14 Homeostasis

Cells function most efficiently if they are kept in near constant conditions. Cells in multicellular animals are surrounded by tissue fluid. The composition, pH and temperature of tissue fluid are kept constant by exchanges with the blood as discussed in the topic on Transport in mammals. In mammals, core temperature, blood glucose concentration and blood water potential are maintained within narrow limits to ensure the efficient operation of cells. Prior knowledge for this topic includes an understanding that waste products are excreted from the body – a role that is fulfilled by the kidneys – and an outline of the structure and function of the nervous and endocrine systems. In plants, guard cells respond to fluctuations in environmental conditions and open and close stomata as appropriate for photosynthesis and conserving water.

14.1 Homeostasis in mammals

Homeostasis in mammals requires complex systems to maintain internal conditions near constant.

By the end of this section you should be able to:

a) discuss the importance of homeostasis in mammals and explain the principles of homeostasis in terms of internal and external stimuli, receptors, central control, co-ordination systems, effectors (muscles and glands)
b) define the term negative feedback and explain how it is involved in homeostatic mechanisms
c) outline the roles of the nervous system and endocrine system in co-ordinating homeostatic mechanisms, including thermoregulation, osmoregulation and the control of blood glucose concentration
h) explain how the blood glucose concentration is regulated by negative feedback control mechanisms, with reference to insulin and glucagon
i) outline the role of cyclic AMP as a second messenger with reference to the stimulation of liver cells by adrenaline and glucagon
j) describe the three main stages of cell signalling in the control of blood glucose by adrenaline as follows:
   - hormone-receptor interaction at the cell surface
   - formation of cyclic AMP which binds to kinase proteins
   - an enzyme cascade involving activation of enzymes by phosphorylation to amplify the signal
k) explain the principles of the operation of dip sticks containing glucose oxidase and peroxidase enzymes, and biosensors that can be used for quantitative measurements of glucose in blood and urine

Maintaining a constant internal environment – homeostasis

Living things face changing and sometimes hostile environments. Some external conditions change slowly, others dramatically. For example, temperature changes quickly on land exposed to direct sunlight, but the temperature of water exposed to sunlight changes very slowly.

How do organisms respond to environmental changes?

Some animals are able to maintain their internal environment, keeping it more or less constant, allowing them to continue normal activities, at least over quite a wide range of external conditions. These are the '**regulators**'. For example, mammals and birds maintain a high and almost constant body temperature. Their bodies are kept at or about the optimum temperature for the majority of the enzymes that drive their metabolism. Their muscles contract efficiently and the nervous system co-ordinates responses precisely, even when external conditions are unfavourable.

Regulators are often able to avoid danger and they may also benefit from the vulnerability of prey organisms which happen to be '**non-regulators**'. So regulators may have greater freedom in choosing where to live. They can exploit more habitats with differing conditions than 'non-regulators' can, too. But whether an organism is a 'regulator' or not, some of control of the internal environment is essential.

Homeostasis is the name we give to the ability to maintain a constant internal environment. Homeostasis means 'staying the same'. Mammals are excellent examples of animals that keep their internal conditions remarkably constant. Their internal environment is the blood circulating in the body and the fluid circulating among cells (tissue fluid) that forms from the blood plasma, delivering nutrients and removing waste products whilst bathing the cells. Mammals successfully regulate and maintain the pH, the concentrations of oxygen, carbon dioxide and glucose, the temperature and the water content of their blood. All these are maintained at constant levels or within very narrow limits.

How is homeostasis brought about and maintained?

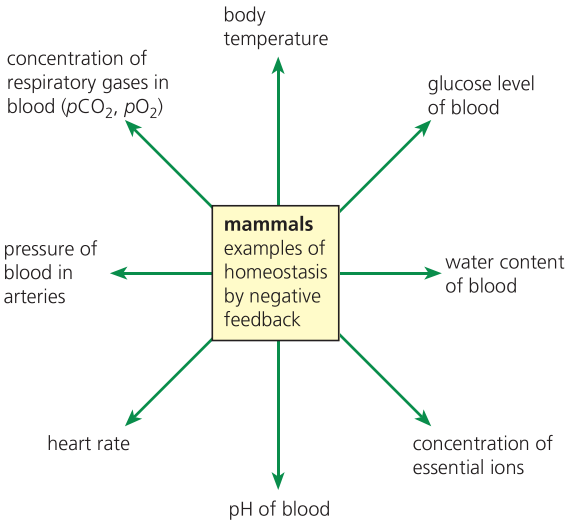
polar bear on ice

otter in fresh water

whale in the sea

camels in the desert

bat in the air



Mammals are a comparitively recent group in terms of their evolutionary history, yet they have successfully settled in significant numbers in virtually every type of habitat on Earth. This success is directly linked to their ability to control their internal environment by homeostasis.

Figure 14.1 Homeostasis in mammals

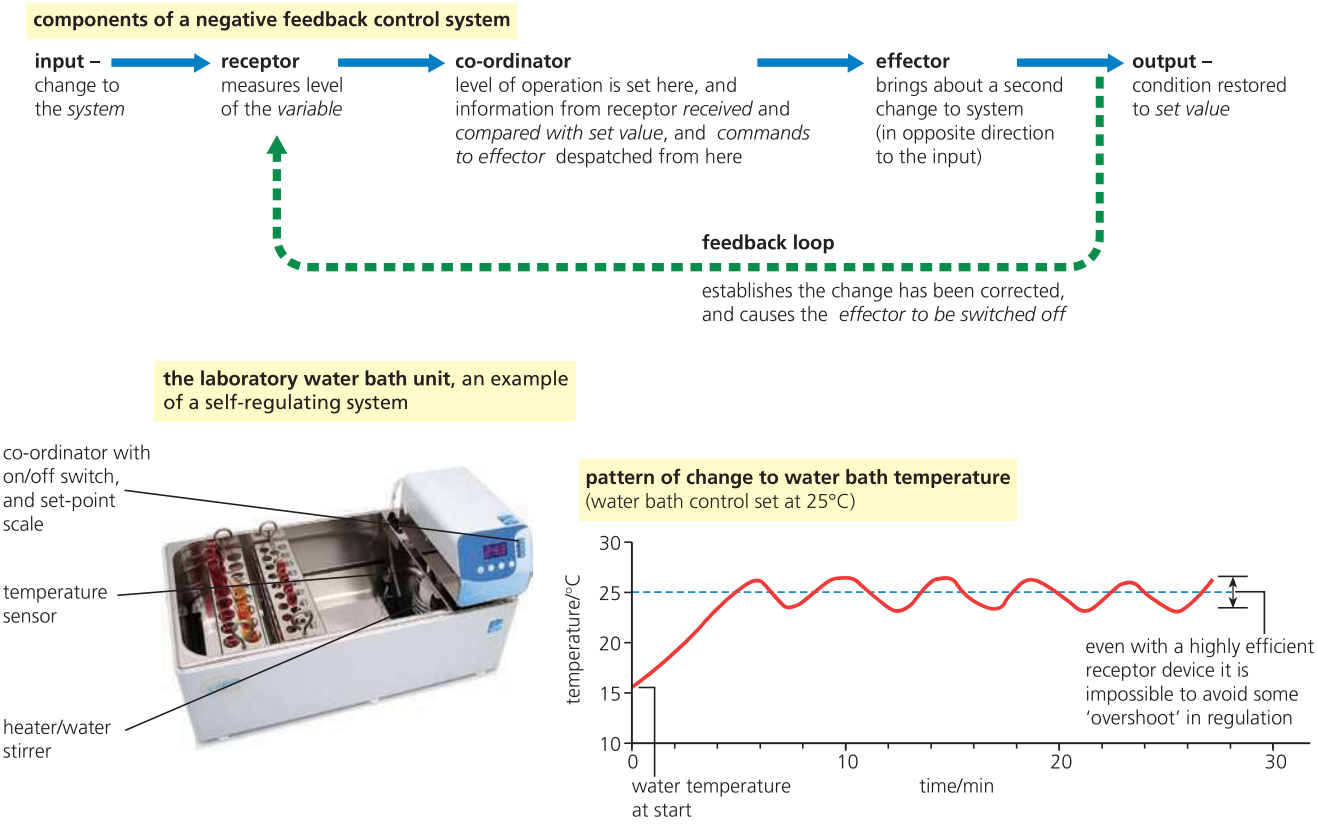


Figure 14.2 Negative feedback: the mechanism

Negative feedback – the mechanism of homeostasis

Negative feedback is a type of control in which the conditions being regulated are brought back to a set value as soon as it is detected that they have deviated from it. We see this type of mechanism at work in a laboratory water bath. Analysis of this familiar example will show us the components of a negative feedback system.

A negative feedback system requires a **receptor** device that measures the value of the variable (in this case, the water temperature of the water bath) and transmits this information to a **co-ordinator** (in this case, the control unit). The co-ordinator compares data from the receptor with a **pre-set value** (the desired water temperature of the water bath). When the value is below the required value the co-ordinator switches on an **effector** device (a water heater in the water bath) so that the temperature starts to increase. Once the water reaches the required temperature, data from the receptor to this effect is received in the co-ordinator, which then switches off the response (the water heater). How precisely the variable is maintained depends on the sensitivity of the receptor, but negative feedback control typically involves some degree of 'overshoot'.

In mammals, regulation of body temperature, blood sugar level and the concentration of water and ions in blood and tissue fluid (osmoregulation) are all regulated by negative feedback. The receptors are specialised cells either in the brain or in other organs, such as the pancreas. The effectors are organs such as the skin, liver and kidneys. Information passes between them either by impulses in neurones within nerves of the **nervous system** or by **hormones** released into the blood by **endocrine organs**. The outcome is an incredibly precisely regulated internal environment. We shall return to examine these two systems in turn, shortly.

Question

1 Homeostasis is illustrated in the way our bodies regulate carbon dioxide level. (Remind yourself of the control of ventilation of the lungs by looking at Figure 9.8, page 177).
   a Why is it essential that carbon dioxide in the blood does not exceed a certain level?
   b In this example of homeostasis, identify where the receptor, co-ordinator and effectors occur in our bodies.

Homeostasis in action – control of body temperature

Heat may be transferred between an animal and the environment by **convection**, **radiation** and **conduction**, and the body loses heat in **evaporation** (Figure 14.3).

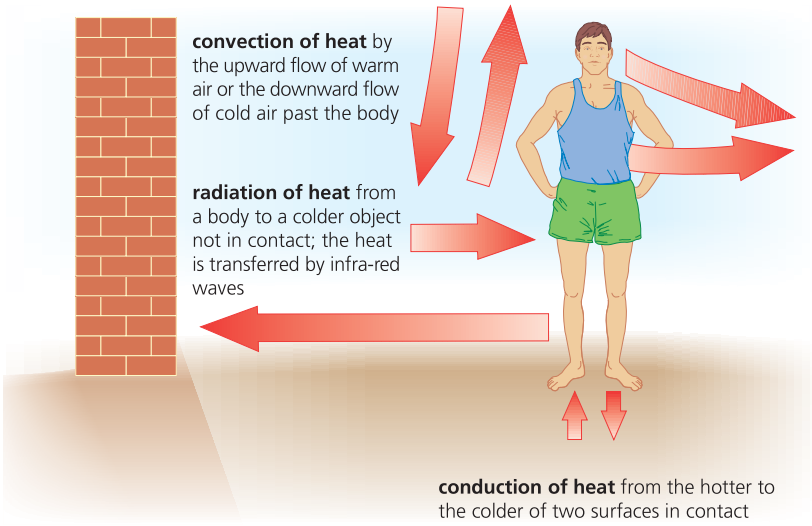


Figure 14.3 How heat is transferred between organism and environment

The regulation of body temperature, known as **thermoregulation**, involves controlling the movement of heat across the body surface. Mammals maintain a high and relatively constant body temperature, using the heat energy generated by metabolism within their bodies (or by generating additional heat in the muscles when cold) and carefully controlling the loss of heat through the skin. An animal with this form of thermoregulation is called an **endotherm**, meaning 'inside heat'. Humans hold their inner body temperature (core temperature) just below 37 °C. In fact, human inner body temperature only varies between about 35.5 and 37.0 °C within a 24 hour period, when we are in good health.

Heat production in the human body

The major sources of heat are the biochemical reactions of metabolism that generate heat as a waste product. Heat is then distributed by the blood circulation. The organs of the body vary greatly in the amount of heat they yield (see Figure 12.13). When at rest, the bulk of our body heat (over 70 per cent) comes from other abdominal organs, mainly from the heart and kidneys, but also from the lungs and brain (which, like a computer central processing unit, needs to be kept cool). Of course, in times of intense physical activity, the skeletal muscles generate a great deal of heat as a waste product of respiration and contraction.

If the body experiences a sudden loss of heat, then heat production in increased. Heat output from the body muscles is raised by non-co-ordinated contraction of skeletal muscles, known as '**shivering**'. This raises muscle heat production about five times above basal rate.

The roles of the skin in thermoregulation

Heat exchange occurs largely at the surface of the body. Here in the skin, the following structures and mechanisms are combined in the regulation of heat loss (as detailed in Figure 14.4):

- at capillary networks, by the arteriole supplying them being dilated (vasodilation) when the body needs to loose heat, but constricted (vasoconstriction) when the body needs to retain heat
- by the hair erector muscles, which contract when heat must not be lost but relax when heat loss must be increased
- by the sweat glands, which produce sweat when the body needs to lose heat, but do not when the body needs to retain heat.

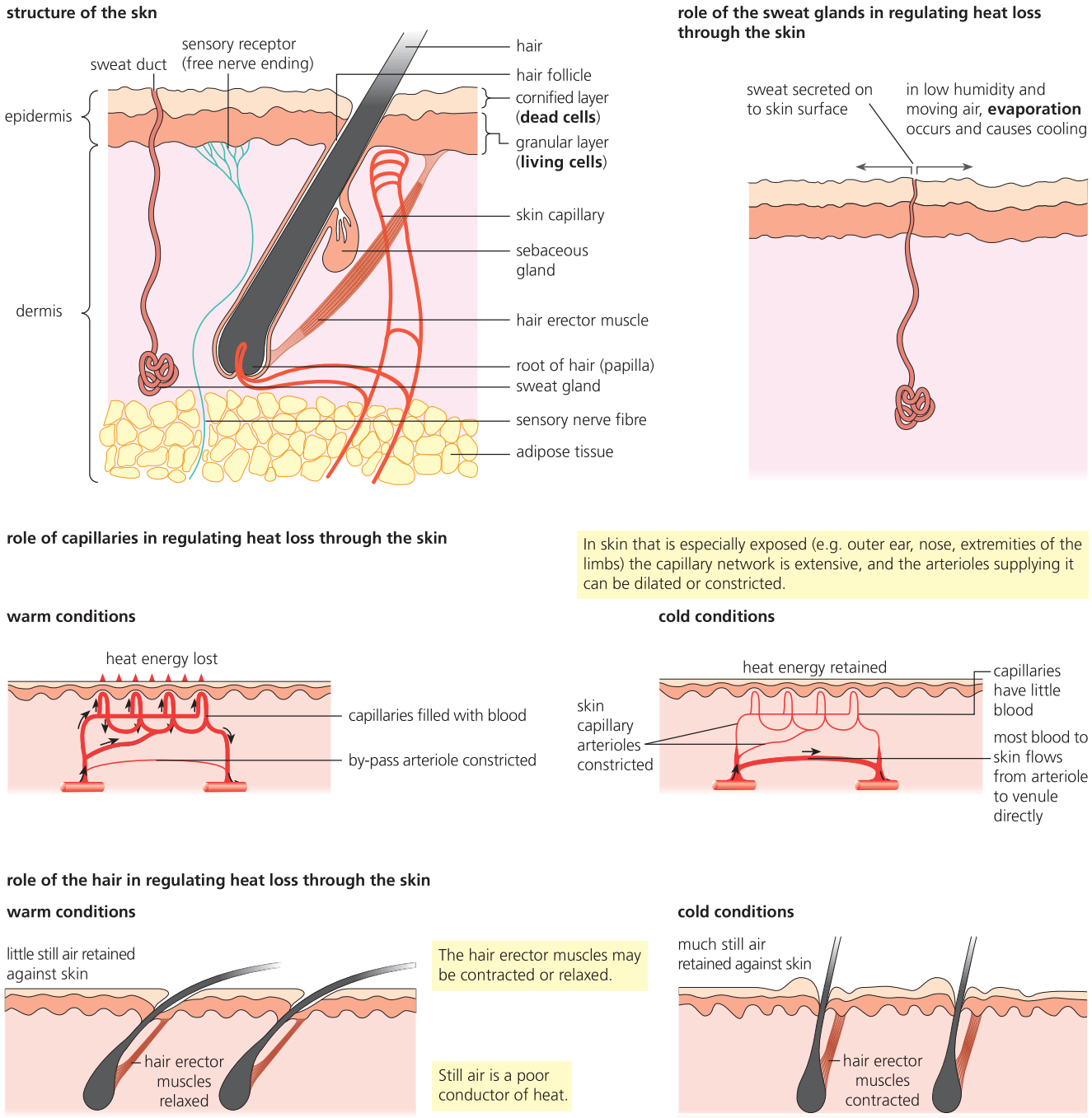


Figure 14.4 The skin and temperature regulation

The hypothalamus as the control centre

The 'control box' for temperature regulation in mammals is a region of the forebrain called the **hypothalamus**. It is called the thermoregulation centre, and it consists of a 'heat loss centre' and a 'heat gain centre' (Figure 14.5). Here, temperature-sensitive nerve cells (neurones) detect changes in the temperature of the blood flowing through the brain (*internal* stimuli). The thermoregulation centre of the hypothalamus also receives information via sensory nerves from temperature-sensitive receptors located in the skin (*external* stimuli), and in many internal organs.

The hypothalamus communicates with the rest of the body via the **nervous system**. For example, when the body temperature is lower than normal, the heat gain centre inhibits activity of the heat loss centre, and sends impulses to the skin, hair erector muscles, sweat glands and

elsewhere that decrease heat loss (such as vasoconstriction of skin capillaries) and increase heat production (such as shivering, and enhanced 'brown fat' respiration). When body temperature is higher than normal the heat loss centre inhibits the heat gain centre activity, and sends impulses to the skin, hair erector muscles, sweat glands and elsewhere that increase heat loss (such as vasodilation of skin capillaries), and decrease heat production.

Another mechanism in thermoregulation

Thyxoxin is an iodine-containing **hormone** produced in the thyroid gland. On secretion it stimulates oxygen consumption and basal metabolic rate of the body organs. Variation in secretion of thyroxin helps to control body temperature (Figure 14.5).

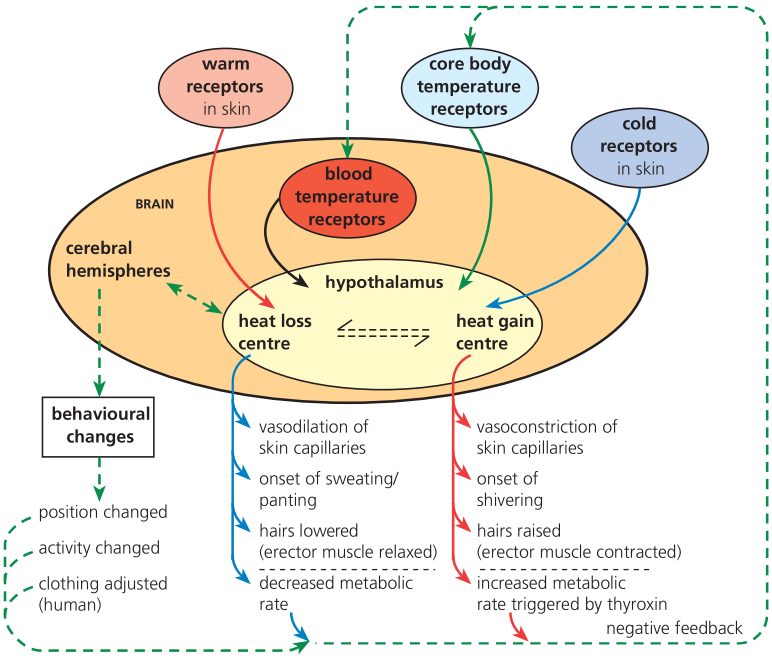


Figure 14.5 Temperature regulation of the body by the hypothalamus

The roles of the endocrine and nervous systems compared

In the processes of thermoregulation we have seen that both the nervous and endocrine systems are involved. The endocrine system and the nervous system work in distinctive and different ways in the control and co-ordination of body activities. However, many of the activities of the nervous and endocrine systems are **co-ordinated** by the pituitary gland, the master gland of the endocrine system, working in tandem with the hypothalamus of the brain. The hypothalamus secretes hormones that regulate the functioning of the pituitary. The hypothalamus also monitors the level of hormones in the blood and regulates secretion by negative feedback control.

Table 14.1 The endocrine and nervous systems compared

Endocrine system	Nervous system
Communication by chemical messengers transmitted in the bloodstream	Communication by electrochemical action potentials (impulses) transmitted via neurones
Hormones 'broadcast' all over the body but influence target cells and tissues only	Action potentials are targeted on specific cells
Causes changes in metabolic activity	Causes muscles to contract or glands to secrete
Have their effects over many minutes, several hours or longer	Produces effects within milliseconds
Effects tend to be long lasting	Effects tend to be short lived and reversible

Homeostasis in action – control of blood glucose concentration

Respiration is a continuous process in all living cells, and glucose is the principle respiratory substrate for most tissues. To maintain tissue respiration, cells need a regular supply of glucose. Transport of glucose to all cells is a key function of the blood circulation. Fortunately, blood glucose can be quickly absorbed across the cell membrane. In humans, the **normal level of blood glucose** is about 4 mM/L of blood, but it varies, typically between 3.6 and 5.8 mM/L. The lower values arise during an extended period without food, or after prolonged and heavy physical activity; the highest values occur after a meal rich in carbohydrate has been digested.

Most cells (including muscle cells) hold reserves in the form of glycogen. This polysaccharide is quickly converted to glucose during prolonged physical activity. However, glycogen reserves may be used up quickly. (In the brain, glucose is the only substrate the cells can use and there are no glycogen stores held in reserve there at all.)

The maintenance of a constant level of this monosaccharide in the blood plasma is the norm, but two extreme conditions can arise:

- **Hypoglycaemia**, in which our blood glucose falls below 2.0 mM/L. If this is not quickly reversed, we may faint. If the body, and particularly the brain, continue to be deprived of adequate glucose levels, convulsions and coma follow.
- **Hyperglycemia**, in which an abnormally high concentration of blood glucose occurs. Since a high concentration of any soluble metabolite lowers the water potential of the blood plasma, water is drawn immediately from the cells and tissue fluid by osmosis, back into the blood. As the volume of blood increases, water is excreted by the kidney to maintain the correct concentration of blood. As a result, the body tends to become dehydrated and the circulatory system is deprived of fluid. Ultimately, blood pressure cannot be maintained.

For these reasons, it is critically important that the blood glucose is held within set limits.

Question

2 Explain what liver cells receive from blood from the hepatic artery that is not present in blood from the hepatic portal vein.

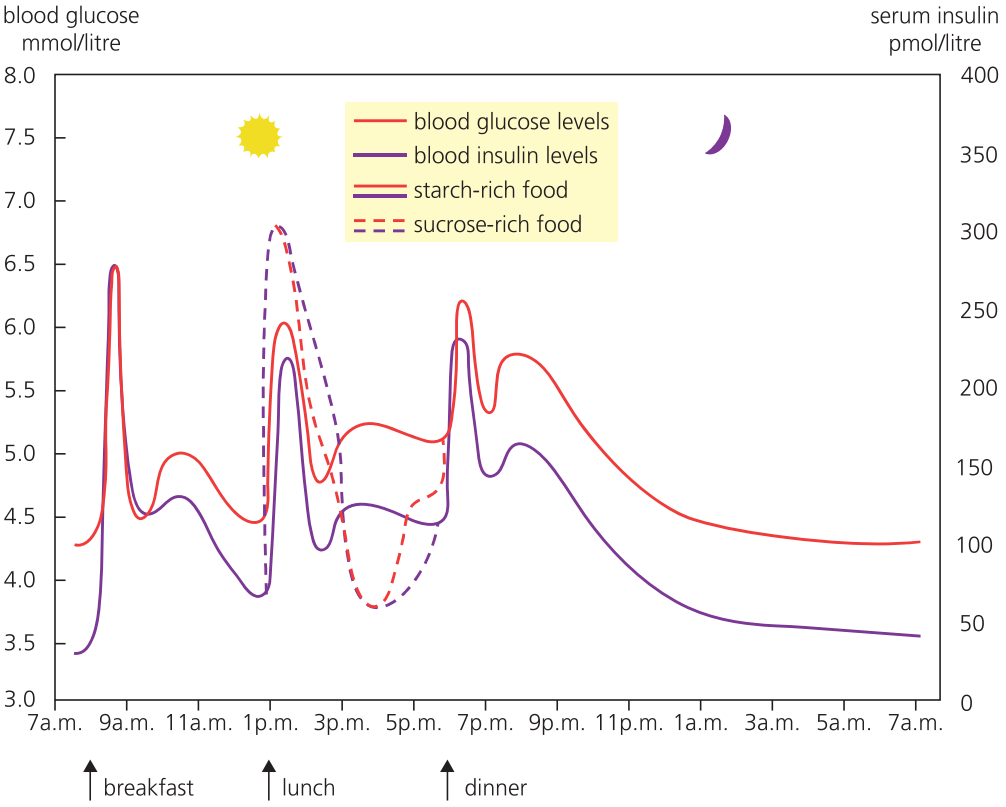


Figure 14.6 How blood glucose and insulin levels vary with time

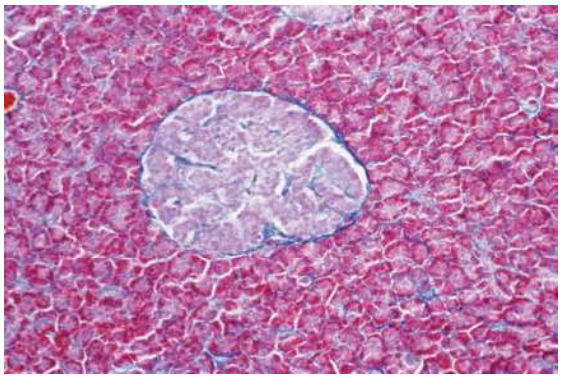
Regulation of blood glucose

Regulation of blood glucose is the result of the actions of two hormones, released from groups of special cells, found in the pancreas.

After the digestion of carbohydrates in the gut, glucose is absorbed across the epithelium cells of the villi (finger-like extensions of the inner surface of the small intestine) into the hepatic portal vein (Figure 8.7, page 158). The blood carrying the glucose reaches the liver first. If the glucose level is too high, then glucose starts to be withdrawn from the blood and is stored as glycogen. However, not all of the glucose can be removed immediately. Blood circulating in the body immediately after a meal has a raised level of glucose (Figure 14.6).

At the pancreas, the presence of an excess of blood glucose is detected in patches of cells known as the **islets of Langerhans**. These islets are hormone-secreting glands (endocrine glands); they have a rich capillary network, but no ducts that would carry secretions away. Instead, they are transported all over the body by the blood. The islets of Langerhans contain two types of cell, **alpha (α) cells** and **beta (β) cells** (Figure 14.7).

TS of pancreatic gland showing an islet of Langerhans



drawing of part of pancreatic gland

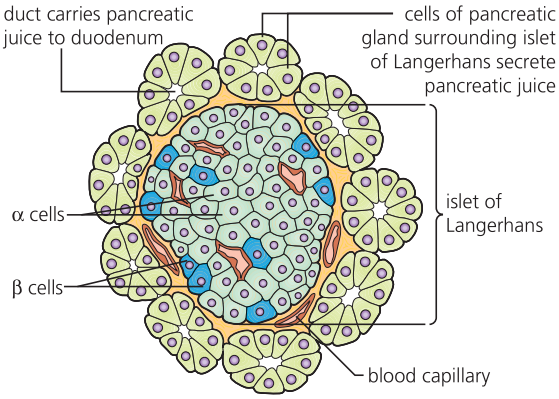


Figure 14.7 An islet of Langerhans in the pancreas

In the presence of a **raised blood glucose level**, the **beta cells** are stimulated. They secrete the hormone **insulin** into the capillary network. Insulin stimulates the uptake of glucose by cells all over the body, but especially by the liver and the skeletal muscle fibres. Another effect of insulin is to trigger the conversion of glucose to glycogen (**glycogenesis**) and of glucose to fatty acids and fats in liver cells. Insulin also promotes the deposition of fat around the body.

As the blood glucose level reverts to normal this is detected in the islets of Langerhans, and the beta cells respond by stopping insulin secretion. Meanwhile the hormone is excreted by the kidney tubules and the blood insulin level falls.

When the **blood glucose level falls below normal**, the **alpha cells** are stimulated. These secrete a hormone called **glucagon**. This hormone activates the enzymes that convert glycogen and amino acids to glucose (**gluconeogenesis**). Glucagon also reduces the rate of respiration.

As the blood glucose level reverts to normal, glucagon production ceases, and this hormone in turn is removed from the blood in the kidney tubules.

Question

3 Given the role of alpha cells and beta cells (the production and discharge of hormones), identify the organelles that are involved directly and list their specific roles.

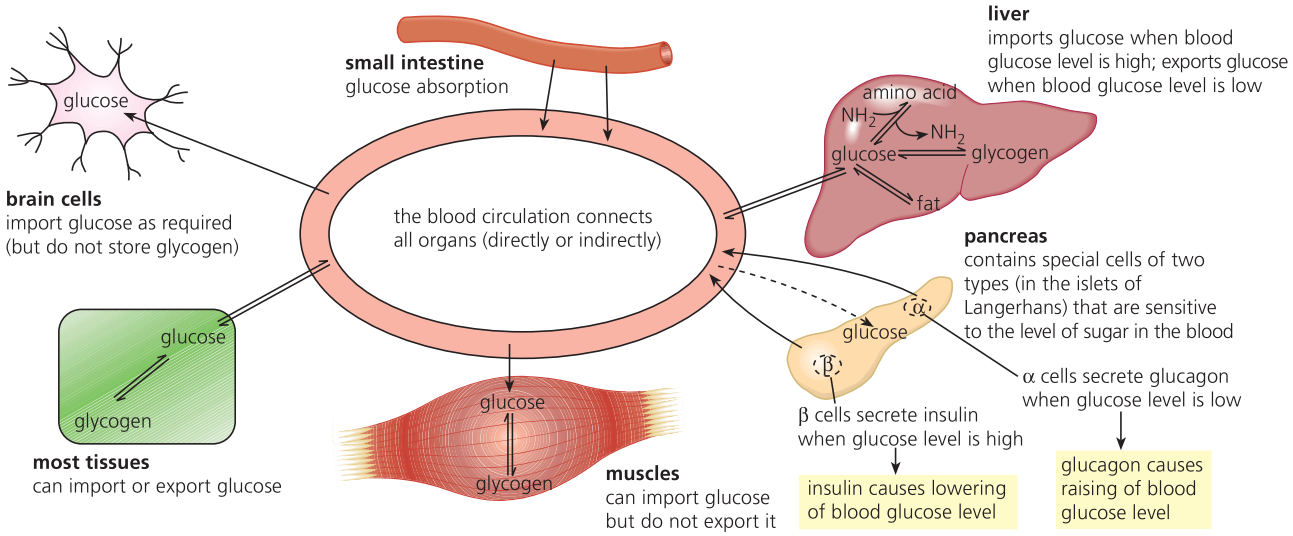
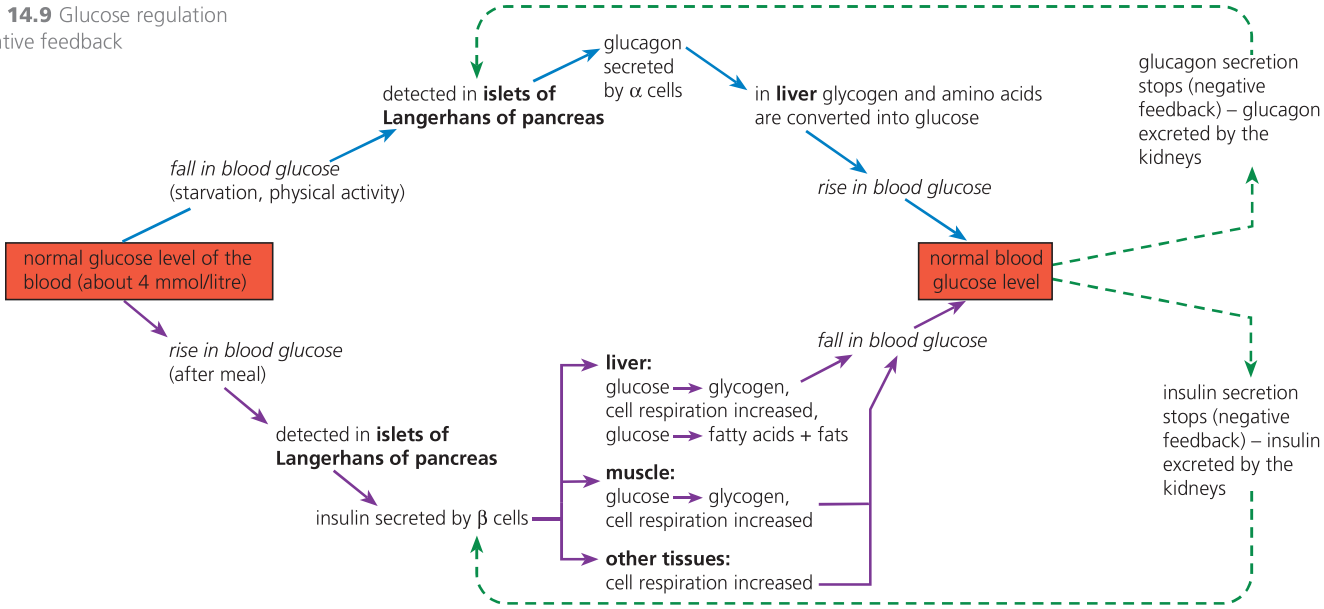


Figure 14.8 Distribution and metabolism of blood glucose

Figure 14.9 Glucose regulation by negative feedback



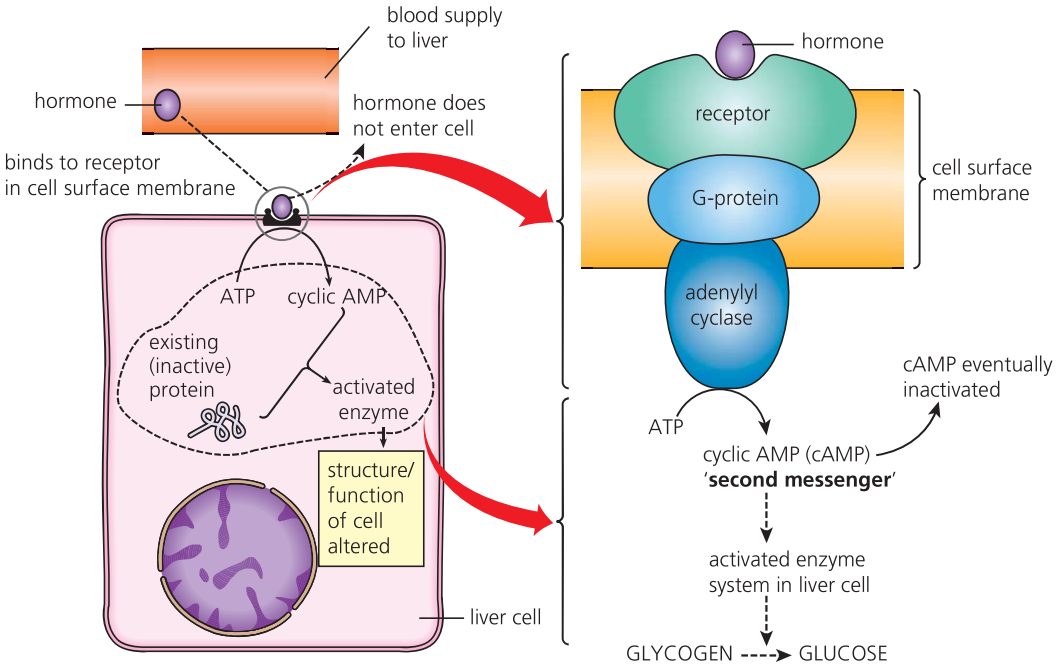
The role of cyclic AMP in the effects of adrenalin and glucagon on liver cells

Both adrenalin and glucagon are peptide hormones, which, whilst circulating in the bloodstream, stimulate liver cells to convert stored glycogen to glucose. The glucose formed then passes out from the liver cells and contributes to blood glucose levels.

The actions triggered by these two hormones are brought about within the liver cells without the hormones having passed through the cell's cell surface membrane. Instead, the hormones bind to specific receptors in the cell surface membrane, and this event triggers the following changes:

- First, another membrane-embedded protein, known as a G-protein, is activated.
- The activated G-protein in turn activates an enzyme known as adenylyl cyclase, also embedded in the cell surface membrane.

Figure 14.10 The role of cyclic AMP as a second messenger



- Activated adenylyl cyclase catalyses the formation of cyclic AMP (cAMP) from ATP within the cell cytosol.

cAMP is known as a '**second messenger**'. It is a small, non-protein molecule that is water soluble, and so spreads quickly through the cytosol by diffusion. The presence of this second messenger triggers a cascade of reactions in liver cells in which specific enzymes are activated by reaction with ATP. The outcomes are:

- the hormone signal is amplified
- the glycogen stored in the liver cells is hydrolysed to glucose.

These events are summarised in Figure 14.10.

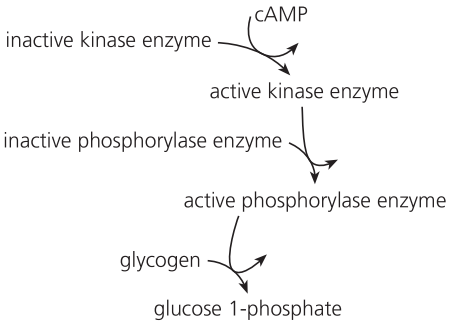


Figure 14.11 The three stages of cell-signalling that adrenalin triggers

The impact of adrenalin on liver cells as a three-stage process of cell-signalling

The impact of adrenalin on a liver cell is a **three-stage process** of cell signalling (Figure 14.11). After the first stage, when a hormone molecule interacts at the cell surface, subsequent events are activated by a succession of relay molecules, initiated by the formation of a second messenger, cAMP, within the cytosol.

The relay molecules are activated kinases and phosphorylases. These proteins catalyse specific types of reaction:

- **Kinases** are enzymes that transfer a phosphate group from ATP to an acceptor.
- **Phosphorylases** are enzymes that break down glucose-based polysaccharides (e.g. glycogen) to glucose 1-phosphate.

The critical role of the second and third stages of signal transduction is the **amplification** of the hormone signal. So, from one activated receptor molecule, 10000 (10^4) molecules of cAMP are formed. As a result of the presence of cAMP in the cytosol, approximately 10^6 molecules of active phosphorylase enzyme will be formed, and these will then trigger the formation of perhaps 10^8 molecules of glucose 1-phosphate.

Table 14.2 Stages of signal transduction leading to amplification

Stage	Events	Consequences
1	hormone interaction at the cell surface	a single hormone initiates events
2	formation of cyclic AMP, which binds to kinase proteins ATP → cAMP	about 10^4 molecules of cAMP become active in the cytosol
3	an enzyme cascade involving activation of enzymes by phosphorylation to amplify the signal	approximately 10^8 molecules of glucose 1-phosphate are formed and become available to pass out into the bloodstream

Extension

The disease of diabetes

Diabetes is the name for a group of diseases in which the body fails to regulate blood glucose levels. **Type I diabetes** results from a failure of insulin production by the beta cells. It is also referred to as insulin-dependent diabetes, early onset diabetes or juvenile diabetes (because it typically appears early on in a person's life). **Type II diabetes** is a failure of the insulin receptor proteins on the cell surface membranes of target cells. It is also referred to as diabetes mellitus, late onset diabetes or adult onset diabetes.

As a consequence of either form of the disease, blood glucose regulation is more erratic and, generally, the level of glucose is permanently raised – to dangerous levels in untreated cases of Type I diabetes. Glucose is also regularly excreted in the urine. If this condition is not diagnosed and treated, it carries a risk of circulatory disorders, renal failure, blindness, strokes and heart attacks.

The production of **human insulin** for treatment of diabetes by the genetic engineering of bacteria is discussed in Topic 19.

Type I diabetes (insulin-dependent diabetes, early onset diabetes or juvenile diabetes)
affects young people, below the age of 20 years
due to the destruction of the β cells of the islets of Langerhans by the body's own immune system
symptoms:
– constant thirst
– undiminished hunger
– excessive urination
treatment:
– injection of insulin into the blood stream daily
– regular measurement of blood glucose level

Type II diabetes (diabetes mellitus, late onset diabetes or adult onset diabetes)
the common form (90% of all cases of diabetes are of this type)
common in people over 40 years especially if overweight, but this form of diabetes is having an increasing effect on human societies around the world, including on young people and even children in developed countries, seemingly because of poor diet
symptoms:
mild sufferers usually have sufficient blood insulin, but insulin receptors on cells have become defective
treatment:
largely by diet alone

Dip-sticks and biosensors for quantitative measurements of glucose

Dip sticks, such as Clinistix™ or, alternatively biosensors, are used to measure glucose levels in urine or blood.

Glucose is not present in the urine of a healthy person because, although it appears in the filtrate in the Bowman's capsule of the kidney, it is selectively reabsorbed in the proximal convoluted tubules (page 301). However, people with diabetes cannot control their blood sugar levels effectively. Glucose may appear in the urine when the blood sugar levels rise steeply, for example after a meal. Diabetics may need to inject insulin to reduce blood sugar levels. The urine may be tested to find out if an injection is needed using Clinistix™. Alternatively, a glucose biosensor may be used (see Figure 14.13).

The Clinistix™ strip contains two enzymes, glucose oxidase and peroxidase, together with a colourless hydrogen donor compound called chromogen. When the strip is dipped into the urine sample, if glucose is present it is oxidised to gluconic acid and hydrogen peroxide. The second enzyme catalyses the reduction of hydrogen peroxide and the oxidation of chromogen. The product is water and the oxidised dye, which is coloured. The more glucose present in the urine, the more coloured dye is formed. The colour of the test strip is then compared to the printed scale to indicate the amount of glucose in the urine (Figure 14.12).

the principles

glucose + oxygen $\xrightarrow{\text{glucose oxidase}}$ gluconic acid + H_2O_2

$DH_2 + H_2O_2 \xrightarrow{\text{peroxidase}} 2H_2O + D$

reduced chromagen (colourless) → chromagen (coloured)

the process

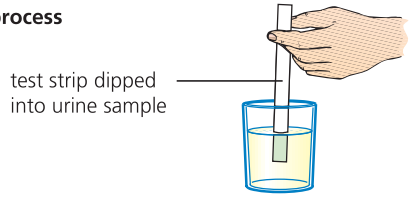


Figure 14.12 Measuring glucose in urine using a Clinistix™

An alternative approach for the diabetic is to measure the glucose level in the blood itself using a **glucose biosensor** (Figure 14.13). A biosensor is a device which makes use of a biological molecule (or sometimes a cell) to detect and measure a chemical compound.

The glucose biosensor has an immobilised enzyme, **glucose oxidase**, held between two membranes positioned at the tip of a platinum electrode. In use, the outer membrane is momentarily brought in contact with a tiny drop of blood, squeezed from a pinprick puncture of the skin at the tip of a finger. In contact with the immobilised enzyme, glucose in the blood plasma is immediately oxidised to gluconic acid and hydrogen peroxide. The electrode measures the drop in oxygen used to produce the hydrogen peroxide and an electrical signal is generated. The size of this signal is proportional to the concentration of glucose in the patient's blood. A digital read-out gives the concentration of blood glucose.

Question

4 What are the advantages to a diabetic patient of measuring blood glucose by means of a biosensor, compared to the Clinistix™ method?

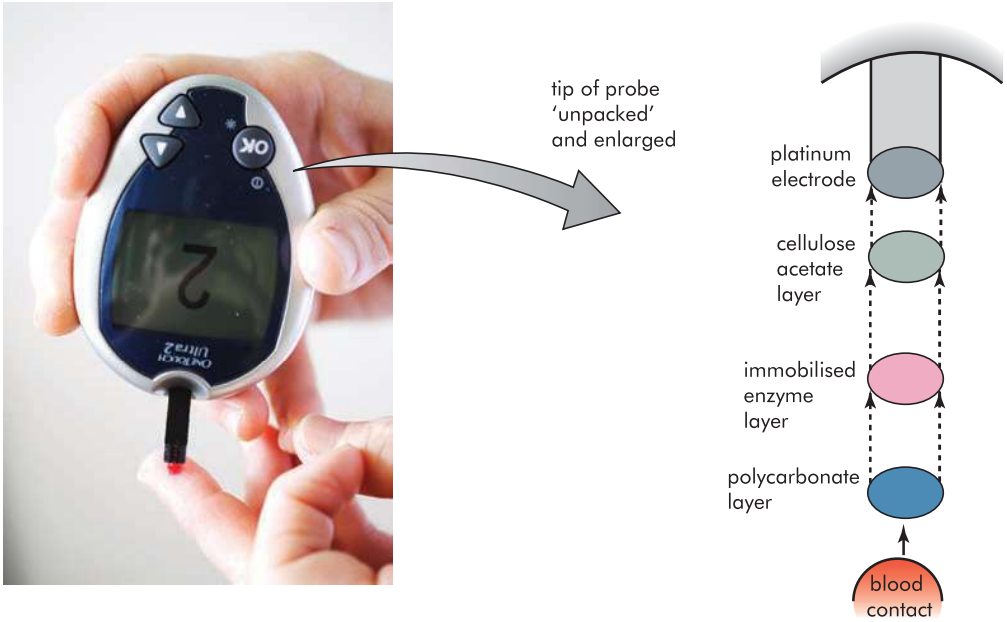


Figure 14.13 Biosensor for blood glucose testing

14.1 *continued* … Kidneys – structure and function

The kidneys remove wastes from the blood and are the effectors for controlling the water potential of the blood.

By the end of this section you should be able to:

d) describe the deamination of amino acids and outline the formation of urea in the urea cycle
e) describe the gross structure of the kidney and the detailed structure of the nephron with its associated blood vessels using photomicrographs and electron micrographs
f) describe how the processes of ultrafiltration and selective reabsorption are involved with the formation of urine in the nephron
g) describe the roles of the hypothalamus, posterior pituitary, ADH and collecting ducts in osmoregulation
l) explain how urine analysis is used in diagnosis with reference to glucose, protein and ketones

Excretion, blood water balance and metabolic waste

Excretion: the elimination from the body of waste compounds produced during the metabolism of cells, including, for a human, carbon dioxide (excreted through the lungs) and urea (excreted through the kidneys in urine).

Excretion is a characteristic activity of all living things. It is essential because the chemical reactions of metabolism produce byproducts, some of which would be toxic if allowed to accumulate. Excretion is the removal from the body of the waste compounds produced during the metabolism of cells. Humans excrete carbon dioxide from the lungs and urea in urine produced by our kidneys.

In mammals, excretion is a part of the process of homeostasis. Excretion of nitrogenous compounds is important in animals because they do not store protein. Proteins in the diet are broken down to their constituent amino acids. Amino acids that are excess to requirements for protein synthesis are respired. The first step is called **deamination**. This occurs in the liver and is the removal from each amino acid of its amino group, which becomes **ammonia**. Ammonia is a very soluble and extremely toxic compound. However, the ammonia is promptly converted into a safer nitrogenous compound. In mammals that compound is **urea** – formed by reaction of ammonia with carbon dioxide (Figure 14.14). In dilute solution, urea is safely excreted from the body.

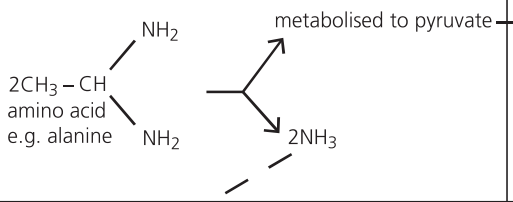
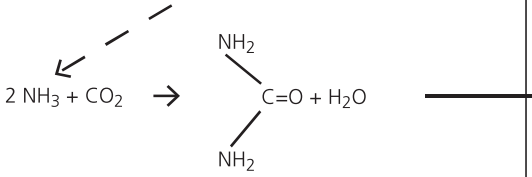
Biochemical change:	Fate of products:
1. proteins → digested to amino acids	
2. Excess amino acids are then deaminated: 	respired via the Krebs Cycle
3. Formation of urea: 	excreted by the kidneys

Figure 14.14 Deamination

Associated with excretion, and very much part of it, is the process of osmoregulation. Osmoregulation is the maintenance of a proper balance in the water and dissolved substances in the blood. Excretion and osmoregulation together, are the work of our kidneys.

The kidney – an organ of excretion and osmoregulation

The role of our kidneys is to regulate the internal environment is by constantly adjusting the composition of the blood. Waste products of metabolism are transported from the metabolising cells by the blood circulation, removed from the blood in the kidneys and excreted in a solution called **urine**. At the same time, the concentrations of inorganic ions, such as sodium (Na^+) and chloride (Cl^-) ions, and water in the body are also regulated.

The position of the kidneys is shown in Figure 14.15. Each kidney is served by a **renal artery** and drained by a **renal vein**. Urine from the kidney is carried to the bladder by the **ureter** and from the **bladder** to the exterior by the **urethra**, when the bladder sphincter muscle is relaxed. Together these structures are known as the **urinary system**.

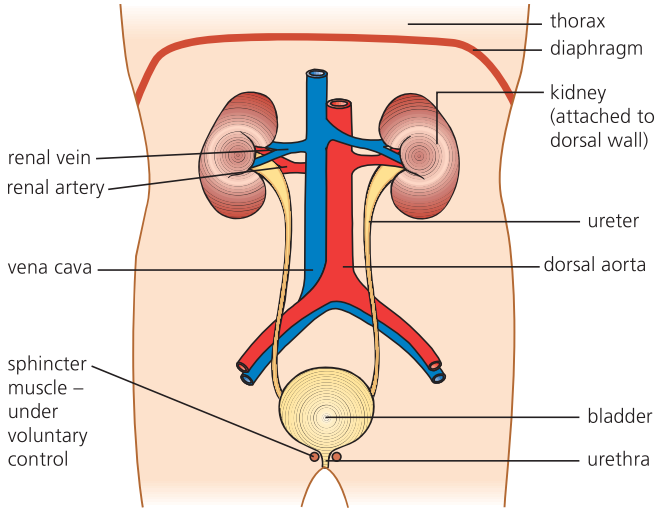


Figure 14.15 The human urinary system

In section, each kidney consists of an outer **cortex** and inner **medulla**, and these are made up of a million or more **nephrons**. A nephron is thin-walled tubule about 3 cm long, part in the cortex and part in the medulla. The shape of a nephron and its arrangement in the kidney are shown in Figure 14.16.

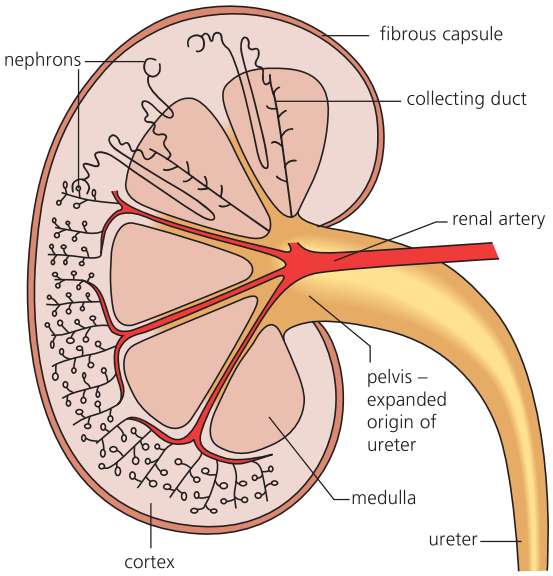
Blood vessels are closely associated with each of the distinctly-shaped regions of the nephrons. For example, the first part of the nephron is formed into a cup-shaped **renal capsule** and the capillary network here is known as the **glomerulus**. Collectively, these are known as the **Malpighian body**. They occur in the cortex. The **convoluted tubules** occur partly in the cortex and partly in the medulla, but notice that the extended **loops of Henle** and **collecting ducts** largely occur in the medulla.

Each region of the nephron has a specific role to play in the work of the kidney, and the capillary network serving the nephron plays a key part, too, as we shall now see.

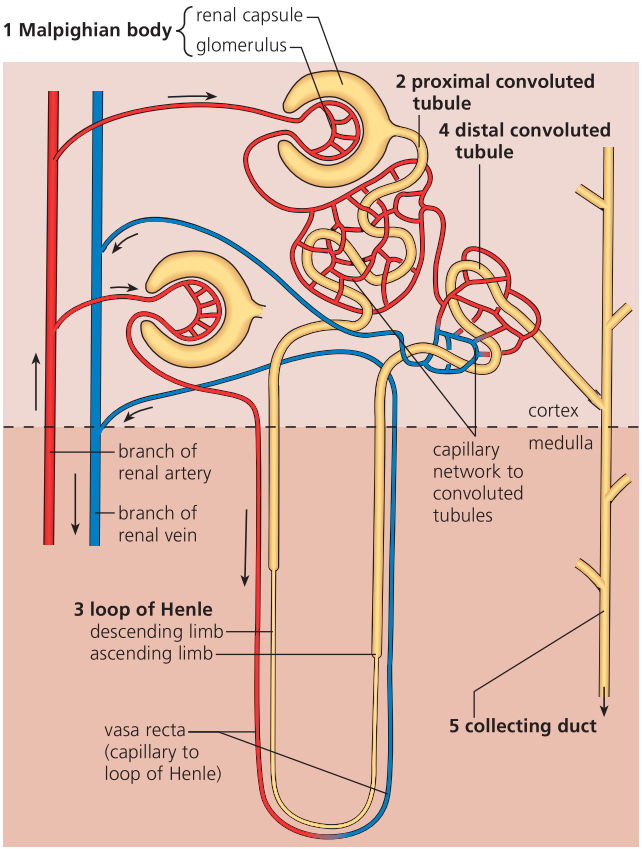
The formation of urine

In humans, about 1–1.5 litres of urine are formed each day, typically containing about 40–50 g of solutes, of which **urea** (about 30 g) and **sodium chloride** (up to 15 g) make up the bulk. The nephron produces urine in a continuous process which we can conveniently divide into five steps, to show just how the blood composition is so precisely regulated.

LS through kidney showing positions of nephrons in cortex and medulla



nephron with blood capillaries



Roles of the parts of the nephron

1 Malpighian body = ultrafiltration
2 proximal convoluted tubule = selective reabsorption from filtrate
3 loop of Henle = water conservation
4 distal convoluted tubule = pH adjustment and ion reabsorption
5 collecting duct = water reabsorption

Photomicrograph of the cortex of the kidney in section, showing the tubules, renal capsules and capillary networks

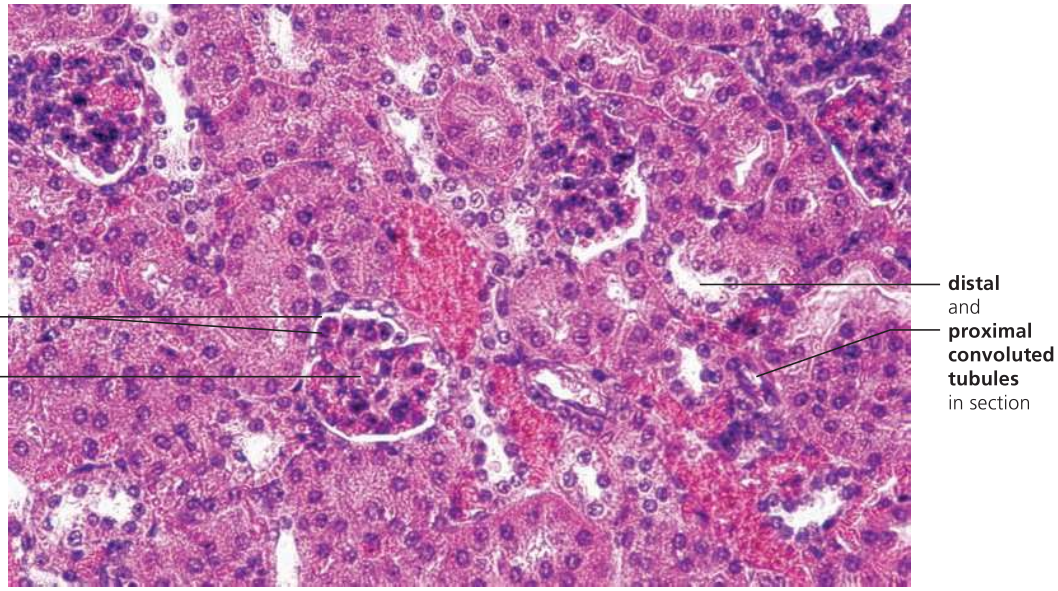


Figure 14.16 The kidney and its nephrons: structure and roles

Step 1: Ultrafiltration in the renal capsule

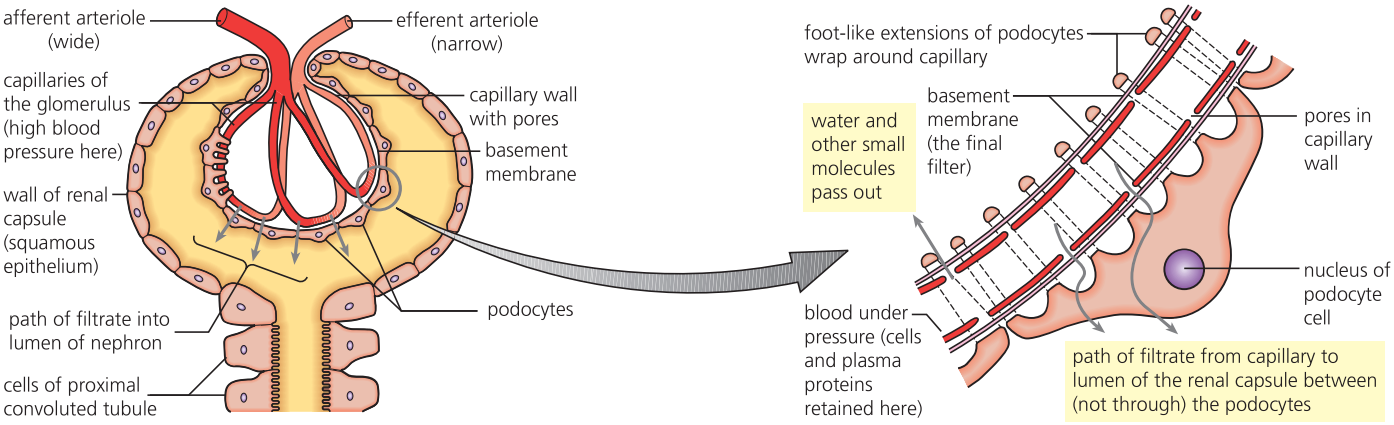
In the glomerulus, water and relatively small molecules of the blood plasma, including useful ions, glucose and amino acids pass out of the capillaries, along with urea, into the lumen of the capsule. This process is described as ultrafiltration because it is powered by the pressure of the blood.

The **blood pressure** is raised at this point by the input capillary (**afferent arteriole**) being wider than the output capillary (**efferent arteriole**). This increase in hydrostatic (blood) pressure exceeds the water potential of the plasma. This forces water and the soluble components of plasma that are able to pass out through the extremely fine sieve-like wall structure here, between the podocytes, into the capsule. This '**sieve**' is made of two layers of cells (the endothelium of the capillaries of the glomerulus and the epithelium of the capsule), between which is a basement membrane. You can see this arrangement in Figure 14.17.

Notice that the cells of the capsule wall are called **podocytes** for they have feet-like extensions that form a network with tiny slits between them. Similarly, the endothelium of the capillaries has **pores**, too. This detail was discovered using the electron microscope, because these filtration gaps are very small indeed. So small, in fact, that not only are blood cells retained, but the majority of blood proteins and polypeptides dissolved in the plasma also remain in the circulating blood. It is the presence of the **basement membrane** that stops large proteins passing out. So, the fluid that has been filtered through into the renal capsule is very similar to blood plasma but with the significant difference that protein molecules are largely absent.

Question

5 **a** What is the source of the force that drives ultrafiltration in the glomerulus?
b List the main components of the blood that are likely to be filtered in the nephron.



False-colour SEM of podocytes (pale purple) with their extensions wrapped around the blood capillaries (pink/red) (× 3500)

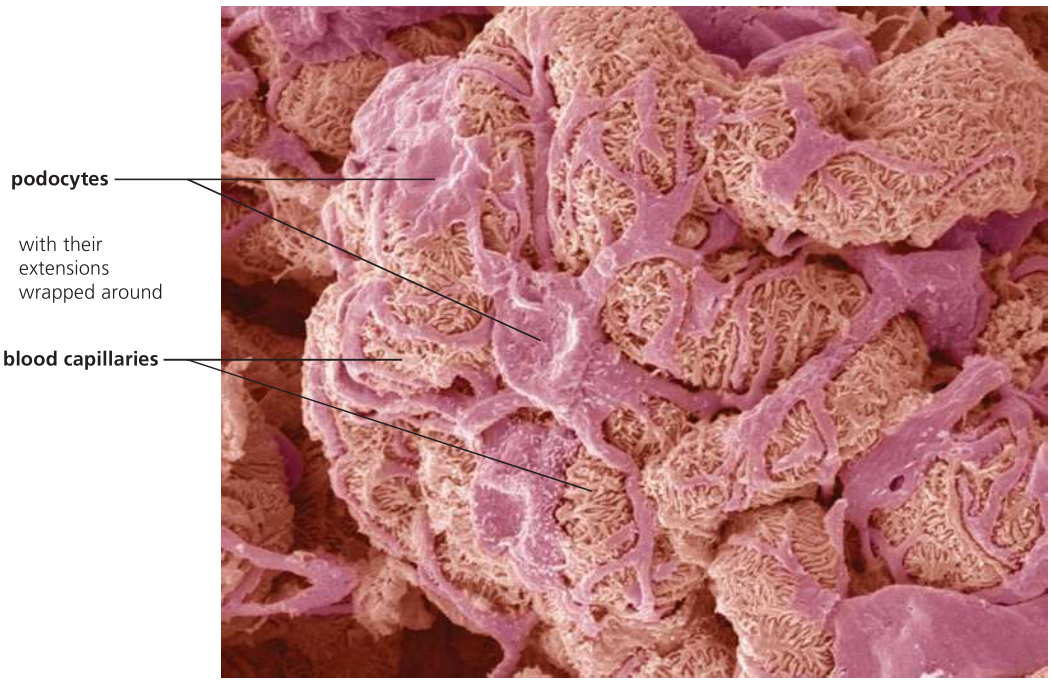


Figure 14.17 The site of ultrafiltration

Step 2: Selective reabsorption in the proximal convoluted tubule

The proximal convoluted tubule is the longest section of the nephron and it is here that a large part of the filtrate is reabsorbed into the capillary network. The walls of the tubule are one cell thick and their cells are packed with mitochondria. (We would expect this, if active transport is part of the way reabsorption is brought about.) The cell surface membranes of the cells of the tubule wall in contact with the filtrate all have a 'brush border' of microvilli. These microvilli increase enormously the surface area where reabsorption occurs. The mechanisms of reabsorption are:

- **active transport** of **sugars** and **amino acids** across the cell surface membrane by the activity of special carrier proteins in a process known as co-transport. In this, the carrier protein uses the diffusion of hydrogen ions (protons) down their electrochemical gradient into the cell to drive the uptake of molecules of sugars such as glucose or sucrose, typically against their concentration gradient. Other essential metabolites are transported similarly.
- movement of mineral ions by a combination of **active transport**, **facilitated diffusion** and some **exchange of ions**
- **diffusion** of urea
- movement of proteins by **pinocytosis**
- some movement of water by **osmosis**.

Question

6 a Cells of the walls of the proximal convoluted tubule have a brush border (Figure 14.19). Explain why this feature is helpful to the process of reabsorption.

b What does facilitated diffusion involve?

The electrochemical gradient in H^+ ions between the exterior and the interior of the cell drives the active transport of metabolites (e.g. sugars, amoni acids) across the membrane as the H^+ flow down their electrochemical gradient via the co-transporter pump.

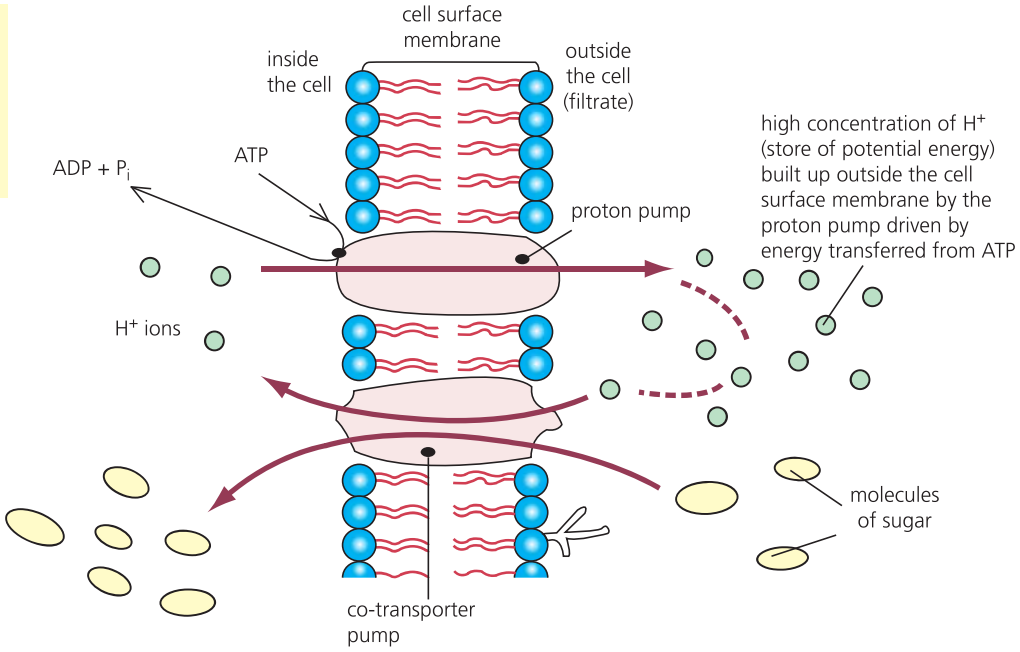


Figure 14.18 Co-transport: active transport driven by a concentration gradient

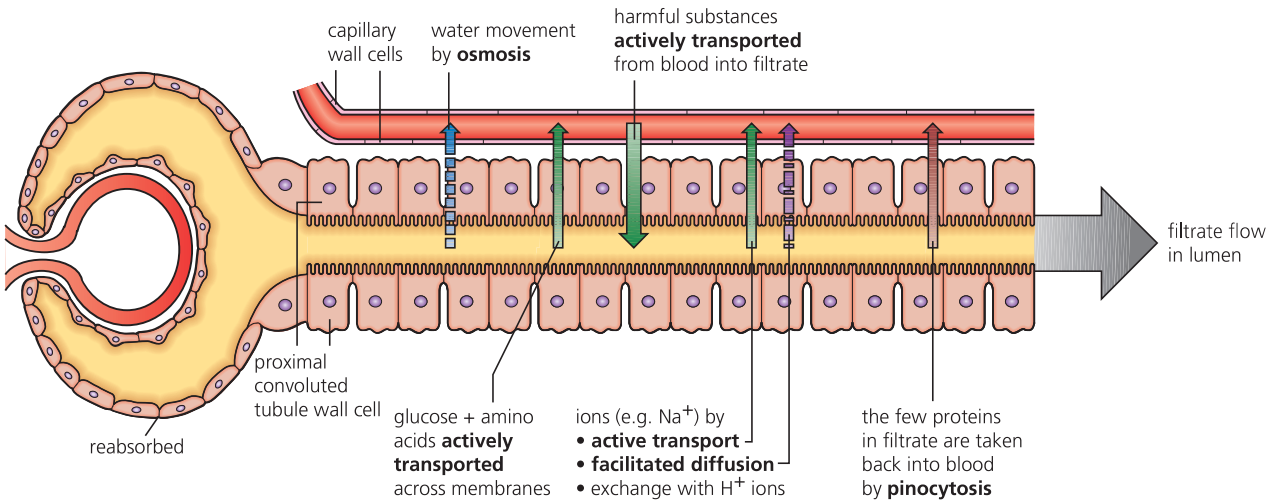


Figure 14.19 Reabsorption in the proximal convoluted tubule

Step 3: Water conservation in the loop of Henle

The function of the loop of Henle is to enable the kidneys to conserve water. Since urea is expelled from the body in solution, some water loss during excretion is inevitable. There is a potential problem here. Water is a major component of the body and it is often a scarce resource for terrestrial organisms. It is important, therefore, that mammals are able to form urine that is more concentrated than the blood (when necessary), thereby reducing the water loss to a minimum. Human urine can be up to five times as concentrated as the blood.

The structure of the loop of Henle with its **descending** and **ascending limbs**, together with a parallel blood supply, the **vasa recta**, is shown in Figure 14.20. The vasa recta is part of the same capillary network that surrounds a nephron. The role of the loops of Henle and their capillary loops is to create and maintain an osmotic gradient in the **medulla of the kidney**. The gradient across the medulla is from a less concentrated salt solution near the cortex to the most concentrated salt solution at the tips of the pyramid region of the medulla (Figure 11.5). The pyramid region of the medulla consists mostly of the collecting ducts. The osmotic gradient allows water to be withdrawn from the collecting ducts if circumstances require it. How this is occurs we shall discuss shortly. First, there is the question of how the gradient itself is created by the loops of Henle.

The gradient is brought about by a mechanism known as a **counter-current multiplier**. The principles of counter-current exchange here involve exchange between fluids flowing in opposite directions in two systems. The annotations in Figure 14.20 help show how the counter-current mechanism works. In following these annotations, remember that the descending and ascending limbs lie close together in the kidney.

Look first at the *second* half of the loop, the **ascending limb**. The energy to create the gradient is transferred from ATP to drive ion pumps in the wall cells of the ascending limbs. Here, sodium and chloride ions are pumped out of the filtrate into the fluid between the cells of the medulla, called the interstitial fluid. The walls of the ascending limbs are unusual in being impermeable to water. So water in the ascending limb is retained in the filtrate as salt is pumped out.

Opposite is the *first* half of the loop, the **descending limb**. This limb is fully permeable to water and also to most salts. Here, water passes out into the interstitial fluid by osmosis, due to the salt concentration in the medulla. At the same time and for the same reason, sodium, chloride and other ions tend to pass in.

Exchange in this counter-current multiplier is a dynamic process occurring down the whole length of the loop. At each level of the loops, the salt concentration in the descending limb is slightly higher than the salt concentration in the adjacent ascending limb. As the filtrate flows, the concentrating effect is multiplied and so the fluid in and around the hairpin bend of the loops of Henle is the saltiest.

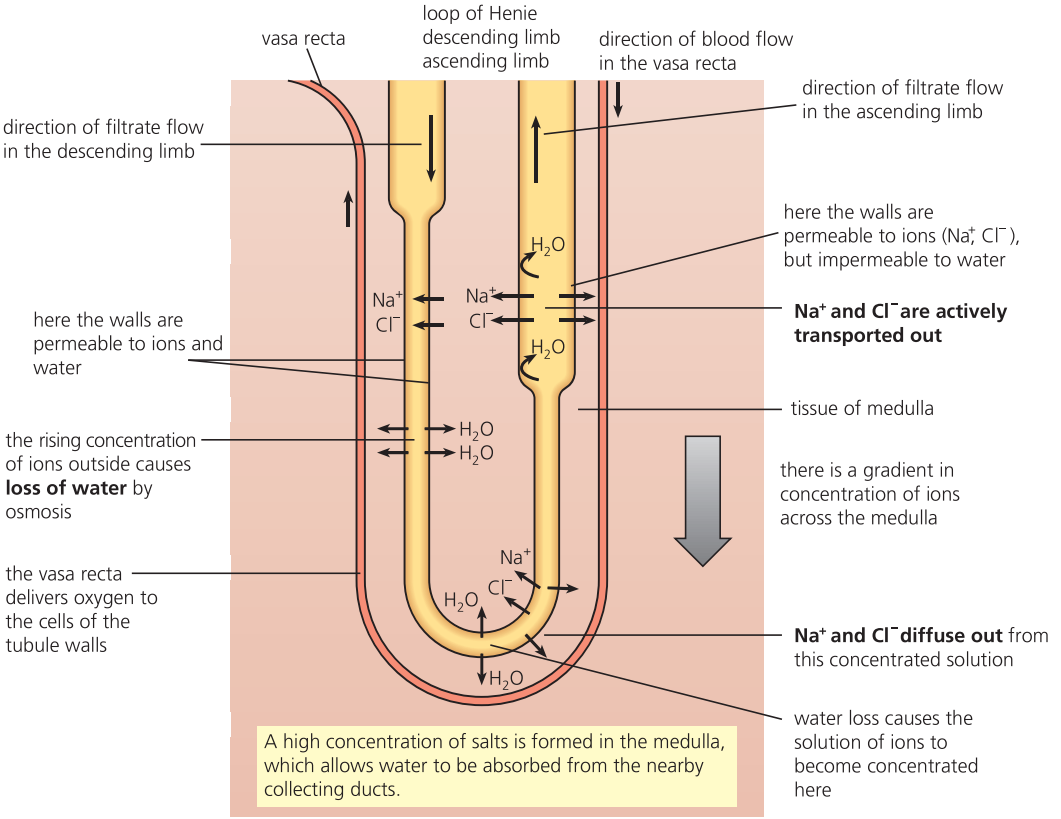


Figure 14.20 The functioning of the loop of Henle

Question

7 What is the essential feature of a counter-current flow system?

The role of the vasa recta is first to deliver oxygen to and remove carbon dioxide from the metabolically active cells of the loop of Henle. As it does this, the blood in the vasa recta also becomes saltier as it flows *down* beside the ascending limb and less salty as it flows back up and out of the medulla. In this way the cells of the loop are serviced without removing the accumulated salts from the medulla. The vasa recta does absorb water that has passed into the medulla at the collecting ducts. We discuss the working of these ducts in step 5, on the next page.

Step 4: Blood pH and ion concentration regulation in the distal convoluted tubule

The cells of the walls of the distal convoluted tube are of the same structure as those of the proximal convoluted tubule, but their roles differ somewhat.

Here the cells of the tubule walls adjust the composition of the blood, in particular, the **pH**. Any slight tendency for the pH of the blood to change is initially prevented by the blood proteins. Protein acts as a pH buffer. (You can read about how a pH buffer works in Appendix 1: Background chemistry for biologists, on the CD).

However, if the blood does begin to deviate from pH 7.4, then here in the distal convoluted tubule there is a controlled secretion of hydrogen ions (H^+) combined with reabsorption of hydrogencarbonate ions (HCO_3^-). Consequently, the pH of the blood remains in the range pH 7.35–7.45, but the pH of urine can vary widely, in the range pH 4.5–8.2.

Also in the distal convoluted tubule, the **concentration of useful ions is regulated**. In particular, the concentrations of potassium ions (K^+) is adjusted by secretion of any excess present in the plasma into the filtrate. Similarly, the concentration of sodium ions (Na^+) in the body is regulated by varying the quantity of sodium ions reabsorbed from the filtrate.

Step 5: Water reabsorption in the collecting ducts

When the intake of water exceeds the body's normal needs then the urine produced is copious and dilute. We notice this after we have been drinking a lot of water. On the other hand, when we have taken in very little water or when we have been sweating heavily (part of our temperature regulation mechanism) or if we have eaten very salty food perhaps, then a small volume of concentrated urine is formed.

Osmoregulation, the control of the water content of the blood (and therefore of the whole body) is a part of homeostasis – another example of regulation by negative feedback.

How exactly is this brought about?

The **hypothalamus**, part of the floor of the forebrain (Figure 14.21), controls many body functions. The composition of the blood is continuously monitored here, as it circulates through the capillary networks of the hypothalamus. Data is also received at the hypothalamus from sensory receptors located in certain organs in the body. All these inputs enable the hypothalamus to accurately control the activity of the pituitary gland.

The **pituitary gland** is situated below the hypothalamus, but is connected to it (Figure 14.21). The pituitary gland as a whole produces and releases hormones (it is part of our endocrine system, *see below*) – in fact it has been called the master hormone gland. In the process of osmoregulation, it is the posterior part of the **pituitary** that stores and releases **antidiuretic hormone** (**ADH**) – amongst others. (Other parts of the pituitary secrete hormones regulating a range of other body activities and functions.)

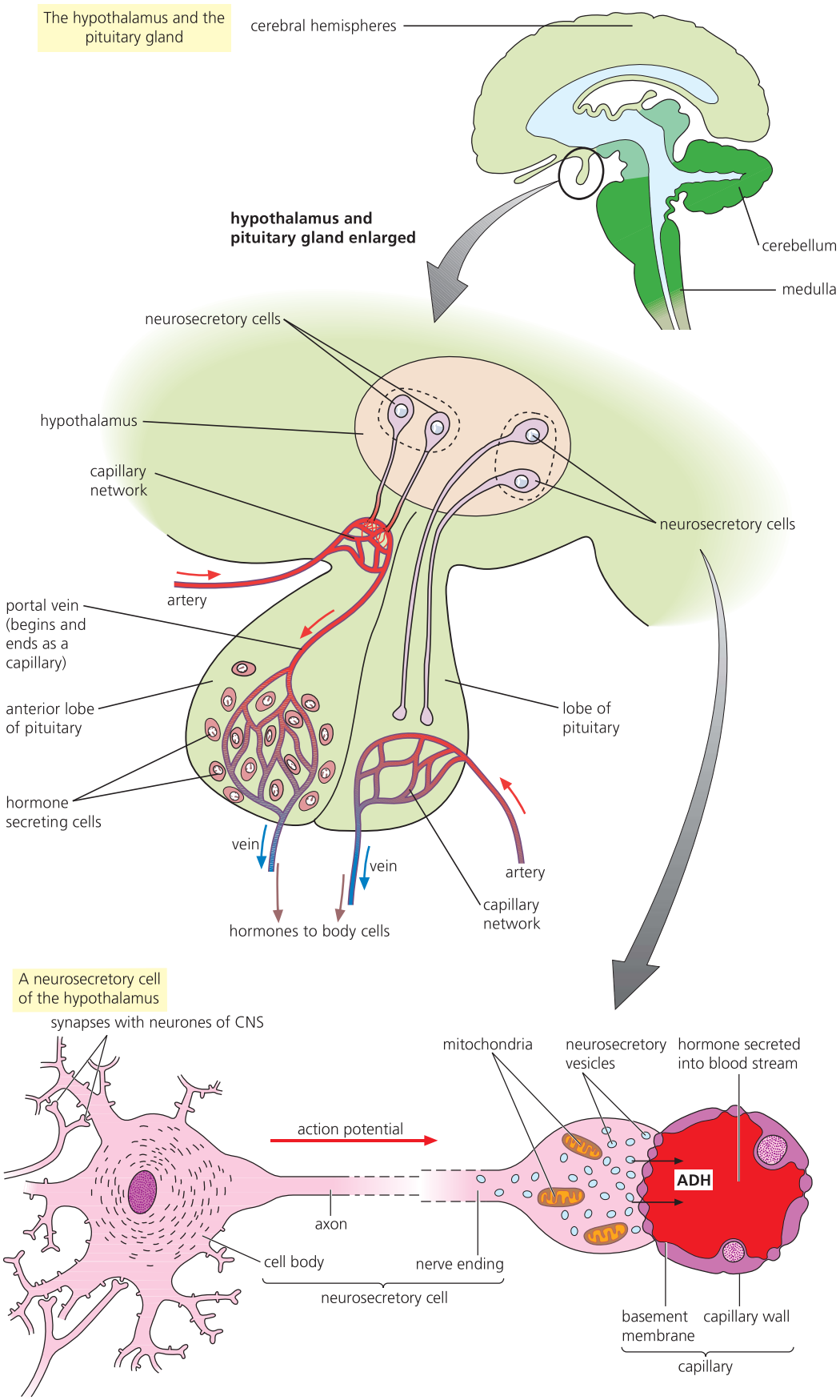


Figure 14.21 The hypothalamus and pituitary gland, and the release of ADH

Antidiuretic hormone (ADH) is actually produced in the hypothalamus and stored in vesicles at the ends of neurosecretory cells in the posterior pituitary gland. When nerve impulses from the hypothalamus trigger the release of ADH into the capillary networks in the posterior pituitary, ADH circulates in the blood stream. However, the targets of this hormone are the walls of the collecting ducts of the kidney tubules.

When the water content of the blood is low, antidiuretic hormone (ADH) is secreted from the posterior pituitary gland. When the water content of the blood is high, little or no ADH is secreted.

How does ADH change the permeability of the walls of the collecting ducts?

The cell surface membranes of the cells that form the walls of the collecting ducts contain a high proportion of channel proteins that are capable of forming an open pore running down their centre. You can see the structure of a fluid mosaic membrane and its channel proteins in Figure 4.3 (page 76) and Figure 4.9 (page 82).

When ADH is present in the blood circulating past the kidney tubules, this hormone causes the protein channels present in the collecting duct cell surface membranes to be open. As a result, much water diffuses out into the medulla and very little diffuses from the medulla into the collecting ducts.

Can you explain why? You may need to go back to step 3 above.

The water entering the medulla is taken up and redistributed in the body by the blood circulation. Only small amounts of very concentrated urine are formed. Meanwhile, as ADH circulates in the blood, the actions of the liver continually remove this hormone and inactivate it. This means that the presence of freshly released ADH has a regulatory effect.

When ADH is absent from the blood circulating past the kidney tubules, the protein channels in the collecting duct cell surface membranes are closed. The amount of water that is retained by the medulla tissue is now minimal. The urine become copious and dilute.

Questions

8 **a** List the components of a negative feedback system and identify these components in the process of osmoregulation.

b How is the effect of ADH on the collecting ducts fed back to the co-ordinator?

9 Why is too much water rarely a problem for plant cells, but potentially hazardous to animal cells?

Urine analyses in medical diagnosis

An analysis of a urine sample for the presence of glucose, protein or ketone bodies is an aid to the early diagnosis of serious but treatable conditions, as summarised in Table 14.2.

Table 14.2 The value of urine analyses in medical diagnosis

Metabolite	Tested for by	Health significance
glucose	Clinistix™ or biosensor	Presence of glucose may be an indicator of **diabetes**.
protein	dipstick test for albumin	Presence of protein is an indicator of **proteinura** – a possible indicator of kidney disease arising from glomerula membrane damage, or severe hypertension.
ketones	dipstick test – Ketostix™	Ketones are a normal product of fatty acid metabolism, but are not normally present in the urine. However, if the body is short of glucose, then fats are used as an energy source and ketones may then appear in the urine. Typically this is the result of **type 1 diabetes**, or **advanced/untreated type 2 diabetes**, but **eating disorders** are another possibility.

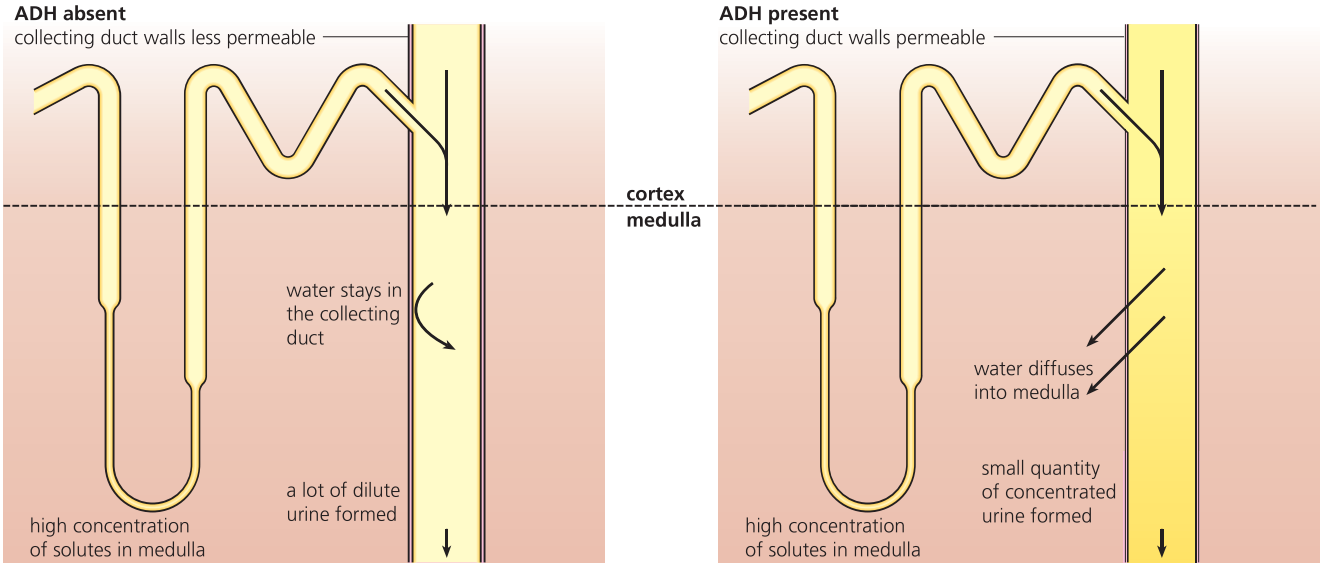
Water reabsorption in the collecting ducts

When we have:
- drunk a lot of water

the hypothalamus detects this and stops the posterior pituitary gland secreting ADH.

When we have:
- taken in little water
- sweated excessively
- eaten salty food

the hypothalamus detects this and directs the posterior pituitary gland to secrete ADH.



Osmoregulation by negative feedback

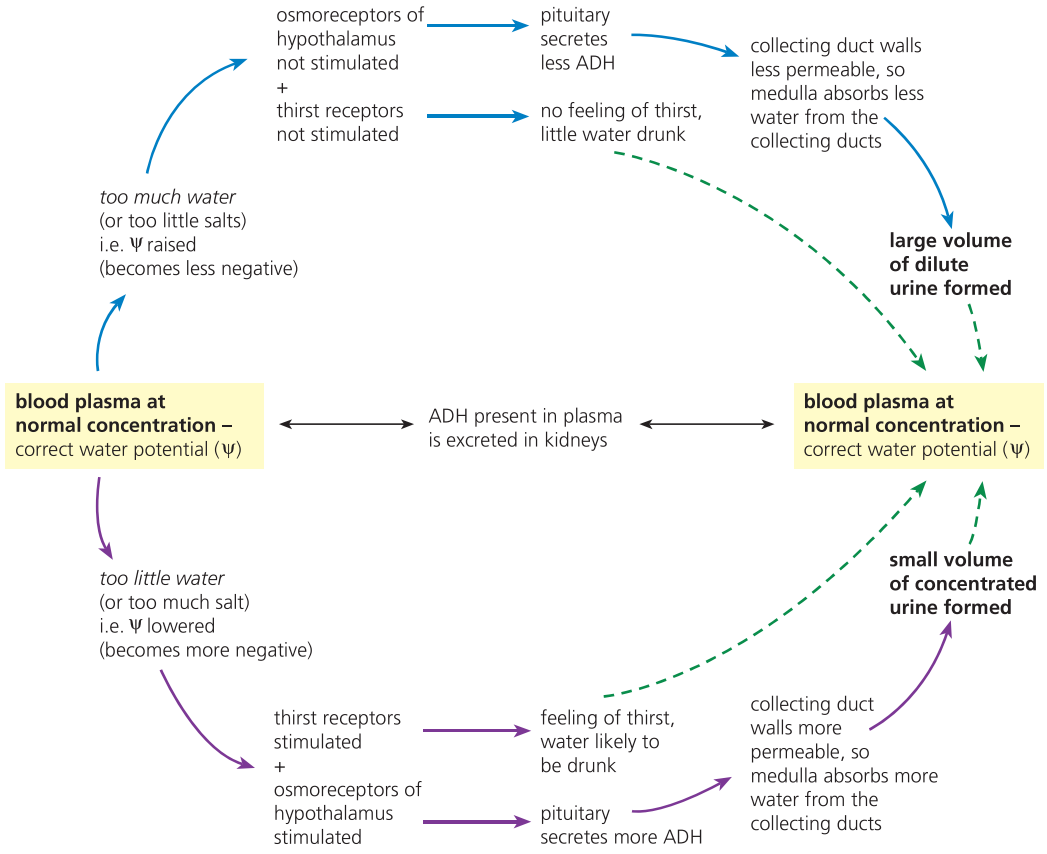


Figure 14.22 The collecting ducts and their role in osmoregulation

14.2 Homeostasis in plants

Stomatal aperture is regulated in response to the requirements for uptake of carbon dioxide for photosynthesis and conserving water.

By the end of this section you should be able to:

a) explain that stomata have daily rhythms of opening and closing and also respond to changes in environmental conditions to allow diffusion of carbon dioxide and regulate water loss by transpiration
b) describe the structure and function of guard cells and explain the mechanism by which they open and close stomata
c) describe the role of abscisic acid in the closure of stomata during times of water stress (including the role of calcium ions as a second messenger)

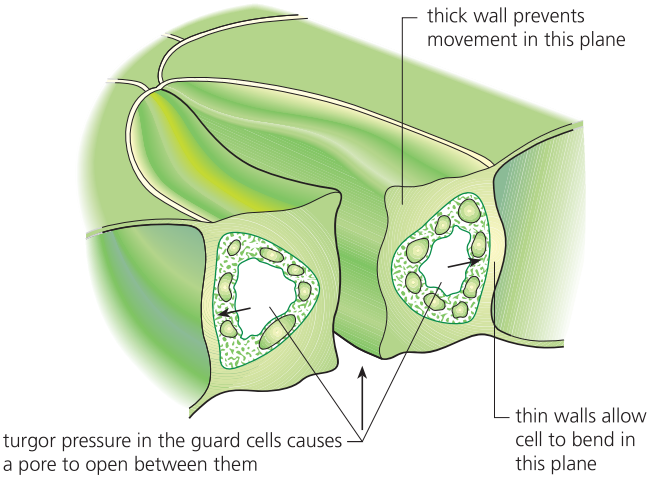


Figure 14.23 The thickness of guard cell walls and opening/closing movements

The stomata – structure and role

The tiny pores of the epidermis of leaves through which gas exchange can occur are known as stomata. Most stomata occur in the leaves, but some do occur in stems. In the broad-leaved plants, stomata are typically concentrated in the lower epidermis of the leaves. In the narrow, pointed leaves typical of many grasses for example, stomata may be equally distributed on both surfaces. The structure of stomata was introduced in Topic 7 (Figure 7.11 on page 139).

Remind yourself of their structure, now.

Each stoma consists of two elongated **guard cells**. These cells are attached to ordinary epidermal cells that surround them and are securely joined together at each end, but are detached and free to separate along their length, forming a pore between them. When open, stomatal pores connect the atmosphere external to the leaf with the air spaces between the living cells of leaf and stem. All these air spaces are interconnected. This is the pathway of diffusion of carbon dioxide into the leaf, and of water vapour out.

Stomata open and close due to changes in **turgor pressure** of the guard cells. They open when water is absorbed by the guard cells from the surrounding epidermal cells. The guard cells then become fully turgid and they push into the epidermal cell besides them. This is because of the variable thickness of cellulose in the walls, and because of the way cellulose fibres are laid down there (Figure 14.23). A pore then develops between the guard cells. When water is lost and the guard cells become flaccid, the pore closes again. This has been demonstrated experimentally (see Figure 14.25 on the next page).

Stomata tend to open in daylight and close in the dark (but there are exceptions to this diurnal pattern). This pattern of opening and closing of stomata, over a 24-hour period, is shown in Figure 14.24.

This daily pattern is over-ridden, however, if and when the plant becomes short of water and starts to wilt. For example, in very dry conditions when there is an inadequate water supply, stomata inevitably close relatively early in the day (because turgor cannot be maintained). This closure curtails water vapour loss by transpiration and halts further wilting. Adequate water reserves from the soil may be taken up subsequently, thereby allowing the opening of stomata again, for example, on the following day. The effect of this mechanism is that stomata regulate transpiration in that they prevent excessive water loss when this is threatened. Of course, when the stomata are forced to close, inward diffusion of carbon dioxide is interrupted.

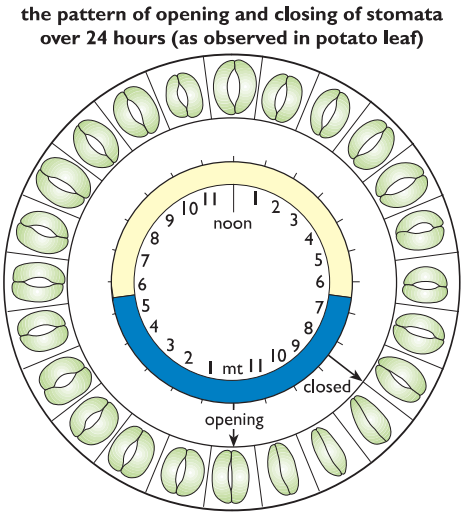


Figure 14.24 The diurnal pattern of stomatal opening and closing

In an experimental demonstration that turgor pressure of the guard cells causes the opening of the stomatal pore, a microdissection needle was inserted into a guard cell.

Observation: on release of the turgor pressure in one guard cell, the distinctive shape of the cell when the pore is open was lost. 'Half' of the pore disappeared.

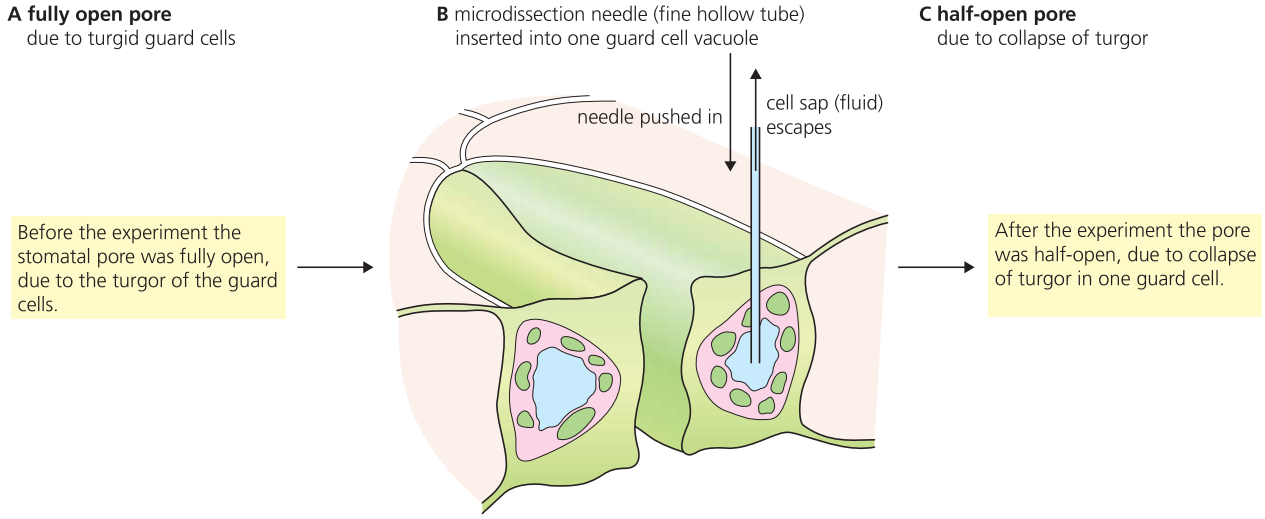


Figure 14.25 The opening of stomata – it's turgor pressure that does it!

The opening and closing of stomata

We have seen that, because of the structure of guard cell walls, stomata open when water is absorbed by the guard cells from the surrounding epidermal cells. Fully turgid guard cells push into the epidermal cell besides them, and the pore develops.

The guard cells contain chloroplasts (all the other epidermal cells do not), but opening is not due to the slow build-up of sugar by photosynthesis in these chloroplasts, leading to the turgor pressure change of opening. Opening is a much quicker process.

Stomatal opening depends on two biochemical changes:

1 **Potassium ions** (K^+ – a cation) are pumped into the guard cell vacuole, from surrounding cells, by proteins of the cell surface membranes, triggered by light (blue wavelengths). Calcium ions play a part in this process.

2 Starch, stored in the guard cells, is **converted to organic acids**, particularly malate. These anions accompany the K^+ cations in the guard cell vacuole.

Question

10 Examine Figure 14.26. Suggest why the stomatal apertures of the plant in the very dry conditions differed in both maximum size and duration of opening from those of the plant with adequate moisture.

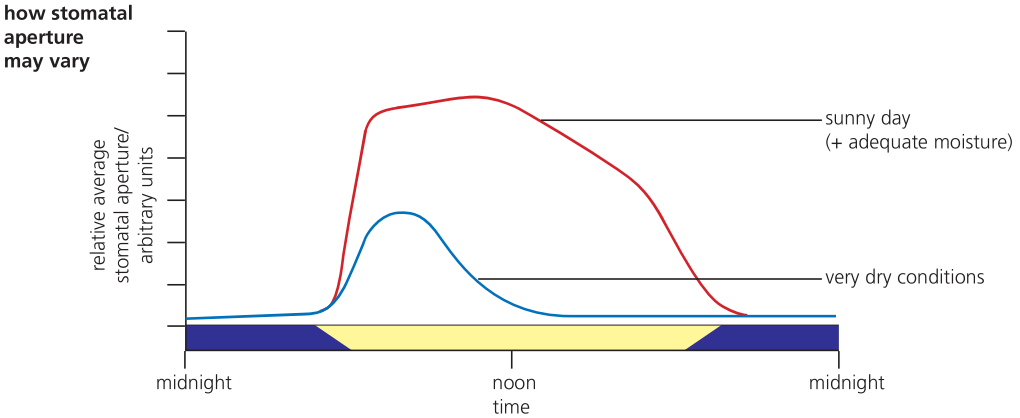


Figure 14.26 Stomatal opening and environmental conditions

The accumulation of these substances in the guard cell vacuole causes the water potential there to become more negative. So, net uptake of water from the surrounding ordinary epidermal cells occurs – making the guard cells extremely turgid (Figure 14.27).

Closing is brought about by the reversal of these steps in the dark. Alternatively closure occurs when triggered by the stress hormone abscisic acid (**ABA**), produced in leaf cells during wilting. We will discuss this situation next.

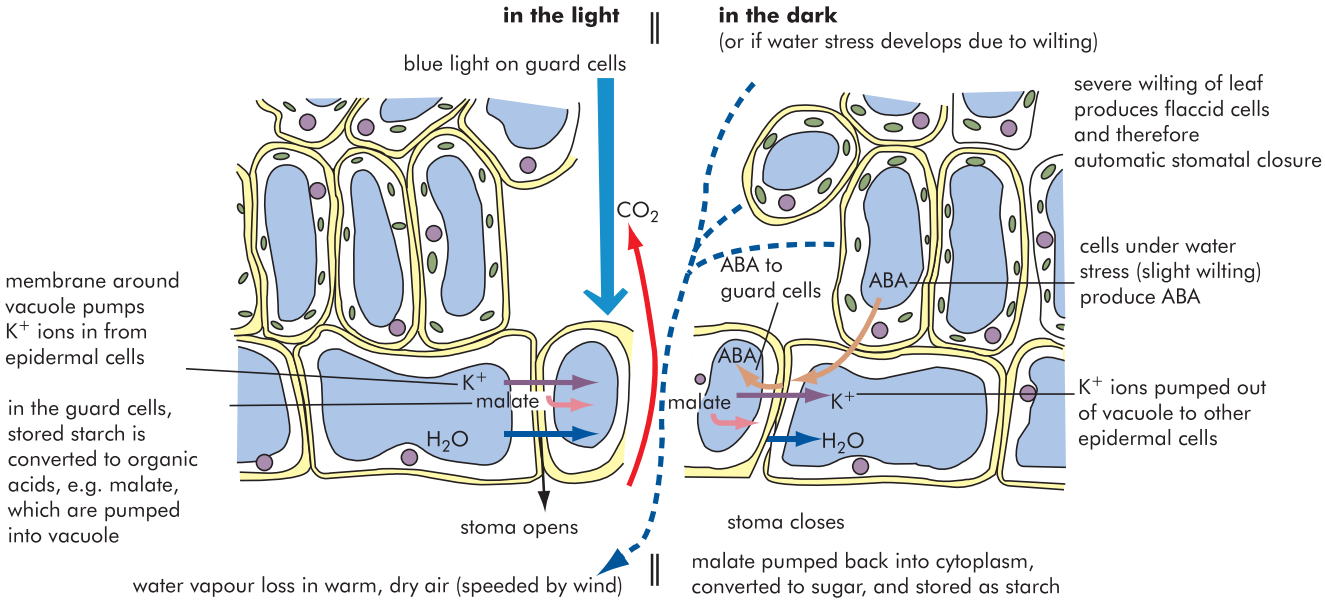


Figure 14.27 How opening and closing of stomata occurs

Abscisic acid and water stress in the leaf

Abscisic acid (ABA) is a plant growth inhibitor substance. The discovery of growth inhibitors in plants came from investigations of dormancy in buds and seeds. ABA is formed in mature leaves, in ripe fruits and seeds, and is present in dormant seeds. It accumulates in leaves of deciduous trees in late summer, just before their winter buds become dormant, and also in deciduous tropical plants at the onset of the dry season.

Of particular interest is the fact that ABA is also involved in the **closure of stomata under conditions of drought**. Green plants that are experiencing drought produce ABA in their chloroplasts, including those in the guard cells, and this 'stress hormone' triggers stomatal closure. This response involves calcium ions as the 'second messenger', as follows.

ABA triggers release of calcium ions from the cell sap in the guard cell vacuoles into the guard cell cytosol, via activated calcium ion channels in the tonoplast. Consequently, the concentration of calcium ions in the cytosol is abruptly increased, and directly triggers:

1 a sudden efflux of anions such as chloride ions from the cytosol, across the cell surface membrane, by activated anion channels
2 a sudden efflux of potassium ions from the cytosol, across the cell surface membrane, by activated potassium ion pumps.
3 inhibition of efflux of potassium ions into the guard cells (a feature of the stomatal opening mechanism).

As a result, the water potential of the guard cells is abruptly raised. It is now higher than the water potential of the surrounding cells, and a net efflux of water occurs from the guard cells. The guard cells become flaccid and the pores close.

Summary

- **Homeostasis** is the maintenance of a constant internal environment despite fluctuating external conditions. The ability to do this efficiently has allowed mammals as a group to live in very diverse habitats. **Negative feedback control** mechanisms operate in homeostasis. When departure from the normal or set value of conditions within an organism is detected (such as an abnormal blood sugar level), responses are set in motion which restore normal conditions and switch off the 'disturbance' signal.
- The **nervous system** and the endocrine system have interconnected roles in co-ordinating homeostatic mechanisms. The nervous system consists of receptors (sense organs) linked to effectors (muscles or glands) by neurones. **Hormones** are produced in endocrine glands, transported all over the body in the blood, and effect specific target organs.
- **Thermoregulation**, the process of body temperature control, is brought about by regulating heat loss and heat gain by the body, and is an example of a homeostatic mechanism. As endotherms, our main heat source comes from the level of respiratory metabolism in the tissues. The body temperature is held at or close to the optimum for the action of metabolic enzymes.
- **Blood glucose** regulation is essential because cells need a more or less constant supply, especially brain cells. Too high a glucose level lowers the water potential of the blood to the point where the circulation takes water by osmosis from tissue fluid and dehydrates cells and tissues. Too low a glucose level may lead to loss of consciousness and coma.
- The **kidney** is an organ of **excretion and osmoregulation**. In excretion the waste products of metabolism are removed from the blood and made ready for discharge from the body. In osmoregulation, the balance of water and solutes in body fluids is maintained at a constant level despite variations in intake. Kidney tubules (nephrons) work by pressure filtration of some of the liquid and soluble components of blood, followed by selective reabsorption of useful substances from the filtrate, active secretion of unwanted substances and adjustments to water and ion content according to their status in the body.
- Adrenalin and glucagon, peptide hormones that stimulate liver cells to convert stored glycogen to glucose, work by binding to external receptors on liver cells cell surface membranes, and indirectly triggering cyclic AMP (cAMP) within the cell cytosol. This '**second messenger**' triggers a cascade of reactions in liver cells in which the hormone signal is amplified. The impact of adrenalin on a liver cell is a **three-stage process** of cell signalling resulting in the **amplification** of the hormone signal. So, from one activated receptor molecule, perhaps 10^8 molecules of glucose 1-phosphate are formed from glycogen.
- Plants carry out gaseous exchange between their living cells and the air spaces between them, which are continuous throughout the plant. Carbon dioxide gas enters and oxygen and water vapour leave the leaves through the **pores** in **stomata**. Stomata consist of guard cells surrounding a pore which permits this gaseous exchange between leaves and environment. There is a daily rhythm of opening and closing of guard cells that is over-ruled in the event of excess water loss (leading to water stress within the plant). It is the plant growth regulator, **abscisic acid** that then triggers premature closure of stomata, so conserving water.

Examination style questions

1 **a)** Describe how nitrogenous waste products are formed and explain why they need to be removed from the body. [6]

b) Describe how the kidney removes metabolic wastes from the body. [9]

[Total: 15]

(Cambridge International AS and A Level Biology 9700, Paper 04 Q7 November 2005)

2 **a)** After the digestion of carbohydrates in the gut, glucose is absorbed into the blood stream and the concentration of blood glucose initially rises. Describe how a surge in blood glucose is normally regulated by the body and what happens to the bulk of this metabolite.

b) Draw a flow diagram showing the steps by which the concentration of blood glucose is held constant by a process of negative feedback.

[Total: 20]

3 **a)** Give an illustrate account of the structure of a stoma. [7]

b) Outline the mechanism by which the stomatal pore opens. [6]

c) How do stress conditions within leaves due to water shortage affect stomatal opening, and what part do plant growth regulators play in this response? [7]

[Total: 20]

4 **a)** Identify the distinctive roles of the endocrine and nervous systems in homeostasis, illustrating your answer by reference to the mechanism of thermoregulation in mammals. [10]

b) Outline the role of a 'second messenger' in the impact of a peptide hormone such as adrenalin on a liver cell. [10]

[Total: 20]