

## Endocrine system

### Components

Endocrine glands include the pineal, thyroid, parathyroids, adrenals, pancreas, gonads, placenta, kidneys, stomach, duodenum, liver, skin, thymus, heart, pituitary gland and hypothalamus of the brain. Unlike in other systems, they are not connected. They are scattered throughout the body, often interacting with one another, and form a functional system that secretes hormones into the bloodstream.

- Some hormones are secreted by glands which are purely endocrinal, such as the adrenal glands or thyroid.
- Some are produced by glands which have both endocrine and exocrine (secretions pass through ducts to site of action) functions, such as the stomach and pancreas.
- Some are made by neurosecretory neurones.
- The ovaries and testes manufacture both hormones and gametes.

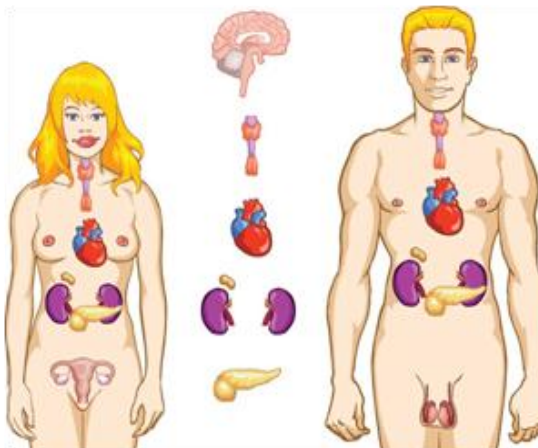


Figure 1 Components of the endocrine system.

### Functions

With the nervous system, the endocrine system regulates and coordinates all the other body systems. While the nervous system can respond rapidly and usually for short intervals, the endocrine system can regulate activities over the long term. This is done by secreting hormones into the blood. Hormones<sup>1</sup> have a key role in controlling growth and reproduction. They regulate the composition of body fluids and stabilise the water content of the body.

Overall the functions of the endocrine system are to:

- regulate metabolism and water and inorganic ion balance;
- enable adaptations to adjust to stress;
- regulate red blood cell production;
- control reproduction;
- promote smooth sequential growth and development;
- act with the autonomic nervous system to control blood circulation and the digestion, absorption and assimilation of food.

### Key mechanisms

#### Target cells

Only specific target cells can respond to each hormone. Each target cell has a receptor which can bind with the specific hormone. This may be in its cell membrane or inside the cell. Binding the hormone triggers a chain of events inside the target cell which regulates the activity of the cell.

A target cell may be influenced by more than one hormone. For example, liver cells have receptors for insulin, which promotes the conversion of glucose into glycogen and receptors for glucagon which reverses that process.

<sup>1</sup> See *Hormones* for examples.

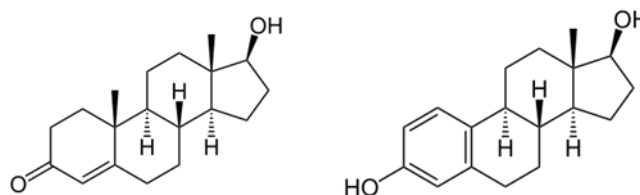
A single hormone may affect more than one type of target cell, for example testosterone stimulates sperm production by the testes, but also enhances a spurt in bone growth during puberty.

### Trophic hormones

Some hormones control the production and secretion of other hormones. For example, thyroid stimulating hormone (TSH) is a trophic (or tropic) hormone that maintains the thyroid gland and stimulates the secretion of thyroxine.

### Chemical classification

Hormones may be amines, steroids, or peptides (includes proteins). Most are peptides. The amines are derived from tyrosine and include those secreted by the thyroid gland and adrenal medulla (those from the latter are called catecholamines). Steroids include those secreted by the adrenal cortex and gonads and are derived from cholesterol.



**Figure 2** Minor differences in chemical structure may give rise to major differences in activity and physiological responses. For example, the structure of testosterone (left) is very similar to that of oestradiol (right), a form of oestrogen.

### Solubility

Variation in structure affects solubility, which determines the mechanism of action at the target cell and how a hormone is transported by the blood.

- Peptides are hydrophilic and highly water-soluble, but have low lipid solubility – they are transported dissolved in the plasma.
- Steroids and amines are lipophilic, dissolving well in lipids but poorly in water – they are transported reversibly bound to plasma proteins.
- Catecholamine hormones are hydrophilic, but 50% are transported reversibly bound to plasma proteins.

### Therapeutic administration

The digestive system does not secrete enzymes that hydrolyse steroid and amine hormones, so when used as medicinal drugs, such as in the case of sex steroids in birth control pills, these can be taken orally and absorbed intact from the gut into the blood.

Peptide hormones cannot be taken orally as they will be hydrolysed by proteases into inactive fragments. Insulin deficiency is therefore treated by daily injections.

### Mode of action

When a hormone binds with a particular receptor in its target cell membrane, it elicits a highly specific response. Receptors may be outside or inside the target cell. Hydrophilic hormones are poorly lipid soluble and cannot pass through membranes – they bind with receptors on the outer cell membrane surface. Lipophilic hormones pass easily through the phospholipid layer of the target cell membrane – they bind with receptors inside.

### Hydrophilic hormone action

A few hydrophilic hormones alter cell membrane permeability when they bind to surface receptors, for example, by altering the conformation of neighbouring proteins to open or close channels.

Most activate second-messenger systems inside the target cell. This may either alter the activity of pre-existing proteins or activate specific genes to initiate protein synthesis. The precise response depends on the hormone, target cell and enzyme system that is activated.

### Lipophilic hormone action

All lipophilic hormones activate specific genes to synthesise new intracellular proteins which have the required effect, either as structural proteins or as enzymes to initiate chemical changes within the cell. Lipophilic hormones diffuse through the cell membrane and bind to receptors inside the cell, usually within the nucleus. This alters the receptor so it can bind with DNA at a specific attachment site (called the hormone response element). Each hormone and receptor complex has a different attachment site and switches on a specific gene. Activated genes transcribe mRNA which enters the cytoplasm for translation and protein synthesis at ribosomes. The new proteins cause the physiological responses regulated by the hormone.

### Onset and duration

Hormone action is usually relatively slow and prolonged, compared to activity within the nervous system. Hormones are greatly diluted by the blood, but can be effective at concentrations as low as  $1 \text{ pg cm}^{-3}$ . Second messenger systems amplify the action of single hormone molecules and can act quite quickly. Responses requiring synthesis of new proteins may take hours to initiate changes, but are also amplified as each hormone molecule results in many mRNA molecules.

### Activity

Most hormones regulate homeostatic mechanisms. Their concentration in the blood is closely controlled according to homeostatic need. Regulation is primarily through negative feedback. Any change in a controlled variable reverses that change, therefore a variable will fluctuate within a range around a set point or norm. For thyroxine, for example, this feedback loop is quite rapid, keeping thyroxine (which affects general metabolic rate) within narrow limits.

Some feedback loops are slow and some are complex. In the case of the menstrual cycle, follicle stimulating hormone (FSH), leuteinising hormone (LH), oestrogen and progesterone interact to give slow measured responses. FSH is involved in a negative feedback loop with oestrogen and LH with progesterone.

Hormones are mainly inactivated by the liver, but are metabolised by the kidneys, blood or target cells. Hormones may also be excreted by the kidneys. Liver or kidney disease may therefore lead to over activity of certain hormones.

### Role in homeostasis

As a system that can respond slowly to regulate body activities over long periods of time, the endocrine system is important in many homeostatic mechanisms, including:

- control of water and salt balance, mainly through hormonal regulation of water and  $\text{Na}^+$  reabsorption by kidney tubules, to maintain osmolarity of the extracellular fluid (and therefore correct cell volumes) and arterial blood pressure;
- regulation of many different target cells to maintain extracellular concentrations of  $\text{Ca}^{2+}$  and other inorganic ions (this also affects other homeostatic mechanisms, for example, neuromuscular excitability and blood clotting);

- adjustments to stressful situations, for example by increasing heart rate and blood pressure, releasing extra glucose from storage and diverting blood circulation from the skin and gut to the muscles and brain;
- coordination of the circulatory and digestive systems to maintain nutrient levels;
- coordination of the circulatory and respiratory systems to maintain oxygen supplies and regulate pH.

## Examples of what can go wrong

### Rickets and osteomalacia

The thyroid is involved in the regulation of  $\text{Ca}^{2+}$  plasma concentration through negative feedback. An increase in  $\text{Ca}^{2+}$  above the set point stimulates the thyroid to secrete calcitonin. This acts on bone which absorbs  $\text{Ca}^{2+}$  so plasma levels fall (negative feedback). A decrease of  $\text{Ca}^{2+}$  below the set point stimulates the parathyroids to secrete parathormone. This acts on bone which releases  $\text{Ca}^{2+}$  so  $\text{Ca}^{2+}$  plasma level rises above the set point starting the cycle again.

However, vitamin D acts as a hormone to enhance the absorption of  $\text{Ca}^{2+}$  in the small intestine. In the case of vitamin D deficiency parathyroid maintains the plasma  $\text{Ca}^{2+}$  at the expense of bones, which become demineralised, soft and deform. Muscular weakness and pain also occur. This condition is called rickets in children, whose legs may become bowed, and osteomalacia in adults.

Vitamin D deficiency is most often caused by nutritional deficiency and vitamin D supplements are recommended for all people at risk of a deficiency, including all pregnant and breastfeeding women, children under five years old, people aged over 65, and people at risk of not getting enough exposure to sunlight. Around 1 billion people worldwide are thought to have vitamin D deficiency. In the UK, about 14.5% of adults are deficient, possibly more than 30% of those over 65 years old.

### Diabetes

In diabetes the body either is unable to make sufficient insulin or unable to respond to insulin to keep blood glucose levels down within the normal range. Type 2 diabetes is the most common form – the body does not use insulin as it should. Sometimes this can be treated without the need for extra insulin. In type 1 diabetes patients take insulin because they are no longer able to make it.

Over time, high levels of blood glucose can cause major health problems including heart disease, heart attacks, strokes, kidney disease, nerve damage, digestive problems, eye disease, and tooth and gum disease. Worldwide, over 350 million people suffer from diabetes and the numbers are expected to more than double in the next 30 years.

Insulin is a peptide hormone which is hydrolysed in the gut. Patients therefore have to use one of three methods to get the hormone past the skin barrier:

- a syringe or insulin 'pen' with a hollow needle to give injections;
- an insulin pump, a small device the size of a mobile phone, worn outside the body and connected to a small plastic tube and a very small needle which stays inserted under the skin for several days;
- an insulin jet injector (which looks like a large pen) to send a fine spray of insulin through the skin with high-pressure air instead of a needle.

There has therefore been considerable pressure to develop an insulin pill so that diabetics can avoid the discomfort of injecting insulin. Research has centred around lipid coatings, allowing the insulin to avoid hydrolysis while remaining absorbable into capillaries in the wall of the ileum to be transported to the liver.

Since 2007, Oramed have been conducting clinical trials of an oral insulin capsule, ORMD-0801. They have claimed that the results show that it is safe and effective.<sup>2</sup>

### Finding out

The successful synthesis of human growth hormone has raised many ethical and scientific dilemmas. Find out about the uses of growth hormone.

- What conditions is growth hormone used to treat?
- Why was it not possible to use animal sources of growth hormone to treat humans?
- Do you think that growth hormone should be used for cosmetic or athletic reasons?

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<sup>2</sup> See <http://www.dailymail.co.uk/health/article-59513/Insulin-pill-free-diabetics-jabs.html> and <http://www.oramed.com/index.php?page=14>