

The pituitary gland and hypothalamus

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After reading this chapter you should have gained an understanding of:

- The anatomy of the pituitary and hypothalamus
- The role of the CNS in the regulation of the endocrine system via the hypothalamic-pituitary axis
- The actions of the hormones of the anterior pituitary gland and the regulation of their secretion
- The actions of the hormones of the posterior pituitary gland, oxytocin and vasopressin (antidiuretic hormone)

15.1 Introduction

The nervous and endocrine systems are closely linked via the control that the hypothalamus exerts over the pituitary gland. Two different modes of control are employed:

- direct neural connection between the hypothalamus and posterior pituitary via the hypothalamo-hypophyseal tract
- hormonal regulation via a dedicated portal vascular system linking the hypothalamus to the anterior pituitary.

This chapter explores the hypothalamo-pituitary system and provides a brief description of the principal hormones of the anterior and posterior lobes of the pituitary gland. The actions of the individual hormones are discussed in further detail in the chapters dealing with their target glands: hormonal control of the thyroid, parathyroid and adrenal glands is discussed in Chapter 16, hormonal control of the reproductive system is discussed in Chapters 33 and 34, and the control of growth is discussed in Chapter 36.

15.2 The hypothalamo-pituitary axis

Fig. 15.1 illustrates the anatomical relationship between the pituitary gland and the hypothalamus, the part of the brain to which it is attached by the pituitary stalk. The pituitary gland is situated in a depression of the sphenoid bone at the base of the skull called the

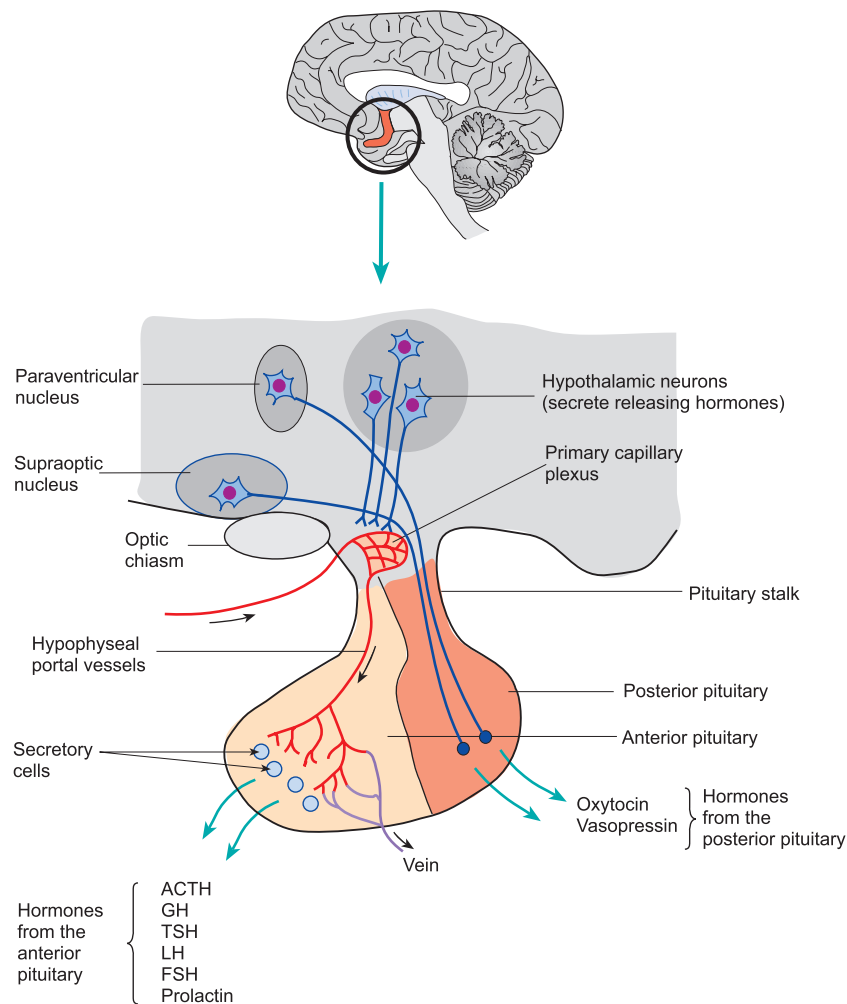


Fig. 15.1 The relationship between the hypothalamus and the pituitary gland. Note the prominent portal system that links the hypothalamus to the anterior pituitary gland. The anterior pituitary has no direct neural connection with the hypothalamus. In contrast, nerve fibres from the paraventricular and supraoptic nuclei pass directly to the posterior pituitary where they secrete the hormones they contain into the blood stream.

sella turcica and consists of two anatomically and functionally distinct regions, the **anterior lobe** or **adenohypophysis** and the **posterior lobe** or **neurohypophysis**. Between these lobes lies a small sliver of tissue called the **intermediate lobe**.

Fig. 15.2 illustrates the way in which the pituitary gland is formed during the first trimester of gestation. The various parts of the pituitary gland have different embryonic origins: the anterior and intermediate lobes are derived from embryonic ectoderm as an upgrowth from the pharynx while the posterior lobe is neural in origin. In the early embryo, the roof of the mouth lies adjacent to the third ventricle of the brain and both sheets of tissue bulge towards each other: the buccal cavity bulges upwards to form Rathke's pouch, and the neural ectoderm bulges downwards to form the infundibulum of the hypothalamus. Eventually, Rathke's pouch pinches off from the rest of the pharyngeal ectoderm and folds around the infundibulum to form the pituitary stalk. Embryogenesis is complete at around 11 or 12 weeks of gestation in humans. The neural tissue, which remains as part of the brain, forms the posterior pituitary and the non-neural tissue forms the anterior pituitary.

The **adenohypophysis** consists of two portions, the anterior pituitary itself (also called the pars distalis) and the much smaller

pars tuberalis, which is wrapped around the infundibular stem to form the pituitary stalk. The **neurohypophysis** strictly consists of three parts: the median eminence, which is the neural tissue of the hypothalamus from which the pituitary protrudes, the posterior pituitary itself, and the infundibular stem, which connects the two.

The anterior pituitary gland plays a central role in the regulation of the endocrine system. It secretes at least seven different hormones most of which regulate the secretions of other endocrine organs. Although the anterior pituitary receives no direct neural input from the median eminence, it is now known that the hypothalamus plays a key role in regulating anterior pituitary function. Between the hypothalamus and the anterior pituitary, there is a system of blood vessels known as the **hypothalamic-hypophyseal portal system** which originates in the primary capillary plexus—a series of capillary loops in the median eminence. Most of the arteries that supply the anterior pituitary do not form a capillary network amongst the epithelial cells; rather, they course upwards into the pituitary stalk where they empty into a network of capillary sinusoids. The blood leaving this primary capillary plexus then flows in parallel veins, the long portal vessels, down the pituitary stalk to the anterior lobe. Here the portal

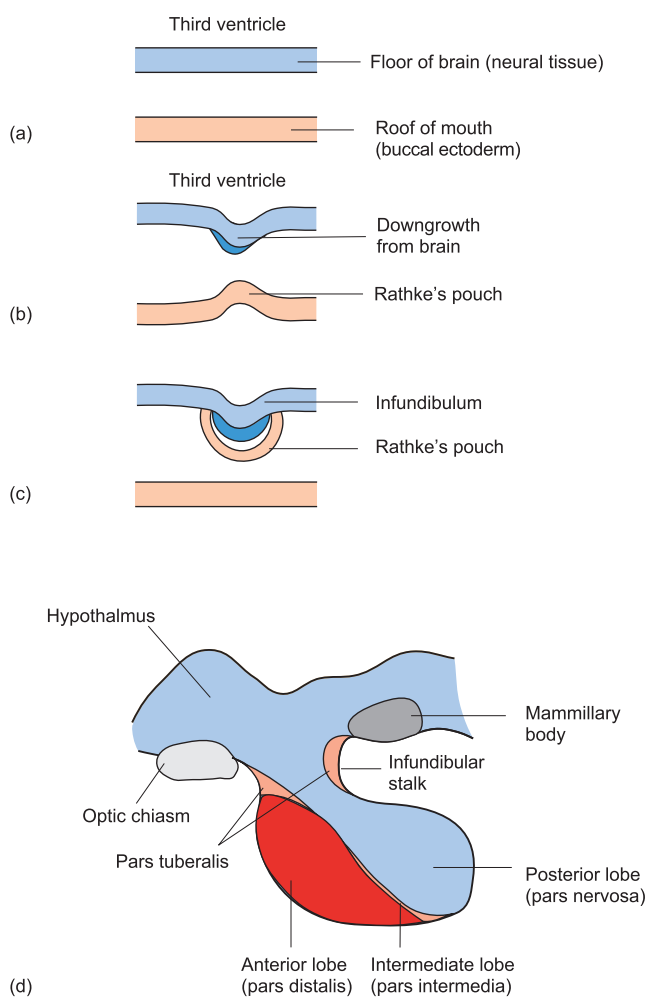


Fig. 15.2 (a–c) The embryonic development of the pituitary gland from outgrowths of neural and ectodermal tissue, with separation of Rathke's pouch. (d) The structure of an adult gland in which the colouring corresponds to that shown in (a–c).

veins break up into sinusoids which form the main blood supply of the anterior pituitary. A diagram of this arrangement is shown in Fig. 15.1. The role of the hypophyseal portal system is to transport specific hormones secreted by the neurons of the median eminence to the anterior pituitary where they regulate the output of the hormones of the anterior pituitary. The hypothalamus, the pituitary, and the products of its target tissues therefore form a complex functional unit.

The hormones of the anterior pituitary

The hormones of the anterior pituitary are listed in Table 15.1 along with their major target tissues and the cells that synthesize and secrete them. All the anterior pituitary hormones are proteins or polypeptides. The major hormones are:

- 1 growth hormone (GH or somatotrophin)
- 2 prolactin
- 3 adrenocorticotrophic hormone (ACTH or corticotrophin)

4 melanocyte-stimulating hormone (MSH)

5 thyroid-stimulating hormone (TSH or thyrotrophin)

6 the gonadotrophins—follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

The various cell types that secrete the anterior pituitary hormones line the blood sinusoids. On the basis of microscopic examination of granule size and number, and of immunological staining reactions, the cells secreting certain pituitary hormones can be identified as shown in Fig. 15.3. At least five different endocrine cell types may be distinguished. The **somatotrophs** secrete growth hormone and account for the majority of pituicytes (~50 per cent). The **lactotrophs** secrete prolactin and account for a further 15–20 per cent of pituicytes. Both somatotrophs and lactotrophs are mainly located in the lateral wings of the anterior pituitary. The **gonadotrophs** secrete **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)** and are scattered throughout the anterior pituitary. They account for about 10 per cent of the pituicyte population. The **corticotrophs** secrete **adrenocorticotrophic hormone (ACTH)** and are mainly located in the central wedge of the anterior pituitary. The corticotrophs account for 15–20 per cent of pituicytes while the **thyrotrophs** secrete **thyroid-stimulating hormone (TSH)** and are mainly located in the anterior part of the central portion. They amount to about 5 per cent of the pituicyte population.

Although many of the cells secrete only one type of hormone (e.g. lactotrophs secrete prolactin and somatotrophs secrete growth hormone), it is now known that some of the pituitary cells are able to produce more than one hormone. The best example of this is provided by the gonadotrophs, many of which secrete both FSH and LH. Furthermore the corticotrophs whilst chiefly secreting ACTH, also secrete β -lipotrophin and **melanocyte-stimulating hormone (α -MSH and β -MSH)**.

The secretion of the anterior pituitary hormones is controlled by hormones released by the hypothalamus into the hypophyseal portal blood

The hypothalamus controls the secretory activity of the anterior pituitary gland. The rates of secretion of TSH, FSH, LH, ACTH, MSH, and the other peptides related to ACTH are all stimulated by hypothalamic hormones (known as **releasing hormones**) while the secretion of prolactin is mainly regulated by the inhibitory effect of dopamine (also secreted by neurons in the hypothalamus). The release of **growth hormone (GH)** is under dual control by the hypothalamus: its secretion is stimulated by **growth hormone-releasing hormone (GHRH)** but suppressed by another peptide, somatostatin (also known as growth hormone-inhibiting hormone (GHIH)).

The hypothalamic hormones are synthesized in the cell bodies of neurons lying within discrete areas of the hypothalamus (see later). They reach the upper part of the hypophyseal stalk (the median eminence) by axonal transport along the fine axons that constitute the tuberoinfundibular tract. The axons terminate in the median eminence and their endings lie next to the capillaries of the primary plexus. In response to neural activity, the

Table 15.1 The anterior pituitary hormones

Class of hormone	Specific hormones	Synthesized and secreted by:	Target tissues	Number of amino acid residues
Somatotrophic hormones				
These hormones have a single peptide chain	Growth hormone (GH) also known as somatotrophin	Somatotrophs	Most tissues except CNS	191
	Prolactin (PRL)	Lactotrophs	Mammary glands	198
Corticotrophin-related peptide hormones				
These are all derived from a single common precursor	Corticotrophin (ACTH)	Corticotrophs	Adrenal cortex	39
	β -Lipotrophin (β -LPH)	Corticotrophs	?Adipose tissue	91
	β -Endorphin (β -LPH 61-91)	Corticotrophs	Adrenal medulla, gut	31
	α -Melanocyte-stimulating hormone (α -MSH)	Corticotrophs	Melanocytes	13
Glycoprotein hormones				
These are composed of a common α -peptide chain associated with a variable β -peptide chain	Thyrotrophin (TSH)	Thyrotrophs	Thyroid gland	α -chain 89 β -chain 112
	Follicle-stimulating hormone (FSH)	Gonadotrophs	Ovaries (granulosa cells)	α -chain 89
			Testes (Sertoli cells)	β -chain 115
	Luteinizing hormone (LH)	Gonadotrophs	Ovaries (thecal and granulosa cells)	α -chain 89
Testes (Leydig cells)			β -chain 115	

hypothalamic hormones are released from the nerve endings into the hypophyseal portal blood and are then carried down the pituitary stalk by the long portal veins to the anterior lobe. Here they act on specific pituitary cells to modify the rate of secretion of one, or sometimes several, of the anterior pituitary hormones. The major hypothalamic releasing and inhibiting hormones along with their target hormones and alternative names are listed in Table 15.2.

Specific hypothalamic nuclei synthesize and secrete the releasing hormones

The neurons that synthesize and store the various hypothalamic releasing hormones have been identified by immunocytochemistry (a specific staining technique that identifies substances by their immunological reactivity). Most of the releasing hormones seem to be produced by relatively discrete groups of neurons in the hypothalamus. A simple diagram showing the positions of these nuclei is shown in Fig. 15.4.

Neurons in the arcuate nucleus secrete GHRH while somatostatin is secreted by cells of the periventricular nucleus (not shown in Fig. 15.4). (The *periventricular* nucleus is a thin layer of nerve cells adjacent to the third ventricle and should not be confused with the *paraventricular* nucleus). **Corticotrophin-releasing hormone (CRH)** is synthesized mainly in neurons of the paraventricular nucleus. **Luteinizing hormone-releasing hormone (LHRH)** is found mainly in neurons of the medial preoptic area and in the arcuate nucleus. LHRH is also known as gonadotrophin-releasing

hormone (GnRH). Dopamine is present in neurons of the arcuate region while **thyrotrophin-releasing hormone (TRH)** is located in neurons of both the preoptic and paraventricular nuclei.

The neurosecretory neurons send their axons to the median eminence at the top of the pituitary stalk from where the hormones are secreted into the blood stream. Fig. 15.5 shows the accumulation of GHRH in the median eminence. Other hypothalamic hormones show similar accumulations.

A further point to note is that some of the hypothalamic hormones may be found in parts of the body other than the hypothalamus, where they act in different ways. Somatostatin, for example, is found acting as a neurotransmitter in other parts of the brain, as a hormone throughout the gut, and in the pancreas where it acts as an inhibitor of the release of insulin and glucagon.

Feedback mechanisms operate within the hypothalamo-pituitary-target tissue axes to ensure fine control of endocrine function

Chapter 14 includes a brief discussion of the regulatory role played by both negative and positive feedback mechanisms throughout the endocrine systems of the body. Such processes are of the utmost importance in determining the responsiveness of the anterior pituitary to the hypothalamic releasing hormones and contribute to the overall control of the secretion of the anterior pituitary hormones.

In many cases, the output of a pituitary hormone is increased by the removal of its target gland. For example, removal of the

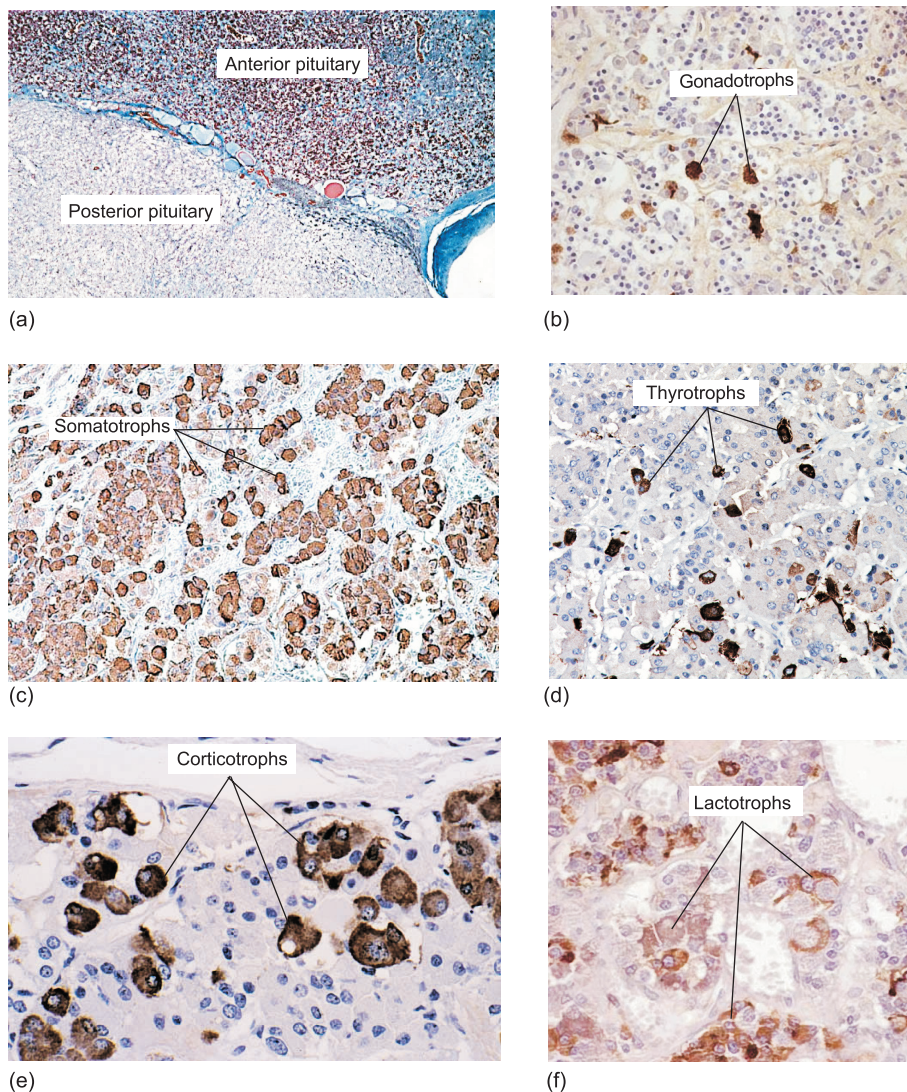


Fig. 15.3 (a) A section of the anterior pituitary gland stained with Masson's triple stain. (b–f) Sections of pituitary treated with antibodies to label specific cell populations: (b) gonadotrophs (which secrete FSH and LH), (c) somatotrophs (which secrete growth hormone), (d) thyrotrophs (which secrete thyroid-stimulating hormone TSH), (e) corticotrophs (which secrete ACTH), and (f) lactotrophs (which secrete prolactin). Note the predominance of somatotrophs in (c) and the relative scarcity of gonadotrophs (b) and thyrotrophs (d).

thyroid gland and the subsequent loss of the thyroid hormones stimulates an increase in the output of thyroid-stimulating hormone (TSH) from the anterior pituitary. It is believed that the responsiveness of the TSH-secreting pituitary cells to hypothalamic TRH is enhanced in the absence of thyroid hormones. Conversely, administration of exogenous thyroxine depresses the output of TSH by reducing pituitary sensitivity to TRH. There may also be a direct effect of thyroid hormones on the output of TRH itself.

Other feedback loops are thought to operate in a similar fashion to modulate pituitary function. ACTH secretion, for example, is depressed by the adrenal steroids as a result of both a direct inhibition of CRH release and a reduction in the responsiveness of the ACTH-secreting cells of the anterior pituitary. Although the secretion of prolactin is largely controlled by the inhibitory action of dopamine, its release is stimulated by TRH. Like the other hormones discussed above, prolactin secretion is subject to negative feedback control. In this case, however, prolactin inhibits its own release by stimulating further output of dopamine.

Summary

The pituitary gland consists of two principal lobes, the anterior lobe (or adenohypophysis) and the posterior lobe (or neurohypophysis). The intermediate lobe, is sandwiched between the two main divisions. The anterior pituitary secretes growth hormone, thyroid stimulating hormone, adrenocorticotrophic hormone, the gonadotrophins (FSH and LH) and prolactin. Secretion of the anterior pituitary hormones is regulated by hormones from the median eminence region of the hypothalamus. The posterior pituitary secretes vasopressin (ADH) and oxytocin.

15.3 Growth hormone (GH) and prolactin

Growth hormone and prolactin have considerable structural similarities. They are both large single chain peptides with prolactin having 198 amino acid residues while the human form of growth hormone (hGH) has 191. Prolactin is synthesized and stored in the

Table 15.2 The hypothalamic releasing and inhibitory hormones with their alternative names

Hypothalamic hormone	Alternative names	Structure	Stimulates	Inhibits
Vasopressin	Antidiuretic hormone (ADH)	9 amino acid peptide	ACTH	-
Corticotrophin-releasing hormone	CRH	41 amino acid peptide	ACTH	-
Gonadotrophin-releasing hormone (GnRH)	Luteinizing hormone-releasing hormone (LHRH) FSH-releasing factor	10 amino acid peptide	LH, FSH	-
Thyrotrophin-releasing hormone	TRH	3 amino acid peptide	TSH, prolactin	-
Growth hormone releasing-hormone	GHRH	44 amino acid peptide	GH	-
Growth hormone-inhibiting factor	Somatostatin, GHIH	14 amino acid peptide	-	GH, prolactin, TSH
Dopamine	Prolactin-inhibiting factor (PIF)	Catecholamine	-	Prolactin

anterior pituitary lactotrophs. It has a weakly somatotrophic action (reflecting its structural closeness to GH) but its predominant role is to promote growth and maturation of the mammary gland during pregnancy to prepare it for the secretion of milk during lactation. The secretion of prolactin is normally inhibited by dopamine (previously known as prolactin inhibitory hormone) secreted by hypothalamic neurons. In lactating women, however, stimulation

of the nipple by the baby during breastfeeding inhibits the secretion of dopamine. Prolactin secretion is thus allowed to rise and milk synthesis by the mammary tissue is stimulated (galactopoiesis); see Chapter 34 (p 707).

GH is synthesized and stored in somatotrophs, which are the most abundant pituitary cell type (Fig. 15.3c). The anterior pituitary contains around 10 mg of growth hormone, which, in adults, is

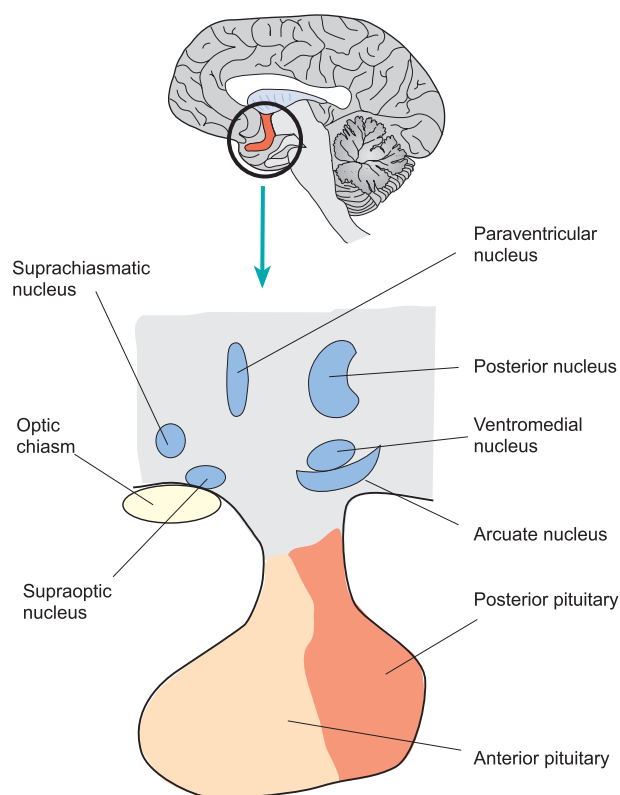


Fig. 15.4 A diagrammatic representation of the location of the principal nuclei of the hypothalamus that are associated with the production and secretion of many of the releasing hormones.

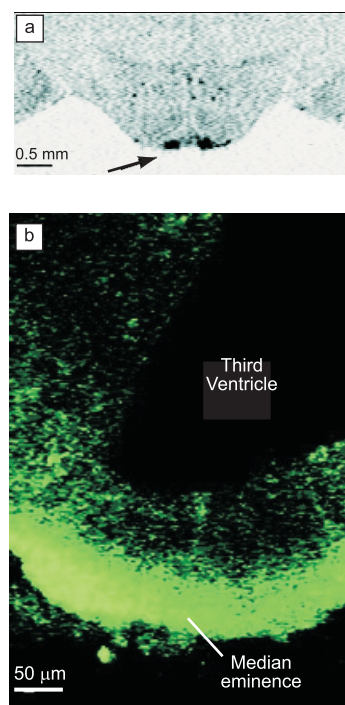


Fig. 15.5 A section of mouse brain which contains nerve cells and nerve terminals in which GHRH has been tagged with green fluorescent protein. (a) A low-power view of the hypothalamus in which the mRNA for GHRH has been labelled to show where the hormone is synthesized. The arcuate nucleus (arrow) shows a strong signal. (b) Intense labelling in the median eminence where the axons terminate adjacent to the primary capillary plexus. Bars, 0.5 mm (a), 50 μm (b).

secreted at a rate of around 1.4 mg/day, greater than that of any of the other pituitary hormones. It is important to note, however, that over a 24-hour period the rate of GH secretion fluctuates considerably, as discussed later in this chapter. In the plasma, about 70 per cent of GH is bound to various proteins, including a specific GH-binding protein which is derived by cleavage of the extracellular region of the GH receptor present on target cells.

Actions of growth hormone

Growth hormone exerts a wide range of metabolic actions that involves virtually every type of cell except neurons. Its principal targets, however, are the bones and skeletal muscles. It stimulates growth in children and adolescents but continues to have important metabolic effects throughout adult life.

For the purposes of discussion, it is convenient to divide the actions of growth hormone into two categories. These are its direct

effects on the metabolism of fats, proteins, and carbohydrates and its indirect actions that result in skeletal growth. The principal actions of GH are illustrated in Fig. 15.6.

Direct metabolic effects of growth hormone

Essentially, growth hormone is anabolic, i.e. it promotes protein synthesis. It is also a glucose-sparing agent with an anti-insulin-like, diabetogenic action. Growth hormone stimulates the uptake of amino acids by cells (particularly those of the liver, muscle, and adipose tissue) and the incorporation of amino acids into proteins in many organs of the body. There is an increase in the rates of synthesis of both RNA and DNA and ultimately of cell division. This effect is particularly important during the growing years when it contributes to the increase in bone length and soft tissue mass. There is also an increase in the rate of chondrocyte differentiation from fibroblasts in cartilage. The net effects of GH on protein

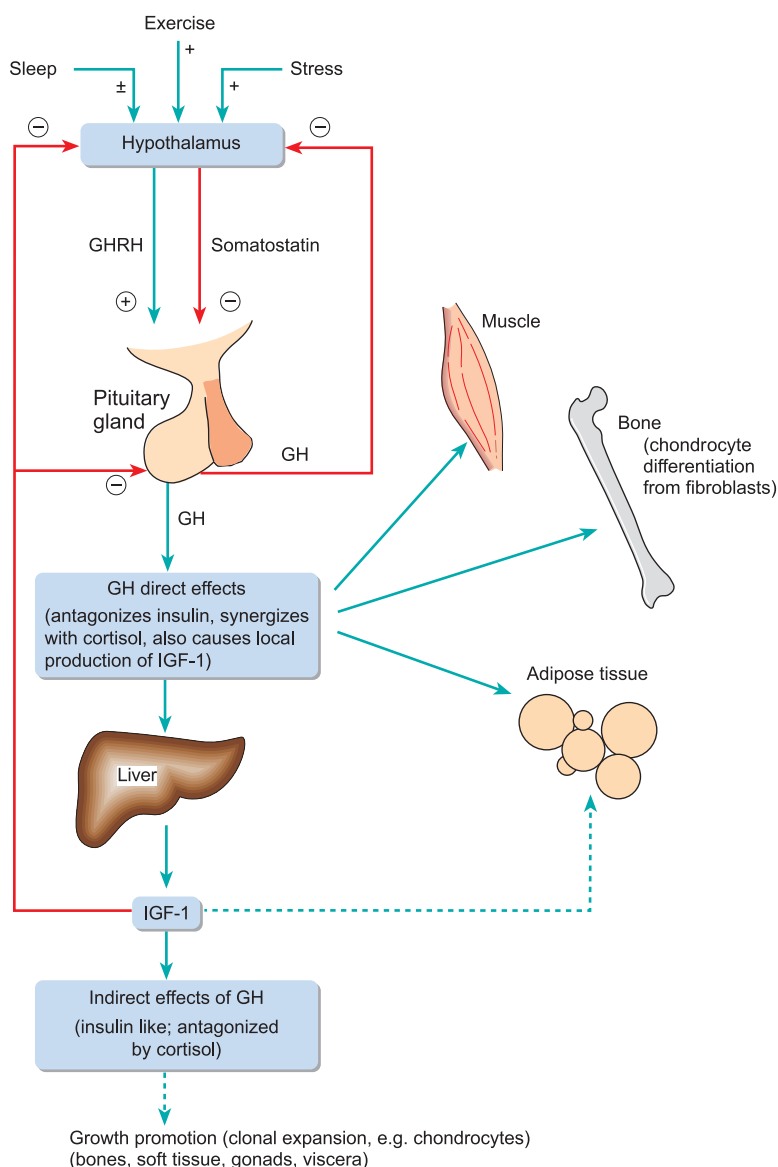


Fig. 15.6 A schematic diagram showing the principal actions of growth hormone and the factors that regulate its secretion.

metabolism are an increase in the rate of protein synthesis, a decrease in plasma amino acid content, and a positive nitrogen balance (defined as the difference between daily nitrogen intake in food and excretion in urine and faeces as nitrogenous wastes).

The actions of GH on lipid and carbohydrate metabolism are essentially diabetogenic. GH increases plasma glucose levels in two ways. It decreases the rate of glucose uptake by cells (largely those of muscle and adipose tissue) and increases the rate of glycogenolysis by the liver. GH promotes the breakdown of stored fat in adipose tissue and the release of free fatty acids into the plasma. This action is important for providing a non-carbohydrate source of metabolic substrate for ATP generation by tissues such as muscle and this action is enhanced during fasting. As a result of the increased oxidation of fat, there is a reduction in the respiratory quotient (see Chapter 37).

The direct actions of GH on the various metabolic substrates may be summarized as follows: GH is essentially an anabolic hormone, it promotes protein synthesis, and it encourages the use of fats for ATP synthesis, thus conserving glucose for use by the CNS.

Indirect actions of GH on skeletal growth

The main indirect physiological actions of GH are the maintenance of tissues and the promotion of linear growth during childhood and adolescence. These actions, particularly the latter, are considered further in Chapter 36. It is important to remember that growth is a highly complex process that is under the control of numerous agents including a variety of growth factors and hormones in addition to GH itself.

The growth-promoting effects of GH are mediated partly by its actions on amino acid transport and partly by its stimulation of protein synthesis. Skeletal growth results from the stimulation of mitosis in the epiphyseal discs of cartilage (also called growth plates) present in the long bones of growing children. GH exerts direct actions on both cartilage and bone to stimulate growth and differentiation, aided by polypeptides called **insulin-like growth factors (IGFs)** that are synthesized chiefly by the liver but also in the growing tissues themselves. These agents encourage the cartilage cells to divide and to secrete more cartilage matrix. As growing cartilage is eventually converted to bone, the growth of cartilage enables the bone to increase in length (see Chapter 36). Growth of the long bones in response to GH ceases once the epiphyseal discs themselves are converted to bone at the end of adolescence (a process known as fusion of the epiphyses). No further increase in stature can then occur despite the continued, though declining secretion of GH throughout adulthood.

What are the IGFs and how do they promote growth?

The IGFs show significant amino acid sequence homology with the pancreatic hormone insulin and share some of its effects. Two such factors have been identified, IGF-1 and IGF-2, the former having the most potent growth-promoting effect and the latter the strongest insulin-like action. An important action of GH is to stimulate IGF-1 production from the liver. IGF-1 stimulates a variety of the cellular

processes that are responsible for tissue growth. In many cells (e.g. fibroblasts, muscle, and liver), it stimulates the production of DNA and increases the rate of cell division. It also encourages the incorporation of sulphate into chondroitin in the chondrocytes (the cells which make cartilage for bones) and the synthesis of glycosaminoglycan for cartilage and collagen formation.

The growth-promoting effects of GH seem to be crucial for growth during childhood, particularly from the age of about 3 to the end of adolescence. IGF-1 levels reflect the rate of growth during this time and there is a marked increase at puberty. GH and IGF-1 seem to be less important to growth during the fetal and neonatal periods, when IGF-2 may be more significant.

Growth hormone secretion is governed by the hypothalamic secretion of GHRH and somatostatin

As described earlier, growth hormone is under dual control by hormones released from hypothalamic neurons. Its secretion is stimulated by GHRH and inhibited by somatostatin. The rate at which GH is released from the somatotrophic cells of the anterior pituitary is therefore determined by the balance between these two hormones. Since GH secretion declines when all hypothalamic influences are removed (either experimentally or in disease), it may be assumed that the positive effects of GHRH on GH release are normally dominant.

GH, like all the anterior pituitary hormones, is released in discrete pulses, these pulses being most frequent in adolescence. The detailed mechanism of pulsatile release is unclear but peaks of output appear to coincide with peaks of GHRH output while troughs coincide with increased rates of somatostatin release. GH secretion also shows a definite circadian rhythm, with marked elevations in output associated with periods of deep sleep during which bursts of secretion occur every 1–2 hours (Fig. 15.7). Serotonergic pathways in the brain are believed to mediate this response. It is important to be aware of these characteristics of GH secretion when carrying out measurements of plasma GH levels in clinical practice. A single measurement will be insufficient for diagnostic purposes and it will be necessary to perform frequent serial assays.

A number of physical and psychological stresses promote the secretion of GH. Examples include anxiety, pain, surgery, cold, haemorrhage, fever, and strenuous exercise. Adrenergic and cholinergic pathways in the brain are believed to mediate these effects. The significance of the raised GH output is not fully understood, but it seems likely that the glucose-sparing effect of the hormone would be of value in circumstances of this kind.

Metabolic factors influencing GH secretion

The most potent metabolic stimulus for GH release is hypoglycaemia. This is an appropriate homeostatic response since GH acts as a glucose-sparing hormone, promoting the breakdown of fats to make fatty acids available for oxidation. At the same time, GH inhibits the uptake of glucose by the peripheral tissues and conserves glucose for use by the brain. By contrast with the effect of hypoglycaemia, an oral glucose load rapidly suppresses the release of GH.

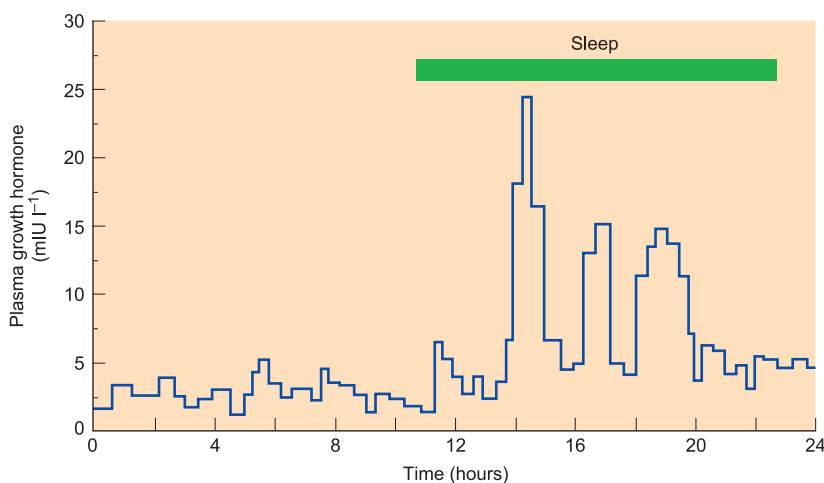


Fig. 15.7 The diurnal variation in growth hormone secretion recorded for a normal 9-year-old child. Note the pronounced pulsatile release of GH during sleep.

Growth hormone is secreted during prolonged fasting. Again, its glucose-sparing effects and its effects on lipid metabolism ensure that tissues which rely entirely on glucose as their metabolic substrate (the CNS and the germinal epithelium) are adequately supplied. Other metabolic factors known to increase the rate of GH secretion include a rise in plasma amino acid levels and a reduction in the plasma concentration of free fatty acids. All of these metabolic actions are mediated by changes in the output of GHRH and somatostatin.

GH promotes lipolysis thus providing a non-carbohydrate source of substrate for ATP generation. GH promotes protein synthesis and is crucial for normal skeletal growth between the ages of about 3 years and puberty. Skeletal growth occurs in response to IGFs whose synthesis and secretion is stimulated by GH. The IGFs encourage cartilage cells to divide and enhance the deposition of cartilage at the epiphyses (growth plates). In adults GH helps to maintain tissues.

Feedback actions of GH and the IGFs

The secretion of growth hormone appears to be influenced by the plasma concentration of GH itself. High plasma GH levels inhibit the release of further GH. This is an example of a short negative feedback loop in which GH depresses its own release by altering the rates of secretion of GHRH and somatostatin by the hypothalamus, or by altering the sensitivity of the anterior pituitary to these hypothalamic factors. In addition to the direct feedback effects of GH itself, IGF-1 can also inhibit GH release via a feedback action on GH synthesis by the pituitary gland. These interactions are shown in Fig. 15.6.

Both hypersecretion and hyposecretion of GH may result in disorders of growth. Hypersecretion in children results in **gigantism**, a condition in which growth is exceptionally rapid, while GH deficiency in children results in **pituitary dwarfism** in which the growth of the long bones is slowed. These conditions are discussed in more detail in Chapter 36.

Summary

Growth hormone is a peptide hormone secreted by the somatotrophs of the anterior pituitary gland. Its secretion is stimulated by GHRH and suppressed by somatostatin. GH exerts a wide range of metabolic actions. Hypoglycaemia, increased plasma levels of amino acids, and reduced plasma levels of free fatty acids all stimulate GH secretion. GH inhibits glucose uptake by most tissues. This anti-insulin action conserves glucose for use by the brain.

15.4 Adrenocorticotrophic hormone (ACTH) and melanocyte-stimulating hormone (MSH)

Both adrenocorticotrophic hormone (ACTH) and melanocyte-stimulating hormone (MSH) are synthesized and secreted by the anterior pituitary corticotrophs. ACTH is a small polypeptide hormone consisting of a chain of 39 amino acid residues that is derived from a much larger precursor molecule, pre-pro-opiomelanocortin which is also a precursor for several other physiologically active peptides. The relationships between the peptides derived from this common precursor are illustrated in Fig. 15.8. Pre-pro-opiomelanocortin splits to form β -lipotrophin and a 146 amino acid peptide. The latter gives rise to ACTH and N-terminal peptide, while the β -lipotrophin forms γ -lipotrophin and β -endorphin (an endogenous opioid, part of which may further split to form met-enkephalin). A variety of other peptides, including α -MSH, CLIP (corticotrophin-like peptide), and some with unknown physiological properties, are also derived from pre-pro-opiomelanocortin.

ACTH regulates the function of the adrenal cortex, playing a crucial role in the stimulation of glucocorticoid secretion in response to a variety of stressors. It also has an important trophic action, maintaining the integrity of the adrenal tissue itself. In the absence of ACTH, the adrenal glands will eventually begin to atrophy. The pattern of ACTH secretion varies during the day showing a typical circadian rhythm (see Fig. 14.2 p 254). ACTH secretion is under the control of hypothalamic CRH and is subject to negative feedback

regulation of the kind discussed in Chapter 14. ACTH secretion is markedly inhibited by glucocorticoids (steroid hormones secreted from the adrenal cortex, see Chapter 16).

The chemical structure of melanocyte-stimulating hormone (α -MSH) is very similar to that of ACTH (Fig. 15.8) but although ACTH has some MSH-like activity MSH does not appear to share any of the actions of ACTH. In certain species, it plays a role in skin pigmentation through the stimulation of melanocytes in the epidermis, and in the control of sodium excretion, but the physiological significance of these effects in humans is unclear. It is known, however, that α -MSH binds to a receptor (MC-1) on the human melanocyte membrane and that this binding activates tyrosinase, an enzyme required for the synthesis of the pigment **melanin**. Furthermore, melanocytes taken from individuals who tan poorly (usually those with red hair) appear to have mutations in the MC-1 receptor. Four additional receptor sub-types for MSH have recently been identified. While their functions remain unclear, they appear to be responsible for some additional effects of MSH including mediation of the actions of ACTH on the adrenal gland, effects on food intake and energy expenditure, and control of exocrine secretions.

Summary

Adrenocorticotrophic hormone (ACTH) is secreted by anterior pituitary corticotrophs. It is derived from a much larger precursor molecule called pre-pro-opiomelanocortin. ACTH maintains the structural integrity of the adrenal cortex and regulates the secretion of glucocorticoid steroid hormones in response to stress. ACTH secretion is under the control of hypothalamic corticotrophin-releasing hormone (CRH) and is subject to negative feedback regulation.

15.5 Pituitary glycoprotein hormones: thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH)

The pituitary glycoprotein hormones consist of two interconnected amino acid chains (α - and β -subunits) containing sialic acids (a family of 8- and 9-carbon monosaccharides) and the carbohydrates hexose and hexosamine. The α -subunits of all three hormones are identical while the β -subunits confer biological specificity (another example of a “family” of related hormones). The α -subunit is also identical to that of human chorionic gonadotrophin (hCG) (see Chapter 34) and is considered to be the effector region responsible for the activation of adenylyl cyclase and the generation of cAMP in the target cells. All three pituitary glycoproteins are trophic hormones, which means that they not only regulate the secretions of their target glands but they are also responsible for the maintenance and integrity of the target tissue itself.

TSH is secreted by pituitary thyrotrophs (Fig. 15.3 d), which contain numerous small secretory granules. It controls the function of the thyroid gland, and the output of the thyroid hormones thyroxine and tri-iodothyronine (see Chapter 16). The secretion of TSH is stimulated by hypothalamic TRH and is under strong negative feedback control by thyroxine and tri-iodothyronine.

The gonadotrophins, FSH and LH, are secreted by the anterior pituitary gonadotrophs shown in Fig. 15.3b. Although many gonadotrophs secrete both FSH and LH, some secrete only FSH while others secrete only LH. As their name suggests, the gonadotrophins control the functions of the ovaries and testes (the gonads). The secretion of both hormones is controlled by a single hypothalamic

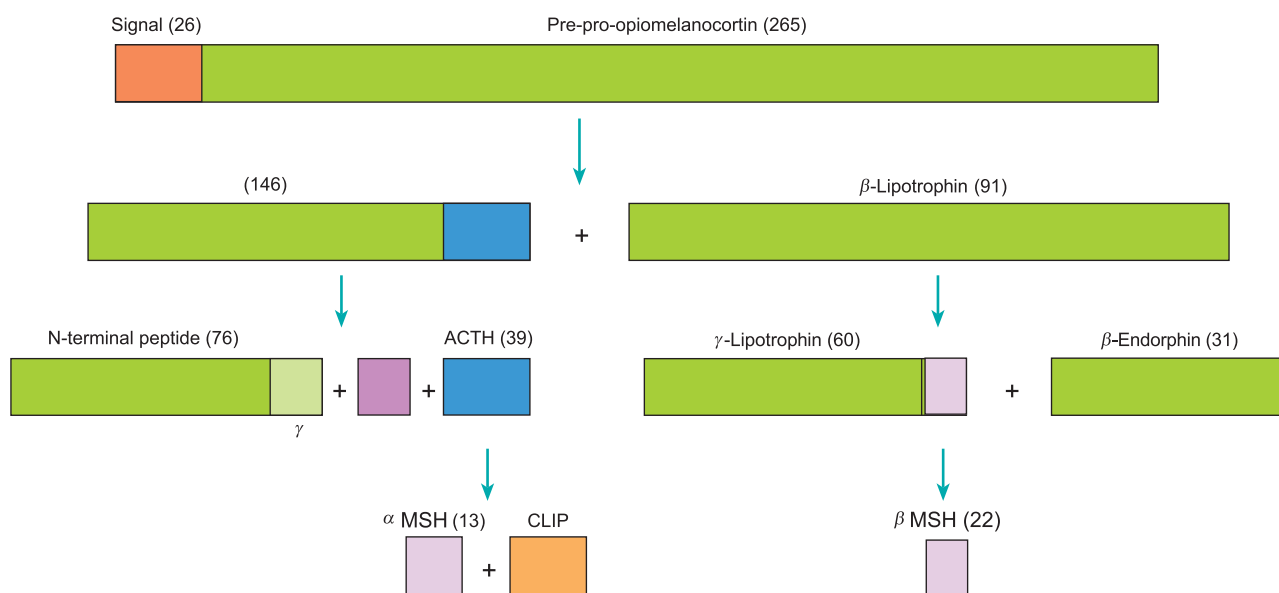


Fig. 15.8 The relationship between the amino acid sequences of the various hormones derived from pre-pro-opiomelanocortin. ACTH, β -lipoprotein, β -endorphin, and a 76 amino acid peptide are the end products that are secreted by the anterior lobe of the pituitary gland. The numbers in brackets after the peptide name give the number of amino acid residues in each peptide.

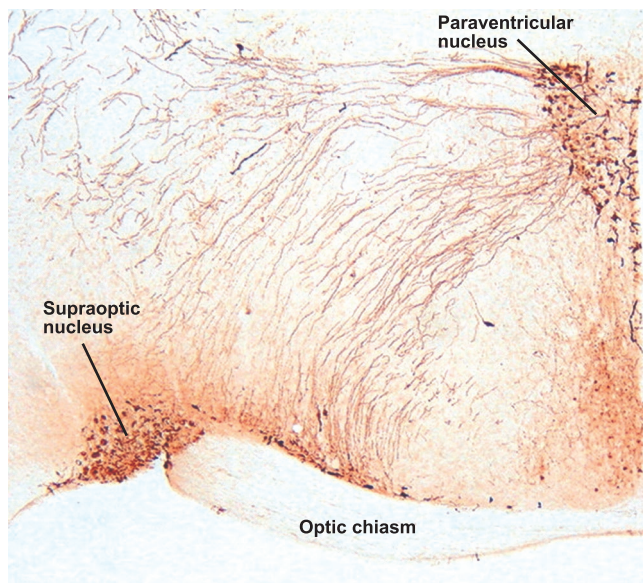


Fig. 15.9 A section of hypothalamus treated with antibodies to neurophysin to label neurons and axons that synthesize and secrete oxytocin and ADH. The reaction product is brown to black in colour. Staining is mainly confined to the neurons of the paraventricular and supraoptic nuclei and the fibres of the hypothalamo-hypophyseal tract.

releasing hormone called gonadotrophin-releasing hormone (GnRH), also known as LHRH or luteal releasing hormone, and both negative and positive feedback control mechanisms may operate to control their release.

In females, FSH stimulates the growth and development of follicles during the first half of each menstrual cycle in preparation for ovulation. It is also needed for the secretion of oestrogens by the developing follicle. LH stimulates ovulation itself and is required for the development and secretory activity of the corpus luteum. In males, FSH is required for normal spermatogenesis and LH is responsible for stimulating the secretion of testosterone by the Leydig cells of the testes. The physiological actions of the gonadotrophins are discussed in detail in Chapters 33 and 34.

Summary

Thyroid stimulating hormone (TSH) maintains the structural integrity of the thyroid gland and regulates the secretion of thyroxine and tri-iodothyronine. Its secretion is regulated by hypothalamic thyrotrophin-releasing hormone (TRH).

FSH and LH regulate the functions of the ovaries and testes. Their secretion is under the control of hypothalamic gonadotrophin-releasing hormone (GnRH). In females, FSH stimulates growth and development of follicles in preparation for ovulation and the secretion of oestrogens by the maturing follicle. LH triggers ovulation and stimulates the secretion of progesterone by the corpus luteum. In males, FSH is required for spermatogenesis while LH stimulates testosterone secretion by Leydig cells.

15.6 The role of the posterior pituitary gland (neurohypophysis)

The posterior lobe of the pituitary gland develops as a down-growth from the hypothalamus as described above (p 257) and, unlike the anterior pituitary, it is directly connected to the hypothalamus via a nerve tract (the hypothalamo-hypophyseal nerve tract). For this reason the posterior pituitary is also known as the neurohypophysis, pars nervosa, or neural lobe.

The posterior pituitary secretes two hormones: **oxytocin** and **vasopressin** (or **ADH**). The hormones are synthesized within the cell bodies of large (magnocellular) neurons lying in the supraoptic and paraventricular nuclei of the hypothalamus. Fig. 15.9 is a photomicrograph of the hypothalamus stained to reveal the oxytocin- and vasopressin-secreting cells and the fibres of the hypothalamo-hypophyseal tract.

The posterior pituitary hormones are transported in association with specific proteins, the neurophysins, along the axons of these neurons to end in nerve terminals that lie within the posterior lobe. Prior to secretion, these hormones are stored in secretory granules either in the terminals themselves or in varicosities called Herring bodies that are distributed along the length of the axons (Fig. 15.10). The hormones are secreted in response to nerve impulses originating in the supra-optic and paraventricular nuclei and enter the blood of the capillaries that perfuse the neural lobe. Both oxytocin and vasopressin are secreted by calcium-dependent exocytosis similar to the secretion of neurotransmitters at other nerve terminals (see Chapter 7).

Oxytocin and vasopressin (ADH) are closely related structurally but have different functions

Oxytocin and vasopressin are both nonapeptides and differ in only two of their amino acid residues, as shown in Fig. 15.11. Although they are secreted along with the neurophysin molecules to which they are bound in the neurons, once released they circulate in the blood largely as free hormones. The kidneys, liver, and brain are the main sites of clearance of these peptides, which have a half-life in the bloodstream of around a minute.

Both oxytocin and vasopressin act on their target cells via G protein-linked cell surface receptors (see Chapter 6). Interaction of oxytocin with its receptors stimulates phosphoinositide turnover and thereby raises the level of intracellular calcium in the myoepithelial cells of the mammary gland. In turn, the increased intracellular calcium activates the contractile machinery to cause milk ejection (see Chapter 34). It also acts as a uterine spasmogen and plays a role in parturition.

There are three subtypes of vasopressin receptor: V_{1A} , V_{1B} , and V_2 . Activation of V_{1A} and V_{1B} receptors increases phosphoinositide turnover and elevates intracellular calcium. V_{1A} receptors mediate the effects of vasopressin on vascular smooth muscle. V_{1B} receptors are found throughout the brain and on the corticotrophs of the anterior pituitary where vasopressin plays a role in the control of ACTH secretion. The renal actions of the hormone are mediated

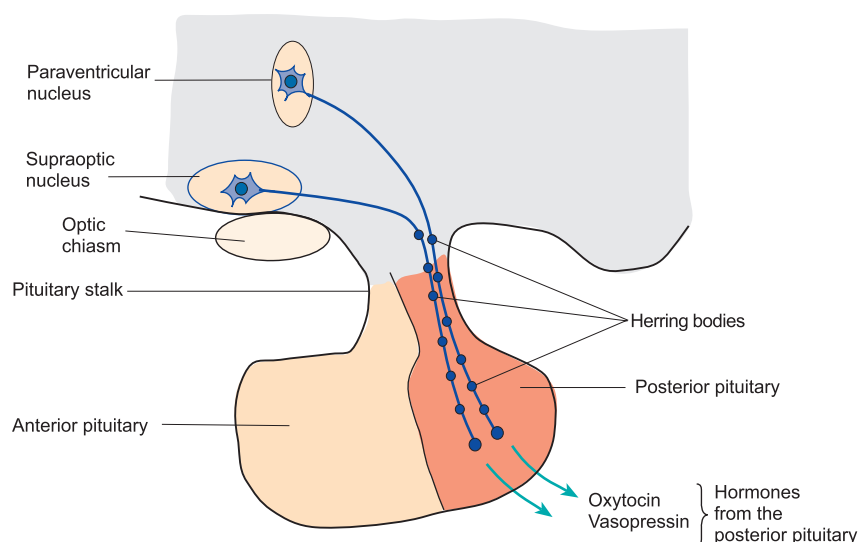


Fig. 15.10 A diagrammatic representation of the relationship between the supraoptic and paraventricular nuclei and the posterior pituitary gland (the neurohypophysis). The neurosecretory fibres originate in these nuclei and terminate in the posterior pituitary gland itself. The axons of the hypothalamo-hypophyseal tract exhibit local swellings known as Herring bodies that contain oxytocin or vasopressin bound to neurophysin.

by V_2 receptors, with cyclic AMP as the second messenger (see Chapter 27 p 531).

Actions of vasopressin (ADH)

The principal physiological action of vasopressin is as an antidiuretic hormone. For this reason it is also known as ADH. This role is discussed in more detail in Chapter 27 (pp 531–533). Briefly, when V_2 receptors are activated they facilitate the reabsorption of water from the final third of the distal tubule and the collecting ducts of the kidney by increasing the permeability of these cells to water. The net result of its actions is an increase in urine osmolality and a decrease in urine flow. Additional renal effects of vasopressin include stimulation of sodium reabsorption and urea transport from lumen to interstitial fluid in the medullary collecting duct. By this action, vasopressin helps to maintain the osmotic gradient from cortex to papilla which is crucial for the elaboration of a concentrated urine.

Vasopressin, as its name suggests, is also a potent vasoconstrictor that acts particularly on the arteriolar smooth muscle of the skin and splanchnic circulation. In spite of this, the increase in blood pressure brought about by vasopressin is small under normal circumstances because the hormone also causes bradycardia and a decrease in cardiac output, both of which tend to offset the increase in total peripheral resistance. However, the vasoconstrictor effect of

vasopressin is important during severe haemorrhage or dehydration (see Chapter 28). Vasopressin also exerts a CRH-like activity whereby it stimulates the release of ACTH from the anterior pituitary. It may also play a role in the control of thirst.

The circumstances under which vasopressin (ADH) is secreted are discussed in Chapters 27 and 28. Only a brief résumé will be given here. Fig. 15.12 illustrates the changes in plasma osmolality and volume that control vasopressin release. The principal physiological stimulus for its release is an increase in the osmolality of the circulating blood. Osmoreceptors located in the hypothalamus detect this increase and activate neurons in the supraoptic and paraventricular nuclei. As a result of the increased rate of action potential discharge of these neurons, vasopressin secretion into the circulation is increased.

Vasopressin is also secreted in response to a fall in the effective circulating volume (ECV), for example during haemorrhage and in response to other factors including pain, stress, and other traumas. The amount of vasopressin secreted when there is a fall in the ECV increases proportionately as the central venous pressure and arterial pressure fall (see Fig. 28.3). Central venous pressure is sensed by the low-pressure receptors (volume receptors) of the atria and great veins while the arterial blood pressure is sensed by the arterial baroreceptors, which are located in the carotid sinuses and aortic arch (see Chapters 23 and 28).

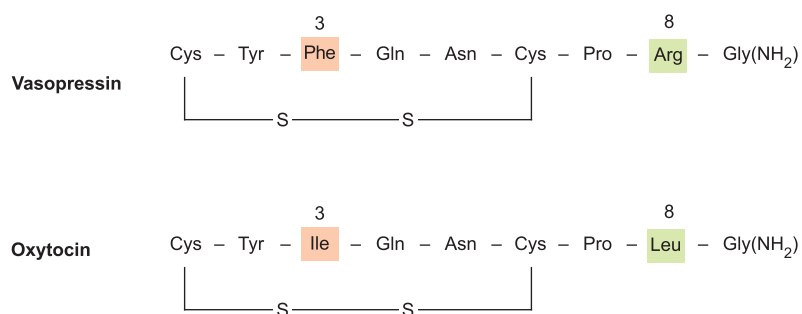


Fig. 15.11 The amino acid sequences of vasopressin and oxytocin. The small differences in structure result in molecules that have very different physiological effects.

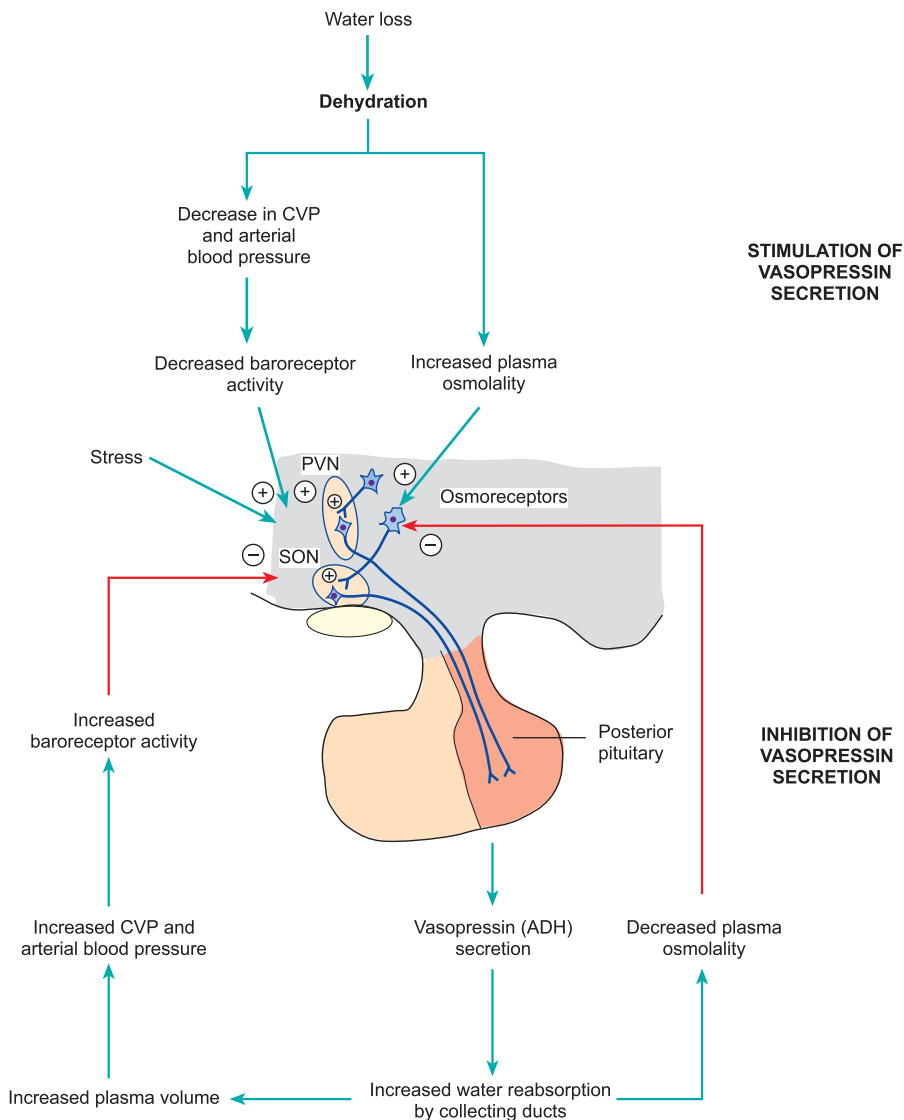


Fig. 15.12 A schematic diagram showing the factors that regulate vasopressin release in response to changes in plasma osmolality and blood volume. Green arrows directed towards the hypothalamus indicate stimulation; red arrows indicate inhibition. CVP, central venous pressure; PVN, paraventricular nucleus; SON, supraoptic nucleus.

Disorders of vasopressin secretion

The consequences of under- or overproduction of vasopressin may easily be predicted from the descriptions of its actions given above. Abnormally high circulating levels of vasopressin may result from certain drug treatments, brain traumas, or from vasopressin-secreting tumours. Such patients will have highly concentrated urine, with water retention, lowered plasma osmolality, and sodium depletion.

A lack of vasopressin leads to a condition known as **diabetes insipidus**, in which the individual is unable to produce a concentrated urine or to limit the production of urine even when the plasma osmolality is raised. To counteract the loss of water via the kidneys, the sufferer has to drink a large amount of fluid. This condition may result from head injuries or tumours that damage the posterior pituitary (central diabetes insipidus). The deficiency is treated by the administration of a synthetic analogue of vasopressin

(desmopressin). Diabetes insipidus may also arise as a consequence of a loss of vasopressin receptors in the distal nephron (nephrogenic diabetes insipidus).

Actions of oxytocin

The main actions of oxytocin are described in some detail in Chapter 34. Briefly, this hormone stimulates the ejection of milk from the mammary glands in response to suckling (the milk ejection or 'let down' reflex). It causes the myoepithelial cells surrounding the ducts and alveoli of the gland to contract thus squeezing milk into the lactiferous sinuses and towards the nipple. Oxytocin is known to promote contractions of the uterus and to increase the sensitivity of the myometrium to other spasmogenic agents and plays a role in expelling the fetus and placenta during labour. Synthetic analogues of oxytocin (e.g. syntocinon and pitocin) are often administered to women in whom labour has

begun but is failing to progress due to inadequate uterine contraction. In males, oxytocin appears to play a role in erection, ejaculation, and sperm progression.

Control of oxytocin secretion

Like vasopressin, oxytocin is released in response to afferent neural input to the hypothalamic neurons that synthesize the hormone. Although oxytocin is released in response to vaginal stimulation (particularly during labour), the most potent stimulus for release is the mechanical stimulation of the nipple by a suckling baby. Impulses from the breast travel to the hypothalamus via the spinothalamic tract and the brainstem (see Fig. 34.22). This explains the so-called 'after pains' experienced by many women when they first breastfeed their babies following delivery. The uterus, which is still highly sensitive to spasmogenic agents, begins to contract once more in response to the oxytocin released during suckling. Certain psychogenic stimuli can also influence the secretion of oxytocin. The milk-ejection reflex is known to be inhibited by certain forms of stress and to be stimulated by the cry of the hungry infant or during play prior to feeding.

Disorders of oxytocin secretion

Excessive oxytocin secretion has never been demonstrated but oxytocin-deficiency results in failure to breastfeed an infant because of inadequate milk ejection.

Summary

The posterior pituitary gland (the neurohypophysis) secretes vasopressin (also called antidiuretic hormone or ADH) and oxytocin. These hormones are synthesized in neurons of the paraventricular and supraoptic nuclei and are transported to the posterior pituitary by axoplasmic flow. Oxytocin and vasopressin are structurally similar but have very different actions. Vasopressin is released in response to an increase in the osmotic pressure of the plasma or a fall in blood volume and stimulates the reabsorption of water in the renal collecting ducts. Vasopressin also exerts a pressor effect on vascular smooth muscle. Oxytocin stimulates the ejection of milk from the lactating breast and increases the contractile activity of the uterine myometrium during parturition. In males oxytocin appears to play a role in erection, ejaculation, and sperm progression.



Checklist of key terms and concepts

The hypothalamo-pituitary axis

- The pituitary gland is situated within a depression in the base of the skull.
- It is connected to the brain via the pituitary stalk and consists of two principal lobes: the anterior lobe (or adenohypophysis) and the posterior lobe (or neurohypophysis).
- The anterior lobe is derived from non-neural embryonic tissue while the posterior lobe is a down-growth from the hypothalamus.
- The anterior pituitary secretes growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and a number of related peptides.
- A system of blood vessels (the hypophyseal portal vessels) carries regulatory hormones from the hypothalamus to the anterior pituitary to control the release of the anterior pituitary hormones.
- The secretion of the hypothalamic hormones, the hormones of the anterior pituitary and their target organs form a complex feedback system—the hypothalamo-hypophyseal axis.
- The posterior pituitary secretes vasopressin (ADH) and oxytocin.
- The secretion of these hormones is directly controlled by nerve activity in the hypothalamo-hypophyseal tract.

Growth hormone and prolactin

- Growth hormone and prolactin are structurally related peptide hormones secreted by the anterior pituitary gland.

- GH secretion is stimulated by hypothalamic growth hormone-releasing hormone and suppressed by hypothalamic somatostatin.
- Prolactin secretion is normally inhibited by the hypothalamic prolactin-inhibiting hormone dopamine.
- The secretion of GH shows a circadian rhythm with the highest rates occurring during deep sleep.
- GH secretion is stimulated by hypoglycaemia, increased plasma levels of amino acids, and reduced plasma levels of free fatty acids.
- GH exerts a wide range of direct metabolic actions in addition to indirect effects that are mediated by insulin-like growth factors (IGFs) which are produced mainly by the liver. GH promotes protein synthesis.
- GH promotes lipolysis, thus providing a non-carbohydrate source of energy. This, together with its anti-insulin action on muscle, spares glucose for use by the CNS and germinal epithelium.
- GH is crucial to normal skeletal growth between the ages of about 3 and puberty. IGFs encourage cartilage cells to divide and enhance the deposition of cartilage at the epiphyses (growth plates) of long bones.
- Prolactin stimulates the manufacture of milk during lactation (galactopoiesis).
- Prolactin secretion is stimulated in response to suckling, which inhibits the release of hypothalamic dopamine.

ACTH and MSH

- Adrenocorticotrophic hormone (ACTH) and melanocyte-stimulating hormone (MSH) are secreted by anterior pituitary corticotrophs.

Both are derived from a much larger precursor molecule, pre-pro-opiomelanocortin.

- ACTH maintains the structural integrity of the adrenal cortex and regulates the secretion of glucocorticoid hormones in response to stress.
- ACTH secretion is under the control of hypothalamic corticotrophin-releasing hormone (CRH) and is subject to negative feedback regulation.
- The role of MSH in humans is unclear but it may be concerned with skin pigmentation and the regulation of food intake and energy expenditure.

TSH, FSH, and LH

- Thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) are all glycoproteins secreted by the anterior pituitary.
- TSH is a trophic hormone that maintains the structural integrity of the thyroid gland and regulates the secretion of thyroxine and tri-iodothyronine.
- The secretion of TSH is regulated by thyrotrophin-releasing hormone (TRH) secreted by neurons in the preoptic and paraventricular hypothalamic nuclei.
- FSH and LH (the gonadotrophins) regulate the functions of the ovaries and testes and are themselves under the control of hypothalamic luteinizing hormone-releasing hormone (LHRH).
- In females, FSH stimulates growth and development of follicles in preparation for ovulation and the secretion of oestrogens by the maturing follicle.

- In males, FSH is required for spermatogenesis.
- In females, LH triggers ovulation and stimulates the secretion of progesterone by the corpus luteum.
- In males, LH stimulates the secretion of testosterone by Leydig cells.

The posterior pituitary hormones

- The posterior pituitary gland (the neurohypophysis) secretes two peptide hormones: vasopressin (antidiuretic hormone or ADH) and oxytocin. They are synthesized in the cell bodies of neurons within the paraventricular and supraoptic nuclei and reach the posterior pituitary by axonal transport.
- They are secreted in response to nerve activity in the hypothalamo-hypophyseal tract.
- Oxytocin and vasopressin are structurally similar but have very different actions.
- Vasopressin is secreted in response to an increase in the osmotic pressure of the plasma or a fall in blood volume.
- The antidiuretic action of vasopressin stimulates the reabsorption of water from the collecting ducts of the renal nephrons. As a result, urinary volume is reduced and urinary osmolality is increased.
- Oxytocin stimulates the ejection ('let-down') of milk from the lactating breast.
- It also increases the contractile activity of the uterine myometrium and may play a role in expulsion of the fetus during parturition.



Recommended reading

Biochemistry

Berg, J.M., Tymoczko, J.L., and Stryer, L. (2011) *Biochemistry* (7th edn), Chapters 14, 27. Freeman, New York.

A classic text with helpful accounts of signal transduction and the integration of metabolism.

Histology

Mescher, A. (2009) *Junqueira's basic histology* (12th edn), Chapter 20. McGraw-Hill, New York.

A recent revision of Junqueira and Carneiro's classic text. Good text, fewer pictures than some alternatives.

Pharmacology

Rang H.P., Dale, M.M., Ritter, J.M., Flower, R. and Henderson, G. (2011) *Pharmacology* (7th edn), Chapter 32. Churchill-Livingstone, Edinburgh.

The first part of this chapter provides an easily digested introduction to pituitary disorders and their treatment.

Endocrine physiology

Griffin, J.E., and Ojeda, S.R. (2004) *Textbook of endocrine physiology* (5th edn), Chapters 6, 7. Oxford University Press, Oxford.

An authoritative account of the pituitary gland. Well referenced.

Medicine

Hall, R., and Evered, D.C. (1990) *A colour atlas of endocrinology* (2nd edn). Wolfe Medical, London.

An informative collection of colour plates illustrating the physical changes associated with various endocrine disorders.

Ledingham, J.G.G., and Warrell, D.A. (2000) *Concise Oxford textbook of medicine*. Chapters 7.1, 7.2 Oxford University Press, Oxford.

These chapters provide a useful introduction to disorders of the pituitary gland and their treatment.

Maitra, A., and Kumar, V. (2007) Chapter 20. In: *Robins basic pathology* (8th edn), Kumar, V., Abbas, A.K., Fausto, N., and Mitchell, R. (eds.). Saunders, New York.



To check that you have mastered the key concepts presented in this chapter, go to the **Online Resource Centre** and complete the self-assessment questions: www.oxfordtextbooks.co.uk/orc/pocock4e/