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A2 2 Biochemistry, Genetics and Evolutionary Trends

Unit A2 1: Physiology, Coordination and Control, and Ecosystems

Chapter 1 – Homeostasis and the Kidney

Students should be able to:

- **4.1.1** Demonstrate knowledge and understanding of the concept of homeostasis and the components of homeostatic mechanisms.
- **4.1.2** Demonstrate knowledge and understanding of the role of the mammalian kidney in excretion and osmoregulation.
- **4.1.3** Demonstrate knowledge and understanding of the gross structure of the mammalian kidney and excretory system.
- **4.1.4** Demonstrate knowledge and understanding of the structure of the nephron.
- **4.1.5** Demonstrate knowledge and understanding of the structure of the filter.
- **4.1.6** Demonstrate knowledge and understanding of the mechanism of ultrafiltration.
- **4.1.7** Demonstrate knowledge and understanding of the mechanism of selective reabsorption.
- **4.1.8** Demonstrate knowledge and understanding of the role of the loop of Henlé.
- **4.1.9** Demonstrate knowledge and understanding of the mechanism of osmoregulation in a mammal.
- **4.1.10** Demonstrate knowledge and understanding of the principle of negative feedback as exemplified by the role of ADH in osmoregulation in mammals.

Homeostasis

Mammalian tissue is essentially made up of a collection of cells bathed in a fluid medium or 'extracellular' fluid (tissue fluid). The composition of this fluid (and consequentially the **blood** due to the permeable nature of the capillary walls) must be kept **constant** in terms of factors such as water and ion content, temperature, pH and oxygen levels, **irrespective of the external conditions** outside the body.

Homeostasis is the maintenance of constant or steady state conditions within the body. Most homeostatic responses have three basic features:

- A **control system** with **sensors (receptors)** which provides information allowing the **monitoring** of the factor being controlled. The receptors can be in the brain or localised throughout the body. However, the monitor (control centre) is usually in the brain.
- If the receptors show a departure from normal levels (the **set point**) for the factor being controlled, for example temperature, then a **corrective mechanism** brings about the changes required to return the factor to its normal level. For example, if mammals overheat, the corrective measures can include sweating and the vasodilation of capillaries in the skin.
- The corrective mechanism involves a **negative feedback** system. *Negative* feedback occurs as the return of the factor being controlled to its normal level (set point) causes the corrective measures to be turned off. This prevents over-correction. In our example of temperature regulation, the stimulation of the sweat glands and the degree of vasodilation of blood capillaries is reduced as blood (body) temperature returns to normal.

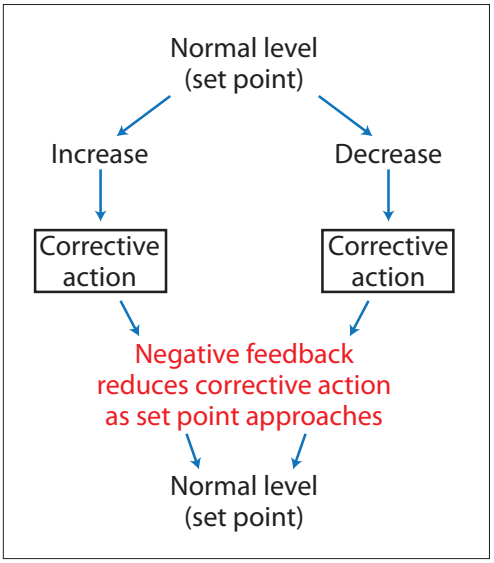
Communication between the sensors/receptors and the monitor (and between the monitor and the effectors that bring about the corrective response) can be by **nervous**

or **hormonal** control. The control of temperature, as described on page 5, is primarily under nervous control, whereas control of blood glucose levels is under hormonal control.

Homeostatic control of mammalian body systems is essential for many reasons including:

- providing the optimum conditions for enzyme reactions in terms of pH and temperature.
- avoiding osmotic problems in cells and in body fluids.

While mammals have complex and effective homeostatic controls, many other animals have simpler controls that are less able to keep the internal environment constant, for example, the body temperature of insects usually varies with the external environment. Consequently, many species of less complex animals avoid large swings in body conditions by living in an environment where the external environment is relatively constant, such as the sea.



The general principles of homeostatic control

The kidney

A major homeostatic organ in mammals is the kidney. The kidney has two very important functions:

Excretion is the removal of the toxic waste of metabolism. The main toxic waste product excreted by the kidneys is **urea**, a nitrogenous waste produced during the breakdown of excess amino acids (and nucleic acids) in the liver. Other toxic products are also excreted by the kidneys, for example creatinine, a waste product produced from the breakdown of creatine phosphate (a molecule important in ATP synthesis) in muscles.

Osmoregulation is the control of the water potential of body fluids. The kidney helps regulate the water potential of the blood through controlling both the volume and concentration of urine produced.

The structure of the urinary (excretory) system

Note: Traditionally the body system including the kidneys, ureters, bladder and urethra has been called the excretory system. However, this is perhaps not the best term as excretion is also carried out by other parts of the body (for example, CO_2 is excreted from the lungs); consequently, many textbooks now refer to it as the urinary system.

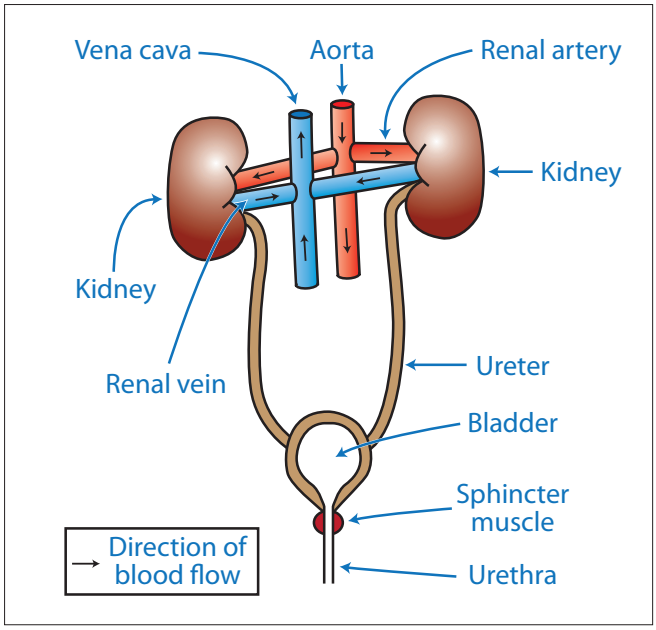
The following figure shows the urinary (excretory) system. Blood travelling through the aorta and renal artery reaches the kidney at the high pressures required for filtration. In essence, the kidney operates as a complex filter, keeping useful products in the blood and eliminating excretory products and excess water.

Filtered blood leaves the kidney via the renal vein whereas the excretory products and excess water pass into the ureter as urine, which takes it to the bladder for storage. Sphincter muscles in the base of the bladder control the release of the urine, which exits the body through the urethra.

Kidney structure

A section through a kidney shows that it contains two main zones (regions) of tissue:

- The **cortex** is the outer dark region immediately under the thin covering layer (capsule).
- The **medulla** is the inner lighter region. The medulla is subdivided into a number of pyramids whose apices extend down into a large central cavity called the **pelvis**.

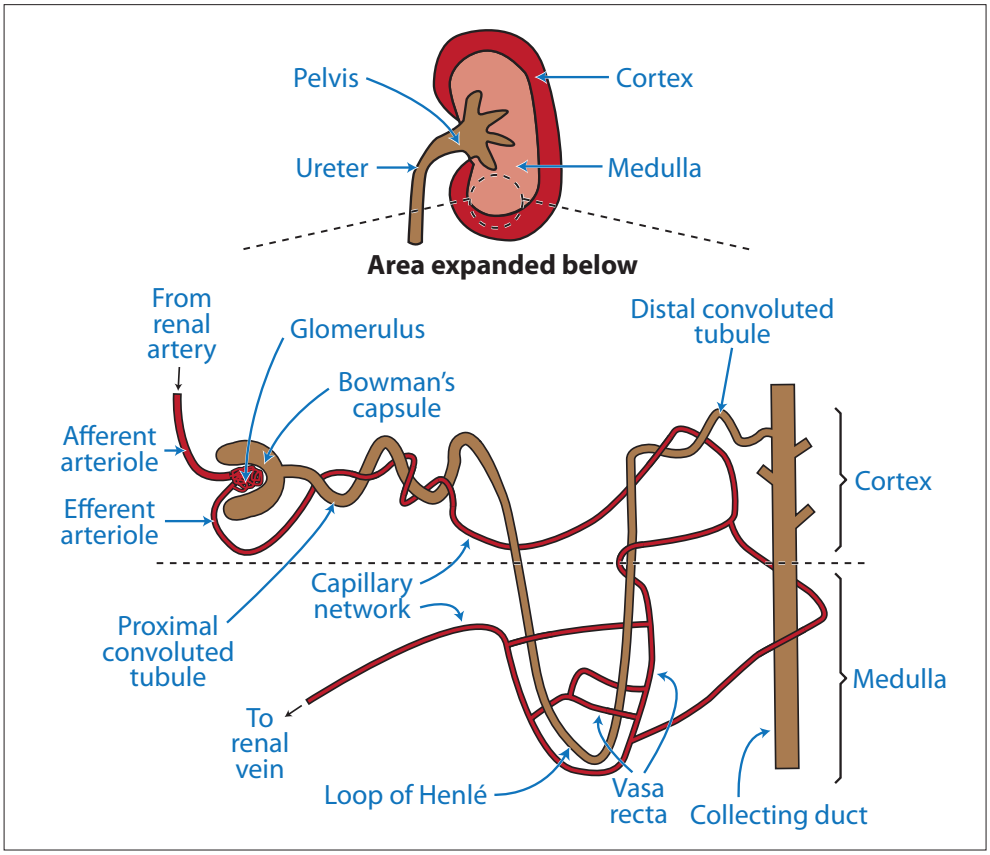


The urinary (excretory) system

The functional unit of the kidney is the **nephron**. There are over one million nephrons in each kidney – each operating as an individual filter. As seen in the diagram below, the nephron originates and ends in the cortex, with a long central region (the loop of Henlé) extending down into the medulla. Many nephrons join with a collecting duct, which also extends down through the medulla.

The structure of the nephron

The nephron originates as a cup-shaped **Bowman's capsule** (also called the **renal capsule**). Each Bowman's capsule is supplied with blood from an **afferent arteriole**



The location and structure of a nephron

(a branch of the renal artery) and the blood leaves through an **efferent arteriole**. Within the 'cup' of the capsule, the arteriole branches to form a tightly coiled knot of capillaries called the **glomerulus** – capillaries which subsequently unite before forming the efferent arteriole.

After leaving the Bowman's capsule, the efferent arteriole branches to form a capillary network (the **vasa recta**) that remains closely associated with the rest of the nephron.

In the nephron itself, the Bowman's capsule extends into a coiled tube called the **proximal convoluted tubule** (proximal = first; convoluted = coiled). The proximal convoluted tubule extends into the **loop of Henlé** which dips down into the medulla of the kidney. The descending part of the loop is, unsurprisingly, called the descending limb. The loop of Henlé then bends sharply and returns back up through the medulla (the ascending limb) to reach the cortex again. At this stage it becomes the **distal convoluted tubule**. The distal convoluted tubule (and the distal convoluted tubules from many other nephrons) joins a **collecting duct**. The collecting ducts converge at the base of the pelvis and empty their contents (now called urine) into the ureter which takes the urine to the bladder.

Kidney function 1 (excretion – producing urine)

Kidney (and nephron) function involves two main processes:

- **Ultrafiltration** – The filtration of plasma and substances below a certain size into the Bowman's capsule (nephron).
- **Reabsorption** – As ultrafiltration is based purely on molecular size (and not whether products are useful or not), it is essential that filtered useful products are selectively reabsorbed back into the bloodstream from the nephron.

Ultrafiltration

Blood entering the glomerulus has a **high hydrostatic pressure** for a number of reasons:

- The **short distance** from the heart that the blood travels down the aorta and into the renal artery before branching into the kidney arterioles.
- The fact that the afferent arteriole of each glomerulus is **wider** than its efferent arteriole.
- The **coiling of the capillaries** in the glomerulus further restricts blood flow therefore increasing pressure.

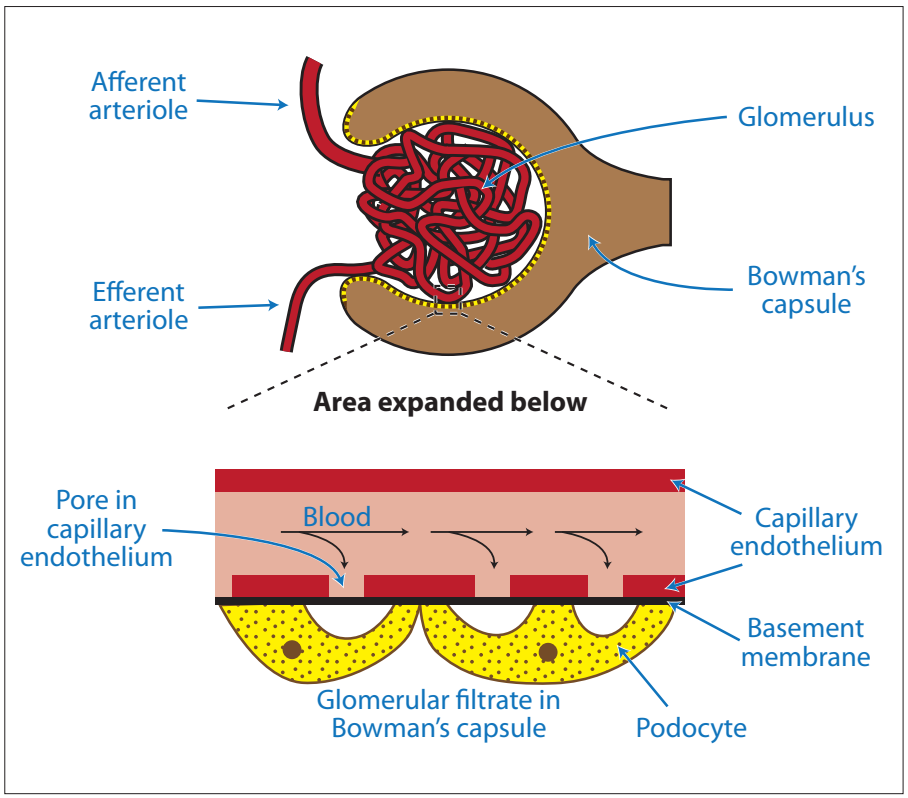
The high hydrostatic pressure produced forces the smaller components in the blood (glucose, amino acids, salts, water and urea) out of the capillaries and into the Bowman's capsule. However, the larger components of the blood, including blood cells and plasma proteins, are too large to pass through into the nephron.

The process of ultrafiltration is aided by the structure of the capillary walls of the glomerulus and the lining of the Bowman's capsule itself.

As seen in the following diagram, the single layer of **squamous** (flattened) **endothelial cells** that form the walls of glomerular capillaries contain small **pores** and the Bowman's capsule is lined with specialised cells known as **podocytes**. Podocytes have extensions in two planes that allow the filtered material to pass through easily. It is the **basement membrane** (separating the capillary and podocytes) that is the **effective filter**

and determines which components of the blood enter the Bowman's capsule – it is the basement membrane that prevents the blood cells and plasma proteins from leaving the blood.

Note: The basement membrane is an extracellular matrix (gel) formed of many different substances including proteins. It is effectively a molecular sieve.



The site of ultrafiltration

In effect, each of the **three layers** separating the blood in the capillary and the inside of the Bowman's capsule is specialised through either being porous (capillary endothelial cells and podocytes) or through acting as a filter (basement membrane).

The **glomerular filtrate** (the substances that pass through the basement membrane and enter the Bowman's capsule) is similar to blood (except for the plasma proteins and blood cells that are too large to penetrate the membrane).

Note: Apart from the podocytes lining the Bowman's capsule, the remaining epithelial cells lining the nephron (and the collecting duct) are cuboidal (cube-shaped) epithelial cells.

The filtration force – Ultrafiltration is a necessary process in kidney function. However, the hydrostatic pressure forcing through water and small molecules is not the only force involved. In terms of water potential, it is important to compare the forces on each side of the membrane. For filtration to occur, the water potential within the glomerular capillaries (blood plasma) must exceed the water potential within the Bowman's capsule (glomerular filtrate), ie the glomerular filtrate must have a more negative water potential. How is this difference in water potential produced?

Remember that water potential has two components – pressure potential and solute potential. The hydrostatic pressure **(pressure potential)** of the blood is much greater than the hydrostatic pressure (back pressure) created by the filtrate in the nephron for reasons listed above.

The **solute potential** is represented by the plasma proteins, as there are plasma proteins in the blood in the glomerular capillaries but not in the filtrate. The filtrate has a less negative solute potential than the blood in the glomerulus. Therefore, although the difference in solute potential **opposes** filtration, this effect is insignificant when compared to the differences in hydrostatic pressure across the basement membrane;

a difference that very strongly promotes filtration. Consequently, the **net filtration pressure** causes fluid to move from the glomerular capillaries into the Bowman's capsule.

Worked example

In this example the water potential of the blood plasma in the glomerulus is higher, ie more positive or less negative (2.0 kPa) compared to the water potential of the glomerular filtrate in the Bowman's capsule (0.7 kPa), therefore producing the net filtration force or pressure (+ 1.3 kPa) that forces liquids and small molecules through the basement membrane.

Blood plasma (in glomerulus)	Glomerular filtrate (in Bowman's capsule)
$\psi_S = -3.5$ kPa (due to presence of plasma proteins) $\psi_P = 5.5$ kPa (high hydrostatic pressure)	$\psi_S = -0.7$ kPa (less negative due to absence of plasma proteins) $\psi_P = 1.4$ kPa (low hydrostatic pressure)
$\psi_{plasma} = 2.0$ kPa	$\psi_{filtrate} = 0.7$ kPa
Net filtration force = +1.3 kPa	

Reabsorption

Useful blood products temporarily lost to the glomerular filtrate are reabsorbed back into the blood, mainly as the filtrate passes along the **proximal convoluted tubule**. **Glucose** and **amino acids** – small enough to pass through the basement membrane but too valuable to be lost in the urine – are **selectively reabsorbed** by **facilitated diffusion** and **active transport**.

Note: The term selectively reabsorbed is used as toxic substances such as urea are not actively reabsorbed but (mainly) remain in the filtrate.

As glucose, amino acids and some salts are actively reabsorbed into the blood the osmotic effect created causes over **70%** of the **water** in the filtrate to re-enter the blood capillaries passively by **osmosis**. **Small plasma proteins** which may have passed through the basement membrane in the glomerular filtrate are reabsorbed by **pinocytosis**.

Note: The reabsorption of glucose, amino acids and salts reduces the solute potential in both the (reabsorbing) epithelial cells of the tubule and the blood in the capillaries, thus creating the osmotic gradient required for the reabsorption of water.

The table below shows relative values of some of the substances filtered into the nephron and subsequently reabsorbed in the proximal tubule.

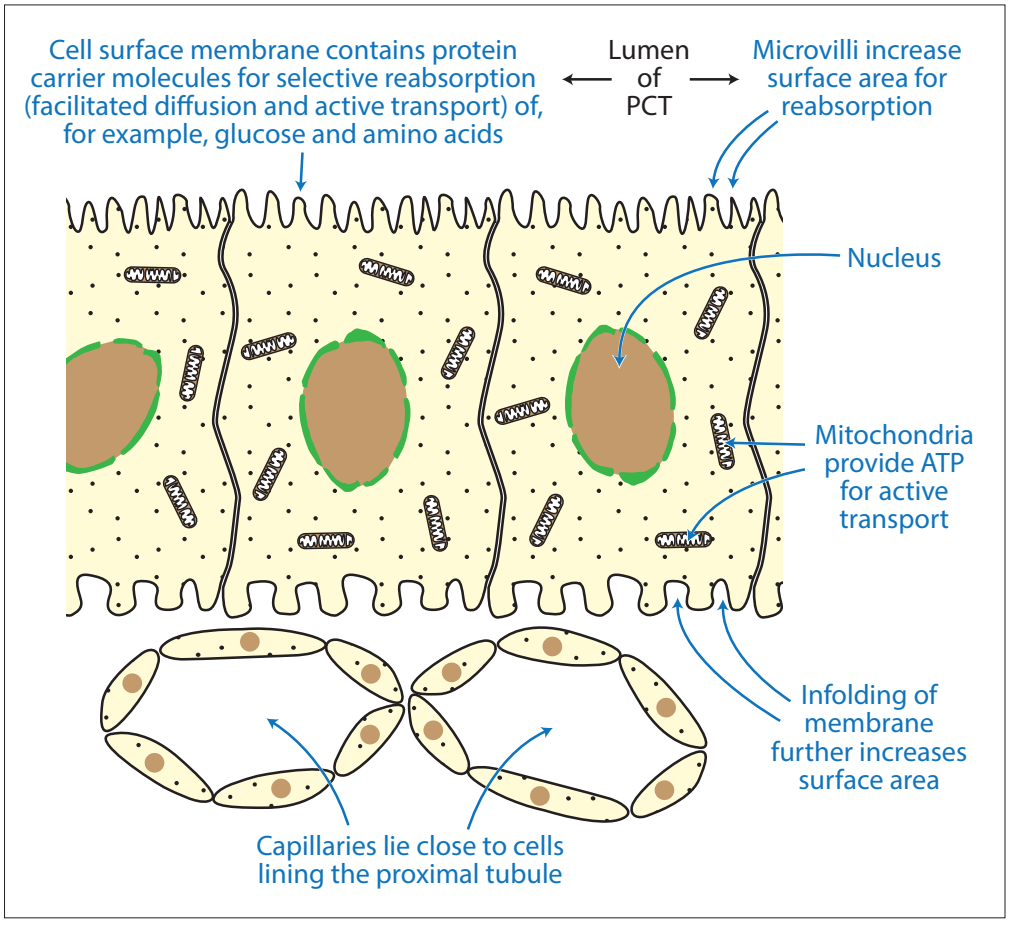
Substance	Amount in blood plasma / %	Amount filtered into glomerular filtrate / %	Amount reabsorbed back into blood in proximal convoluted tubule / %
Large plasma proteins	100	0	N/A
Glucose	100	100	100
Amino acids	100	100	100
Urea	100	100	< 50 (by diffusion)

Note 1: Although urea (being a toxic metabolic waste) is not selectively reabsorbed, some urea passes from the nephron back into the blood by diffusion. Theoretically up to 50% can diffuse back into the blood.

Note 2: The glucose and amino acids can be absorbed by **facilitated diffusion** as long as the concentration gradient permits. **Active transport** is necessary to ensure that all the glucose is reabsorbed from the nephron back into the capillary network.

The epithelial cells of the proximal convoluted tubule have high levels of metabolic activity and continually carry out energy-demanding processes such as active transport. Consequently, they are highly adapted for this role as seen in the diagram below.

By the time the filtrate reaches the end of the proximal tubule, it will have no glucose or amino acids present as they all will have been reabsorbed. Although some urea diffuses back into the blood by diffusion along the length of the proximal convoluted tubule, as noted in the table, the **concentration of urea** in the filtrate increases along its length due to the reabsorption of water. At the end of the proximal convoluted tubule, the filtrate is **isotonic** with the blood plasma.



Adaptations of the epithelial cells lining the proximal tubule

Further regulation of blood composition takes place in the **distal convoluted tubule**. The pH and ionic composition of the blood in the capillaries surrounding the tubule are adjusted and some toxic substances, for example, creatinine (a byproduct from muscle metabolism), are secreted from the blood into the filtrate for disposal.

Kidney function 2 (osmoregulation)

Osmoregulation is a homeostatic process that controls water balance in the body. It does this through controlling water balance in the blood; consequently the water content of the tissue fluid and the cells is also controlled.

The collecting duct is where the water regulation takes place. Although **most water** is reabsorbed in the proximal convoluted tubule (and some from the descending limb of the loop of Henlé – see page opposite), the process is passive and the exact amount of water reabsorbed back into the blood cannot be controlled. However, reabsorption in the collecting ducts can be controlled by varying the permeability of the collecting duct walls – this is where the fine control of water balance takes place. The **antidiuretic hormone (ADH)** is crucial in this process as it can control the degree of permeability of the collecting duct walls.

The role of the antidiuretic (ADH) hormone

ADH is *produced* in the **hypothalamus** (part of the brain just above the junction with the spinal cord) and then secreted into the **posterior lobe** of the **pituitary body** where it is *stored*. The solute potential of the blood is monitored by **osmoreceptors** (specialised cells) in the **hypothalamus**.

What happens if the blood becomes too concentrated? Blood can become too concentrated, ie a more negative solute potential, for many reasons. For example, sweating after exercise or on a hot day, not drinking enough water or eating a very salty meal. If this happens:

- the solute potential of the blood becomes ***more* negative** and this is detected by the osmoreceptors in the hypothalamus.
- the posterior lobe of the pituitary body releases ***more* ADH** into the blood.
- this causes the walls of the distal convoluted tubules and the collecting ducts to become ***more* permeable** – special channel proteins (aquaporins) open which helps make the walls of the collecting ducts more permeable.
- therefore ***more* water is reabsorbed** from the collecting ducts back into the blood.
- the net result is that the solute potential of the blood returns to normal (becomes less negative) and a smaller volume of ***more* concentrated (hypertonic) urine** is produced.
- this process exemplifies **negative feedback**. As the blood concentration changes it sets in train a process (as described above) that returns the solute potential back to normal; as the blood concentration returns to normal the release of ADH reduces, returning to normal levels.

What if the blood is too dilute? This is most likely to happen when drinking (hypotonic) liquid. In this situation the opposite happens: the blood develops a higher solute potential (becomes less concentrated) and this is detected by the osmoreceptors in the hypothalamus, ***less*** ADH is released, the walls of the collecting ducts become ***less*** permeable and ***less*** water is reabsorbed back into the blood (large quantities of **dilute (hypotonic) urine** are produced).