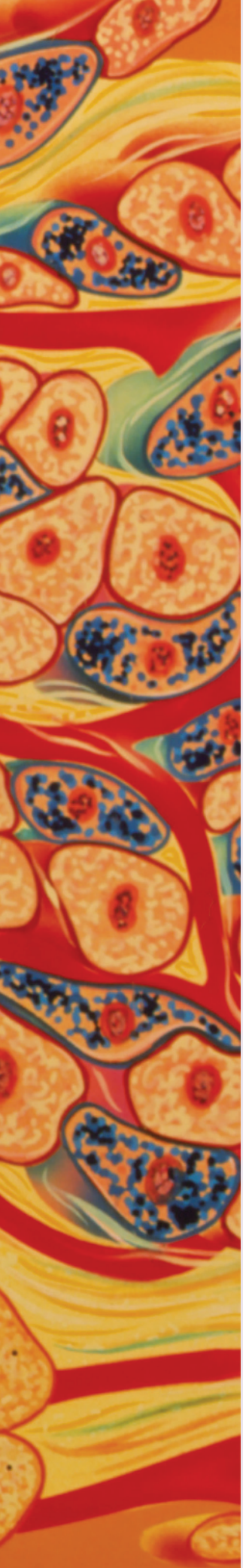

CHAPTER 1

Overview of endocrinology

Key topics

Learning objectives

- To be capable of defining endocrinology
- To understand what endocrinology means as a basic science and a clinical specialty
- To appreciate the history of endocrinology
- To understand the classification of hormones into peptides, steroids and amino acid derivatives
- To understand the principle of how feedback mechanisms regulate hormone levels in the circulation

This chapter introduces endocrinology and diabetes including some of the basic principles that underpin the following chapters

Essential Endocrinology and Diabetes, Seventh Edition. Richard I.G. Holt and Neil A. Hanley.

Box 1.1 The endocrine and nervous systems are the two main communication systems in the body

- Monitor internal and external environments
- Allow appropriate adaptive changes
- Communicate via chemical messengers

} Ensure homeostasis

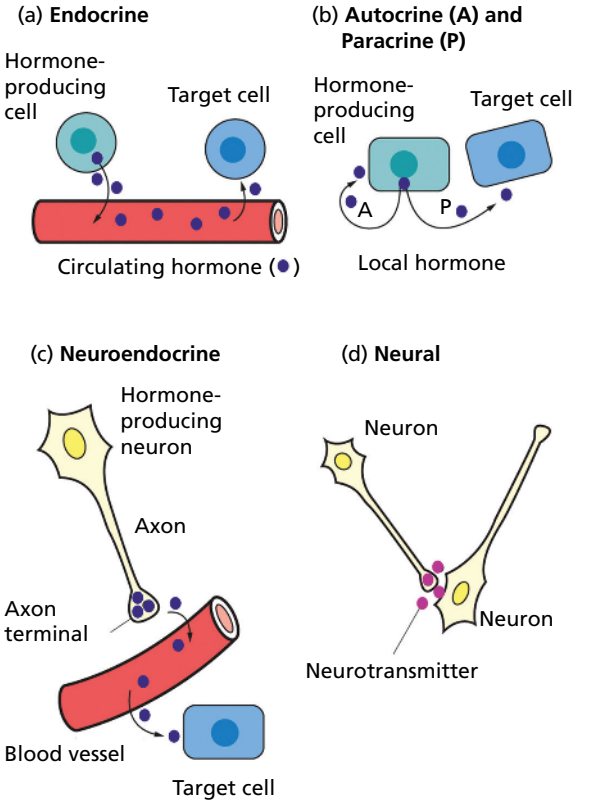

Figure 1.1 Chemical signalling in the endocrine and neural systems. (a) In endocrine communication, the producing cell secretes hormone into the blood vessel, where it is carried, potentially over large distances, to its target cell. (b) Sometimes hormones can act on the cell that produces them (autocrine, A) or nearby cells (paracrine, P) without the need for transport via the circulation. For instance, glucagon from α-cells and somatostatin from δ-cells can regulate insulin secretion by adjacent β-cells within the pancreatic islet. (c) In neuroendocrine communication, neurons can secrete hormones into the surrounding blood vessels to reach a more distant target. A good example is hypothalamic regulation of the anterior pituitary. (d) In pure neural communication, neurons activate other neurons via neurotransmitters released from axonic terminals into the synaptic space. Conceptually, neurotransmitters are similar to hormones and in some instances, such as for norepinephrine/noradrenaline, can actually be the same chemical.

All organisms need to be able to analyze and respond to their surroundings in order to provide a constant internal environment. Maintaining this internal constancy is called homeostasis. For an organism comprised of a single or a few cells homeostasis is relatively easy as no cell is more than a short diffusion distance from the outside world or its neighbours. This simplicity has been lost with the evolution of more complex, larger, multicellular organisms. Diffusion alone is inadequate in larger animal species where discrete functions localize to specific organs. In humans, there are ~10^{14} cells of more than 200 different types. With this compartmentalized function comes the need for effective communication to disseminate information throughout the whole organism – only a few cells face the outside world, yet all need to respond to it. Two communication systems facilitate this: the endocrine and nervous systems (Box 1.1).

Whereas gastrointestinal cells tend to secrete chemicals into ducts, the specialized cells that make up the glands and tissues of the endocrine system release their chemical messengers, called hormones, into the extracellular space, from where they enter the bloodstream. Historically, this blood-borne transit of hormones was what defined 'endocrinology'; however, the principle is identical for hormone action on a neighbouring cell (called a paracrine effect) or, indeed, the endocrine cell itself (an autocrine or intracrine effect) (Figure 1.1).

The nervous and endocrine systems interact. Endocrine glands can be under nervous control; the adrenal medulla is an excellent example (Chapter 6). Conversely, neural cells can themselves release hormones into the bloodstream. This is particularly relevant in the hypothalamus (Chapter 5). Indeed, this interplay between the body's two main communication systems has led to the composite specialty of 'neuroendocrinology' (Figure 1.1).

A brief history of endocrinology and diabetes

The term 'hormone', derived from the Greek word 'hormaein' meaning 'to arouse' or 'to excite', was first used in 1905 by Sir Ernest Starling in his Croonian Lecture to the Royal College of Physicians. However, endocrinology is built on foundations that are far older. Although Aristotle described the pituitary, gigantism, caused by excess growth hormone (GH) from the somatotrophs of the anterior pituitary, was referred to in the Old Testament. It was only two millennia or so later in the 19th century that the gland's anterior and posterior components were appreciated by Rathke, and Pierre Marie connected GH-secreting pituitary tumours to acromegaly and excess growth.

Diabetes was recognized by the ancient Egyptians. Areateus later described the disorder in the second century AD as 'a melting down of flesh and limbs into urine'. Consequently, diabetes comes from the Greek word meaning 'siphon'. The pancreas was only implicated relatively recently when Minkowski realized in 1889 that the organ's removal in dogs mimicked diabetes in humans.

The roots of reproductive endocrinology are equally long. The Bible refers to eunuchs and Hippocrates recognized that mumps could result in sterility. Oophorectomy in sows and camels was used to increase strength and growth in ancient Egypt. The dependence of endocrinology on technology is also long standing. It took the invention of the microscope in the 17th century for Leeuwenhoek to visualize spermatozoa and later, in the 19th century, for the mammalian ovum to be discovered in the Graafian follicle.

During the last 500 years, many endocrine organs and systems ('axes') have been identified and characterized. In 1564, Bartolomeo Eustacio noted the presence of the adrenal glands. Almost 300 years later (1855), Thomas Addison, one of the forefathers of clinical endocrinology, described the consequences of their inadequacy. Catecholamines (epinephrine/adrenaline and norepinephrine/noradrenaline) were identified at the turn of the 19th century, in parallel with Oliver and Schaffer's discovery that these adrenomedullary substances raised blood pressure. This followed shortly after the clinical features of myxoedema were linked to the thyroid gland, when, in 1891, physicians in Newcastle-upon-Tyne treated hypothyroidism with sheep thyroid extract. This was an important landmark, but long after the ancient Chinese recognized that seaweed, as a source of iodine, held valuable properties in treating swelling of the thyroid gland ('goitre').

These early aspects of clinical endocrinology and diabetes tended to rely on recognition and description. Since then our understanding has advanced through:

- Successful quantification of circulating hormones
- Molecular unravelling of complex hormone action
- Mechanistic identification of pathophysiology underlying endocrine dysfunction
- Molecular genetic diagnoses

Some of the landmarks from the last 100 years are shown in Box 1.2. Endocrinology and diabetes is notable for researchers who have been awarded the Nobel Prize for Medicine, Physiology or Chemistry for their landmark discoveries (Table 1.1).

Box 1.2 Some landmarks in endocrinology over the last century or so

1905	First use of the term 'hormone' by Starling in the Croonian Lecture at the Royal College of Physicians
1909	Cushing removed part of the pituitary and saw improvement in acromegaly
1914	Kendall isolated an iodine-containing substance from the thyroid
1921	Banting and Best extracted insulin from islet cells of dog pancreas and used it to lower blood glucose
Early 1930s	Pitt-Rivers and Harrington determined the structure of the thyroid hormone, thyroxine
1935–1940	Crystallization of testosterone
1935–1940	Identification of oestrogen and progesterone
1940s	Harris recognized the relationship between the hypothalamus and anterior pituitary in the 'portal-vessel chemotransmitter hypothesis'
1952	Gross and Pitt-Rivers identified tri-iodothyronine in human serum
1955	The Schally and Guillemin laboratories showed that extracts of hypothalamus stimulated adrenocorticotrophic hormone (ACTH) release
1950s	Adams and Purves identified thyroid stimulatory auto-antibodies
	Gonadectomy and transplantation experiments by Jost led to the discovery of the role for testosterone in rabbit sexual development
1955	Marcel Janbon and colleagues first recognized the hypoglycaemic effects of sulphonamide antibiotics during a typhoid epidemic in Marseilles in 1942. This led to the introduction of sulphonylureas into clinical practice
1955	Sanger reported the primary structure of insulin
1956	Doniach, Roitt and Campbell associated antithyroid antibodies with some forms of hypothyroidism – the first description of an autoimmune phenomenon
1957	Growth hormone was used to treat children with short stature
1966	First transplant of human pancreas to treat type 1 diabetes by Kelly, Lillehei, Goetz and Merkel at the University of Minnesota
1969	Hodgkin reported the three-dimensional crystallographic structure of insulin
1969–1971	Discovery of thyrotrophin-releasing hormone (TRH) and gonadotrophin-releasing hormone (GnRH) by Schally's and Guillemin's groups
1973	Discovery of somatostatin by the group of Guillemin
1981–1982	Discovery of corticotrophin-releasing hormone (CRH) and growth hormone-releasing hormone (GHRH) by Vale

1983	Cloning of gene encoding glucagon and two glucagon-like peptides, including GLP-1, by Bell and colleagues
1994	Identification of leptin by Friedman and colleagues
1994	First transplantation of pancreatic islets to treat type 1 diabetes by Pipeleers and colleagues in Belgium
1999	Discovery of ghrelin by Kangawa and colleagues
1999	Sequencing of the human genome – publication of the DNA code for chromosome 22
2000	Advanced islet transplantation using modified immunosuppression by Shapiro and colleagues to treat type 1 diabetes
2005	GLP-1 receptor agonists introduced into clinical practice
2010	SGLT-2 inhibitors entered clinical practice

Table 1.1 Nobel prizewinners in endocrinology and diabetes or those whose discoveries have profoundly affected the specialty

Year	Prizewinner(s)	For work on . . .
1909	Emil Theodor Kocher	Physiology, pathology and surgery of the thyroid gland
1923	Frederick Grant Banting and John James Richard Macleod	Discovery of insulin
1928	Adolf Otto Reinhold Windaus	Constitution of the sterols and their connection with the vitamins
1939	Adolf Friedrich and Johann Butenandt	Sex hormones
1943	George de Hevesy	Use of isotopes as tracers in the study of chemical processes
1946	James Batcheller Sumner, John Howard Northrop and Wendell Meredith Stanley	Discovery that enzymes can be crystallized and prepared in a pure form
1947	Carl Ferdinand Cori, Getty Theresa Cori (neé Radnitz) and Bernardo Alberto Houssay	Discovery of the course of the catalytic conversion of glycogen
1950	Edwin Calvin Kendall, Tadeus Reichstein and Philip Showalter Hench	Discoveries relating to the hormones of the adrenal cortex, their structure and biological effects
1955	Vincent du Vigneaud	Biochemically important sulphur compounds, especially for the first synthesis of a polypeptide hormone
1958	Frederick Sanger	Structures of proteins, especially that of insulin
1964	Konrad Bloch and Feodor Lynen	Discoveries concerning the mechanism and regulation of cholesterol and fatty acid metabolism
1964	Dorothy Hodgkin	X-ray crystallography, a method used to determine the three-dimensional structures of molecules, including insulin
1966	Charles Brenton Huggins	Discoveries concerning hormonal treatment of prostatic cancer
1969	Derek HR Barton and Odd Hassel	Development of the concept of conformation and its application in chemistry
1970	Bernard Katz, Ulf von Euler and Julius Axelrod	Discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release and inactivation
1971	Earl W Sutherland Jr	Discoveries concerning the mechanisms of the action of hormones
1977	Roger Guillemin, Andrew V Schally and Rosalyn Yalow	Discoveries concerning peptide hormones in the production in the brain and the development of radioimmunoassay from peptide hormones
1979	Allan M Cormack and Godfrey N Hounsfield	Development of computer-assisted tomography

Table 1.1 (*Continued*)

Year	Prizewinner(s)	For work on . . .
1982	Sune K Bergström, Bengt I Samuelson and John R Vane	Discoveries concerning prostaglandins and related biologically active substances
1985	Michael S Brown and Joseph L Goldstein	Discoveries concerning the regulation of cholesterol metabolism
1986	Stanley Cohen and Rita Levi-Montalcini	Discoveries of growth factors
1992	Edmond H Fischer and Edwin G Krebs	Discoveries concerning reversible protein phosphorylation as a biological regulatory mechanism
1994	Alfred G Gilman and Martin Rodbell	Discovery of G-proteins and the role of these proteins in signal transduction in cells
2003	Peter Agre and Roderick MacKinnon	Discovery of water channels, and the structural and mechanistic studies of ion channels
2003	Paul Lauterbur and Sir Peter Mansfield	Discoveries concerning magnetic resonance imaging
2010	Robert G Edwards	Development of *in vitro* fertilisation

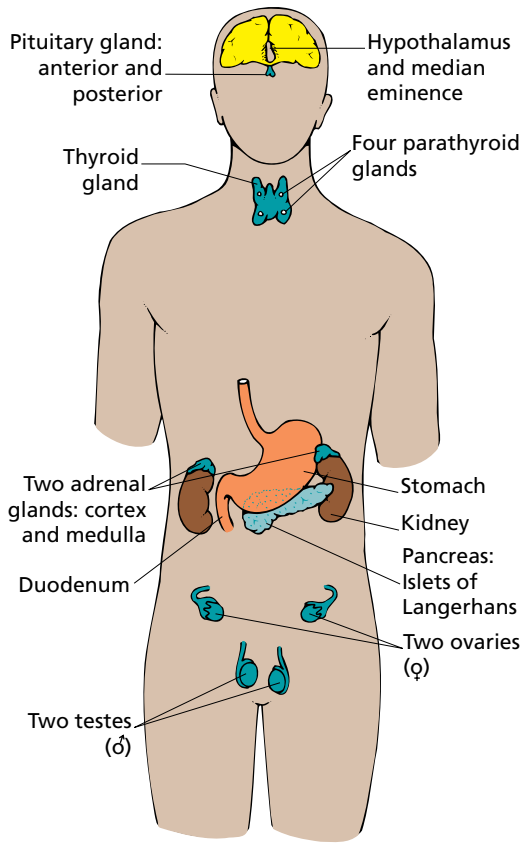

Figure 1.2 The sites of the principal endocrine glands. While the stomach, kidneys and duodenum are shown, a multitude of different hormones are secreted right the way along the gastrointestinal tract.

Traditionally, endocrinology has centred on specialized hormone-secreting organs (Figure 1.2), largely founded on the 'endocrine postulates' of Edward Doisy (Box 1.3). While the focus of this textbook remains on these organs, virtually all tissues make hormones of some description or, equally relevant, modulate the action of hormones from other sites. All of these different aspects are important for a complete appreciation of endocrinology and its significance.

Box 1.3 The 'Endocrine Postulates': Edward Doisy, St Louis University School of Medicine, USA, 1936

- The gland must secrete a substance (an 'internal secretion')
- Methods of detecting the secretion must be available
- The purified substance (the hormone) must be recoverable from gland extracts
- The hormone must be capable of isolation for its structure to be determined and for synthesis

To this could be added:

- The hormone must act on specific target cells via a receptor such that excess or deficiency causes a specific phenotype

The role of hormones

Endocrine (i.e. hormone-secreting) cells may exist as distinct glands or be located as single cells within other organs, such as the gastrointestinal tract (Table 1.2). The chapters in Part 2 are largely organized on this anatomical basis.

Hormones act by binding to specific receptors, either on the surface of or inside the target cell, to initiate a cascade of intracellular reactions, which frequently amplifies the original stimulus and generates a final response. These responses are altered in hormone deficiency or excess: for instance, GH deficiency leads

Table 1.2 The endocrine organs and their hormones*

Gland	Hormone	Molecular characteristics
Hypothalamus/ median eminence	Releasing and inhibiting hormones:	
	Thyrotrophin-releasing hormone (TRH)	Peptide
	Somatostatin (SS; inhibits GH)	Peptide
	Gonadotrophin-releasing hormone (GnRH)	Peptide
	Corticotrophin-releasing hormone (CRH)	Peptide
	Growth hormone-releasing hormone (GHRH)	Peptide
	Dopamine (inhibits prolactin)	Tyrosine derivative
Anterior pituitary	Thyrotrophin or thyroid-stimulating hormone (TSH)	Glycoprotein
	Luteinizing hormone (LH)	Glycoprotein
	Follicle-stimulating hormone (FSH)	Glycoprotein
	Growth hormone (GH) (also called somatotrophin)	Protein
	Prolactin (PRL)	Protein
	Adrenocorticotrophic hormone (ACTH)	Peptide
Posterior pituitary	Vasopressin [also called antidiuretic hormone (ADH)]	Peptide
	Oxytocin	Peptide
Thyroid	Thyroxine (T4) and tri-iodothyronine (T3)	Tyrosine derivatives
	Calcitonin	Peptide
Parathyroid	Parathyroid hormone (PTH)	Peptide
Adrenal cortex	Aldosterone	Steroid
	Cortisol	Steroid
	Androstenedione	Steroid
	Dehydroepiandrosterone (DHEA)	Steroid
Adrenal medulla	Epinephrine (also called adrenaline)	Tyrosine derivative
	Norepinephrine (also called noradrenaline)	Tyrosine derivative
Stomach†	Gastrin	Peptide
Pancreas (islets of Langerhans)	Insulin	Protein
	Glucagon	Protein
	Somatostatin (SS)	Protein
	Pancreatic polypeptide	Protein
	Ghrelin	Protein
Small and large intestine†	Secretin	Protein
	Glucagon-like peptide 1 (GLP-1)	Protein
Liver	Insulin-like growth factor I (IGF-I)	Protein
Ovary	Oestrogens	Steroid
	Progesterone	Steroid
Testis	Testosterone	Steroid

*The distinction between peptide and protein is somewhat arbitrary. Shorter than 50 amino acids is termed a peptide in this table.
†The list is far from exhaustive for the gastrointestinal tract (see Chapter 11).

to short stature in children, while excess causes over-growth (either gigantism or acromegaly; Chapter 5).

Hormone responses can be widespread or incredibly focussed according to how widely the hormone's receptor is distributed. For instance, thyroid hormone acts on many, if not all, of the more than 200 cell types in the body. The body's entire metabolic rate increases if it is present in excess and declines if there is a deficiency (Chapter 8). Similarly, insulin acts on most tissues; an importance underlined by its pivotal role in the survival and growth of many cell types in laboratory culture. In contrast, other hormones may act only on one tissue. For instance, thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH) and the gonadotrophins are secreted by the anterior pituitary and regulate specific cell-types in the thyroid gland, the adrenal cortex and the gonads, respectively (Table 1.2).

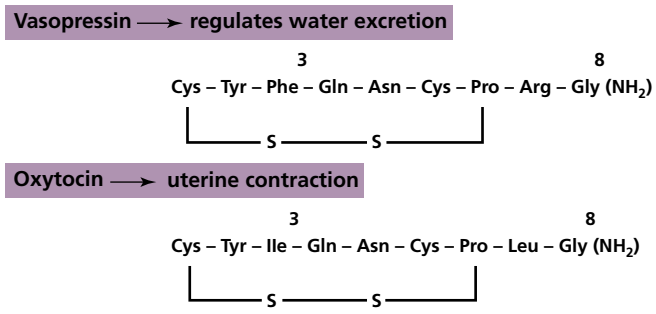

Figure 1.3 The structures of vasopressin and oxytocin are remarkably similar, yet the physiological effects of the two hormones differ profoundly.

Classification of hormones

There are three major groups of hormones, defined according to their biochemical synthesis (Box 1.4). Peptide or protein hormones are synthesized like any other cellular protein. The amino acid derivatives and steroid hormones originate from a cascade of intracellular enzymatic reactions.

Peptide hormones

The majority of hormones are peptides and range in size from tiny, only three amino acids [thyrotrophin-releasing hormone (TRH)], to small proteins of >200 amino acids, such as TSH or luteinizing hormone (LH). While some peptide hormones are secreted directly, a typical feature is their storage in granules, the release from which is commonly controlled by another hormone, as part of a cascade, or by innervation.

Some peptide hormones have complex tertiary structures or comprise more than one peptide chain encoded by multiple genes. Oxytocin and vasopressin, the two posterior pituitary hormones, have ring structures linked by disulphide bridges. Despite being remarkably similar in structure, they have markedly different physiological roles (Figure 1.3). Insulin consists of α- and β-chains linked by disulphide bonds. Like several hormones, it is synthesized as an inactive precursor that requires modification prior to release and activity. To some extent, this regulation protects the synthesizing cell from being overwhelmed by the action of its own hormone. The gonadotrophins, follicle-stimulating hormone (FSH) and LH, TSH and human chorionic gonadotrophin (hCG) also have two chains. However, these α- and β-subunits are synthesized separately from entirely different genes. The α-subunit is common to each of the hormones. It is the distinctive β-subunit of each that confers biological specificity.

Box 1.4 Major hormone groups

- Peptides and proteins
- Amino acid derivatives
- Steroids

Amino acid derivatives

These hormones are small water-soluble compounds. Melatonin is derived from tryptophan, whereas tyrosine derivatives include thyroid hormones, catecholamines, and dopamine, which regulates prolactin secretion in the anterior pituitary. The catecholamine hormones, epinephrine (also called adrenaline) and norepinephrine (noradrenaline) are secreted by the adrenal medulla as well as being sympathetic neurotransmitters, emphasizing the close relationship between the nervous and endocrine systems (Figure 1.2). Like peptide hormones, they are stored in granules prior to release.

Steroid hormones

Steroid hormones are lipid-soluble molecules derived from cholesterol. Cholesterol is present in all cells as a basic constituent of the cell membrane. However, in the steroid hormone synthesizing cells of the adrenal cortex, gonad and placenta, it is also extracted from the circulation and stored intracellularly as cholesterol esters. Steroid hormones are insoluble in water and circulate largely bound to plasma proteins.

Control systems regulating hormone production

The synthesis, release and circulating level of hormones are regulated by control systems, similar to those used in engineering. These mechanisms ensure that hormone signals can be limited in amplitude and duration. Central to the regulation of many different endocrine organs is the anterior pituitary gland, which, in turn, is controlled by several hormones and factors released from specialized hypothalamic neurones (Chapter 5). Thus, the body's major endocrine axes comprise the hypothalamus, anterior pituitary and an end organ, the adrenal cortex, thyroid,

testis or ovary. An understanding of these control mechanisms is crucial for appreciating endocrine physiology and its clinical investigation.

Simple control

An elementary control system is one in which the signal itself is limited, either in magnitude or duration, so as to trigger only a transient response. Certain neural impulses are of this type. Responsiveness of the target cell is set to discriminate between a positive signal, when a cell responds, and background 'noise', when a response is not triggered. An example is the pulsatile release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus.

Negative feedback

Negative feedback is the commonest form of regulation used by biological systems. For example, in enzymology, the product frequently inhibits its own catalyzed reaction. In endocrinology, a hormone may act on its target cell to elicit a response (often secretion of another hormone) that then inhibits production of the original hormone (Figure 1.4a). The same effect can come from a metabolic process. For instance, the pancreatic β-cell makes insulin in response to high surrounding glucose levels. The effect is to lower glucose, which, in turn, inhibits further insulin production. The hypothalamic–anterior pituitary–end organ axes are a slightly more complex extension of this model. The hypothalamic hormone [e.g. corticotrophin-releasing hormone (CRH)] stimulates release of the anterior pituitary hormone (e.g. ACTH), which, in turn, increases peripheral hormone production (e.g. cortisol). The peripheral hormone then feeds back via the circulation to inhibit further production of the anterior pituitary and hypothalamic hormones. Figure 1.4b illustrates the anterior pituitary and end-organ components of this model where hormone 1 could be ACTH and hormone 2 could be cortisol.

Positive feedback

Under certain more unusual circumstances, hormone feedback enhances, rather than inhibits, the initial response. This is called positive feedback (illustrated alongside the more usual negative feedback by the plus sign in Figure 1.4a). This is intrinsically unstable and always has built-in self-limiting features. Transiently, it can be beneficial. For instance, the action of oestrogen on the pituitary gland induces the ovulatory surge of LH and FSH, further stimulating oestrogen production in the developing follicle

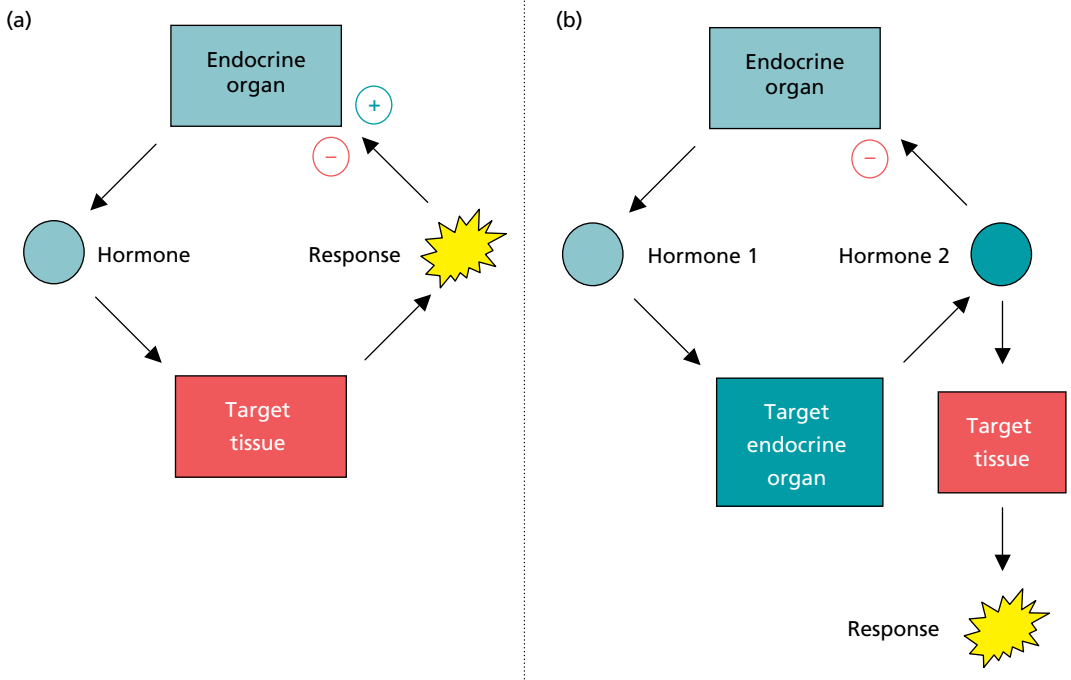

Figure 1.4 Control systems regulating hormone production and circulating levels. (a) The endocrine organ releases a hormone, which acts on the target tissue to stimulate a response. The response usually feeds back to inhibit (−) the endocrine organ and decrease further supply of the hormone. Occasionally, the feedback can act to enhance the hormone secretion (+, positive feedback). (b) In this slightly more complex scenario, the endocrine organ produces hormone 1, which acts on a second endocrine gland to release hormone 2. In turn, hormone 2 acts dually on the target tissue to induce the response and feeds back negatively onto the original endocrine organ to inhibit further release of hormone 1. This model is illustrative of the axes between the anterior pituitary and the peripheral end-organ targets.

Box 1.5 Endocrine cycles

Circadian = 24-h cycle
- Circa = about, dies = day

Ultradian < 24-h cycle
- E.g. GnRH release

Infradian > 24-h cycle
- E.g. menstrual cycle

(Chapter 7). During childbirth, stretch receptors and nerves from the distended vagina stimulate the posterior pituitary to release oxytocin. The rise in oxytocin causes more uterine contraction, further activating the stretch receptors. The role of oxytocin in the suckling–milk ejection reflex is similar. In each instance, the positive feedback amplifies a signal until there is a break in the circuit, either ovulation, birth of the baby or the cessation of suckling.

Inhibitory control

The secretion of some hormones is under inhibitory as well as stimulatory control. Somatostatin, a hypothalamic hormone, prevents the secretion of GH so that when somatostatin secretion is diminished, GH secretion is enhanced. Prolactin is similarly controlled by tonic inhibition from dopamine.

Endocrine rhythms

Superimposed on the regulatory systems described above, many of the body's activities show additional periodic or cyclical changes (Box 1.5). Control of these rhythms commonly arises from the nervous system via the hypothalamus. Some appear independent of the environment, whereas others are coordinated and 'entrained' by external cues (e.g. the 24-h light/dark cycle, which becomes temporarily disrupted in jetlag). Cortisol secretion is maximal between 0400h and 0800h as we awaken and minimal as we retire to bed. In contrast, GH and prolactin are secreted maximally ~1 h after falling asleep. Clinically, this knowledge is important as investigation must be referenced according to hour-by-hour and day-to-day variability. Otherwise, such laboratory tests may be invalid or, indeed, misleading.

Endocrine disorders

The chapters in Part 2 largely focus on organ-specific endocrinology and associated endocrine disorders. Diabetes and obesity in Part 3 has now become its own specialized branch of endocrinology. Nevertheless, it is possible to regard all endocrine abnormalities as *too much*, *too little* or *disordered* production of hormone. Some clinical features occur because of compensatory overproduction of hormones. For example, Addison disease is a deficiency of cortisol from the adrenal cortex (Chapter 6), which reduces negative feedback on ACTH production at the anterior pituitary. ACTH rises and stimulates melanocytes in the skin to increase pigmentation, especially in unusual locations, which is a striking sign of Addison disease.

Imbalanced hormone production may occur when a particular enzyme is missing because of a genetic defect. For example, in congenital adrenal hyperplasia, lack of 21-hydroxylase prevents adequate cortisol synthesis (Chapter 6). Other pathways within adrenocortical cells remain intact, leading to excess production of sex steroids that masculinize aspects of the female body. Endocrine disorders may also arise from abnormalities in hormone receptors or downstream signalling pathways. The commonest example is type 2 diabetes, which is characterized, at least in part, by resistance to insulin action in target tissues (Chapter 13).

For endocrine organs under regulation by the hypothalamus and anterior pituitary, the associated disorders can also be categorized according to site. When disease is located in the end organ it is termed 'primary'. When the end organ is affected because of an upstream problem in the anterior pituitary (either under-activity or over-activity) it is termed secondary, while in tertiary disease, the pathology resides in the hypothalamus.

Tumours affect all organs and tissues. In endocrinology, these tumours are most commonly sporadic and benign but they may over-secrete hormones resulting in organ-specific syndromes. These are described in the appropriate chapters of Part 2. Endocrine tumourigenesis may also affect multiple endocrine organs as unusual clinical syndromes. These are described in Chapter 10.

Key points

- Endocrinology is the study of hormones, defined classically by their secretion into the bloodstream
- The endocrine and nervous systems are the body's two major communication systems
- A hormone is a chemical messenger that elicits specific effects by binding to a receptor on or inside target cells
- The three major types of hormones are peptides and the derivatives of amino acids or cholesterol
- Negative and, occasionally, positive feedback, and cyclical mechanisms operate to regulate hormone production, commonly as part of complex multiorgan systems or axes
- Clinical endocrine disorders usually reflect too much, too little or dysregulated hormone production