Topic 7: Run for your life

Aerobic respiration

Aerobic respiration is the splitting of the respiratory substrate glucose to release carbon dioxide as a waste product and reuniting of hydrogen with atmospheric oxygen with the release of a large amount of energy.

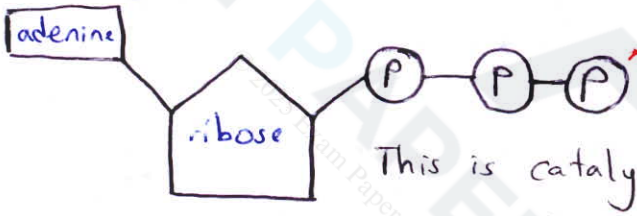
→ The overall reaction of aerobic respiration is:

glucose + oxygen → carbon dioxide + water + energy

Energy is in the form of ATP.

ATP

ATP is a nucleotide with three phosphate groups attached.



When energy is needed, the third phosphate bond can be broken by a hydrolysis reaction. This is catalysed by the enzyme ATPase.

The result of this hydrolysis is adenosine diphosphate (ADP), and a free inorganic phosphate group (P_i) and energy. Some of this energy is lost as heat and wasted, but the rest is used for any energy-requiring biological activity in the cell such as active transport.

The breakdown of ATP into ADP and phosphate is a reversible reaction. ATP can be synthesised from ADP and a phosphate group in a reaction which requires an input of energy and the action of ATPase. The energy needed to drive the synthesis of ATP usually comes from catabolic reactions or redox reactions. As a result, the ATP molecule provides an immediate supply of energy, ready for use when needed.

Cellular respiration

As opposed to what the equation in the previous page suggests, respiration is not a single step reaction. In fact, the complete process is a complex series of reactions which involves many different enzymes and redox reactions.

Respiration takes place 3 steps:

- Glycolysis
- The link reaction and Krebs cycle
- The electron transport chain and oxidative phosphorylation

Glycolysis does not require oxygen whereas the other two stages do. Glycolysis, the first part of the respiratory pathway is not associated with any particular cell organelle. The enzymes controlling glycolysis are found in the **cytoplasm**. However, the reactions of the Krebs cycle and the electron transport system involved in producing ATP, takes place inside the mitochondria. The matrix of the mitochondrion seems to contain the enzymes of the Krebs cycle, while the cristae carry the stalked particles associated with ATP synthesis.

– The hydrogen acceptors

During cellular respiration, hydrogen is removed from compounds and picked up by a hydrogen carrier which is therefore reduced. The hydrogen is then passed to the next hydrogen acceptor and along the electron transport chain. A series of linked redox reactions takes place and it is here that ATP is formed.

The most common hydrogen acceptor in cellular respiration is NAD. NAD is a coenzyme. When it accepts hydrogen atoms from a metabolic pathway it is reduced to form reduced NAD.

FAD is another hydrogen carrier and coenzyme, which accepts hydrogen from reduced NAD and forms reduced FAD. A molecule of ATP is formed in the process.

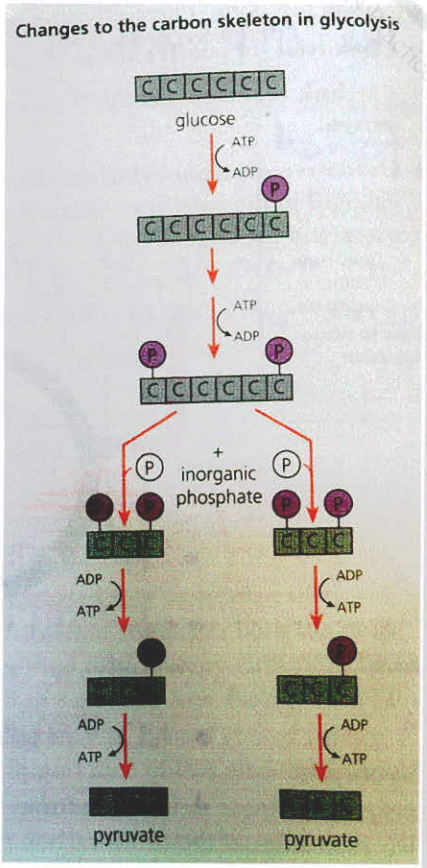
1 Glycolysis

Glycolysis is a linear series of reactions in which a six-carbon sugar is broken down to two molecules of the three-carbon pyruvate ion. Glycolysis occurs in four stages.

- **Phosphorylation**: 2 molecules of ATP activate glucose forming a six-carbon sugar with two phosphate groups attached (fructose bisphosphate).
- **Lysis**: Fructose bisphosphate takes place, forming two molecules of a three-carbon sugar.
- Oxidation of three-carbon sugar molecules occurs by removal of hydrogen. The enzyme for this reaction (a dehydrogenase) works with a coenzyme, NAD^+. NAD^+ is a molecule that can accept hydrogen ions and electrons.

$$NAD^+ + 2H^+ + 2e^- \longrightarrow NADH + H^+$$

- **ATP formation**: Two molecules of triose phosphate (TP) are converted to **pyruvate**, four molecules of ATP are synthesised.



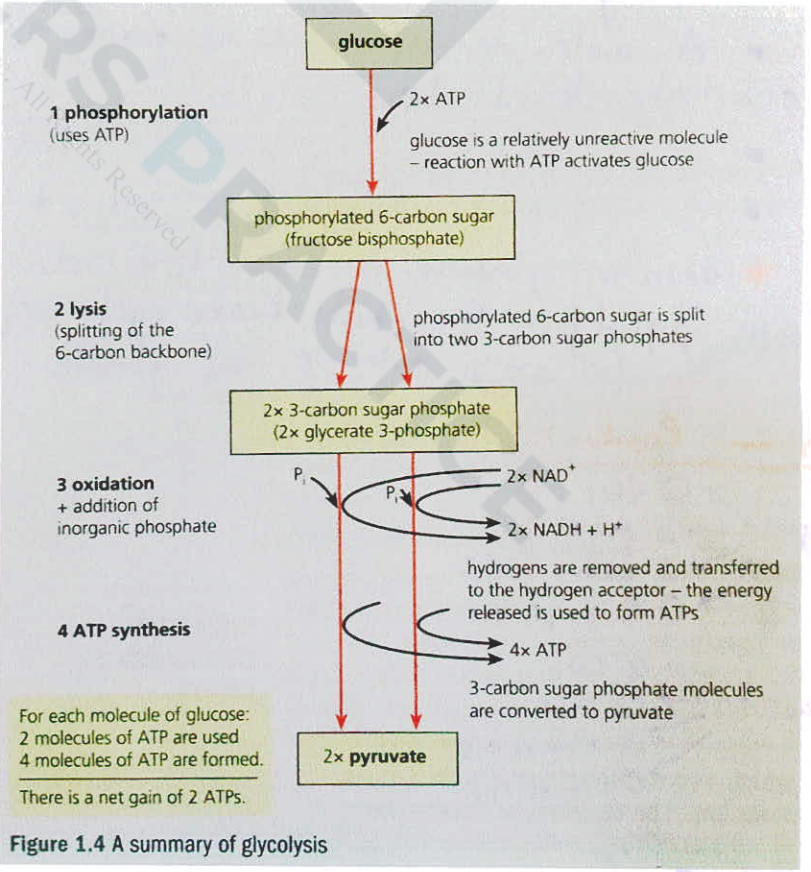
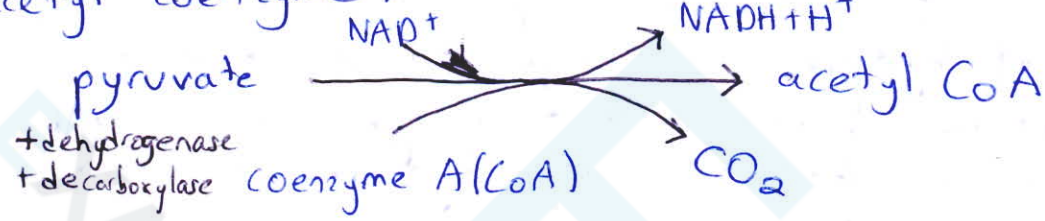


Figure 1.4 A summary of glycolysis

2 The link reaction and Krebs cycle

- The link reaction

In the link reaction, pyruvate diffuses into the matrix of the mitochondrion as it forms, and is metabolised there. First, the three-carbon pyruvate is decarboxylated by removal of carbon dioxide and, at the same time, oxidised by removal of hydrogen. Reduced NAD is formed. The product of this oxidative decarboxylation reaction is an acetyl group. This acetyl group is combined with a coenzyme called coenzyme A, forming acetyl coenzyme A.



- Krebs cycle

- Acetyl CoA reacts with 4C organic acid (oxaloacetate, (OAA). 6C acid citrate and, of course coenzyme A form. The latter is re-used in the link reaction.
- Two molecules of CO_2 are given off in separate decarboxylation reactions.
- A molecule of ATP is formed. This ATP synthesis is at substrate level too.
- Three molecules of reduced NAD are formed.
- One molecule of FAD is reduced.

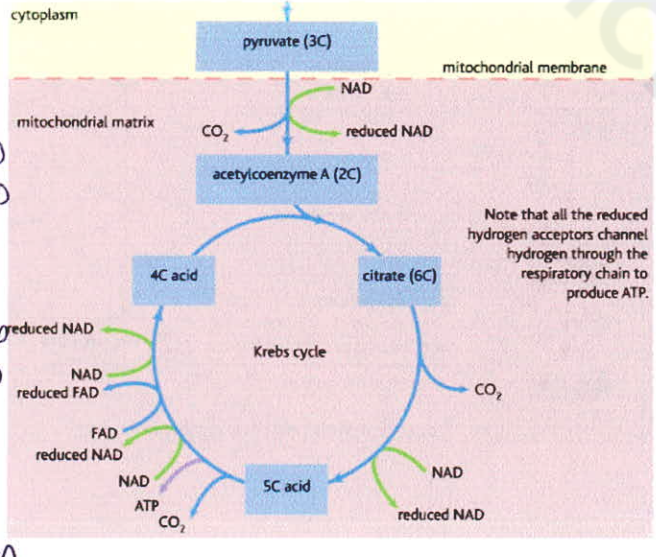
* Because glucose is converted into two molecules of pyruvate in glycolysis, the whole Krebs cycle sequence of reactions turns twice for every molecule of glucose.

Step — Product

Glycolysis → 0 CO_2, 2 ATP, 2 Reduced NAD, 0 Reduced FAD

Link reaction → 2 CO_2, 0 ATP, 2 Reduced NAD, 0 Reduced FAD

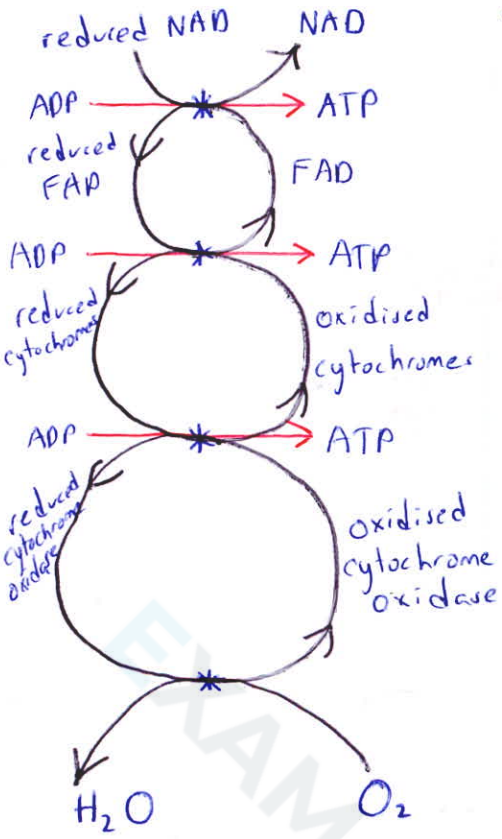
Krebs cycle → 4 CO_2, 2 ATP, 6 Reduced NAD, 2 Reduced FAD



Total:

- 6 CO_2
- 4 ATP (substrate level)
- 10 Reduced NAD
- 2 Reduced FAD

3 Oxidative phosphorylation



- The electron transport chain

$$NADH + H^+ \longrightarrow NAD^+ + 2H^+ + 2e^-$$

The high energy electrons released enter the electron transport chain. Various elements of this chain are at different energy levels. The first member of the chain is the highest level. Each electron is passed down from one energy level to another, releasing energy that powers the production of ATP. The process is known as oxidative phosphorylation because ADP is phosphorylated in a process which depends on the presence of oxygen.

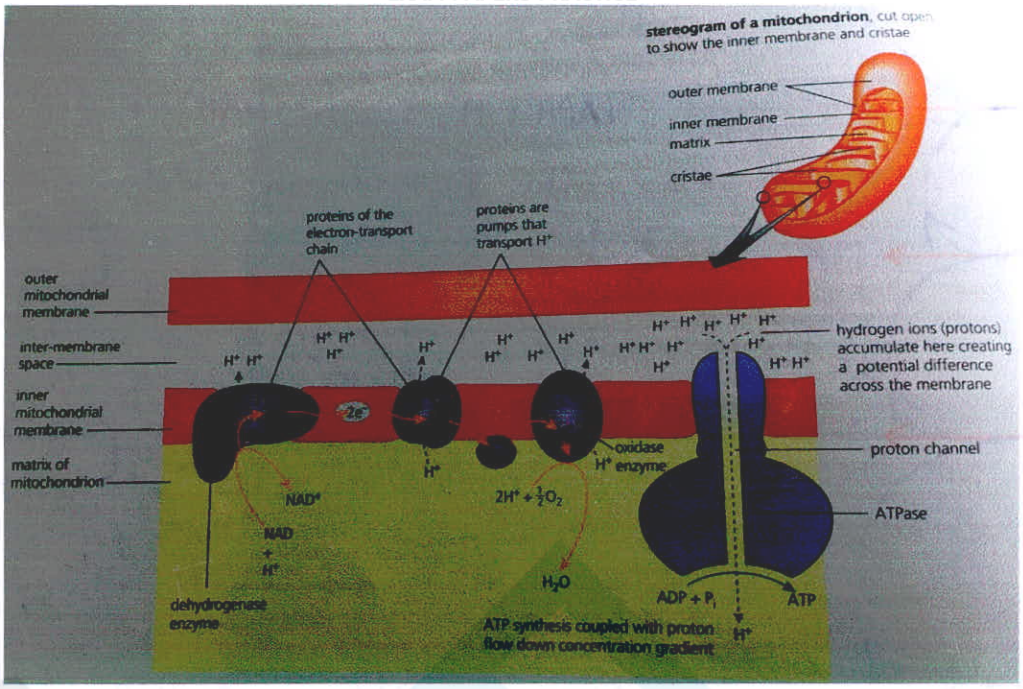
Final reaction: $\frac{1}{2}O_2 + 2H^+ + 2e^- \longrightarrow H_2O$

The chemiosmotic theory of ATP production

Chemiosmosis is a process by which the synthesis of ATP is coupled to electron transport via the movement of protons. Electron-carrier proteins are arranged in a highly ordered way. These carrier proteins oxidise the reduced coenzymes and energy from this process is used to pump hydrogen ions (protons) ~~to~~ from the matrix of the mitochondrion into the space between inner and outer mitochondrial membranes.

Here the H^+ ions accumulate - incidentally causing the pH to drop. Because the inner membrane is largely impermeable to ions, a significant difference in hydrogen ion concentration builds up, generating an electrochemical gradient across the inner membrane.

Eventually, the protons do flow back into the matrix via channels in ATPase enzymes also found in the inner mitochondrial membrane. As the protons flow down their gradient through the enzyme, the energy is transferred and ATP synthesis occurs.



Anaerobic respiration

A knowledge of aerobic respiration shows the effect that a lack of oxygen will have. If oxygen is the final hydrogen acceptor, then without it the carriers of oxidative phosphorylation will all become reduced and the flow of electrons and protons will cease. This will also mean that the supply of NAD^+ will be halted and the Krebs cycle will come to a stop.

With only glycolysis operating, there is a net gain of only 2 ATPs per glucose molecule compared with about 38 ATPs from complete aerobic respiration.

A second consequence of a lack of oxygen is that the end-product of glycolysis, pyruvic acid, will begin to accumulate. In animal cells this results in the formation of lactate as the pyruvate acts as the acceptor for reduced NAD, whilst in plant cells ethanal acts as this acceptor and this results in the formation of ethanol. In effect, these compounds are replacing oxygen as the final hydrogen acceptor to allow glycolysis to continue.

When exercise stops, the levels of lactate in the blood of animals remain raised. The lactate must be oxidised back to pyruvate to enter the Krebs cycle, to be respired.

Muscles and movement

Muscle

Muscle is a specialised tissue. Muscles are made largely of protein. They consist of very long cells known as muscle fibres bound together by connective tissue. They can contract to do work. Muscles have a good blood supply (the energy for contraction is provided).

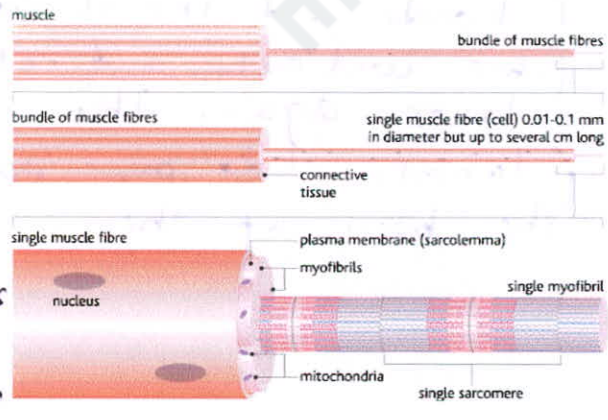
Types of muscle

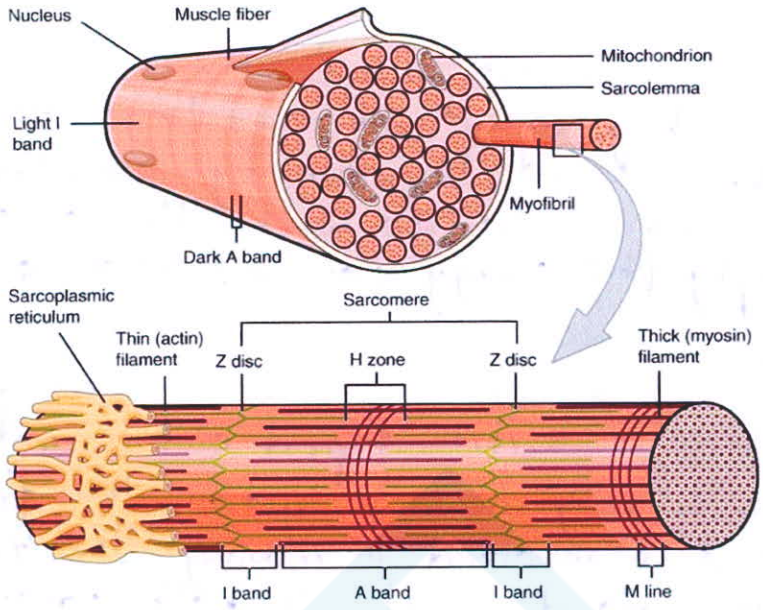
- Smooth muscle: is not striped and is under the control of the involuntary nervous system. It is found in the gut where it is involved in moving the food along, and in the blood vessels. It both contracts and fatigues slowly.
- Cardiac muscle: is found exclusively in the heart. It is striated and the fibres are joined by cross-connections. It contracts spontaneously and does not fatigue.
- Skeletal muscle (striated or voluntary muscle): is the muscle attached to the skeleton and involved in locomotion. It is under the control of the voluntary nervous system. It contracts rapidly but also fatigues or tires relatively quickly.

Detailed structure of a striated muscle

Muscle fibres are made up of many myofibrils lying parallel to each other. Each myofibril is made up of sarcomeres. The proteins actin and myosin make up a large part of the structure of sarcomeres. The cytoplasm of the myofibrils is called the sarcoplasm. It contains many mitochondria. A network of membranes running through the system is called the sarcoplasmic reticulum.

Diagram:





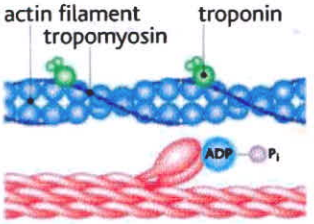
Different types of muscle fibre

Slow-twitch	Fast-twitch
specialised for slower, sustained contraction and can cope with long periods of exercise	specialised to produce rapid, intense contractions in short bursts
many mitochondria – ATP comes from aerobic respiration (electron transport chain)	few mitochondria – ATP comes from anaerobic respiration (glycolysis)
lots of myoglobin (dark red pigment) to store O_2 and lots of capillaries to supply O_2. This gives the muscle a dark colour	little myoglobin and few capillaries. The muscle has a light colour
fatigue resistant	fatigue quickly
low glycogen content	high glycogen content
low levels of creatine phosphate	high levels of creatine phosphate

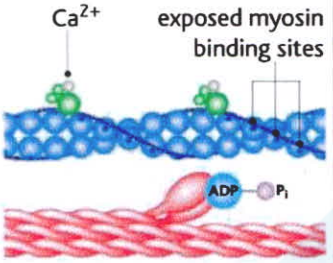
Contraction of muscles

Observations of micrographs show that whether a muscle fibre is contracted or relaxed, the dark A bands remain the same length. However, the light I bands and the H zone get shorter when a muscle fibre contracts and return to normal length when it relaxes again. This suggests that two types of filaments slide over each other during contraction – the basis of the **sliding filament theory**.

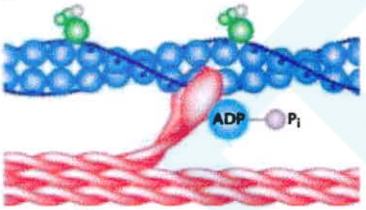
Sliding filament theory



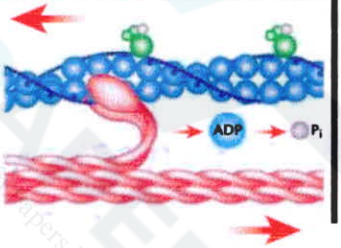
The diagram shows the actin and myosin unit before contraction starts. The myosin heads have ADP and Pi bound closely to them as well.



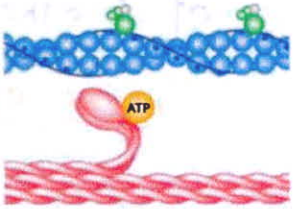
Calcium ions bind to the troponin molecules, changing their shape, so troponin molecules pull on the tropomyosin molecules they are attached to. This moves the tropomyosin away from the myosin binding sites, exposing them ready for action.



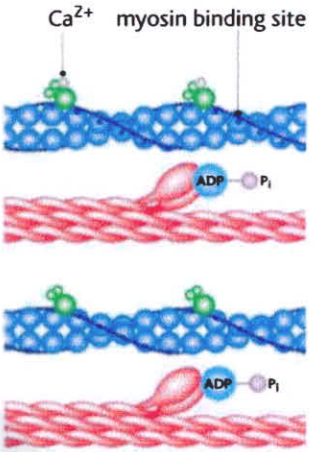
The myosin heads bind to the actin, forming an actomyosin bridge.



ADP and Pi are released from the myosin head. The myosin changes shape – the head bends forward moving the actin filament about 10 nm along the myosin filament, shortening the sarcomere.



Free ATP binds to the head, causing another shape change in the myosin, so the binding of the head to the actin strand is broken. This activates ATPase in the myosin head, which also needs calcium ions to work. The ATP is hydrolysed, providing the energy to return the myosin head to its original position, primed with ADP and Pi, ready to go again.



With continued stimulation, calcium ions remain in the sarcoplasm and the cycle is repeated. If not, calcium ions are pumped back into the sarcoplasmic reticulum using energy from ATP. The troponin and tropomyosin return to their original positions and the contraction is complete. The muscle fibre is relaxed.

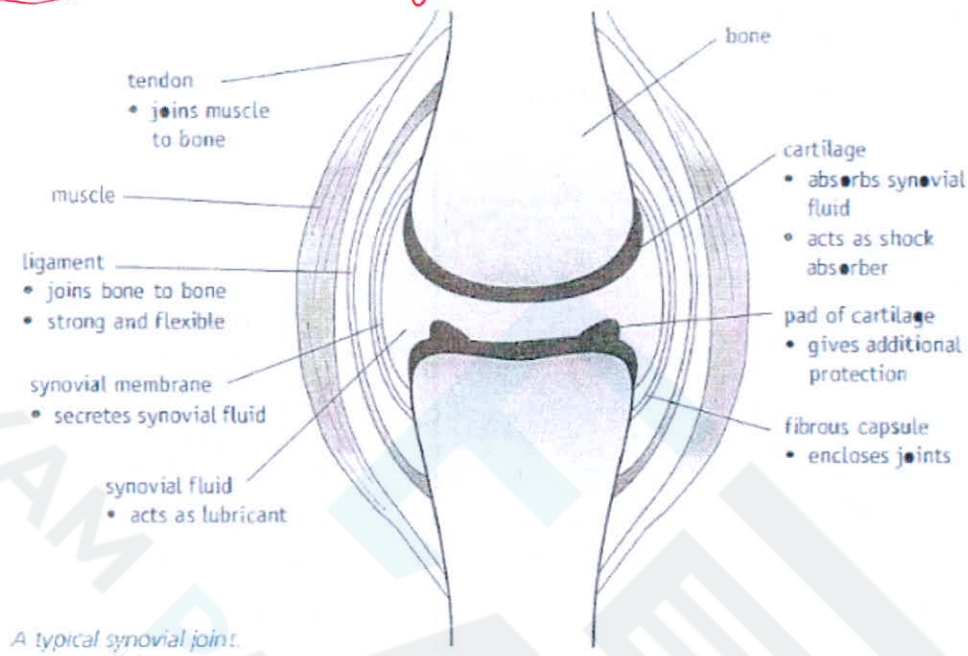
* The shape of myosin molecule enables it to attach to the actin to form cross-bridges of actomyosin. This changes the molecular shape and so pulls the actin filament across the myosin, increasing the interlocking region and shortening the sarcomere. The bridges then break and the process is repeated.
* The process requires Ca^{2+} ions and ATP.

Myosin: A myosin molecule is made up of two long polypeptide chains twisted together, each ending in a large, globular head which has ADP and inorganic phosphate molecules bound to it. The head can act as an ATPase enzyme.

Actin: An actin filament is made up of two chains of actin monomers joined together. The shape of the actin molecule produces myosin binding sites at regular intervals, where the globular heads of the myosin molecules can fit.

However, wrapping around the double chains is another long chain protein called tropomyosin. In a relaxed muscle the tropomyosin chain covers up the myosin bonding sites. In turn, the tropomyosin molecules have molecules of another protein, troponin.

Tissues of the skeletal system



A typical synovial joint

• Bone is strong and hard, and made up of bone cells embedded in a matrix of collagen and calcium salts. It is also light as possible to reduce the weight moved about.

• Cartilage is a hard but flexible tissue made up of cells called chondrocytes within an organic matrix of collagen. Cartilage is elastic. It is frequently found between bones and in the joints.

• Tendons are made up almost entirely of white fibrous tissue. This consists of bundles of collagen fibres and gives a tissue that is strong but relatively inelastic. This makes it ideal for joining muscles to bones. One end of the tendon is attached to a muscle and the other end attached directly to a bone or to the fibrous cover of the bone. This makes a more secure attachment for muscles to bone and provides a little shock absorption if the joint is subjected to sudden stretch.

• Ligaments hold bones together and in correct alignment, both around the joint as a capsule and within the joint itself. They need to be elastic to allow the bones of a joint to move when necessary.

Movement

Movement is brought about by the action of muscles on bones. Each of the skeletal muscles is attached by tendons to two different bones, spaming at least one joint. When muscles contract they exert a pull on a bone and so it moves relative to another. However, when they relax they do not exert a corresponding push – they simply stop contracting and become capable of being pulled back to their original shape.

Thus the muscles of the skeleton are found in pairs. One pulls the bone in one direction, the other pulls it back to its original position. Because they work in direct opposition to each other these muscles are known as antagonistic pairs.

– Flexors contract to flex, or bend a joint.

– Extensors contract to extend, or straighten a joint.

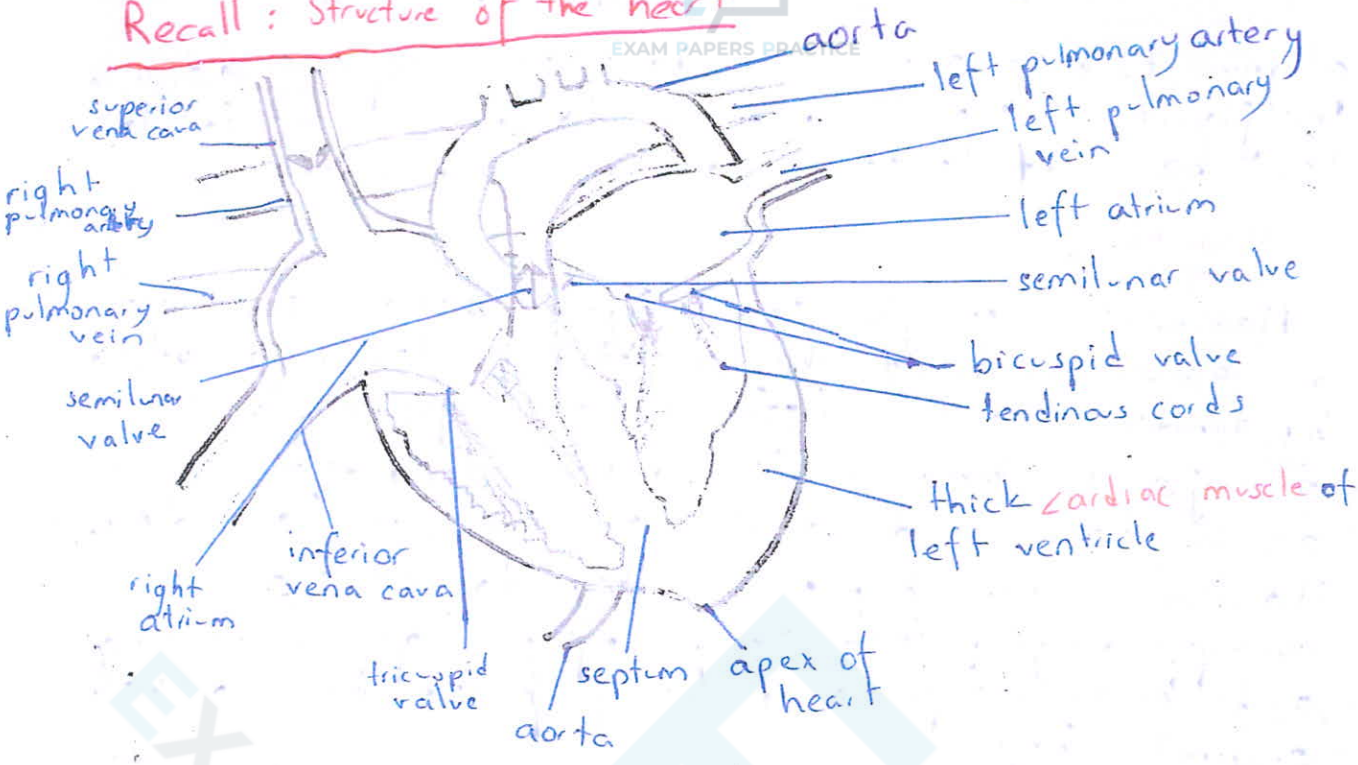
The cardiac cycle

The heart continuosly contracts and then relaxes. The contraction of the heart is called a systole. Systole can be divided into:

- atrial systole, when the atria contract together forcing blood into the ventricles, and
- ventricular systole when ventricles contract forcing blood out of the ventricles into the pulmonary artery and the aorta.

* Between contractions the heart relaxes and the atria fill with blood. This relaxation is called a diastole. One cycle of systole and diastole makes up a single heartbeat. This is known as the cardiac cycle.

Recall : Structure of the heart



* The heart is made of a unique type of muscle known as cardiac muscle which has special properties. It can carry on contracting without resting or getting fatiqued.

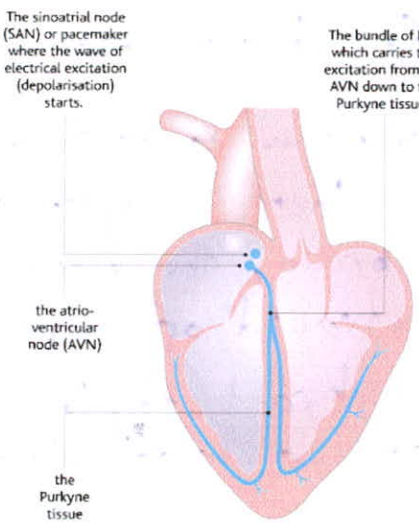
- The inferior vena cava collects blood from the lower parts of the body, while the superior vena cava receives blood from the head, neck, arms and chest.
- The right atrium receives the blood and the blod passes to the ventricle.
- The tricuspid valve (atrioventricular valve) allows blood to pass from the atrium to the ventricle, but not in the other direction. The tough tendinous cords make sure the valves are not turned inside out by the great pressure exerted when the ventricles contract.
- The right ventricle is filled with blood under some pressure when the right atrium contracts. Then, the ventricle contracts forcing blood into the pulmonary arteries. Semilunar valves prevent the the backflow of blood.
- The blood returns from the lungs in the pulmonary veins. The blood returns to the left atrium. It contracts to force blood into the left ventricle. Backflow is prevented by the bicuspid valve.
- Left ventricle contracts to force blood out of the heart and into the aorta. Semilunar valves prevent the blood flowing back from the aorta into the ventricle.

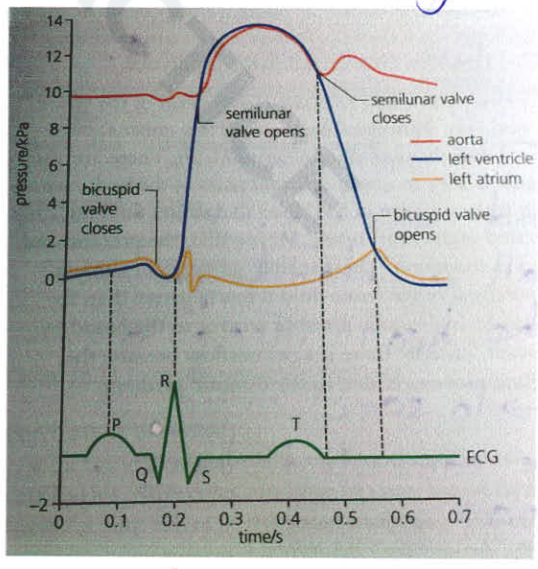
Controlling the heart

The impulse to contract originates within the heart itself. The heart has intrinsic rhythmicity and the cardiac muscle is said to be myogenic. The intrinsic rhythm of the heart is around 60 beats per minute. It is maintained by a wave of electrical excitation similar to a nerve impulse which spreads through special tissue in the heart muscle

The area of the heart with the fastest intrinsic rhythm is a group of cells in the right atrium known as sinoatrial node (SAN), and this acts as the heart's own natural pacemaker.

- Electrical impulses from the SAN spread across the atria walls, causing contraction. This is called atrial systole.
- The boundary between atria and ventricles is made up of connective tissue that does not conduct these impulses. To pass to the ventricles the impulses stimulate another node, the atrio-ventricular node (AVN).
- To reach the ventricles the AVN is connected to a bundle of specially modified muscle fibres called the Bundle of His and then through a network of finer branching Purkyne tissue to the base of the ventricles.
- The impulses spread up through the ventricle walls causing contraction from the apex upwards. Blood is squeezed into the arteries. This is ventricular systole.





Electrocardiograms

An ECG is used to investigate the rhythms of the heart by producing a record of the electrical activity of the heart. The rhythm of the heart results from the spread of a wave of depolarisation (electrical activity) through specialised tissue within the heart muscle itself. This depolarisation in the heart causes tiny electrical changes on the surface of your skin. An ECG measures these changes at the surface of your skin.

- Using ECGs to diagnose heart disease

In a normal ECG the P wave represents the depolarisation of the SAN and the related tissue in the atrium. The QRS complex represents the spread of excitation through the ventricles, and the T wave reflects the rapid depolarisation of the Purkyne tissue in the ventricles

If your heart starts behaving abnormally, e.g during a heart attack, the normal electrical activity of the heart will be disrupted, and the rhythm of the contraction of the muscles will change. These different rhythms - known as arrhythmias - of the heart can be detected using an ECG.

Some conditions

- Ischaemic: Starved of oxygen.
- Atrial fibrillation: The atria of the heart beating too fast and arhythmically.
- Tachycardia: An unusually fast heart rate.
- Ventricular fibrillation: The ventricles contract erratically and weakly. When this happens there is often a rapid fall in blood pressure, so the brain, the body and the heart itself are rapidly starved of blood.

→ In some cases, an abnormal heart rhythm can be corrected by giving the heart a large electric shock.

Homeostasis

The maintenance of a steady internal state in the body almost regardless of changes in either the external or the internal conditions is known as homeostasis.

Homeostasis involves a high level of coordination and control. Changes in the body are detected by a sensor. This sends a message to an effector which either works to reverse the change or to increase it. Negative feedback systems are the most common, and they provide a way of maintaining a condition within a narrow range. A change in conditions is registered by receptors and as a result effectors are stimulated to restore the equilibrium. The communication in a feedback system may be by hormones or by nerve impulses.

Homeostasis plays an important role during exercise when conditions in the body are changing rapidly and demands on the systems are high. Negative feedback systems are vital in the coordinated response which enables you to exercise effectively, as both your heart and respiratory system respond.

Changing cardiac output

* cardiac output = cardiac volume x heart rate
  ($dm^3\ min^{-1}$)

The intrinsic rhythm of the heart is not sufficient to supply the needs of the body except at a most basic level.

- Adjusting the heart rate

→ Nervous control of the heart: The cardiovascular control centre, which controls changes to heart rate, is found in the medulla of the brain. Chemical and stretch receptors in the lining of the blood vessels and the chambers of the heart send nerve impulses to the cardiovascular centre.

Most of the nervous control of your heart is by the autonomic nervous system. The autonomic nervous system is divided into two parts:

- The sympathetic nervous system is usually excitatory.
- The parasympathetic system is usually inhibitory.

→ Nerve impulses travelling down the sympathetic nerve from the cardiovascular centre in the brain to the heart stimulate the SAN. This increases the frequency of the signals from the pacemaker region so that the heart beats more quickly. In contrast, nerve impulses in the corresponding parasympathetic nerve inhibit the SAN and slow the heart down.

→ Hormonal control of the heart: Heart rate changes with emotion. When you are stressed, the hormone adrenaline is produced. This affects the SAN, speeding up the frequency of the excitation and so speeding up the heart, supplying you with extra oxygen and glucose for the muscles.

*Exercise

- As the atria fill with blood at the start of the cardiac cycle, stretch receptors in the muscle walls of the heart respond to the stretching by sending nerve impulses to the cardiovascular control centre.
- As more blood flows into the atria, the receptors are stretched more than usual and send more nerve impulses to the cardiovascular centre in the brain.
- This in turn sends more nerve impulses along the sympathetic nerve to the SAN, causing an increase in the heart rate.
- The increased stretching of the heart atrial muscle as blood returns from the body also makes the muscles contract harder, increasing the volume of blood expelled at each stroke. This is a feature of cardiac muscle.

Baroreceptors found in the sinuses of the carotid arteries in the neck are also important in the feedback control of the heart rate. As blood pressure in the arteries increases, the baroreceptors are stretched. They send nerve impulses to the cardiovascular centre which then sends impulses through the parasympathetic system to slow down the heart rate and cause a widening of the blood vessels.

Regulation of ventilation rate

Terms:

- Tidal volume: is the volume of air that enters and leaves the lungs at each natural resting breath.
- Inspiratory reserve volume: is the volume of air that can be taken in over and above the normal inspired tidal volume.
- Expiratory reserve volume: is the volume of air that can be expelled over and above the normal expired tidal volume.
- Vital capacity: is the total of the tidal volume and the inspiratory and expiratory reserves.
- Residual volume: is the volume of air left in the lungs after the strongest possible expiration.
- Total lung capacity: is the sum of the vital capacity and the residual volume.
- Inspiratory capacity: is the volume that can be inspired from the end of a normal expiration.

* ventilation rate = tidal volume × frequency of inspiration

* The ventilation centre in the medulla controls the rate and depth of breathing in response to impulses from chemoreceptors in the medulla and arteries which detect the pH and concentration of CO_2 in the blood. Impulses are sent from the ventilation centre to stimulate the muscles involved in breathing.

Exercise

- As soon as exercise starts, impulses from the cortex of the brain stimulate the respiratory centre in the medulla.
- This in turn stimulates the respiratory muscles and increases the rate and depth of ventilation.
- Chemoreceptors sensitive to the level of carbon dioxide and pH of the blood send impulses back to the main respiratory centre when carbon dioxide levels rise.
- Impulses are then sent out to the breathing muscles so the breathing rate changes in a negative feedback system which removes the extra carbon dioxide and at the same time matches the oxygen needs of the body.

→ The chemical sensors along with the stretch receptors in the muscles and lungs all act on the respiratory centre to maintain increased ventilation rates until the exercise is complete and oxygen debt has been paid off.

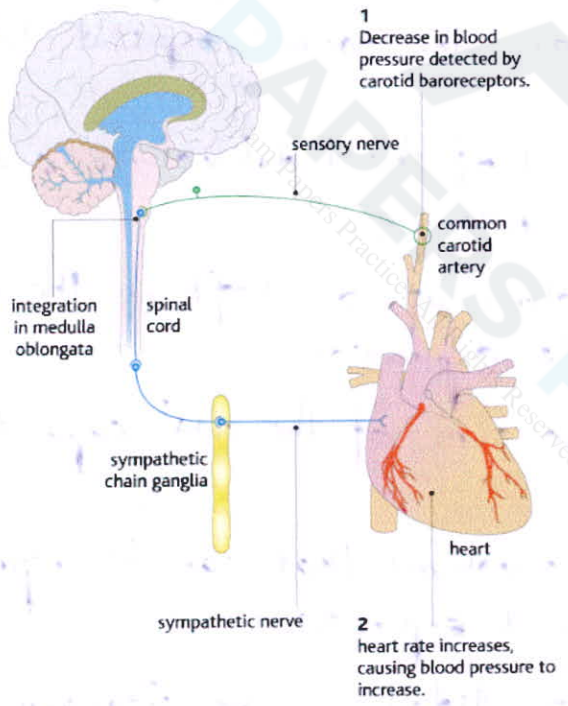


fig. 7.3.6 Negative feedback system for the heart through the baroreceptors.

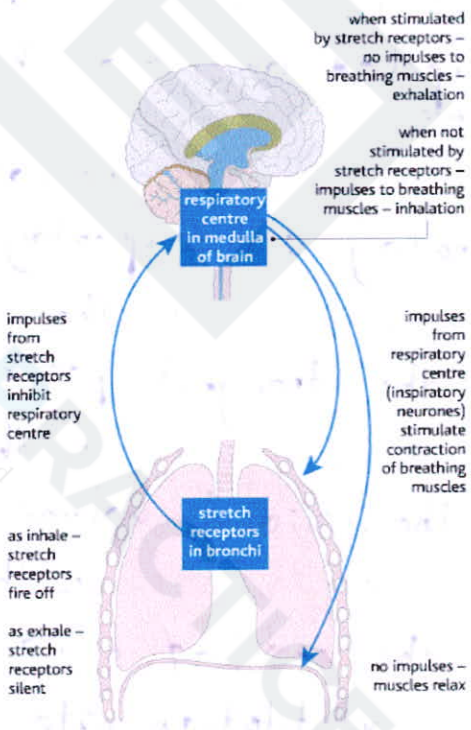


fig. 7.3.9 A simple feedback system controls the basic rate of breathing. The breathing muscles (intercostal muscles) are the muscles between the ribs and the diaphragm.

Regulating heart rate

Regulating ventilation

Human temperature regulation

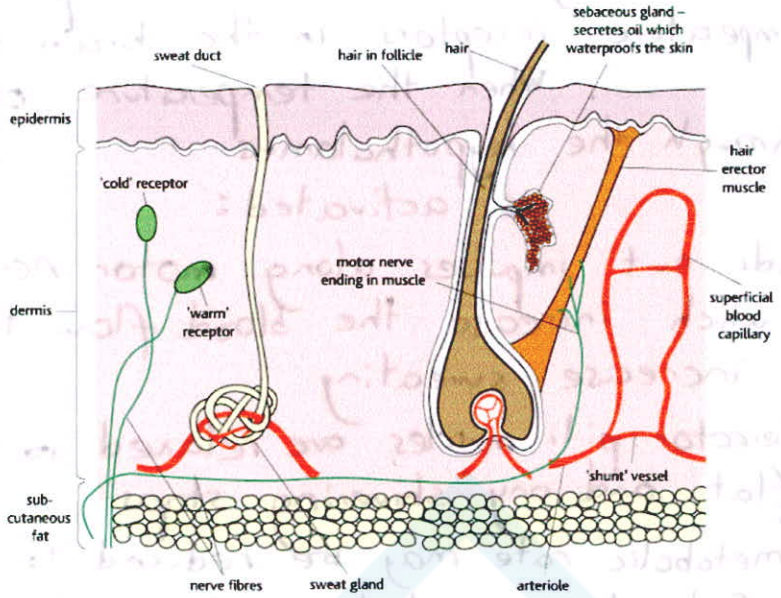


fig. 7.3.16 The human skin and its functions – the same major structures are present in the skin of all other mammals too. Many of the features are involved in thermoregulation.

In a warm environment

- vasodilation occurs
- sphincter muscles around arterioles leading to superficial capillaries are not stimulated to contract and therefore relax
- more blood can flow into these capillaries, dilating them with the pressure; less blood flows through deeper shunt vessels
- more blood flows close to the body surface
- as more blood flows close to the body surface, the temperature gradient between the body surface and the environment becomes steeper, so heat loss by conduction and radiation is increased

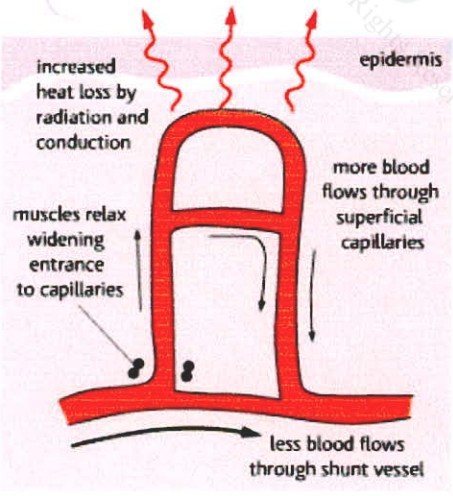


fig. 7.3.17 The superficial blood vessels play an important part in thermoregulation – here in cooling the body down.

In a cold environment

- vasoconstriction occurs
- sphincter muscles around arterioles leading to superficial capillaries contract
- this constricts the passage into these capillaries and more blood flows through deeper shunt vessels
- less blood flows close to the body surface
- as most blood is diverted further from the body surface, the temperature gradient between the body surface and the environment is less steep, so heat loss by conduction and radiation is reduced.

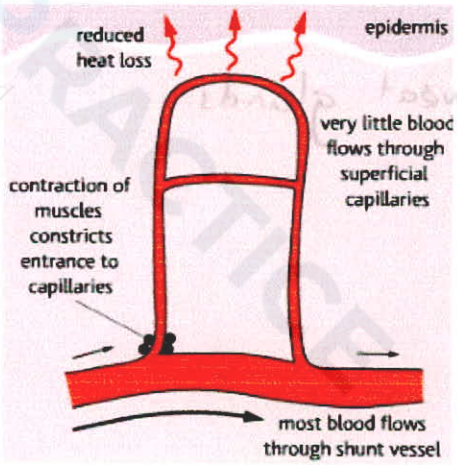


fig. 7.3.19 The superficial blood vessels play an important part in thermoregulation – here in warming the body up.

Receptors in the brain directly monitor the temperature of the blood, while receptors in the skin detects changes in external temperature.

The temperature receptors in the brain are sited in the hypothalamus. When the temperature of the blood flowing through the hypothalamus increases, the heat loss centre is activated:

- It sends out impulses along motor nerves to effectors which increase the blood flow through the skin and increase sweating
- The erector pili muscles are relaxed so that the hairs lie flat and any shivering stops.
- The metabolic rate may be reduced to lower the amount of heat generated in the body.

If the temperature of the blood flowing through the hypothalamus drops, the heat gain centre:

→ stimulates:

- arterioles in the skin to constrict.
- hair erector muscles to contract.
- liver to raise metabolic rate.
- skeletal muscles to contract in shivering

→ inhibits:

- sweat glands

Health and exercise

The possible effects of too little exercise

There are a few possible effects of a lack of exercise over a prolonged period time:

- reduced physical endurance, lung capacity, stroke volume and maximum heart rate
- increased resting heart rate, blood pressure and storage fat in the body
- increased risk of coronary heart disease, type II diabetes, some cancers, weight gain and obesity
- impaired immune response due to lack of natural killer cells
- increased levels of LDL and reduced levels of HDL
- reduced bone density, therefore increased risk of osteoporosis

The possible effects of too much exercise

Overtraining can lead to symptoms such as immune suppression and increased wear and tear on joints. It can also result in fatigue and poor athletic performance.

Too much exercise generally may also increase the amount of wear and tear on joints. Damage to cartilage in synovial joints can lead to inflammation and a form of athritis. Ligaments can also be damaged. Bursae that cushion parts of the joint can become inflamed and tender.

There is also some evidence of a correlation between intense exercise and the risk of infection such as colds and sore throats. This could be caused by an increased exposure to pathogens, or a suppression of the immune system. There is some evidence that the number and activity of some cells of the immune system may be decreased while the body recovers after vigorous exercise. It may also be the case that damage to muscles during exercise and the release of hormones such as adrenaline may cause an inflammatory response which could suppress the immune system.

Medical technology and sports

The development of keyhole surgery using fibre optics has made it possible for surgeons to repair damaged joints with precision and minimal damage. This is because only a small incision is needed so there is less bleeding and damage to the joint, and recovery is much quicker.

A prothesis is an artificial body part designed to regain some degree of normal function or appearance. The design of protheses has improved significantly and many disabled athletes are now able to compete at a very high level, e.g with dynamic response feet that can literally provide them with a spring in their step. Damaged joints can also now be repaired with small prosthetic implants to replace the damaged ends of bones, freeing the patient from a life of pain and restoring full mobility.

* Correlation vs causation

Just because two things happen, it doesn't mean they're connected. In particular it doesn't mean that one caused the other. A correlation does not necessarily mean a connection. If there appears to be a strong correlation between two factors, a causal link is more likely if you can provide a biological explanation for why one factor will affect the other, especially if there aren't many other likely factors or explanations available.

Ethics of using performance-enhancing substances

Some athletes will do anything they can, in pursuit of excellence. This might include the use of illegal performance-enhancing substances. Others may feel they need to follow suit because they don't want to be at a disadvantage.

Ethical absolutists see things as a very clear cut. They would take one of the two positions.

- It is never acceptable for athletes to use performance-enhancing substances (even if they are legal) or,
- It is always acceptable for athletes to use any substance available to them to compete more effectively, even if there are associated risks to their health.

Ethical relativists would realise that people and circumstances may be different, e.g:

- It is wrong for athletes to use performance-enhancing substances, but there may be some cases and circumstances where it is acceptable.

Drugs and genes

Some drugs such as anabolic steroids are closely related to natural steroid hormones. They can pass directly through cell membranes and be carried into the nucleus bound to a receptor molecule. These hormone/receptor complexes act as transcription factors. They bind to the promoter region of a gene allowing RNA polymerase to start transcription. As a result more protein synthesis takes place in the cells. For example, testosterone increases protein synthesis in muscle cells, increasing the size and strength of the muscle tissue. Peptide hormones do not enter cells directly, but they bind with receptors on the cell surface membrane. This starts a process that results in the activation of a transcription factor within the nucleus. For example erythropoietin (EPO) stimulates the production of red blood cells. This means that the blood can carry more oxygen.

- Genes are switched on by successful formation and attachment of the transcription initiation complex to the promoter region.
- Genes remain switched off by failure of the transcription initiation complex to form and attach to the promotor region. This is due to the absence of protein transcription factor(s) or the action of repressor molecules.

Topic 8: Grey matter

The effects of light on plants

Plants detect light using photoreceptors and respond to environmental cues. The photoreceptors are phytochromes, which react with different types of light.

Phytochrome is a blue-green pigment which exists in two interconvertible forms: P_R (P_{660}) absorbs red light; P_{FR} (P_{730}) absorbs far red light. When one form of the pigment absorbs light, it is converted reversibly into the other form. The length of time it takes from one form of the pigment to be converted into the other depends on the light intensity. In low light intensity it takes minutes, but in high light intensity it takes seconds.

The conversion of P_{FR} to P_R also takes place very slowly in the dark. P_R is the more stable form of the pigment, but it is the P_{FR} which is biologically active.

$$P_R \underset{\text{for red light (rapid)}}{\overset{\text{red light (rapid)}}{\rightleftharpoons}} P_{FR}$$

or slow conversion in the dark

* The presence of P_{FR} is needed for germination.
→ P_{FR} is biologically active and initiates germination.

* The lack of P_{FR} leads to flowering in short-day plants and the presence of P_{FR} leads to flowering in long-day plants.

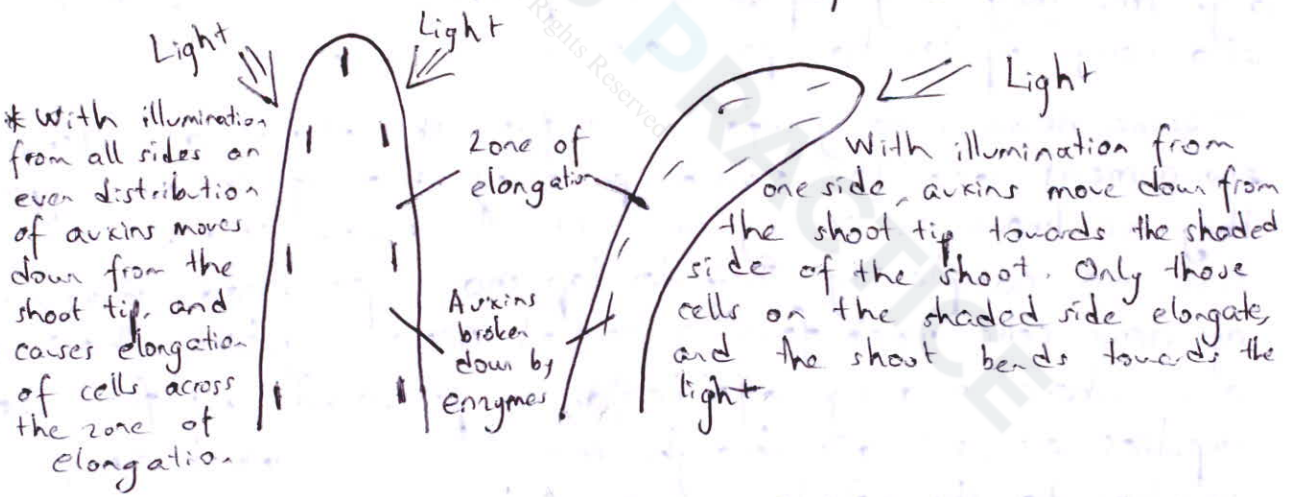
→ As the two forms of phytochrome are almost present to some degree in a plant, it is the balance between them which is affected by varying periods of light and dark, and which in turn affects flowering.

Phototropism in plants

Plant growth responses to environmental cues are known as tropisms. The direction of the growth response is determined by the direction of the external stimulus. If a plant grows towards a stimulus it is said to be a positive tropic response.

Phototropisms are the result of a chemical message made in the tip of the shoot which is transported to the growing region where it has an effect. The message is known as a plant hormone or plant growth substance. The growth substance involved in phototropisms is called an auxin.

Auxins seem to affect the ability of the plant cell walls to stretch. IAA (indoleacetic acid) is an auxin. The molecules of IAA bind to specific receptor sites on the cell surface membranes, activating the active pumping of hydrogen ions into the cytoplasm. This changes the hydrogen ion concentration, providing the optimum pH for the enzymes which break bonds between adjacent cellulose microfibrils and keep it flexible. The cells absorb water by osmosis and the very flexible cell walls stretch and allow the cells to expand. Eventually, as the cells mature, the IAA is destroyed by enzymes, the pH of the cell wall rises and bonds form between the cellulose microfibrils.



Nervous system in mammals	Endocrine system in mammals	Tropisms in plants
Electrochemical changes giving an electrical impulse. Chemical neurotransmitters used at most synapses.	Chemical hormones from endocrine glands carried in the blood plasma around the circulatory system.	Chemical growth substances (e.g. auxins) diffusing from cell to cell – some may go in the plant transport system – the phloem.
rapid acting	slower acting	slower acting
Usually associated with short-term changes, e.g. muscle contraction.	Can control long-term responses, e.g. growth and sexual development. Some are involved in homeostasis, e.g. control of blood sugar. Some can be relatively fast, e.g. effects of adrenaline in response to stress.	Controls long-term growth responses, e.g. cell elongation.
Response is very local and specific such as a muscle cell or gland.	Response may be widespread, or restricted to specific target cells.	Response may be widespread, but normally restricted to cells within a short distance of the growth substance being released.

The nervous system

A nervous system is made up of interconnected neurones specialised for the rapid transmission of impulses throughout the organism. They carry impulses from special receptor cells. Neurones also carry impulses to specialised effector cells.

- Some neurones carry information from the internal or external environment into the central processing areas of the nervous system. They are known as sensory neurones. As animals increase in size and complexity they develop more specialised concentrations of nerve cells which form a central nervous system. This is an area where incoming information is processed, and from where impulses are sent out through motor neurones which carry impulses to the effector organs.

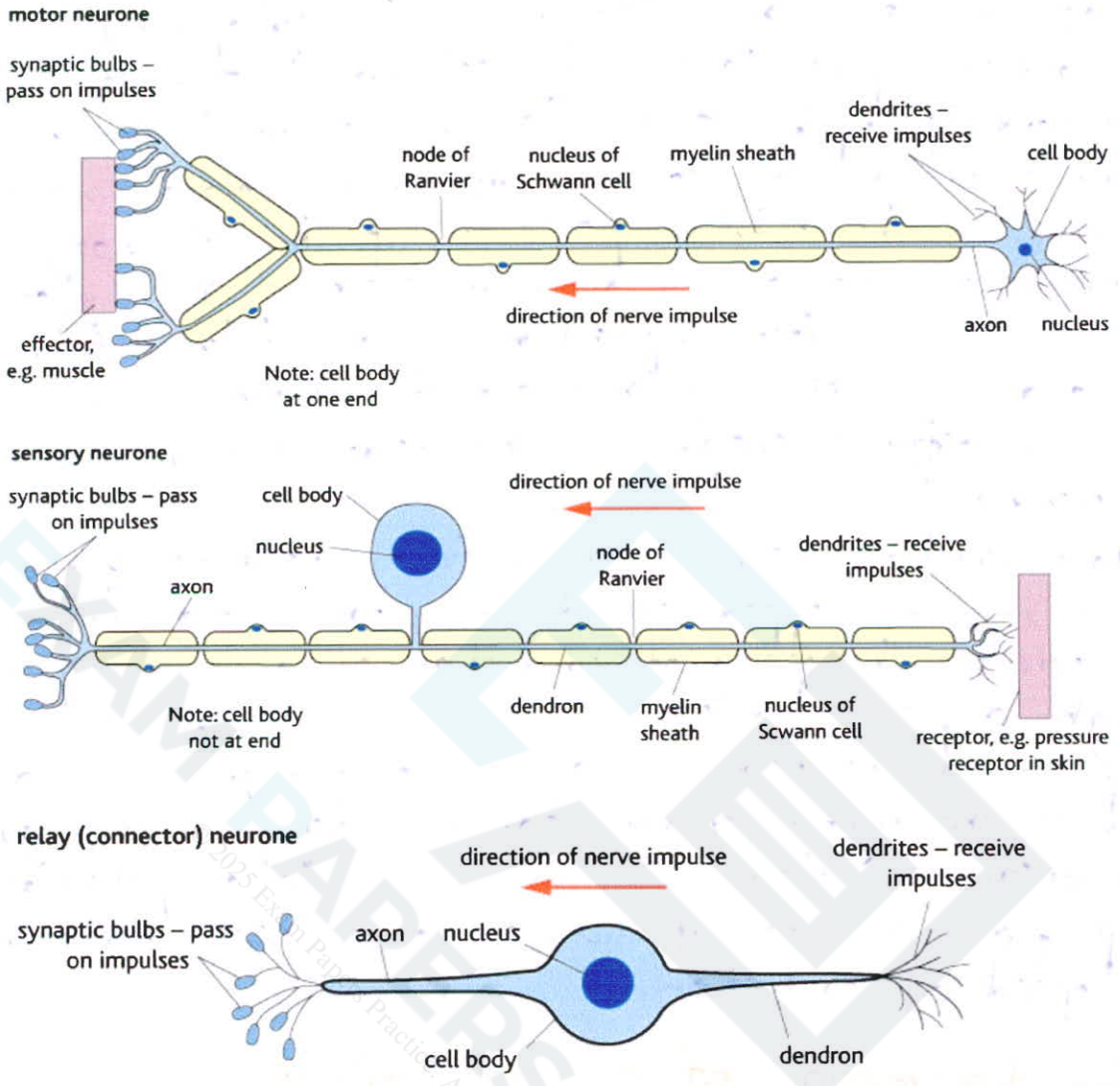


fig. 8.2.1 All neurones have the same basic structure of a cell body, dendrites and axon but the detailed arrangements vary depending on their function.

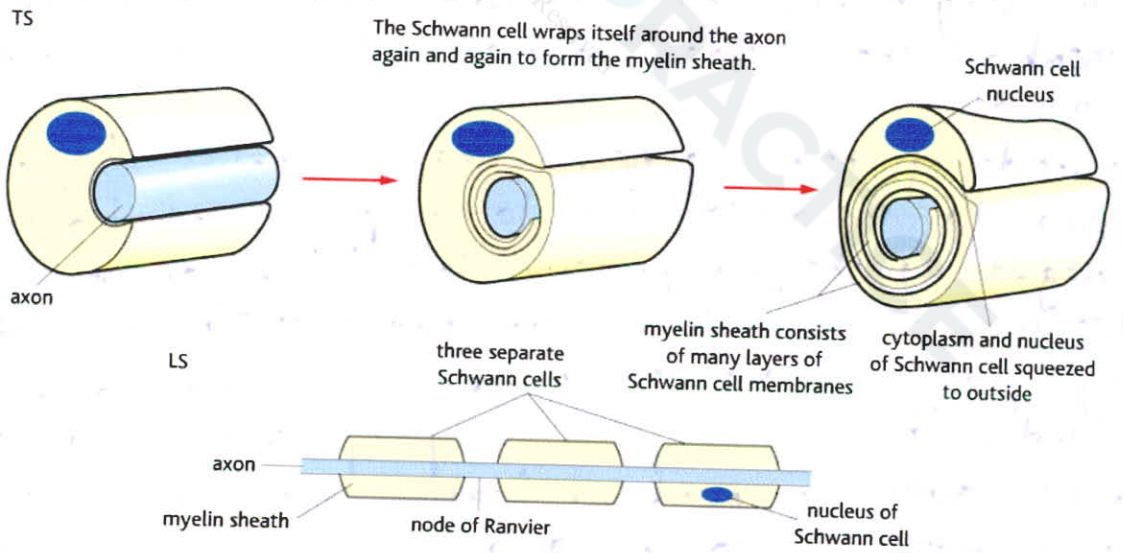


fig. 8.2.2 The myelin sheath which forms a protective, insulating layer around vertebrate nerve fibres.

The structure of neurones

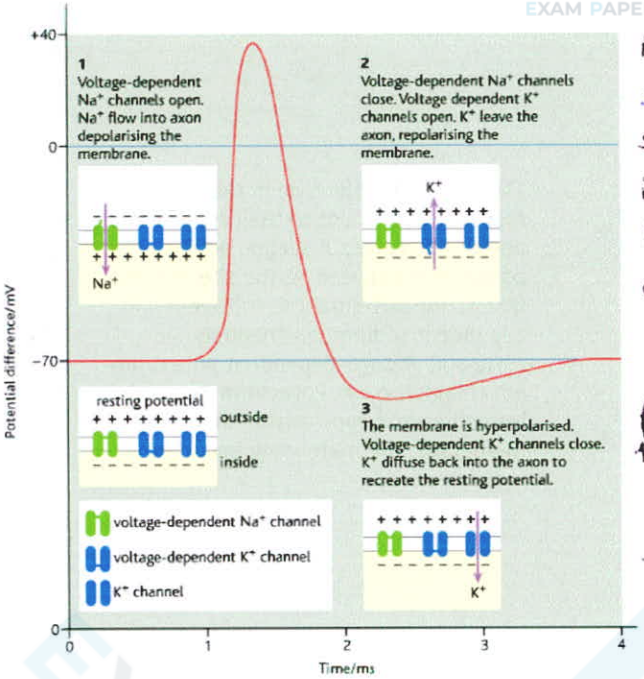
All neurones have a cell body (containing the nucleus and most of the cell's organelles within the cytoplasm), dendrites (that conduct impulses towards the cell body) and an axon (that conducts impulses away from the cell body). The main difference between the structures of sensory, motor and relay neurones is the relative position of the cell body.

Neurones are able to carry waves of electrical activity called action potentials (nerve impulses) over a long distance because the axons can be very long and the membranes are polarised (different charges on the inside and outside of the membrane).

Most vertebrate neurones have a fatty insulating layer of myelin sheath wrapped around the axon and/or dendron. This increases the speed of conduction of a nerve impulse through a process called saltatory conduction. Schwann cells wrap around the neurone, to nourish and protect it and produce the myelin sheath. However, there are small gaps left uncovered called nodes of Ranvier. Action potentials jump from one node of Ranvier to the next, increasing the speed of conduction.

The transmission of a nerve impulse

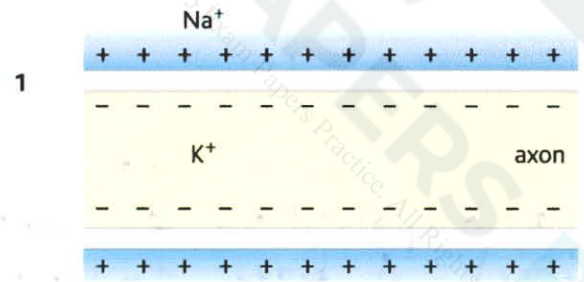
- In a resting neurone there are more sodium ions outside the cell membrane than inside, and more potassium ions inside than outside.
- The inside of the resting neurone has a negative charge in comparison to the outside due to the presence of chloride ions and negatively charged proteins. This distribution of ions creates a potential difference of about $-70\,mV$ called the resting potential and the membrane is said to be polarised. The sodium-potassium pump creates concentration gradients across the membrane (sodium moves out and potassium moves in to the axon).
- Potassium ion channels allow facilitated diffusion of potassium back out of the membrane down their concentration gradient, creating the uneven distribution of charge across the membrane.



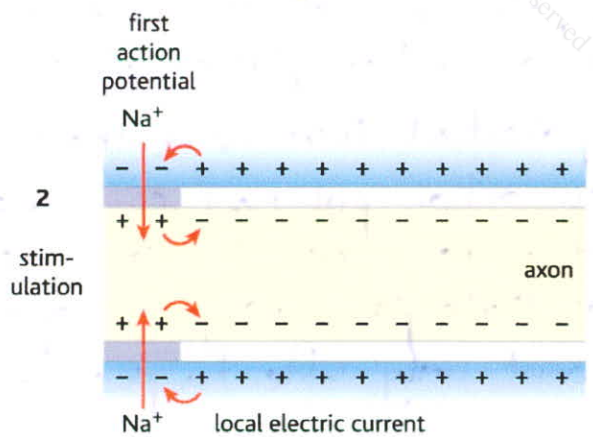
If a neurone cell membrane is stimulated, voltage-dependent sodium ion channels open and sodium ions diffuse in. This increases the positive charge inside the cell, so the charge across the membrane is reversed.

The membrane now carries a potential difference of about +40mV. This is the action potential and the membrane is said to be depolarised. As the charge reverses, the sodium ion channels shut and voltage-dependent potassium ion channels open so that more potassium ions leave the axon, repolarising the membrane.

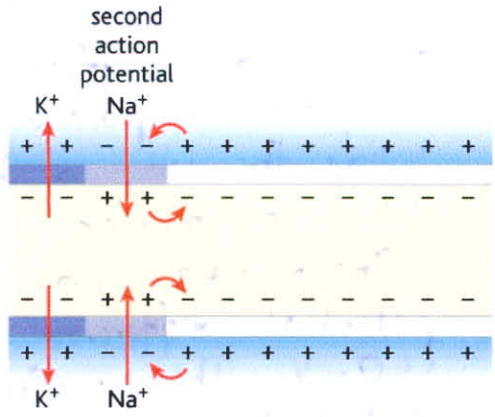
Propagation of a nerve impulse along an axon



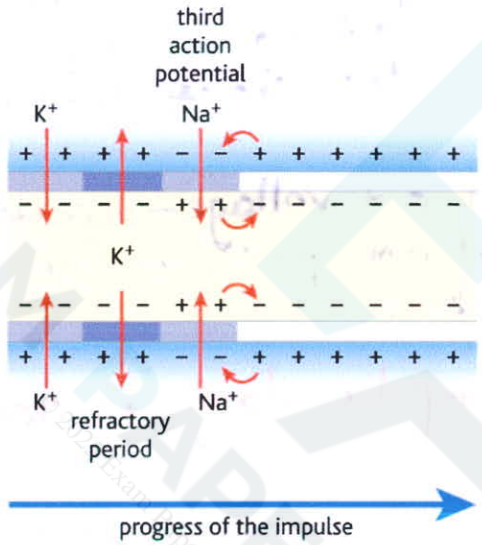
At resting potential there is positive charge on the outside of the membrane and negative charge on the inside, with high sodium ion concentration outside and high potasssium ion concentration inside.



When stimulated, voltage-dependent sodium ion channels open, and sodium ions flow into the axon, depolarising the membrane. Localised electric currents are generated in the membrane.



The potential difference in the membrane adjacent to the first action potential changes. A second action potential is initiated. At the site of the first action potential the voltage-dependent sodium ion channels close and voltage-dependent potassium ion channels open. Potassium ions leave the axon, repolarising the membrane. The membrane becomes hyperpolarised.

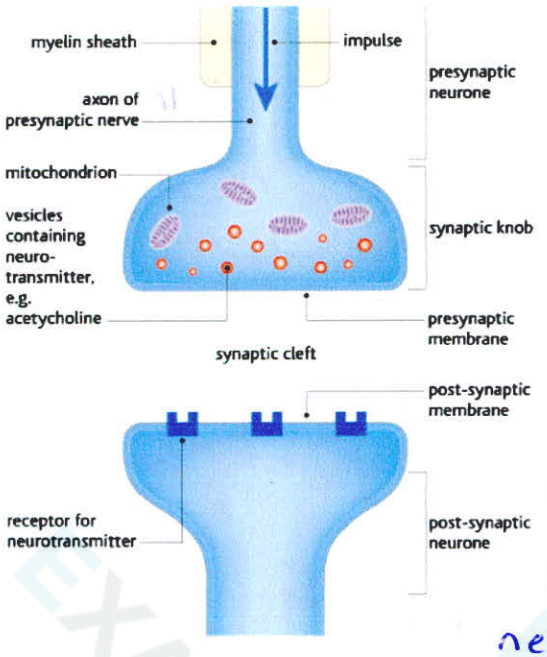


A third action potential is initiated by the second. In this way local electric currents cause the nerve impulse to move along the axon. At the site of the first action potential, potassium ions diffuse back into the axon, restoring the resting potential.

* Action potentials have an all-or-nothing nature (the values of the resting and action potentials are always the same for a specific neurone). A bigger stimulus increases the frequency of the action potentials. A threshold stimulus must be applied to produce an action potential.

* Straight after an action potential there is a short refractory period when a new action potential can't be generated because the sodium ion channels can't reopen. This ensures that action potentials pass along as separate signals and are unidirectional (only able to pass in one direction).

Synapses - junctions between neurones



A tiny gap, called a synapse, is the link point between neurones. Synapses consist of the swollen tip (synaptic knob) of the axon of one neurone (pre-synaptic neurone) and the dendrite or cell body of another neurone (post-synaptic neurone)

The practical effect of the synaptic cleft is that an action potential cannot cross it. Transmission occurs by specific chemicals known as neurotransmitters.

Acetylcholine (ACh) is a commonly occuring neurotransmitter substance; the neurones that release acetylcholine are known as cholinergic neurones.

Transmission at a synapse:

(1) The arrival of an action potential at the synaptic knob opens calcium ion channels in the pre-synaptic membrane. Calcium ions flow in from the synaptic cleft.

(2) The calcium ions cause vesicles of transmitter substance to fuse with the pre-synaptic membrane and they release a transmitter substance into the synaptic cleft. The transmitter substance diffuses across the synaptic cleft.

(3) The transmitter substance binds with a receptor protein on the post-synaptic membrane. In the post-synaptic membrane, there are specific receptor sites for each transmitter substance. Each of these receptors also acts as a channel in the membrane that allows a specific ion to pass. The attachement of a transmitter molecule to its receptor instantly opens the ion channel.

When a molecule of ACh attaches to its receptor site, a Na^+ channel opens. As the sodium ions rush into the cytoplasm of the post-synaptic neurone, depolarisation of the post-synaptic membrane occurs.

As more and more molecules of ACh bind, it becomes increasingly likely that depolarisation will reach the threshold level. When it does, an action potential is generated in the post-synaptic neurone.

(4) The transmitter substance on the receptors is quickly inactivated. For example, the enzyme cholinesterase hydrolyses ACh to choline and ethanoic acid. These molecules are inactive as transmitters. This reaction causes the ion chanel of the protein receptor to close, and so allows the resting potential in the post-synaptic membrane to be re-established.

(5) Meanwhile, the inactivated products of the transmitter re-enter the pre-synaptic neurone, are re-synthesised into transmitter substance and packaged for re-use.

* If two or more excitatory ~~synaps~~ impulses arrive at a synapse at the same time their effect will be combined and you are more likely to depolarise the postsynaptic membrane (spatial summation). If you have a strong stimulus along one neurone many action potentials will arrive one after the other (due to high frequency) and this will have the same effect. (temporal summation)

- Excitatory post synaptic potentials: Small currents making the post synaptic membrane less negative, which makes it more likely to trigger a new action potential.
- Inhibitory post-synaptic potentials: Small currents making the post synaptic membrane more negative, which makes it less likely to trigger a new action potential.

- How do receptors work?

Just like nerve fibres, receptors cells have a resting potential which is dependent on the maintenance of an interior that is negative in relation to the outside by membrane sodium pumps. When a receptor cell recieves a stimulus, sodium ions move rapidly across the cell membrane along ~~their~~ concentration and electrochemical gradients, and this generator current sets up a generator potential. Generator potentials do not oby the all-or-nothing law. If the generator potential produced is large enough to reach the threshold of the sensory neurone, an action potential will result in that neurone.

This process:

stimulus → local change in permeability → generator current → generator potential → action potential

is common in one form or another to most sensory receptors.

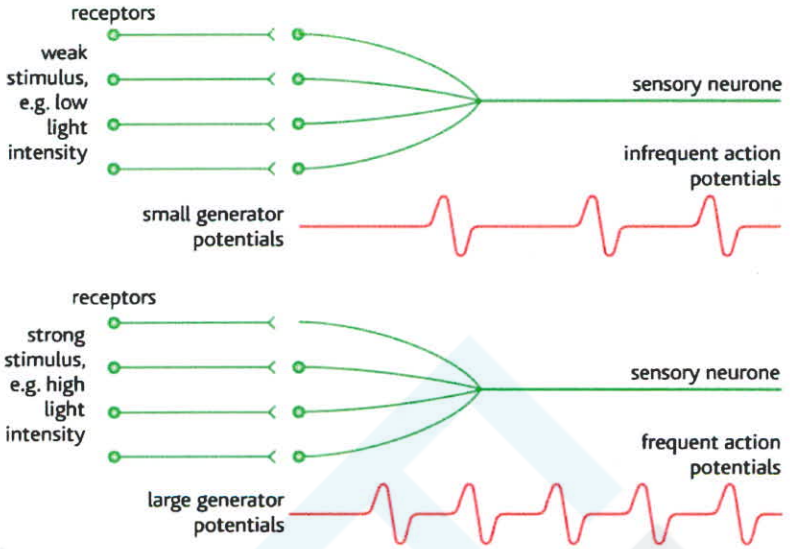
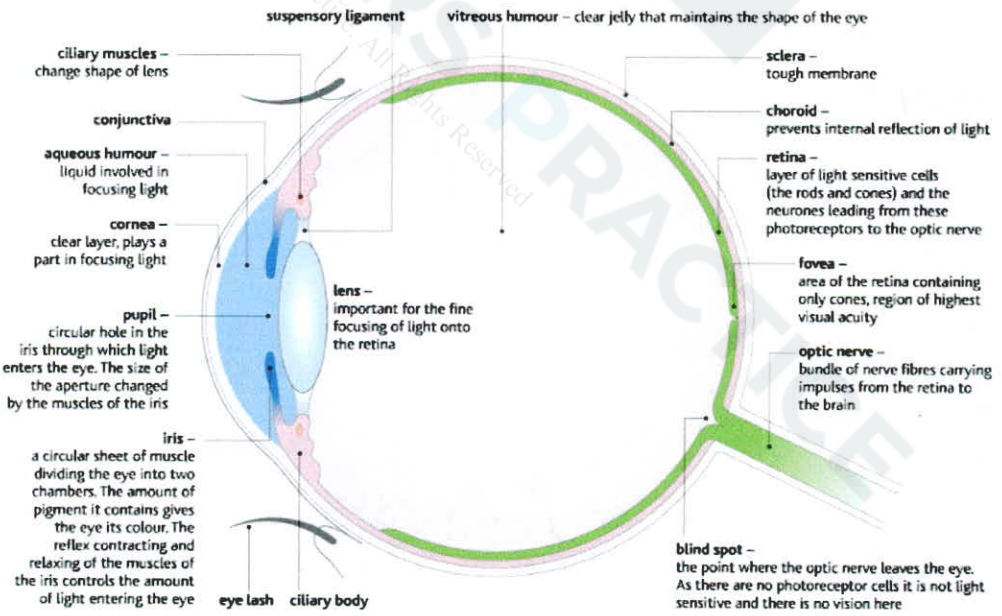


fig. 8.2.17 The interactions of receptors and sensory neurones to give high levels of sensitivity, as found in the eye and other sense organs.

Detection of light by humans

The eye is the sensory organ in humans and is structure is illustrated below.

The structure of the human eye is very closely related to its function, as can be seen in fig. 8.2.18.



Retina and human photoreceptors

The retina contains over a hundred million light-sensitive cells (photoreceptors), along with the neurones with which they synapse. There are two main types of photoreceptors in the retina, known as the **rods** and the **cones**.

Rods are far more numerous than cones and they are evenly distributed throughout the retina, while cones are concentrated at and around a region called the **fovea**. This is an area where vision is most accurate – here there is the greatest density of photoreceptors.

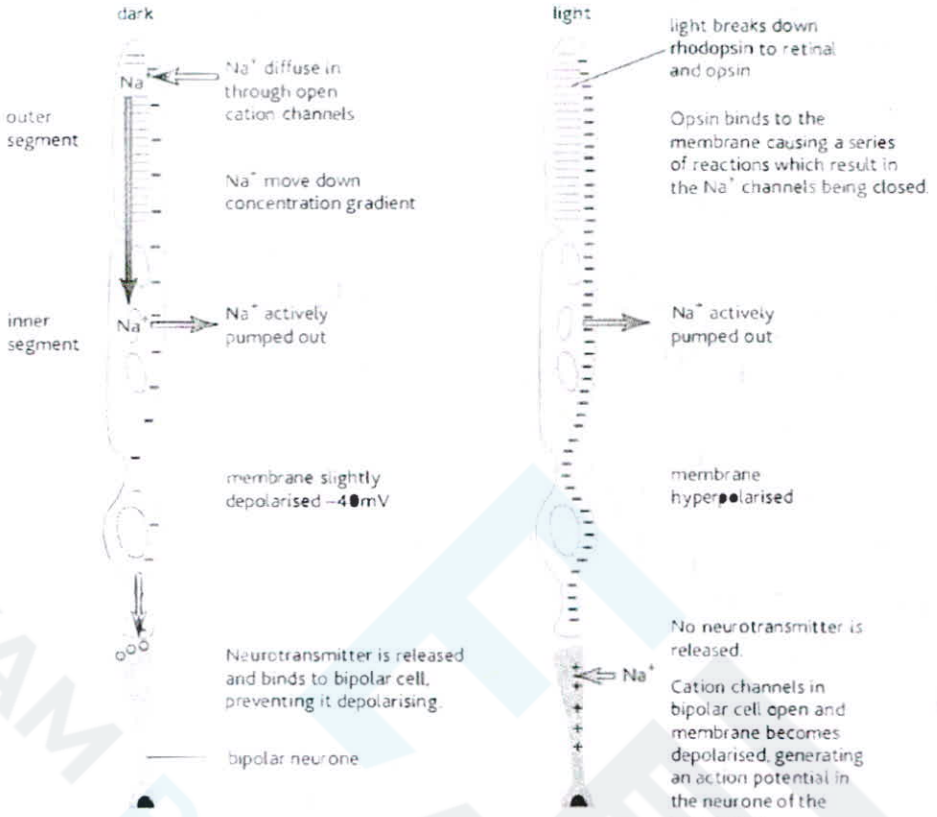
Rod cells are extremely sensitive to light, much more sensitive than the cones, but rod cells do not discriminate colours. Since they respond to lower light intensities than cones, they are principally used for dim light and night vision. The visual pigment molecule is **rhodopsin**.

$$\text{rhodopsin} \underset{\text{dark}}{\overset{\text{light (bleaching)}}{\rightleftharpoons}} \text{opsin (protein)} + \text{retinal (light-absorbing vitamin A derivative compound.)}$$

* Each cone cell synapses with only one optic nerve fibre whereas a single optic nerve fibre has synapses connecting it to several rod cells, a phenomenon known as **convergence**.

* The accuracy of the image is expressed as **visual acuity**. This is the ability of the eye to distinguish between two points close together. The visual acuity of the cones is much higher than that of rods. As points become increasingly closer and closer, there comes a time when they are so close that despite stimulating two different rods, these rods share the same optic nerve fibre so only one signal is sent to the brain, which interprets this as one point. Stimulation of two cones will always result in two separate impulses until the points are so close that they cover the same cone cell.

Rod cells in action



$E = \frac{hc}{\lambda}$

rhodopsin → retinal + opsin + generator potential

generator potential → if threshold reached → action potential → nerve impulse along optic nerve to brain

retinal + opsin → rhodopsin resynthesised in dark conditions → rhodopsin

ATP required for resynthesis of rhodopsin

Explanation

- The bleaching of the rhodopsin changes the permeability of the cell membrane of the rod to Na^+ ions.

→ The membranes of most neurones are impermeable to Na^+ ions but rod cells are normally very permeable to them.

- Na^+ ions move into the rod cell through Na^+ ion channels, and the sodium pump moves them out again.
- When rhodopsin is bleached with light, sodium ion channels are closed. The rod cell becomes much less permeable to Na^+ ions.
- The sodium pump continues to work at the same rate pumping sodium ions out of the cell, so the interior becomes more negative than usual. This **hyperpolarisation** is what is known as the **generator potential** in the rod.

→ The size of the generator potential depends on the amount of rhodopsin bleaching and so the amount of light hitting the rod.

- If the generator potential is large enough to reach the threshold, or if several rods are stimulated at once, neurotransmitter substances are released into the synapse with the bipolar cell.
- An action potential is then set up in the bipolar cell which passes across the synapse to cause an action potential in the sensory neurone.

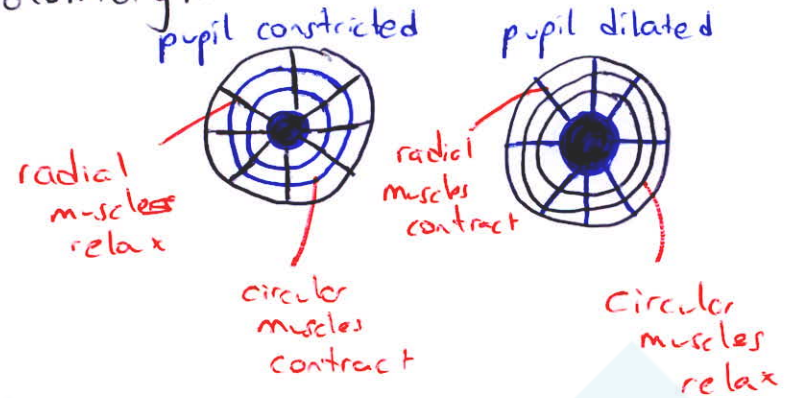
* Once the visual pigment has been bleached, the rod cannot be stimulated again until the rhodopsin is resynthesised. It takes ATP produced by the many mitochondria in the inner segment to convert the trans-retinol back to cis-retinal and rejoin it to the opsin to form rhodopsin again.
* In normal daylight the rods are almost entirely bleached and can no longer respond to dim light. Rhodopsin is formed back again in the dark.

Cones in action

The cones work in a very similar way to rods, except that their visual pigment is known as **iodopsin**. Iodopsin needs to be hit with more light energy than rhodopsin in order to break down, and so it is not sensitive to low light intensities, but the cones provide colour vision.

The pupil reflex

The iris contains pairs of antagonistic muscles (radial and circular muscles) that control the size of the iris under the influence of the autonomic nervous system (involuntary).

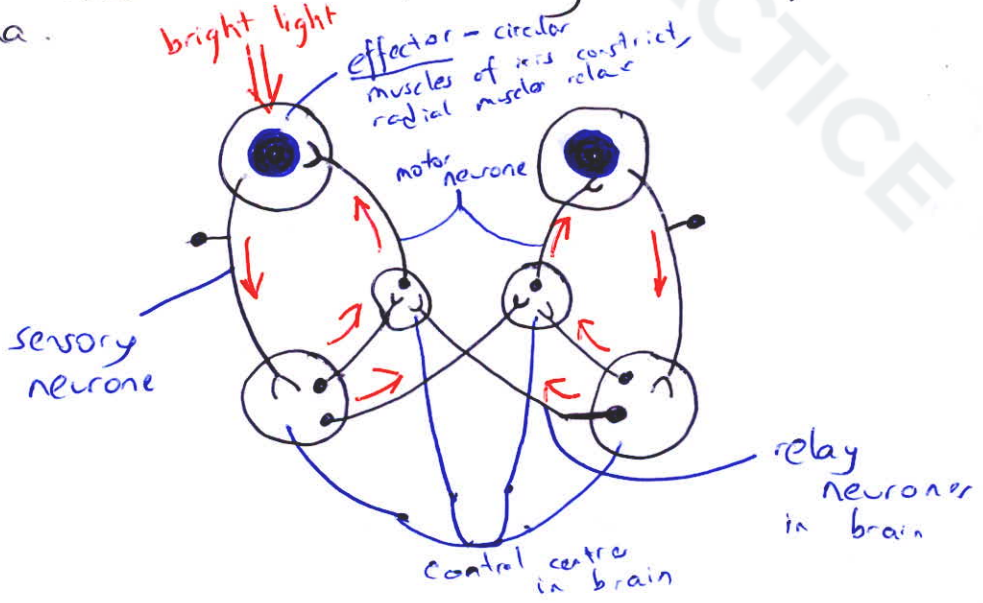


- High light intensity

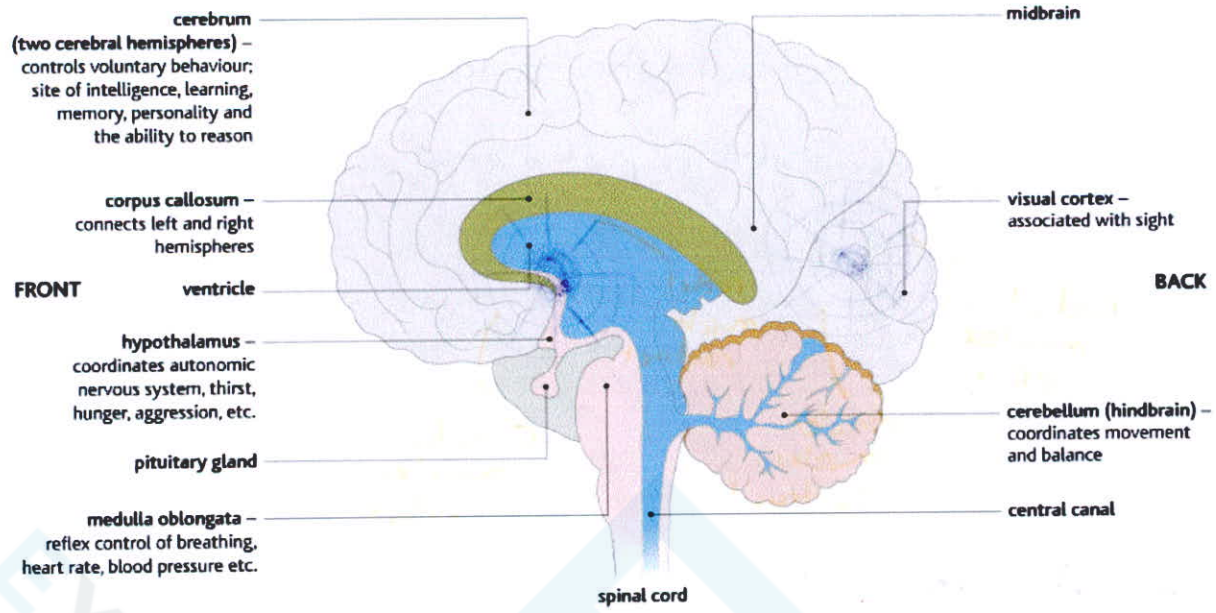
In high light intensities photoreceptors such as rods in the retina cause nerve impulses to pass along the optic nerve to a group of cells in the brain. These then send impulses along parasympathetic **motor neurones** to the circular muscles of the iris. The muscles contract, reducing the diameter of the pupil so that less light can enter the eye, thus preventing damage to the retina.

- Low light intensity

In low light conditions fewer impulses reach the coordinating centre in the brain - impulses are sent down sympathetic motor neurones to the radial muscles of the iris instead. This causes the radial muscles to contract and the pupil becomes dilated, allowing more light to reach the retina.



The human brain



Major areas of the brain

Frontal lobe: It is concerned with the higher brain functions such as decision making, reasoning and consciousness of emotions. It is also concerned with forming associations (by combining information from the rest of the cortex) and with ideas. It includes the primary motor cortex which has neurones that connect directly to the spinal cord and brain stem and from there to the muscles. It sends information to the body via the motor neurones to carry out movements. The motor cortex also stores information about how to carry out different movements.

Parietal lobe: It is concerned with orientation, movement, sensation, calculation, some types of recognition and memory.

Occipital lobe: It is also known as visual cortex – concerned with processing information from the eyes, including vision, colour, shape recognition and perspective.

Temporal lobe: It is concerned with processing auditory information that is hearing, sound recognition and speech. It is also involved in memory.

The cerebrum

The cerebrum is the largest part of the brain. It is divided into two cerebral hemispheres connected by a band of white matter called the corpus callosum. The cerebrum is associated with advanced mental activity like language, memory, calculation, processing information from the eyes and ears, emotion and controlling all the voluntary activities of the body.

* White matter is so called because it mainly consists of lots of myelinated axons. Grey matter is where the synapses occur and therefore where all the processing takes place and your memories are stored.

Imaging techniques for the brain

Several imaging techniques are useful for medical diagnosis and investigating brain structure and function. For example, the effects of drugs and diseases such as Parkinson's on the activity of the human brain can now be seen using imaging techniques such as fMRI.

- Magnetic resonance imaging (MRI): scans use a magnetic field and radio waves to make images of soft tissues like the brain. MRI scans can be used in the diagnosis of tumors, strokes, brain injuries and infections. They can also be used to track degenerative diseases like Alzheimer's by comparing scans over a period of time.
- Functional magnetic resonance imaging (fMRI): is a modified MRI technique that can allow you to see the brain in action during live tasks, because it detects activity in the brain by following the uptake of oxygen in active brain areas.
- Computed tomography (CT): scans use thousands of narrow beam X-rays rotated around the patient. Like MRI they only capture one moment in time and so only look at structures and damage rather than functions. The resolution is worse than MRI so small structures in the brain can't be distinguished; they also use potentially harmful X-rays.

Brain development

We are born with a range of innate behaviours such as crying, grasping and sucking. However, the brain still needs much growth and development after birth through the formation of synapses and the growth of axons.

Evidence for critical windows

Critical windows for development are those periods of time where it is thought that the nervous system needs specific stimuli in order to develop properly.

Evidence for critical windows for development has come from medical observations and from animal models. Hubbel and Wiesel used kittens and monkeys as models to investigate the critical window in visual development because of the similarity of their visual systems to that of humans.

→ The animals were deprived of the stimulus of light into one eye at different stages of development and for different lengths of time. They found that kittens deprived of light in one eye at 4 weeks after birth were effectively permanently blind in that eye. Monocular deprivation before 3 weeks and after 3 months had no effect. It was thought that during the critical period (about 4 weeks after birth) connections to cells in the visual cortex from the light-deprived eye had been lost. This meant that the eye that remained open during development became the only route for visual stimuli to reach the visual cortex.

Eye deprived of light during critical window	Eye that remains open during critical window
- Axons do not pass nerve impulses to cells in the visual cortex.	- Axons pass nerve impulses to cells in the visual cortex.
- Inactive synapses are eliminated.	- Synapses used by active axons are strengthened.
- Eye has no working connection to the visual cortex and is effectively blind, even though the cells of the retina and optic nerve work normally when exposed to light.	- Synapses only present for axons coming from the light-stimulated eye. So the visual cortex can only respond to this eye.

Issues about the use of animals for research

The use of animals as models for understanding how humans develop, or how new drugs may affect us, is a very controversial area. There are those who hold an absolutist view of animal rights and think we should never keep animals or use them in medical research. From the point of view of medical research, a much more widespread position is the relativist view that humans should treat animals well and minimise harm and suffering so far as is possible. Here the emphasis is on animal welfare, respecting their rights to such things as food, water and veterinary treatment and the ability to express normal behaviours. This is pretty much the position in European law. This all assumes that animals can suffer and experience pleasure.

A utilitarian ethical framework allows certain animals to be used in medical experiments provided that the overall expected benefits are greater than the overall expected harms based on the belief that the right course of action is the one that maximises the amount of overall happiness or pleasure in the world.

The role of nature and nurture in brain development

- Nature: Many of our characteristics develop solely under the influence of our genes with little influence from our environment or learning.
- Nurture: Many characteristics are learnt or are heavily influenced by the environment.

Most of our characteristics are actually determined by nature and nurture via nurture. We are the result of a mixture of genetic and environmental factors. Human behaviours, attitudes and skills may have an underlying genetic bases but are modified by experience or the environment in a way which is very complex. For example, the chance of developing some diseases, such as some cancers, has a genetic basis, where a gene or several genes interact to confer susceptibility to the disease with environmental factors contributing to the risk of developing the disease.

Visual development is an example of how the effects of nature and nurture can combine in development. The genes control the development of the responsive cells in the visual cortex (nature) but a stimulus from the environment is needed during the critical window for the correct connections to be made (nurture).

Evidence

- **The abilities of newborn babies:** Newborn babies have some innate capacities. These suggest that genes help to form the brain and some behaviours before the baby is born.
- **Studies of individuals with damaged brain areas:** Some patients who have suffered from brain damage show the ability to recover some of their brain function. This demonstrates that some neurones have the ability to change.
- **Animal experiments:** Hubel and Wiesel's experiments on critical windows for sight, suggest that external stimulation is important in brain development.
- **Twin studies:** Identical twins share all the same genes. Fraternal twins share the same number as any other sibling would. Twin studies can help to estimate the relative contribution of genes and the environment. Any differences between identical twins must be due to the effects of the environment.

  Identical twins raised apart in comparison to those raised together are particularly useful for study. For example if there is a greater difference between those twins raised apart than twins raised together it suggests some environmental influence. However, twins raised apart may not have completely different environments and twins raised together may develop different personalities due to a desire to be different. In general if genes have a strong influence on the development of a characteristic, then the closer the genetic relationship, the stronger the correlation will be between individuals for that trait.
- **Cross-cultural studies:** Investigations into the visual perception of groups from different cultural backgrounds support the idea that visual cues for depth perception are at least partially learnt.

Learning and habituation

Learning is a process that results in a change in behaviour (or knowledge) as a result of experience. For learning to be effective you must remember what you have learnt. Memories (conscious and sub-conscious) are formed by changing or making new synapses in the nervous system.

There are two main types of behaviour:

- Species-characteristic (innate) behaviour
- Individual-characteristic (learned) behaviour

Habituation

Habituation is a very simple example of learning that involves a loss of response to a repeated stimulus which fails to provide any form of reinforcement (reward or punishment). It allows animals to ignore unimportant stimuli so that they can concentrate on more rewarding or threatening stimuli.

The mechanism of habituation can be investigated practically by tapping on giant African snails repeatedly and measuring the time taken for the snail to re-emerge. It will be observed that the time will get less after each tap and after a certain number of taps, the snail will no longer withdraw.

- Mechanism of habituation

- With repeated stimulation Ca^{2+} channels in the presynaptic membrane become less responsive.
- With fewer Ca^{2+} channels open, fewer calcium ions cross into the pre-synaptic knob.
- Fewer vesicles move to the presynaptic membrane and as a result, less neurotransmitter is released.
- With less neurotransmitter available to bind to the post-synaptic membrane, the post-synaptic excitatory potential is not high enough to trigger an action potential in the motor neurone.

Effects of imbalances in brain chemicals

A - Dopamine and Parkinson's disease

Parkinson's disease is associated with the death of a group of dopamine-secreting neurones in the brain (an area of the midbrain known as the substantia nigra). This results in the reduction of dopamine levels in the brain. Dopamine is a neurotransmitter which is active in neurones in the frontal cortex, brain stem and spinal cord. It is associated with the control of movement and emotional responses.

The symptoms of Parkinson's are:

- muscle tremors (shakes)
- stiffness of muscles and slowness of movement
- poor balance and walking problems
- difficulties with speech and breathing
- depression

A variety of treatments are available for Parkinson's disease, most of which aim to increase the concentration of dopamine in the brain.

- Levodopa (L-dopa): dopamine cannot cross the blood-brain barrier, so it cannot be used to treat Parkinson's. However L-dopa which is used to make dopamine can cross the barrier. Supplying the brain with L-dopa allows the remaining cells to make as much dopamine as possible. This can greatly relieve stiffness and slowness of movements.
- Dopamine agonists: these chemicals bind to dopamine receptors in brain synapses and mimic the effect of dopamine. They are often used at the beginning of the disease when they are most effective.
- MAOB inhibitors: Monoamine oxidase B is a similar enzyme to MAOA and it breaks down dopamine in the brain synapses. MAOB inhibitors inhibit the enzyme, reducing the destruction of what little dopamine gets made.
- Gene therapy: adding genes to prevent the dopamine-producing cells from dying and adding genes to enhance the levels of dopamine production in the remaining cells.
- Stem cell therapy: use of embryonic stem cells to replace the failing dopamine-producing cells.

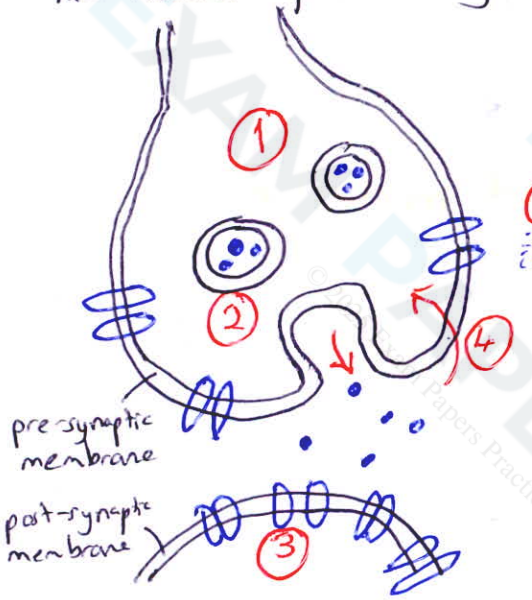
B- Serotonin and depression

Serotonin is a neurotransmitter linked to feelings of reward and pleasure. A lack of serotonin is linked to clinical depression (prolonged feelings of sadness, anxiety, hopelessness, loss of interest, restlessness, insomnia, etc.).

Treatments for depression often involve drugs that can help increase the concentration of serotonin in the synapses. For example, Prozac is a selective serotonin reuptake inhibitor (SSRI) that blocks the process which removes serotonin from the synapse.

The effect of drugs on synapses

Many drugs affect the nervous system by interfering with the normal functioning of a synapse



1. Some drugs affect the synthesis or storage of the neurotransmitter. For example, L-dopa used in the treatment of Parkinson's disease is converted into dopamine, increasing the concentration of dopamine to reduce the symptoms of the disease.
2. Some drugs may affect the release of the neurotransmitter from the presynaptic membrane.
3. Some drugs may affect the interaction between the neurotransmitter and the receptors on the postsynaptic membrane.

a) Some may be stimulatory by binding to the receptors and opening the sodium channels (Na^+ ion channels) - for example dopamine agonists (which mimic dopamine because they have a similar shape and are used in the treatment of Parkinson's disease) bind to dopamine receptors and trigger action potentials.

b) Some may be inhibitory, blocking the receptors on the post-synaptic membranes and preventing the neurotransmitters binding.

(4) Some drugs prevent the reuptake of the neurotransmitter back into the presynaptic membrane. For example ecstasy (MDMA) works by preventing the reuptake of serotonin. The effect is the maintenance of a high concentration of serotonin in the synapse which brings about the mood changes in the users of the drug. One of the many possible side effects of ecstasy use is depression as a result of the loss of serotonin from the neurones because of the lack of reuptake.

Prozac is a common example of a selective serotonin reuptake inhibitor (SSRI) that blocks the reuptake of serotonin in the treatment of depression.

(5) Some drugs may inhibit the enzymes involved in breaking down the neurotransmitter in the synaptic cleft, resulting in the maintenance of a high concentration of the neurotransmitter in the synapse and therefore repeated action potentials (or inhibition) of the postsynaptic neurone.

The Human Genome Project and medicine

The Human Genome Project was a multinational project that determined the base sequence of the human genome. A genome is all of the DNA (or genes) of an organism.

The project also had specific aims about the storage and analysis of all the data involved, with the ideal that all ~~the data involved, with the ideal~~ of the information about the genome should be freely available to scientists everywhere.

- Pharmacogenomics

The ability to find and manufacture a medicine which has the right effect in the right place is of vital importance in the fight against disease.

Traditionally, most medicines are developed from existing chemicals (often extracted from plants), but the information coming from the human genome project could help develop drugs that are highly specific so that they can be effective in lower doses with fewer side effects. Pharmacogenomics links pharmaceutical expertise (drug development and manufacture) with the knowledge of the human genome.

Many new genes have been identified through the Human Genome Project, including some of those genes responsible for inherited diseases. In addition new drug targets have been identified.

* Information about a patient's genome may help doctors to prescribe the correct drug at the correct dose. The Human Genome Project may also allow some diseases to be prevented. If you understand what genes you carry you may understand what disease you are likely to be at risk from.

The Human Genome Project also helps to provide information about evolution and increases our knowledge of physiology and cell biology.

Social, moral and ethical aspects of pharmacogenics

+ Ethical aspects

- Discrimination
  → Who is entitled to know the information about your genome if it is sequenced? Insurance companies might have access to a person's DNA.
- Expensive medical treatments might be restricted and only be suitable for a few people
- Confidentiality is an issue.
- Who decides whether a person is tested?

+ Social aspects

- Huge financial implications in training doctors and pharmacists to recognise all the possible drug permutations
- Lives of patients

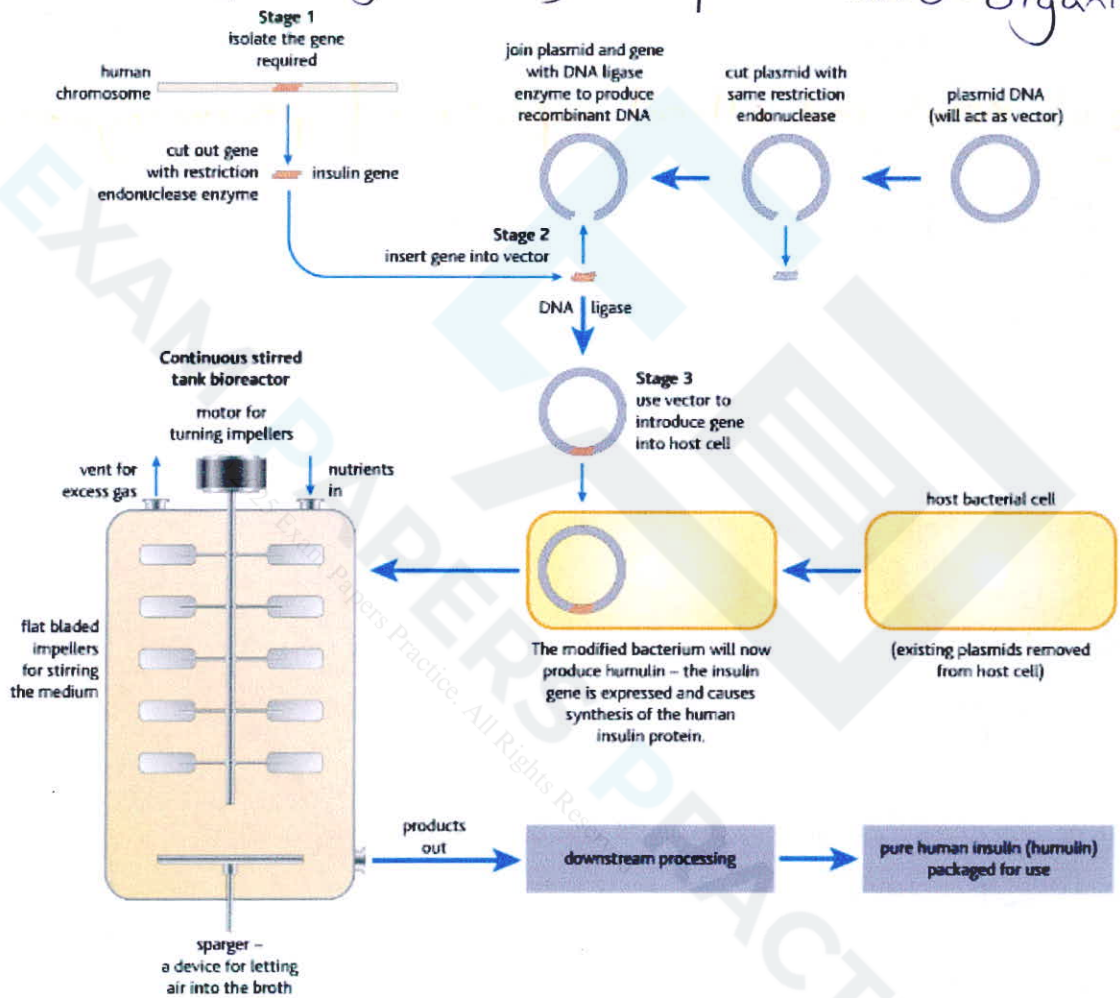
+ Moral aspects

- It may well be possible to tell people a particular drug won't work for their particular genetic makeup before alternatives are available.
- Can we abandon a small number of people who cannot be treated with a common drug?

Drugs from genetically modified organisms

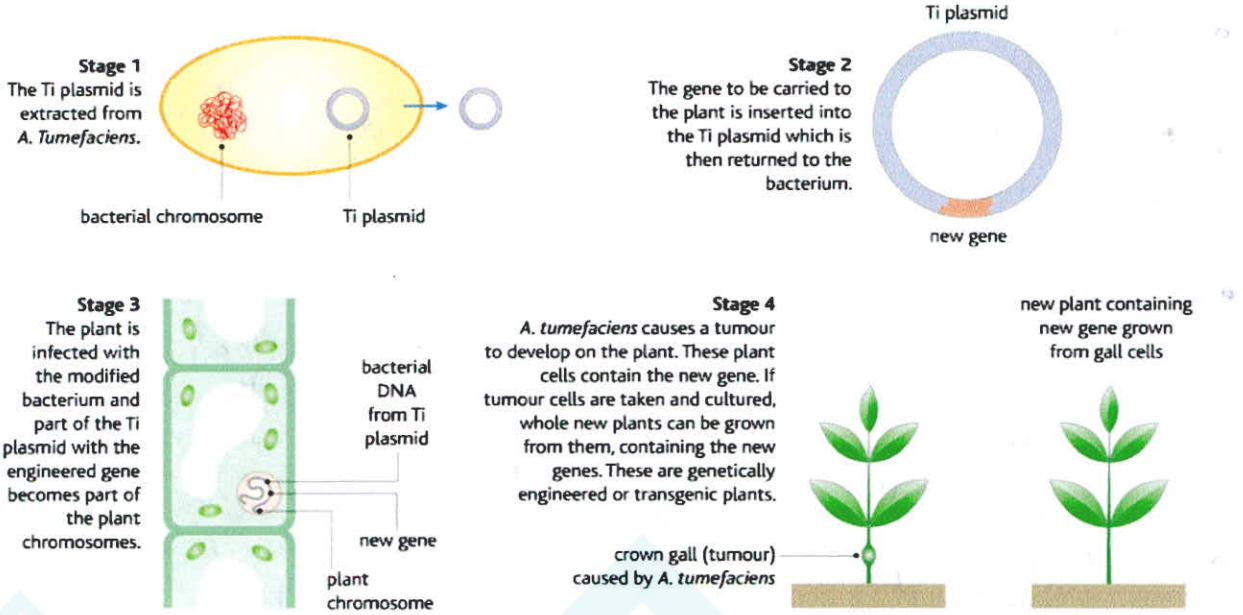
- Microorganisms

Microorganisms such as bacteria are the most common target for genetic modification as they are relatively easy targets for gene transfer and can be grown rapidly in large quantities in fermenters. The drugs produced can be extracted and purified using downstream processing. Insulin, to treat type II diabetes, is an example of a drug produced from genetically modified micro-organisms.



- Plants

GM plants may be useful for edible drugs such as vaccines that can be stored and transported easily in plant products such as bananas and potatoes. Useful genes can be transferred into crop plants using a vector, such as Agrobacterium tumefaciens, gene guns (pellets coated with DNA) or a virus. Restriction enzymes are used to cut DNA at specific sequences and DNA ligase is an enzyme that can be used to stick pieces of DNA together. These make it possible to insert specific DNA into the GM organism. Large numbers of identical GM plants can easily be produced.



- Animals

It is very difficult to transfer new DNA into eukaryotic cells but there have been some notable successes. The production of proteins using transgenic animals involves the introduction of a copy of a human gene which codes for the desired protein into the genetic material of an egg of a different animal species.

There are a number of techniques for getting new DNA into mammalian cells, which are being tried with varying degrees of success. Whatever technique is used it must get the new DNA through the cell membrane and into the cytoplasm – or nucleus – where it can be accepted and incorporated into the host cell DNA. The methods include the following:

- Microinjection where DNA is injected into a cell through a very fine micropipette.
- Microprojectiles – DNA is shot into the cell at high speed carried on minute gold or tungsten ~~particles~~ pellets.
- A harmless virus can be engineered to carry a desirable gene and then used to infect the animal's cells, carrying the DNA with it.
- Liposome wrapping – the gene to be inserted is wrapped in liposomes (spheres formed from a lipid bilayer). These then fuse with the cell membrane and can pass through it to deliver the DNA into the cytoplasm.

Risks of using genetically modified organisms (GMOs)

- genetic pollution (transfer of the genes to natural, wild species) through cross-pollination.
- antibiotic resistance genes are used to identify GM bacteria which could lead to antibiotic resistance developing in other microbes.
- GM crops could become super-weeds that out-compete other plants and may be resistant to herbicides. They could damage natural food chains, resulting in damage to the environment because they would encourage farmers to use more selective herbicides to kill everything but the crop.
- GM crops may not produce fertile seeds. This prevents farmers collecting seed and replanting so they need to return to the biotechnology company to buy new seeds for each planting. This could make them too expensive for some farmers.