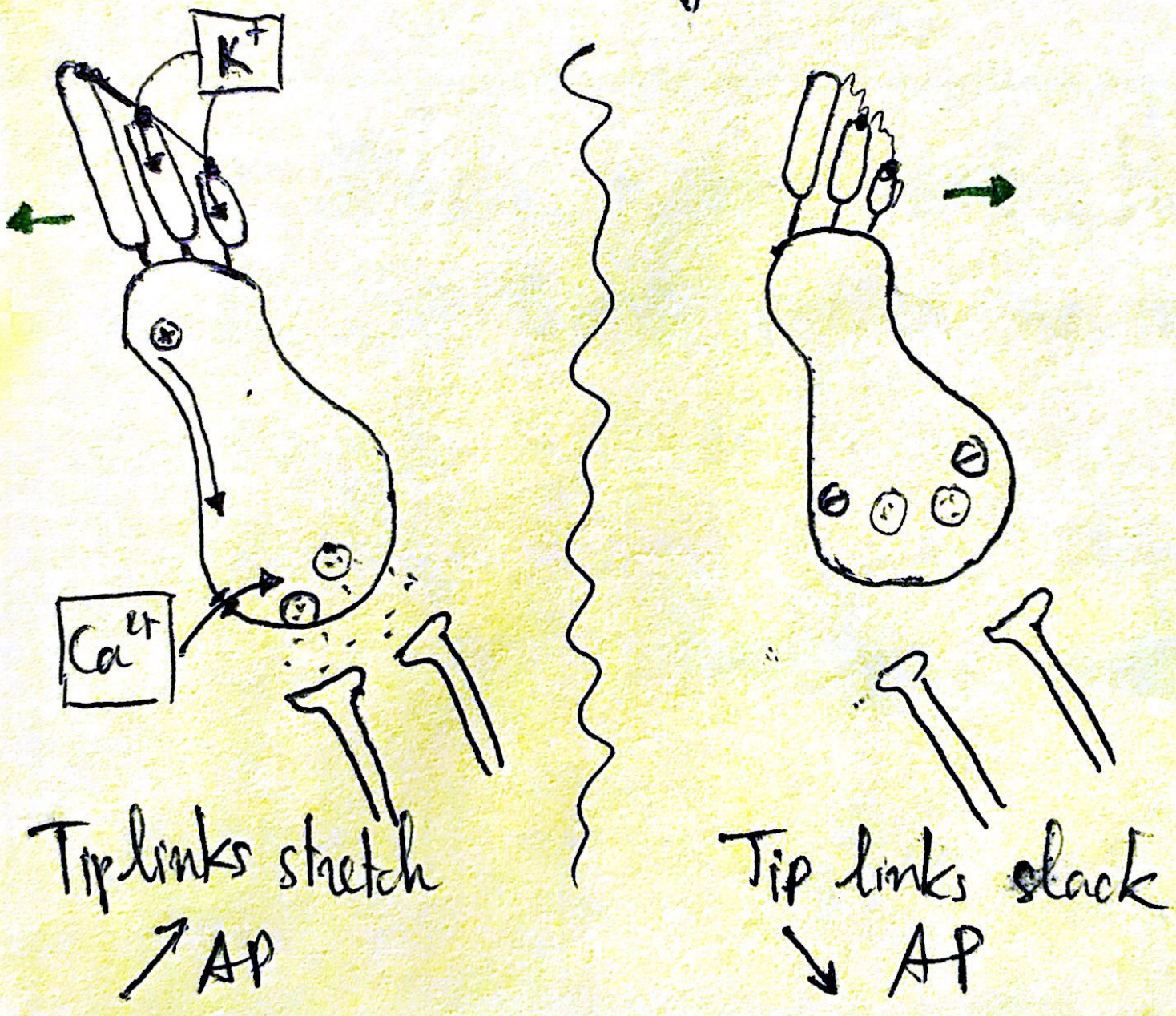
- When a somd enters the ear, the mvt of the fluid in scala vestibuli pushes the membrane between it and cochlear duct
- The Organ of Corti embedded w/ hair cells between Tectorial mem and Basilar membrane
- The fluid mvt in the cochlear duct displace the Basilar membrane, which in turns bends the tectorial membrane → Bending hairs on hair cell → AP to the brain
- Different frequency will be recognised in different area in the cochlea
  - High f somd travels less far → ~~Scala vestibuli~~
  - Medium f somd travels abit further → ~~Scala tympani~~
  - Low f somd travels furthest → ~~Cochlear duct~~

The inner ear & balance



1. Semicircular ducts
2. Semicircular canal
3. Membranous ampullae
4. Utricle
5. Sacaule
6. Cochlea
7. Cochlear nerve
8. Vestibule

The hair cells in Organ of Corti actually does have some kind of "kinocilium":

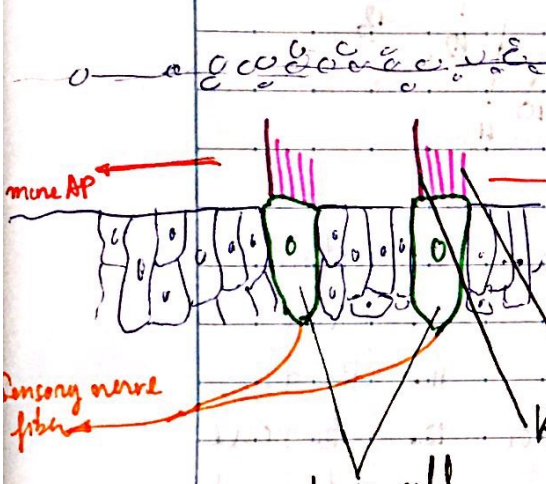


Thứ
Ngày . . No.

- Part of inner ear associated w/ balancing is call **Vestibular apparatus**
  = series of fluid-filled tube that connect to each other, consists of 3 semicircular canal (~90° orientation)

Also contain 2 **Otolith organs**. { Utricle / Saccule

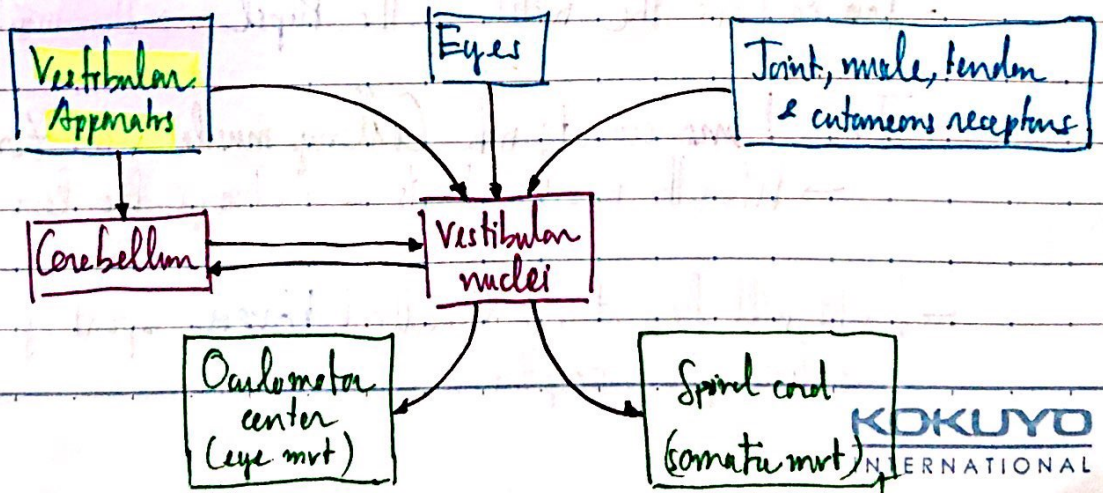
- Semicircular canal : rotation, angular acce., turning, spin, tumbling
- Utricle + Saccule : linear acce., head tilting.



In semicircular & otolith organs contain hair cells, which have **sterocilia**. Each cell has a major hair called **Kinocilium**.

- If the hairs bend toward the kino. → Na^+ influx → ↗ membrane
  → more AP
- If the hairs bend away the kino
  → ion channel close → ↘ membrane
  → less AP

- The info from the vestibular apparatus is only 1 in 3 main inputs to the **Vestibular nuclei** (in brainstem). Combining w/ muscle mvt & eye
  → enough information to balance.



Thứ
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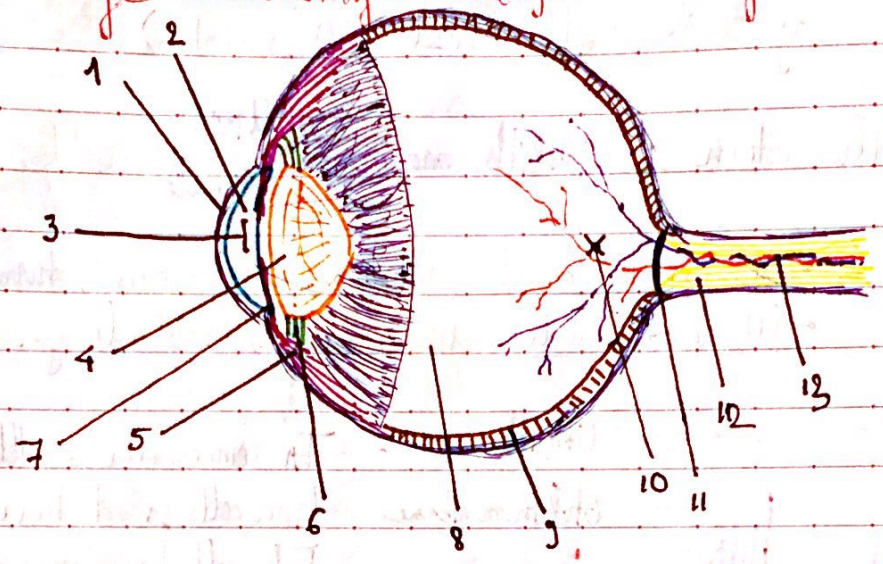
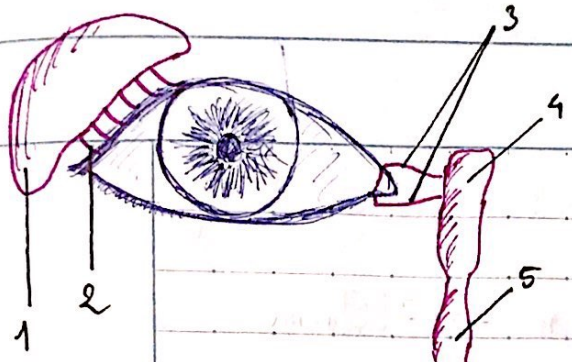
III) The eye

Eye anatomy + adjustment for light



1. Cornea
2. Aqueous humor
3. Pupil
4. Lens
5. Ciliary muscle
6. Zonulas
7. Iris
8. Vitreous chamber
9. Retina
10. Fovea
11. Optic disc
12. Optic nerve
13. Central artery + vein

- Cornea is a thin film, let light go through
- Behind the cornea → chamber contain Aqueous Humer
- Iris controls the width of the Pupil → How much light
- The Lens connects with Ciliary muscle via Zonulas
  → When the muscle retracts → change the lens' shape → refract
- Light will focus at a point called Fovea, apart of Retina which contain photoreceptors



1. Lacrimal gland
2. Duct
3. Superior & inferior canaliculi
4. Lacrimal sac
5 Naso lacrimal duct

Thứ
Ngày . . No.

- Tears are formed from Lacrimal gland
  → eye moist + clean

- Then tears will diffuse into the lacrimal sac and then Nasolacrimal duct to the nasopharyngeal region (nose & mouth)

- The Aqueous humor formed near the Ciliary muscle, perfuses thru the iris into the front chamber of the eye then drain out
  → { Provide nutrients that cannot be brought by blood.
  { Remove waste

- Glaucoma : Aqueous humor build up.

Controlling light into the eye

- 2 sets of muscles:
  - Circular muscle (parasympathetic) : activated by bright light
    → contract → pupil smaller
  - Radial muscle (sympathetic) : activated by low light
    → contract → pupil larger.

Thứ
Ngày : No.

Light focus

- Visible light: $\lambda = 400\,nm \rightarrow 750\,nm$

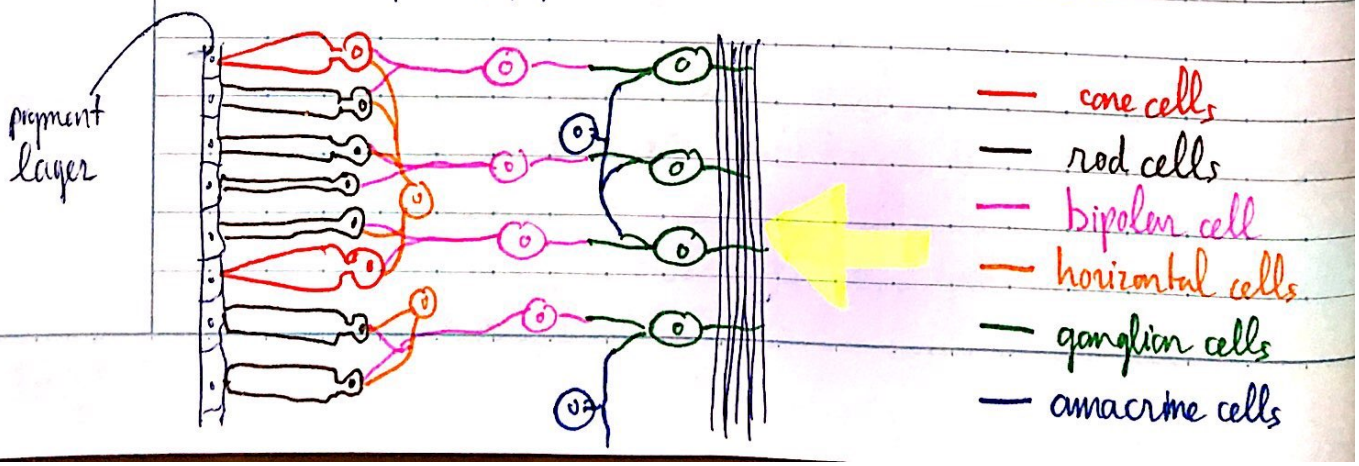
- Light enters → deflect → focus on the retina in the back of the eye
  The retina contain photoreceptors that get energy from light
  → converse to AP

- The Lens is changed by the Ciliary muscle:
  - Contract → Relax Zonulas → Lens more round → near visi
  - Relaxed → Contract Zonulas → Lens more stretched → far visi

- Optical defects:
  - **Hyperopia** (far-sighted): focus behind the retina
    → fix by convex lens
  - **Myopia** (near-sighted): focus infront of the retina
    → fix by concave lens

- The retina has 2 types of photoreceptor cells { cone cells / rod cells

Theses photoreceptors are activated when light produces a chemic
change in pigment molecules within the disc



* ganglion cells, bipolar cells } → signals from cones & rods are intergrated
→ they are neurons.

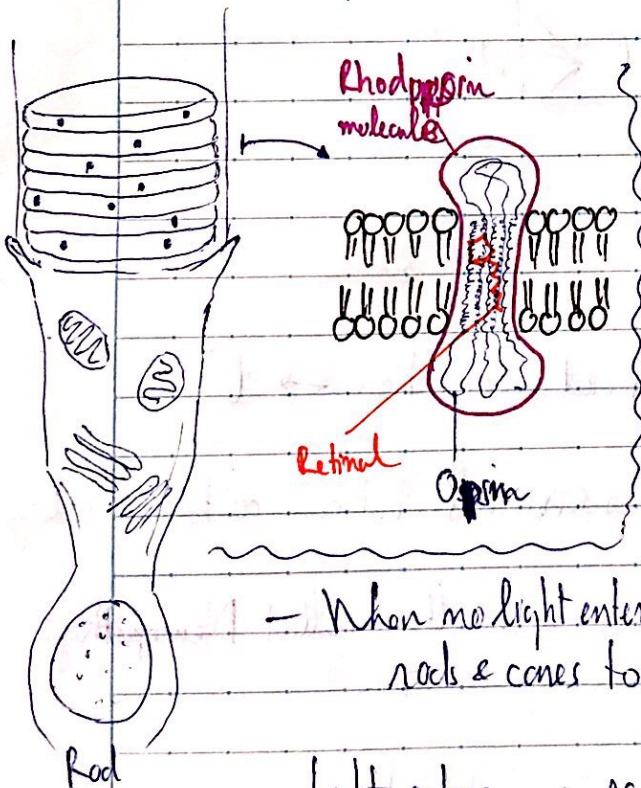
Thứ
Ngày . . No.

- Cones & Rods are furthest from light source, except at the Fovea, where every cells/neurons/synapses are pushed to the side → best { direct light / little convergence
- Out side the Fovea, 40 photoreceptors may converge into 1 single ganglion cells → peripheral vision.

More details

- { Rod: monochrome / Cone: colour

- Some structure:
  - Outer segment: have discs within, facing toward pigment epithelial
  - Inner segment: cell nucleus + organelles
  - Synaptic terminal: contact w/ ganglion cells



- Discs in outer segment contain pigment → light to electrical energy
- Rhodopsin contain Retinal + opsin
  - Cone → 3 Rhodopsin-like structure → RGB

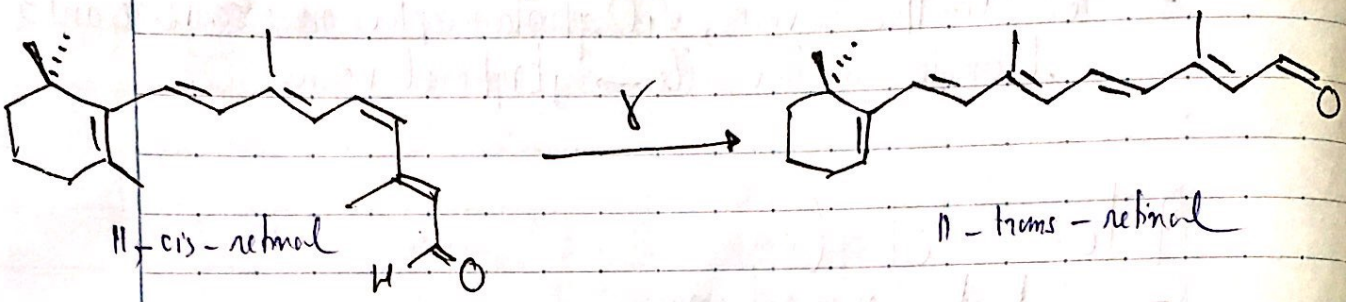
- When no light enters → tonic neurotransmitter release from rods & cones to bipolar cells.

- Light enters → retinal changes conformation → released from opsin (bleaching) → hyperpolarisation, less neurotransmitter

Thứ
Ngày . . No.

- Neuron pass from the retina out of the eye through optic nerve, then "cross over"

Neurons later synapse in the thalamus on the way to visual cortex



IV) The skin

Major roles

- Protection: { mechanical ← ↑ impact, t°
  biological
  radiation
  chemical

Regulation: secrete sweat & grow hair → t°

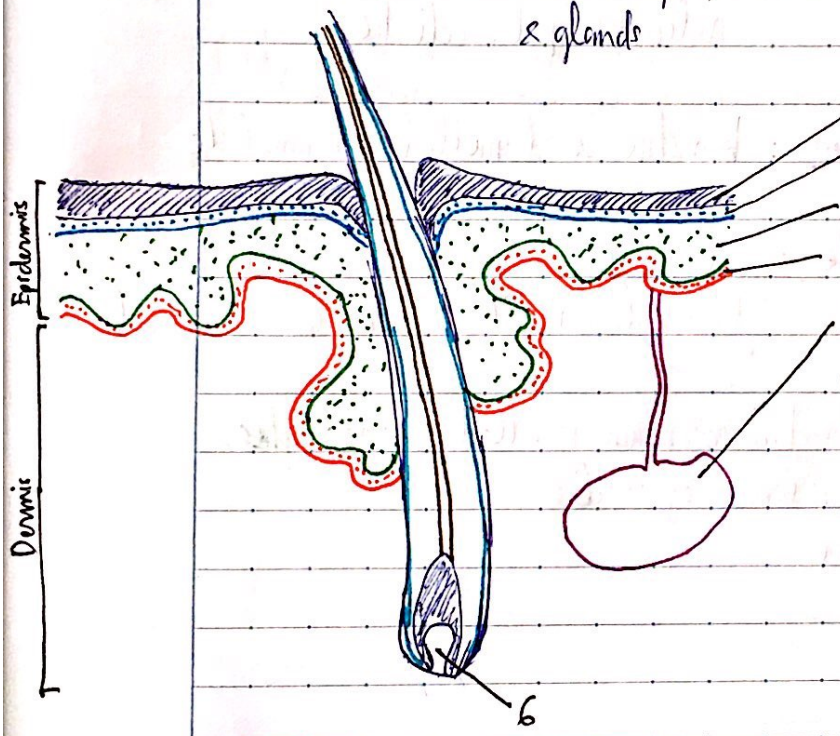
Sensation: • network of nerve cells that can detect & relay info of envi.
• Damage to these nerve cells is called Neuropathy → loss of sensation

- The skin also acts as { H_2O resistant barrier
  Vitamin D synthesis reservoir

Thứ
Ngày . . No.

Skin anatomy + function

- 2 layers:
  - **Epidermis**: upper layer, contains squamous cells (dead). Under squamous cells are basal cells. Also contain melanocytes → melanin
  - **Dermis**: inner layer, contains blood + lymph vessel, hair follicles & glands



Epidermis

- 95% Keratinocytes, but also melanocyte, Langerhans cells & Merkel cells

- The basal layer is primarily made up of basal keratinocytes.
  → Closest to blood supply

This is the only layer that can undergo mitosis.

Thứ
Ngày . . No.

- The epidermis contains 4 layer (or 5 on the palm)
  - **Stratum corneum**: dead cells w/ hard protein envelope
    These contain keratin & surrounded by lipid
  - **Stratum lucidum**: dead cells contain dispersed keratohyalin
  - **Stratum granulosum**: keratohyalin & hard protein envelope form, release lipid, cells die
  - **Stratum spinosum**: keratin & lamellar accumulate
  - **Stratum basale**: cells devide by mitosis, attach to the basal lamina by Hemidesmosome cell junction

- Keratinocyte in stratum corneum is called **corneocytes**
  → Dead, no presence of nucleus
  → Protective layer

Dermis

- Made of elastic connective tissue (collagen, elastin & fibrillin)
- Contains nerve endings, sweat glands, oil gland, hair follicles & blood
  - Nerve endings sense pain (6.2)
  - Blood vessels provide nutrients & t° ⌐ vasoconstriction
    ⌙ vasodilation

Thứ
Ngày . . No.

More skin !!

- **Sweat gland**: produce sweat in response to t°
  - sweat = H_2O, salt, other chemical (like plasma)
  - regulated by SNS

- **Sebaceous gland**: - secrete sebum into hair follicles
  - ↳ oil = TAG + fattyacids + wax ester
  - to lubricate & prevent bacteria by having some antibiotics

- **Hair follicles**:
  - produce hair
  - derma papilla construct hair from keratinised cells from the base of follicle.
  - regulated by SNS

- **Nails**
  - hard structure of keratin
  - facilitate pinching & grabbing

Hair cycle

3 distinct stages:

+ **Anagen**:
  - Hair growth
  - Rapid proliferation
  - Differentiation
  - Duration of the phase determines hair length

+ **Catagen**:
  - Apoptosis
  - Regression
  - No diff.
  - Derma papillain contact w/ epithelium

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Ngày . . No.

+ Telogen: • Resting
• No. diff, apoptosis, proliferation
• Derma papilla near stem cell.

Skin diseases

- Acne: Over production of sebum
→ block skin pore → anaerobic environment for the growth of bacteria, trigger inflammation.

- Sunburn: UV from the sun
→ red, sore, warm
→ may permanently damage the skin

- Eczema: Hypersensitivity to anything
→ trigger overreaction
May disappear over childhood & early adulthood.

- Psoriasis: Chronic autoimmune condition
CTL release growth factors → ↗ keratinocytes.

- Fungal infection: Fungi + weaken of immune system
→ overgrow in keratin