Bio Factsheet
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Negative Feedback Mechanisms

Negative feedback is an important principle of homeostasis**.** When a physiological process or value (for example, blood glucose concentration), varies from the norm or mean value, a mechanism kicks in to bring it back to the mean. When the mean has been reached, the controlling mechanism is damped (reduced in activity, but not completely switched off).

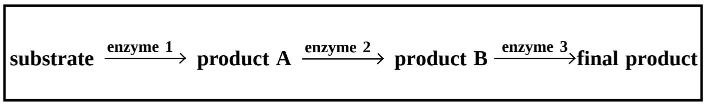
This Factsheet summarises the most important examples of negative feedback in living organisms.

1. Enzyme control of metabolic reactions

Enzymes catalyse almost every metabolic reaction in living organisms. By regulating the synthesis and activity of enzymes, a cell can control the rate of the metabolic reactions that go on inside it.

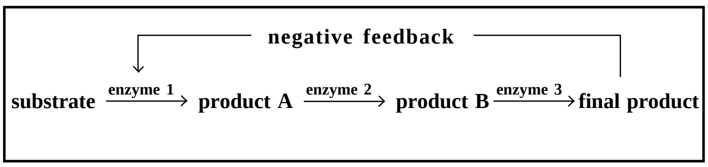
Many metabolic reactions occur in a series of steps. Each of these steps may be controlled by a different enzyme (Fig 1).

Fig 1 A 3-step metabolic reaction



The rate at which a substrate is used up, or the rate at which the final product is formed, can be controlled by altering the rate at which enzymes work. As the reaction proceeds, the amount of the final product increases. At some point, the accumulation of this product then exerts an inhibitory effect on enzyme 1. This stops the reaction proceeding. The amount of final product then begins to go down as it is used up or transported away. At a certain point, the inhibitory effect is removed, enzyme 1 become active again and final product begins to accumulate again – and so on and so on. This is negative feedback; the accumulation of final product set in motion a mechanism (inhibition) that led to its level going down again (Fig 2).

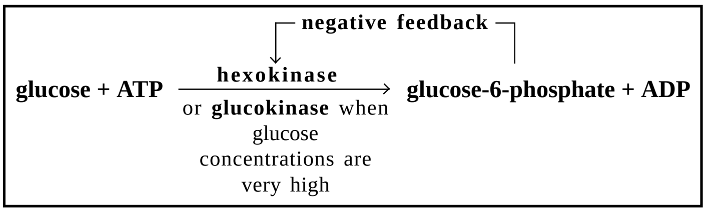
Fig 2 Negative feedback in enzyme activity



One example of this involves the first stage of glycolysis in respiration.

When glucose enters the cells of respiring tissues it is first modified to glucose-6-phosphate in order to make it more reactive. This is the first reaction in the glycolysis pathway (Fig3). High concentrations of glucose-6-phosphate then inhibits hexokinase which prevents too much product (glucose-6-phosphate) accumulating.

Fig 3 Negative feedback in glycolysis



This reaction is important because:
- The addition of a phosphate group (phosphorylation) makes the glucose molecule more reactive.
- The phosphorylation of the glucose molecule makes it more difficult for it to escape out of the cell.
- It is the main regulatory step in the glycolysis pathway.

The regulation of a reaction by the end product is called **end product inhibition**.

2. Regulation of blood glucose concentration

The concentration of glucose in the blood is maintained at about 800mg/dm^3. This is crucial as glucose is a crucial respiratory substrate and most cells need a continuous supply. Brain cells, in particular, are sensitive to any fall in blood glucose concentration.

Two hormones**, insulin and glucagon**, control blood glucose concentration. The release of these two hormones is regulated by negative feedback.

When the blood glucose level falls below the norm, this is sensed by receptors on the alpha cells of the **islets of Langerhans** of the pancreas. This stimulates the alpha cells to release glucagon into the blood. Glucagon eventually arrives at the liver. It then binds with its glycoprotein receptor on the surface of the liver cells. This triggers:
- the conversion of glycogen to glucose
- the conversion of amino acids to glucose
- a slowing of the rate of respiration

So blood glucose levels go back up to their normal concentration. The alpha receptors become switched off.

When the blood glucose concentration rises above the norm, it is sensed by receptors on the beta cells of the islets. Insulin is released into the blood, and binds with its glycoprotein receptors on the surfaces of certain cells. This triggers:
- Muscle and fat cells to absorb glucose faster
- An increase in the rate of respiration
- Muscle and liver cells to convert glucose into glycogen faster

So blood glucose concentration falls back to the norm and so the beta receptors are switched off.

So in each case, the movement of glucose concentration away from the equilibrium value of 800mg/dm^3 has triggered a mechanism that will bring it back to that figure; negative feedback control.

3. Control of metabolic rate

The metabolic rate is the rate at which the cells of the body carry out their anabolic (building-up) and catabolic (breaking-down) reactions. The metabolic rate is carefully controlled via negative feedback.

If the metabolic rate falls:
- The hypothalamus in the brain detects the fall and releases more thyrotropin releasing hormone
- This causes the pituitary gland to release more thyroid stimulating hormone
- This causes the thyroid gland to release more thyroxine
- This causes the metabolic rate of cells to increase

Once the metabolic rate has got back to normal, the hypothalamus slows down its release of thyrotropin releasing hormone.

4. Control of body temperature

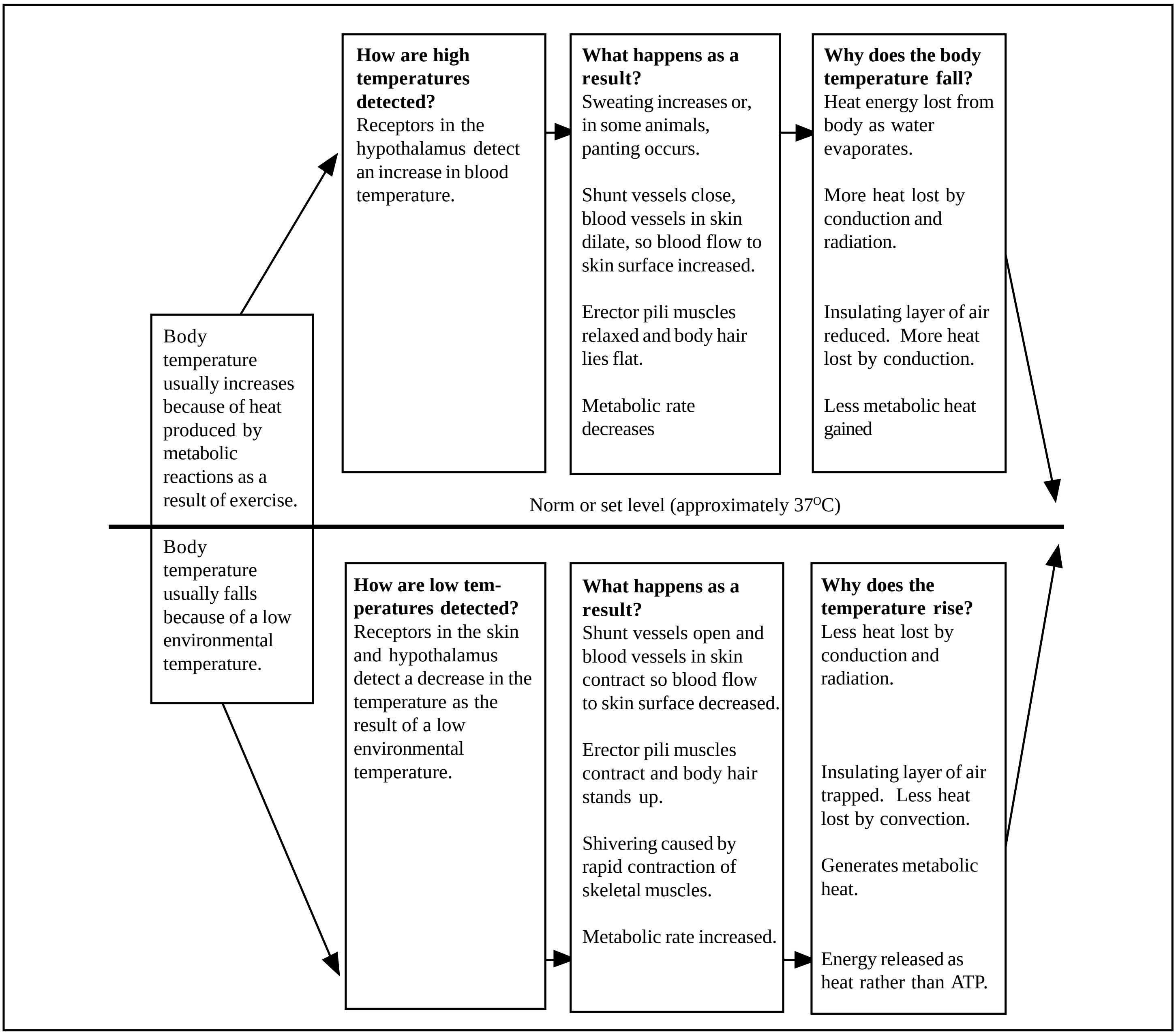
Mammals and birds are **endotherms** – they can maintain a constant body temperature, above that of their surroundings**.** This gives them a huge advantage over the rest of the animal kingdom, all of which are poikilotherms:

Endotherms can:
- maintain an internal temperature close to the optimum for their enzymes
- exploit very cold or very hot habitats and can remain active all year-round or during the day and night.

The big **disadvantage** is that maintaining a constant temperature requires huge amounts of energy!

Changes in the body temperature of a mammal or bird set in motion mechanisms which return the body temperature to its norm or set level. Fig 4 shows how negative feedback is used to control the body temperature of a mammal.

Fig 4. Control of body temperature



5. The actions of the autonomic nervous system (ANS)

Generally, the **sympathetic system** tends to increase or accelerate activity to meet increased demands by the body. The **parasympathetic system** tends to reduce or slow up activity, allowing organs to rest when the body's needs are reduced. The two systems act in harmony to keep the body systems working at the level needed.

Often, this will involve negative feedback. The cardiac cycle is an example.

The cardiac cycle is initiated and co-ordinated by the heart itself. However, the cardiac output must be adjusted to meet the varying needs of the body.

Stimulation of the heart by the **sympathetic nervous system (SNS**) increases cardiac output, by:
- increasing the frequency of the heartbeat, and
- increasing the force with which the cardiac muscle contracts.

Stimulation of the heart by the **parasympathetic nervous system** reduces the cardiac output by:
- reducing the frequency of the heartbeat, and
- reducing the force of contraction.

These two systems operate through **negative feedback control** involving two controlling centres in the medulla of the brain. These are the **cardioacceleratory centre** (CAC) which is concerned with increasing cardiac output (via the hormone noradrenaline) and the **cardioinhibitory centre** (CIC) which reduces cardiac output (via acetylcholine).

Similarly, blood pressure – detected by the carotid sinus in the wall of the carotid artery – is under negative feedback control via the cardiac centers in the medulla. If blood pressure increases, signals are sent to the medulla which then triggers vasodilation and lowered heart rate to bring blood pressure back down. In turn, this leads to the signals from the carotid sinus being switched off.

6. Regulation of water balance

Any increase in blood sodium concentration is detected by receptors in the hypothalamus of the midbrain.
- ADH is then secreted from the posterior pituitary gland into the blood
- The ADH attaches to target receptors on the collecting duct walls and makes them permeable to water
- Water is then reabsorbed back into the blood
- The blood sodium concentration falls

This means that the hypothalamus is no longer stimulated and ADH release is damped or switched off and so the collecting duct walls revert to being water impermeable. Thus, the urine becomes more dilute whilst the blood sodium concentration starts to rise once more, until the ADH release is switched on again (Fig 6).

Negative feedback processes also operate in the production of sperm in males and in the female menstrual cycle. At ovulation, the increased level of estrogens depresses FSH production. Following ovulation, the follicle transforms into the corpus luteum ("yellow body"), which produces the hormone progesterone which helps to maintain the endometrium ready for a fertilized ovum. If pregnancy doesn't occur, the high levels of estrogens and progesterone gradually fall and menstruation occurs. The levels of the ovarian hormones oestrogen and progesterone drop, thus their inhibiting effect on the pituitary hormones is lifted. FSH and LH production now begins to rise, and a new cycle starts.

7. The regulation of calcium

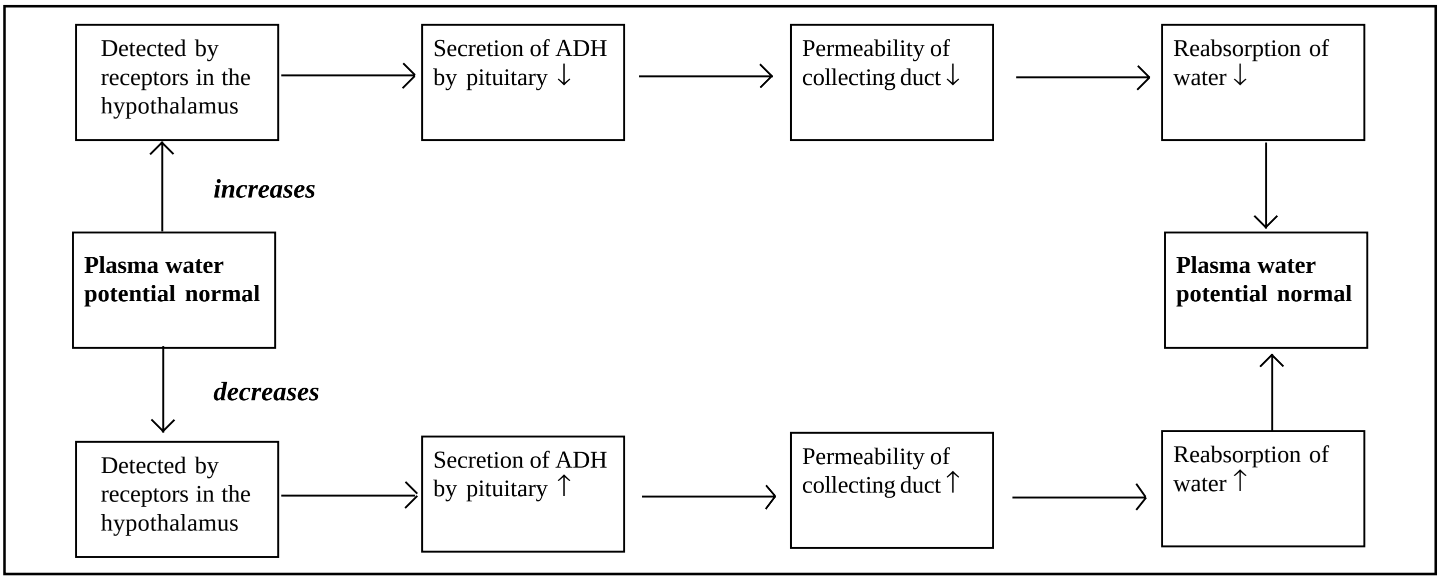
The absorption of calcium ions (and phosphate) from the gastrointestinal tract requires the presence of **vitamin D** in its activated form. If active vitamin D is deficient then calcium cannot be absorbed and abnormalities may appear in the bones. In children this may cause **rickets** with the symptoms of stunted growth and bent limb bones. In adults it can cause **osteomalacia** where the bones become weak and fragile due to loss of calcium and phosphate.

The thyroid hormone calcitonin lowers the levels of calcium and phosphate in blood whilst the hormone parathormone from the parathyroid glands promotes the release of calcium and phosphate from the bone to the blood when required. These actions of calcitonin and parathormone are under negative feedback control from the thyroid and parathyroid glands.

Conclusion

The overall point of negative feedback is that it ensures that our systems always come back to equilibrium. It is an essential part of homeostasis.

Fig 6. Regulation of water balance in the kidney



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