Respiration

Aerobic Respiration

Glycolysis (Cytoplasm)

- Activation of glucose to make it more metabolically active: Glucose is phosphorylated to become glucose-6-phosphate (1 ATP), catalysed by hexokinase
- Isomerisation to fructose-6-phosphate
- Phosphorylation of fructose-6-phosphate to fructose-1,6-phosphate (1 ATP), catalysed by phosphofructokinase (PFK)- regulator of respiration rate
- Fructose-1,6-bisphosphate is cleaved to form 2 molecules of glyceraldehyde-3-phosphate (GALP)
- Each GALP then releases protons and electrons, transferred to oxidised nicotinamide adenine dinucleotide (NAD) to form reduced NAD, and 1,3-bisphosphoglycerate, which then converted to 3-phosphoglycerate and then pyruvate
- 2 net ATP are generated by substrate level phosphorylation per GALP, hence there is a gain of 4 ATP per glucose molecule by the end of glycolysis
- Products per glucose: 2 ATP, 2 reduced NAD, 2 pyruvate (3C)

Link Reaction (Mitochondrial Matrix)

- Decarboxylation: 1 CO_2 molecule is released from pyruvate
- Dehydrogenation: Oxidation of the 2C molecule occurs by transferring protons and electrons to oxidised NAD, forming reduced NAD and acetate
- Coenzyme A is attached to acetate to form acetyl-coA (2A)
- Products per glucose: 2 reduced NAD, 2 CO_2, 2 Acetyl-CoA

Krebs Cycle (Mitochondrial Matrix)

- Acetyl CoA+Oxaloacetate→Citrate (6C)
- Citrate is hydrated to isocitrate, which is oxidised and decarboxylated to α-ketoglutarate (5C) (1 oxidised NAD → 1 reduced NAD, 1 CO_2 released)
- α-ketoglutarate is reduced and decarboxylated to succinyl-coA (1 oxidised NAD→1 reduced NAD, 1 CO_2 released) , which then releases 1 ATP through substrate level phosphorylation to form succinate (4C)
- Succinate is reduced to form fumurate (1 oxidised FAD→1 reduced FAD), where water is added to form malate
- Malate is oxidised (1 oxidised NAD→1 reduced NAD) to form oxaloacetate
- Products per glucose: 4 CO_2, 6 reduced NAD, 2 reduced FAD, 2 ATP, 2 oxaloacetate
- 1.5 ATP will be released from each reduced FAD, 2.5 ATP from each reduced NAD
- Since there are 2 acetyl-coA for each glucose, the Krebs cycle runs twice for each glucose molecule

- 1 molecule of ATP from substrate level phosphorylation per cycle (phosphate from GTP)
- The coenzymes transfer high energy protons and electrons to the electron transport chain to synthesise ATP in oxidative phosphorylation

***Every time you mention transfer protons and electrons, state that it is dehydrogenation.**

***NAD and FAD are electron and proton CARRIERS**

***If the question asks you to OUTLINE, just mention "intermediates are oxidised/decarboxylated/phosphorylated etc, then state the net products**

***ATP is produced by ADP+Pi only in oxidative phosphorylation**

Oxidative Phosphorylation (Inner Mitochondrial Membrane)

Electron Transport Chain

- A series of electron carriers embedded in the mitochondrial membrane, each with decreasing levels of energy
- Extensively folded inner membrane/cristae increases surface area so that more electron carriers can be embedded for faster respiration
- Reduced NAD and reduced FAD transfer high energy protons and electrons to the electron transport chain (ETC) for synthesis of ATP
- Electrons are transferred down the ETC from one electron carrier to the next, each with a lower energy level than the previous one
- Electron carriers alternate between reduced and oxidised states
- The last electron carrier transfers to the final proton and electron acceptor, oxygen, which then forms water, catalysed by cytochrome oxidase. $\frac{1}{2}\ O_2+2H^++2e^- \rightarrow H_2O$

Chemiosmosis

- Energy is released from transferring of electrons from one electron carrier to the next, each with lower energy levels than the previous one. The energy is used to pump protons from the mitochondrial matrix to the intermembrane space
- The high proton concentration of protons in the intermembrane space generates a steep electrochemical proton gradient. The concentration is maintained by the impermeability of the inner mitochondrial membrane to H^+
- Protons diffuse from the intermembrane space to the matrix through the stalked particles containing ATP synthase, providing energy to synthesise ATP by phosphorylation of ADP with inorganic phosphate

Anaerobic respiration

Alcohol Fermentation (Yeast and Plants)

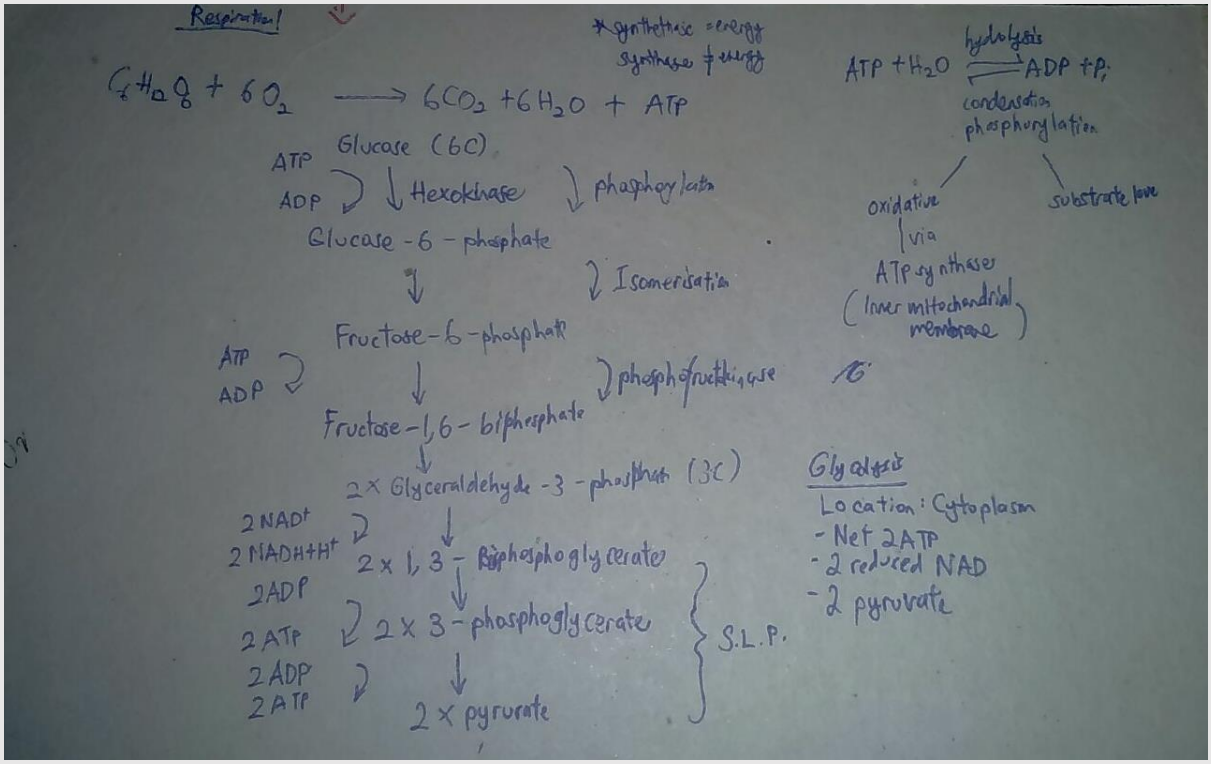
- Glucose is converted to pyruvate in glycolysis
- Pyruvate is decarboxylated to release 1 CO_2 to produce acetaldehyde/ethanal (2C), catalysed by a decarboxylase
- Acetaldehyde/ethanal is reduced to ethanol by reduced NAD, catalysed by alcohol dehydrogenase, allowing oxidised NAD to be regenerated and glycolysis to continue
- Glycolysis results in net release of 2 ATP from substrate level phosphorylation

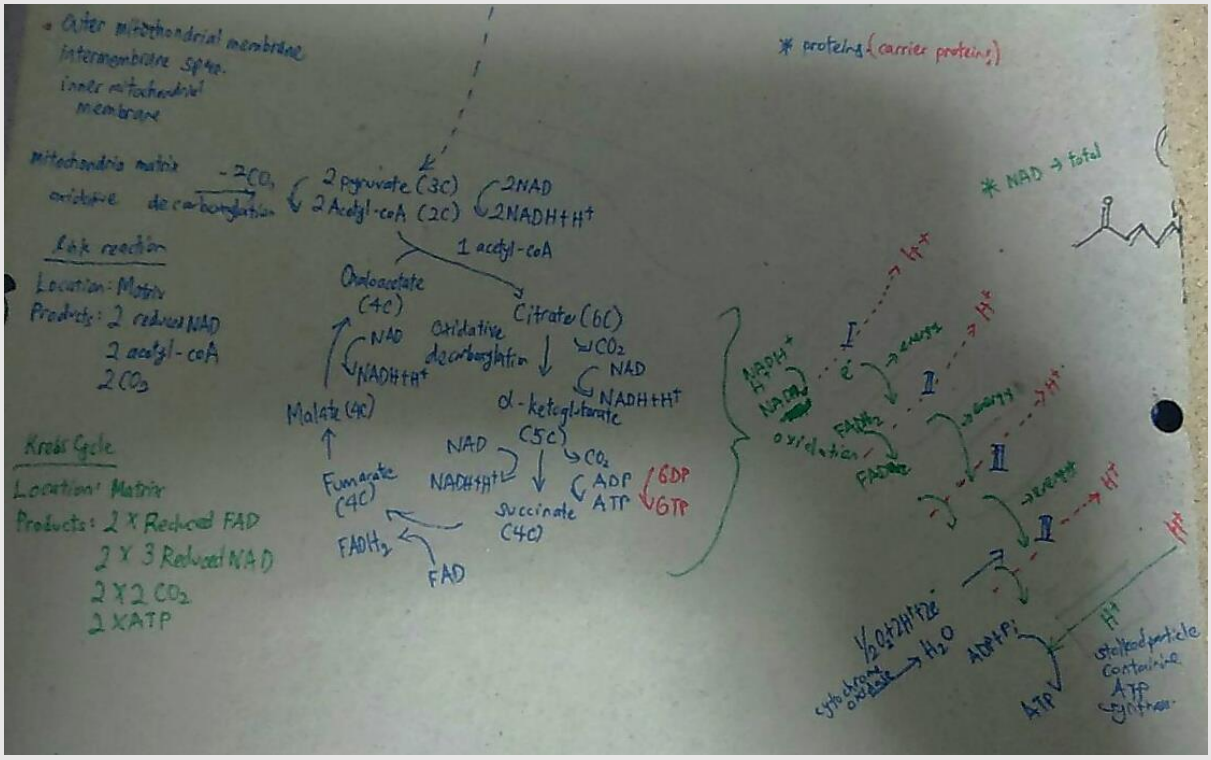
Lactate Fermentation

- Pyruvate is reduced directly to lactate, catalysed by lactate dehydrogenase, by reduced NAD, in a single step process
- Lactate still contains a lot of energy as glucose is incompletely oxidised, hence it is converted to pyruvate when oxygen is restored, and it enters the Krebs cycle

***State that OP cannot occur in anaerobic respiration as there is no oxygen→ Oxygen cannot be the final electron and proton acceptor**

***Always remember to state glucose converted to pyruvate first**





Photosynthesis

Chloroplasts

- Thylakoid membrane has large surface area for embedding of ETC, photosystems and stalked particles
- Thylakoid membrane is impermeable to protons to set up electrochemical proton gradient between the thylakoid space and the stroma

Photosystems

- Light harvesting complexes: made up of accessory pigments- chlorophyll and carotenoids, which function to funnel the energy absorbed by light to the reaction centre
- Reaction centre: contains two special chlorophyll A molecules (primary pigments) and a primary electron acceptor. Each chlorophyll A molecule emits one electron that is accepted by the primary electron acceptor
- Two types of chlorophyll A: P680 (in Photosystem 2) and P700 (in Photosystem 1)
- Primary pigments absorb energy from accessory pigments and when the energy levels in the electrons are boosted, they become excited and emit electrons, leaving 'positive holes' in the molecules

Non-cyclic Photophosphorylation

- Light of a particular wavelength strikes the accessory pigment molecule in light harvesting complex of PSII and PSI
- The energy is relayed to the neighbouring accessory pigment molecules until it accumulates and reaches one of the two P680 chlorophyll A molecules in PSII/P700 in PSI
- This excites one of the P680/P700 electrons to a higher energy level, and the electron is emitted and accepted by the primary electron acceptor in the reaction centre, leaving a positive hole in the P680 and P700 chlorophyll A molecules in PSII and PSI
- Photolysis of water occurs when an enzyme catalyses the splitting of water into hydrogen and oxygen: $H_2O \rightarrow 2H^+ + 2e^- + ½ O_2$. These electrons fill up the positive hole of PSII and return P680 to ground state (two electrons for two chlorophyll A molecules)
- The photoexcited electron from P680 passes from the primary electron acceptor of PSII to P700 in PSI, to fill the positive hole in P700, through an ETC, with each electron carrier at a lower energy level than the one before it
- Energy from the transfer of electrons is used to pump protons from the stroma into the thylakoid space, to generate electrochemical proton gradient, so that ATP can be produced by chemiosmosis as protons diffuses through stalked particles with ATP synthase
- Electrons and protons are passed down a second ETC from the primary electron acceptor of PSI to ferrodoxin, the last electron carrier
- NADP reductase catalyses the transfer of electrons and protons from ferrodoxin to oxidised NADP (final proton and electron acceptor) to form reduced NADP
- Products: ATP, O_2, Reduced NADP

Maintenance of the electrochemical proton gradient

- Water undergoes photolysis to generate protons, in the thylakoid space
- Plastoquinone (Pq) transfers electrons to the cytochrome complex, translocating protons across the membrane into the thylakoid space
- Protons are removed from the stroma as they are taken up by oxidised NADP
- Impermeability of the thylakoid membrane to protons

Cyclic Photophosphorylation

- PSI is a donator and acceptor of electrons
- The excited electrons in the primary electron acceptor of PSI pass to ferrodoxin and back to cytochrome complex in the ETC, and then return to PSI
- No photolysis of water occurs and PSII is not involved
- Only produces ATP

Calvin Cycle

- Carbon fixation: Ribulose bisphosphate (RuBP,5C) is fixated with CO_2, catalysed by RuBP carboxylase-oxygenase (Rubisco), giving an unstable 6C intermediate which immediately breaks down into 2 molecules of glycerate-3-phosphate (GP)
- Rubisco regulates the rate of photosynthesis
- GP can be converted to pyruvate which can be used to synthesise fatty acids. Pyruvate can also be converted to acetyl-CoA which undergoes the Krebs Cycle to form α-ketoglutarate, which can be used to form amino acids
- GP is phosphorylated into 1,3-bisphosphate (6 ATP) and reduced into GALP (6 Reduced NADP), by using ATP and reduced NADP that was produced in non-cyclic photophosphorylation. 1/6 of the GALP that is produced will be used to synthesise glucose and other organic compounds.
- The remaining 5/6 of the GALP will be used to regenerate RuBP, requiring energy from the hydrolysis of ATP (3 ATP)

Limiting Factors

Light Intensity

- Light intensity is an important limiting factor as it is used to excite the chlorophyll A molecules for photophosphorylation to occur
- Light compensation point is when rate of respiration equals rate of photosynthesis

Wavelength of light

- Rate of photosynthesis is highest at the red and blue violet regions of the spectrum and lowest at the green

Temperature

- It affects the rate of enzymatic reactions, like NADP reductase and rubisco

Carbon Dioxide

- It is the raw material for the Calvin Cycle as it is used in Carbon fixation

Cell Signalling

Types

- Cells in multicellular organisms communicate by ligands targeted for cells that are adjacent (local signalling) or non-adjacent (long-distance signalling)
- Local signalling: cell junctions (gap junctions in animals, plasmodesmata in plants) or cell-cell recognition by glycolipids or glycoproteins on the cell surface membrane.
- Short distance travel of signal molecules eg growth factor or neurotransmitters to neighbouring cells
- Long-distance signalling: eg endocrine hormones, or plant hormones like auxin that travel in vessels or diffuse through air

Ligand-receptor Interaction

- The ligand/signal molecule is complementary in shape to the binding site on the receptor confers specificity in binding. Binding of ligand to receptor activates the receptor
- Ligands may be large and/or hydrophilic and cannot pass through cell surface membrane. Examples: insulin, glucagon
    - Receptors lie on the cell surface membrane-→binds at the extracellular side of the receptor, and relay the message across the membrane
- Ligands may also be small and hydrophobic→can pass through cell surface membrane. Examples: steroid hormones like oestrogen/testosterone, thyroid hormones
    - Receptors for these hormones lie in the interior of the target cell and these signal molecules act as gene regulatory proteins

Cell Surface Receptors

- These receptors are usually transmembrane proteins that are embedded in the cell surface membrane of the target cell
- Ion-channel receptors are membrane-bound receptors that cause gates to open when a ligand binds to the extracellular side, causing increased permeability to ions like Na^+/Ca^{2+}, hence causing ions to enter through the channel protein. An example is the ligand gated Na^+ channels on the postsynaptic membrane

G Protein-Coupled Receptor (GPCR)

- The GPCR is closely associated with a G protein which binds to GTP or GDP
- Is a single polypeptide chain with 7 transmembrane α-helices, with an extracellular ligand binding site and an intracellular G protein binding site

Receptor Tyrosine Kinases (RTKs)

- Single polypeptide chain with single transmembrane α-helix
- Extracellular ligand binding site, and an intracellular tail that functions as a tyrosine kinase and contains tyrosine residues

Intracellular Receptors

- Intracellular receptors are located either in the cytosol or in the nucleus
- Ligands that bind at such receptors are small and hydrophobic to pass through the hydrophobic core of the phospholipid bilayer of the cell surface membrane
- Testosterone, a steroid hormone passes through the cell surface membrane of all cells but only cells with testosterone receptors can respond
- In the cytoplasm of the target cell, the testosterone binds to the receptor and activates it. The activated ligand-receptor complex enters the nucleus and binds to the regulatory sequence in DNA, activating transcription of certain genes that give rise to male characteristics

Signal Transduction

Phosphorylation Cascade

- The activated receptor activates other relay molecules (usually proteins) through phosphorylation and the relay molecule activates other relay molecules, until the molecule that produces a final cellular response is activated
- Many of these relay molecules are protein kinases, which activates other protein kinases, in a sequential phosphorylation and activation (phosphorylation) cascade
- Relay molecules are activated by protein kinases (phosphorylation) and deactivated by phosphatases (dephosphorylation)

Second Messengers

- Second messengers are small, non-protein, water soluble molecules or ions that relay signals received at the receptors on the cell surface membrane to target molecules in the cytosol
- Second messengers are small and soluble hence they can readily diffuse throughout the cell
- They also serve to greatly amplify the signal → Ca2+ ions and cyclic AMP (cAMP)
- cAMP
    - Adenylyl cyclase, when activated by the G protein, converts many ATP to cAMP molecules, hence amplifying the signal in the cytoplasm as the concentration of cAMP is elevated by 20 fold in a few seconds
    - Phosphodiesterase converts cAMP to ATP, hence cutting the signal when the hormone (glucagon) no longer binds

- Ca^{2+}
    - Signal molecules like neurotransmitters, growth factors and hormones induce responses in the target cells that increase the cytosolic concentration of Ca^{2+}
    - This increased concentration causes muscle contraction, secretion of substances like acetylcholine, and cell division (this is present in both GPCR and RTK pathways)
    - Ca^{2+} is always present in cells, however, they function as a second messenger as the concentration in the cytosol is usually much lower than outside the cell as Ca^{2+} is actively transported out of the cell/into the smooth ER by protein pumps

Signal Amplification

- Signal amplification occurs when some of the relay molecules in the pathway can transmit the signal to multiple molecules of the next molecule in the series, hence activating many of them
- This allows a small number of extracellular signalling molecules to cause a large cellular response
- Amplification of the cellular response occurs as the number of activated products at each step of the pathway is much greater than at the previous step
- Main occurrences of signal amplification
    1. Each adenylyl cyclase catalyses the formation of many cAMP molecules (from many ATP molecules→not signal amplification per se)
    2. Each PKA phosphorylates many molecules of the next kinase in phosphorylation cascade
- This occurs as proteins are active long enough to catalyse conversion of many substrate molecules before being inactivated
- Hence this can lead to production of many glucose molecules when a small number of signal molecules bind to the receptors (GPCR), as many glycogen phosphorylase molecules are activated to convert many glycogen molecules to glucose-1-phosphate (glycogenolysis)

Cellular Response

- Regulation of activity of protein, for example the activity of an ion channel which regulates membrane permeability to ions and hence entry of ions into cell
- Regulation of protein or hormone synthesis by turning gene expression on or off in the nucleus
- Regulation of enzyme activity (eg glycogen phosphorylase)
- Rearrangement of cytoskeleton of cell
- Death of cell (apoptosis)

Signal Termination

- Dissociation of ligand from receptor when the concentration of the signal molecule drops (as the binding is reversible, the receptor becomes inactive again)
- GTPase in G protein hydrolyses bound GTP to GDP, hence inactivating it
- Protein phosphatases inactivate protein kinases by dephosphorylation
- Phosphodiesterase converts cAMP to ATP

Advantages of a Cell Signalling System

- Specificity in ligand-receptor interaction allows signal molecules to elicit responses in specific target cells
- Regulation and control of response by activating many different target cells
- Signal amplification allows triggering of a large cellular response
- One signal molecule can activate many signal transduction pathways which trigger many cellular responses simultaneously
- Binding of signal molecule to receptor on cell surface membrane can trigger gene transcription in nucleus

Differential Gene Expression

- Only cells that have receptors for the signal molecules can have a cellular response
- Different cell types can have different cell surface receptors that recognise the same signal molecule
- Different cell types may have the same receptors, but these receptors have different affinities for the same signal molecules
- Expression of relay proteins, and proteins triggered by them involved in signal transduction may be different in different cell types (number of proteins, enzyme pathways, etc)

Glucagon and GPCR Signalling

- Ligand-receptor interaction
    - Glucagon binds to the extracellular site of the G protein-coupled receptor (GPCR), activating it and causing change in conformation
    - The cytoplasmic side of the GPCR binds to an inactive G protein, causing it to exchange its bound GDP for GTP (one-for-one exchange), activating it
    - The activated G protein dissociates from the receptor and binds to adenylyl cyclase, which catalyses conversion of many ATP molecules to cAMP molecules
- Signal transduction
    - cAMP (second messenger) binds to and activates a large number of protein kinase A (PKA)
    - Each PKA initiates a sequential phosphorylation and activation of other kinases, triggering a phosphorylation cascade. At each step, ea

activated kinase activates a large number of the next kinase, hence increasing number of activated products (signal amplification)
    - Activated PKA phosphorylates and activates phosphorylase kinase, which phosphorylates and activates glycogen phosphorylase (final product)
- Cellular response
    - A large number of glycogen phosphorylase is activated, catalysing breakdown of glycogen into glucose-1-phosphate (glycogenolysis)
    - Also increases synthesis and activity of enzymes involved in gluconeogenesis
- Signal termination
    - Glucagon is released from the receptor
    - GTPase intrinsic to G protein hydrolyses bound GTP to GDP
    - Phosphodiesterase converts cAMP to AMP

Insulin and RTK Signalling

- Ligand-receptor interaction
    - Insulin binds to extracellular binding sites of receptor tyrosine kinase (RTK), causing two RTK proteins to form a dimer
    - Dimerisation activates the tyrosine kinase function in the intracellular tails of RTK
    - Tyrosine kinase adds phosphate group from ATP to tyrosine residues on the tail of other RTK by autophosphorylation
- Signal transduction
    - Activated RTK triggers assembly of relay proteins on receptor tails and activates them
    - Activated relay proteins further recruit and activate downstream kinases and relay molecules
    - Each PKA initiates a sequential phosphorylation and activation of other kinases, triggering a phosphorylation cascade. At each step, each activated kinase activates a large number of the next kinase, hence increasing number of activated products (signal amplification)
- Cellular response
    - Activated relay proteins cause vesicles embedded with glucose transporters to move to the cell surface membrane and fuse with it, increasing the permeability of cell to glucose and uptake of glucose
    - Large number of glycogen synthase is activated from binding of one insulin molecule, which triggers glycogenesis
    - Decreased synthesis and activity of enzymes involved in gluconeogenesis and glycogenolysis
- Signal termination
    - Insulin is released from receptors and the tyrosine residues are dephosphorylated by phosphatases, causing the dimers to dissociate into individual RTK proteins
    - Protein phosphatases also deactivate other protein molecules by dephosphorylation

Endocrine System

Definition & Principles

- Homeostasis is the ability to maintain relatively stable internal conditions even though external conditions change continuously
- The set point is an optimum value of which a variable is to be maintained at
- A stimulus is a detectable change in the variable above or below the set point
- The receptor detects stimuli and sends information to the control centre (afferent pathway)
- The control centre coordinates information received from the receptors and sends instructions to the effectors to carry out a response to correct the deviation
- The effector carries out the instructions from the control centre to restore variable to set point
- Principles of homeostasis
    - Self-regulatory: The control mechanism is triggered by the variable it serves to regulate. For example, secretion of insulin is triggered by changes in blood glucose level
    - Negative feedback: The response of the system provides feedback to the receptors that the magnitude of the stimulus decreases to set point, hence causing the homeostatic mechanism to stop

Nervous vs Endocrine Control

- Nervous control involves electrical impulses transmitted by neurones, except at the synapse, whereas endocrine control involves hormones transported by blood to target cells
- Nervous control has much faster transmission speed
- In nervous control, impulses are transmitted directly to target, hence it is localised.
- Nervous control has far more short lived effects than endocrine control

Hormones

- Effective in small amounts
- Slow transmission (requires time to be transported by blood to the target organs)
- Long lasting effects (remains in bloodstream for hours)
- Slow but sustained response (requires time for the deviation to be restored to set point)

Homeostatic Response (Increased Blood Glucose)

Release of Insulin

- β cells of the islets of Langerhans detects increase in blood glucose level, and secrete insulin to correct the deviation (β cells are both the receptor and the control centre)
- Insulin secreted binds to receptors on the cell surface membrane on target cells

Effects of Insulin

- Insulin enhances transport of glucose into muscle and fat cells (brain cells can take up glucose without insulin)
- Insulin increases rate of glucose utilisation in cells for cellular respiration
- Insulin stimulates the conversion of excess glucose to glycogen (glycogenesis) for storage in liver and muscles
- Inhibits breakdown of glycogen to glucose (glycogenolysis)
- Inhibits conversion of amino acids and fats to glucose (gluconeogenesis)
- Stimulates amino acid uptake and protein synthesis in muscles
- Stimulates triglyceride formation in adipose tissues from excess glucose
- This causes blood glucose to decrease to set point. Negative feedback is achieved, and when stimulus magnitude decreases, insulin production decreases

Homeostatic Response (Decreased Blood Glucose)

- α cells of islets of Langerhans detects the decrease in blood glucose and secretes glucagon to correct the deviation
- Glucagon binds to receptors on cell surface membrane of liver cells, and stimulates breakdown of glycogen into glucose (glycogenolysis), and stimulates synthesis of glucose from lactate, glycerol, amino acids (gluconeogenesis)
- Blood glucose increases to set point. Negative feedback is achieved, and when stimulus magnitude decreases, glucagon production decreases

Diabetes Mellitus

- Caused by a deficiency of insulin or decreased response to insulin in target cells, causing elevated blood glucose levels
- Cells are unable to take in glucose from the bloodstream, and hence fats and proteins become main respiratory substrates, which cause accumulation of acidic metabolites in the blood and blood pH to decrease

- Glucose in kidney filtrate is excreted, causing it to be in the urine. As glucose is more concentrated in the urine, larger volumes of urine are produced and causes excessive thirst

Type I

- Autoimmune disorder where the immune system attacks the β cells of the islets of Langerhans causing inability to produce insulin
- Appears during childhood
- Treated by insulin injections

Type II

- Target cells do not respond to insulin
- Risk is increased with obesity and lack of exercise
- Generally appears in adulthood
- Treated by healthy diet and exercise

Nervous System

Structure of Neurones

- Contains a cell body with most of its organelles, including the nucleus
- Cell bodies have dendrites that transmit information towards the cell body
- Neurones also have axons that conducts impulses away from the cell body to the axon terminals. Some axons are covered by fatty myelin sheaths formed by Schwann cells, with unmyelinated gaps between Schwann cells (Nodes of Ranvier)
- Each branched end of an axon transmits information to another cell at a junction called a synapse, through neurotransmitters

Maintenance of Resting Potential in a Neurone

- The resting potential of a neurone is the difference in voltages between the outside and inside of an unstimulated neurone when not transmitting signals
- The axon membrane is polarised with a resting potential of -70mV
- Negative resting potential sets up an electrochemical gradient across the membrane due to an unequal distribution of ions across the phospholipid bilayer

1. Sodium-Potassium pump

    - Actively transports 2 K^+ ions into the cell and 3 Na^+ ions out of the cell

2. Facilitated diffusion of Na^+ and K^+ across membrane

    - Concentration of K^+ is higher inside the cell and concentration of Na^+ is higher outside of the cell due to the sodium-potassium pump
    - Due to electrochemical gradient, Na^+ tends to diffuse back into the cell and K^+ tends to diffuse out of the cell, but as ions are charged particles and will get repelled by the hydrophobic fatty acid tails, they have to undergo facilitated diffusion through leak channels
    - The plasma membrane of a resting neurone has more K^+ leak channels and hence is more permeable to K^+, hence net amount of K^+ diffuses out of the cell

3. Impermeability of cell membrane to anions

    - The concentration of anions is higher inside the neurone, but the cell membrane is impermeable to the anions and this contributes to the net negative charge

*Leak channels are <u>always open</u>

<u>Generation of an Action Potential</u>

1. Depolarisation

    - A stimulus causes the opening of voltage-gated sodium channels, which causes a net influx of Na^+ through facilitated diffusion into the cell, causing the membrane to become less negative
    - Influx of Na^+ causes more sodium channels to open, further depolarising the membrane. This is an example of positive feedback
    - Threshold potential is -55mV. When the threshold potential is reached, more rapid influx of Na^+ is triggered as all voltage gated sodium channels open, triggering action potential
    - Positive feedback mechanism rapidly brings the membrane potential to +40 mV
    - The voltage gated potassium channels start to open slowly

*A stronger stimulus causes more neurones to fire, but does not change the peak

2. Repolarisation

    - After the action potential peaks (+40 mV), voltage gated Na^+ channels close, preventing Na^+ influx
    - The opening of K^+ channel increases permeability of the membrane to K^+, causing a net efflux out of the cell, down the electrochemical gradient
    - This causes a rapid decrease in membrane potential to resting potential

- The efflux of K^+ is slower than the influx of Na^+ as voltage gated sodium channels open faster than voltage gated potassium channels

3. Hyperpolarisation

- The membrane becomes slightly more negative than resting potential (-75mV)
- Voltage gated sodium channels are closed whereas the voltage gated potassium channels are still closing, hence the efflux of K^+ occurs until they are closed
- The slower closing of the potassium channels than sodium channels causes the membrane to be more negative than the resting potential
- Absolute refractory period is when no new impulses can form as the membrane cannot respond to further stimuli, no matter how intense the stimulus is. This is from the time sodium channels open at the threshold (-55mV) to the time they are inactivated
- Relative refractory period is when the membrane begins to recover and become more responsive. New impulses form only when the stimulus can produce more polarisation than normal to cause a greater influx of Na^+ ions, to reach the threshold (-55mV). This period is from the sodium channels regain resting condition until resting potential is achieved.

Recovering Resting Potential

- Potassium leak channels facilitate diffusion of K^+ ions into the neurone
- The sodium potassium pump works to maintain resting potential

Importance of Refractory Period

- Allows action potential to only be propagated in a region which is not experiencing a refractory period, hence signals move forward in only one direction from cell body to action terminal
- By the end of the refractory period, the action potential has been transmitted further down the neurone, hence the second action potential will be separated from it. This prevents overlapping of signals and sets an upper limit to frequency of impulses along a neurone

Transmission of an Action Potential

- Unidirectional: The region where an action potential is generated causes depolarisation of neighbouring region due to Na^+ inflow. The depolarised region reaches the threshold and an action potential is reinitiated. This process repeats as the action potential travels the axon. Behind the depolarised zone is a repolarised

zone due to K^+ outflow, and in that zone Na^+ channels are closed, hence an action potential cannot generate behind it. Action potentials hence only move forward to the axon terminal

- All-or-nothing: If the strength of a stimulus is insufficient to depolarise the neurone membrane to reach threshold potential, no action potential is generated. Once the stimulus causes the neurone membrane to be depolarised to reach the threshold potential, action potential is generated. Action potentials are the same magnitude regardless the strength of the stimulus (stronger stimuli only cause more impulses to fire). The magnitude of the action potential remains the same as it travels along the neurone

Factors Affecting Conduction Speed

- Axon diameter: The greater the diameter of the axon the faster the speed of transmission as resistance to electrical flow is inversely proportional to the cross sectional area of the conductor
- Myelination: Nerve impulses travel faster along a myelinated neurone (saltatory conduction) than along a non-myelinated one (continuous conduction). Fatty myelin acts as an electrical insulator, and hence action potentials cannot form there. Action potentials can only form at Nodes of Ranvier, hence they jump from node to node, speeding up transmission. Saltatory conduction also requires less ATP for pumps to maintain ion concentrations as fewer ions need to move across the membrane
- Number of synapses: Tiny gaps at synapses involve chemical release and a brief delay, hence more synapses means slower transmission

Synaptic Transmission

- When a nerve impulse reaches the synaptic knob, it depolarises the pre-synaptic membrane and causes voltage-gated calcium channels to open, and increases membrane permeability to calcium ions, and they diffuse into the neurone
- Ca^{2+} influx causes the synaptic vesicles to move to and fuse with the pre-synaptic membrane, aided by rearrangement of cytoskeleton, which requires ATP
- The synaptic vesicles discharge neurotransmitter (acetylcholine) into the synaptic cleft via exocytosis. Ca^{2+} moves out of the synaptic knob by active transport to maintain ionic gradient for subsequent transmission
- Acetylcholine diffuses across the synaptic cleft. It takes longer for an impulse to travel across a synapse than along the axon, hence there is a synaptic delay (other factors include vesicle fusing to the pre-synaptic membrane, entrance of Ca^{2+} into pre-synaptic neurone, etc)
- Acetylcholine reaches the post-synaptic membrane and binds with acetylcholine receptors (ligand gated sodium channels) and causes the channels to open

- Na^+ enters the post-synaptic neurone and generates a new impulse (EPSP), depolarising the post-synaptic neurone, which may build up as more neurotransmitters arrive or as a sum of the neurotransmitters on different pre-synaptic neurones. A new action potential is generated when the depolarisation exceeds the threshold.
- Once acetylcholine depolarises the post-synaptic neurone it is hydrolysed by acetylcholinesterase which is on the post-synaptic membrane. This is to prevent continuous stimulation of post-synaptic neurone.
- Choline diffuses across the synaptic cleft and actively transported back to the synaptic knob of pre-synaptic neurone. ATP synthesised by mitochondria is used to resynthesize acetylcholine from choline and acetate.

One-direction Transmission Across Synapse

- Acetylcholine receptors/ ligand-gated ion channels, and acetylcholinesterase are only located on the post-synaptic neurone
- Synaptic vesicles containing neurotransmitters are located at the pre-synaptic neurone
- Mitochondria for ATP synthesis found in pre-synaptic neurone (for active transport of acetate and choline into the pre-synaptic neurone, active transport of Ca^{2+} out of the pre-synaptic neurone rearrangement of cytoskeleton to aid synaptic vesicle movement, and exocytosis of acetylcholine

Functions of Synapses

- Transmit information between neurones
- Transmits impulses in one direction: synaptic vesicles are only at pre-synaptic membrane, mitochondria only at pre-synaptic neurone, acetylcholine receptors only at post-synaptic membrane, voltage gated calcium channels only at pre-synaptic membrane
- Junction for a coordinated response: Many pre-synaptic neurones may converge at a synapse, hence spatial summation may occur and action potential generated on a single post-synaptic neurone
- Filter out low level stimuli: Only small amounts of neurotransmitter is released at a synapse, hence it is insufficient to create a new impulse, and the information is carried no further than the synapse and no response is generated
- Adaptation to intense stimulation: The high frequency of impulses causes considerable release of neurotransmitters into the synaptic cleft, and continued high level stimulation will cause rate of release of neurotransmitters to be higher than the rate of which they can be reformed, hence the release of neurotransmitters ceases and prevents further response to the stimulus. The synapse becomes fatigued, and prevents over stimulation which may damage an effector

Transmission at a Neuromuscular Junction

- A neuromuscular junction is where a motor neurone stimulates a muscle fibre
- When an impulse reaches the neuromuscular junction, the synaptic vesicles fuse with pre-synaptic membrane and releases acetylcholine through exocytosis, which diffuses across the synaptic cleft and binds with acetylcholine receptors on the motor end plate at the sarcolemma (membrane of muscle fibre)
- Na^+ channels open, the sarcolemma is more permeable to Na^+ and it diffuses into the sarcoplasm. The sarcolemma is depolarised and an end plate potential is created, causing the muscle fibre to contract as the action potential travels along it
- Sarcolemma contains acetylcholinesterase, which hydrolyses acetylcholine into acetate and choline