Clinical Endocrinology and Diabetes at a Glance

Aled Rees
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WILEY Blackwell

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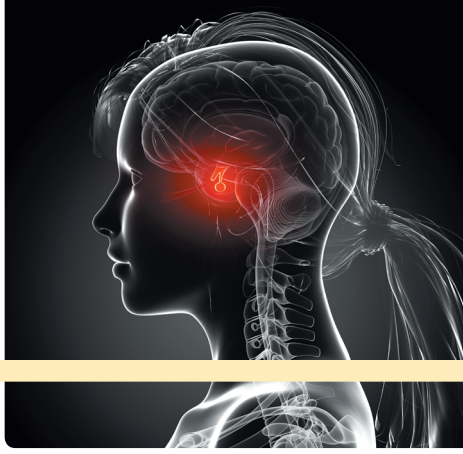

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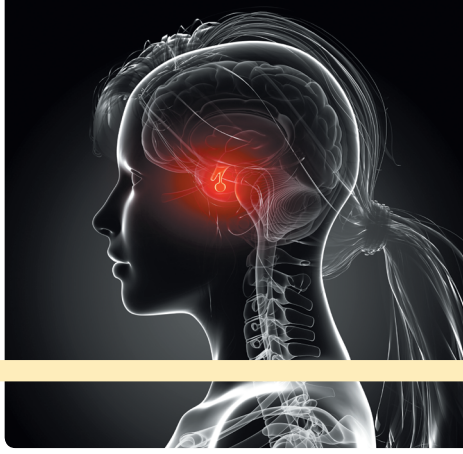
Preface



This concise and informative textbook is aimed primarily at medical undergraduates commencing their clinical rotations, and is the first of its kind to be aligned against a nationally endorsed curriculum (developed by the Society for Endocrinology, Diabetes UK and the Association of British Clinical Diabetologists). Feedback from our students has informed our approach to this book, which seeks to progress the reader from a fundamental understanding of the physiological mechanisms underpinning endocrine regulation through to disease processes which disturb this homeostatic balance. In addition to the core material on common endocrine and diabetes presentations, there is an emphasis on key practical skills and provision of clear guidance on peri-operative management, emergency presentations and acute illness. We therefore anticipate that *Clinical Endocrinology and Diabetes at a Glance* will form a helpful and accessible resource for junior doctors involved in the management of patients with diabetes and endocrine disorders. As with other books in the series there is a major emphasis on the use of clear illustrations and tables to complement the text and consolidate learning.

Parts 1 to 9 cover the regulation and assessment of the endocrine system, pituitary disorders, fluid and electrolyte balance, thyroid disease, metabolic bone disorders, adrenal disease, disorders of the reproductive system, neuroendocrine tumours and endocrine emergencies. Part 10 provides a comprehensive overview of all aspects of diabetes, lipid and weight disorders.

Finally, no textbook makes it to publication without the hard work of a number of contributors. We are particularly grateful to Karen Moore for her diligence in keeping our writing endeavours on track, and to Jan East and Kathy Syplywczak for their help in taking us through the production process.

We welcome any feedback, and hope you enjoy reading the book as much as we have enjoyed writing it.

Aled Rees
Miles Levy
Andrew Lansdown
February 2017

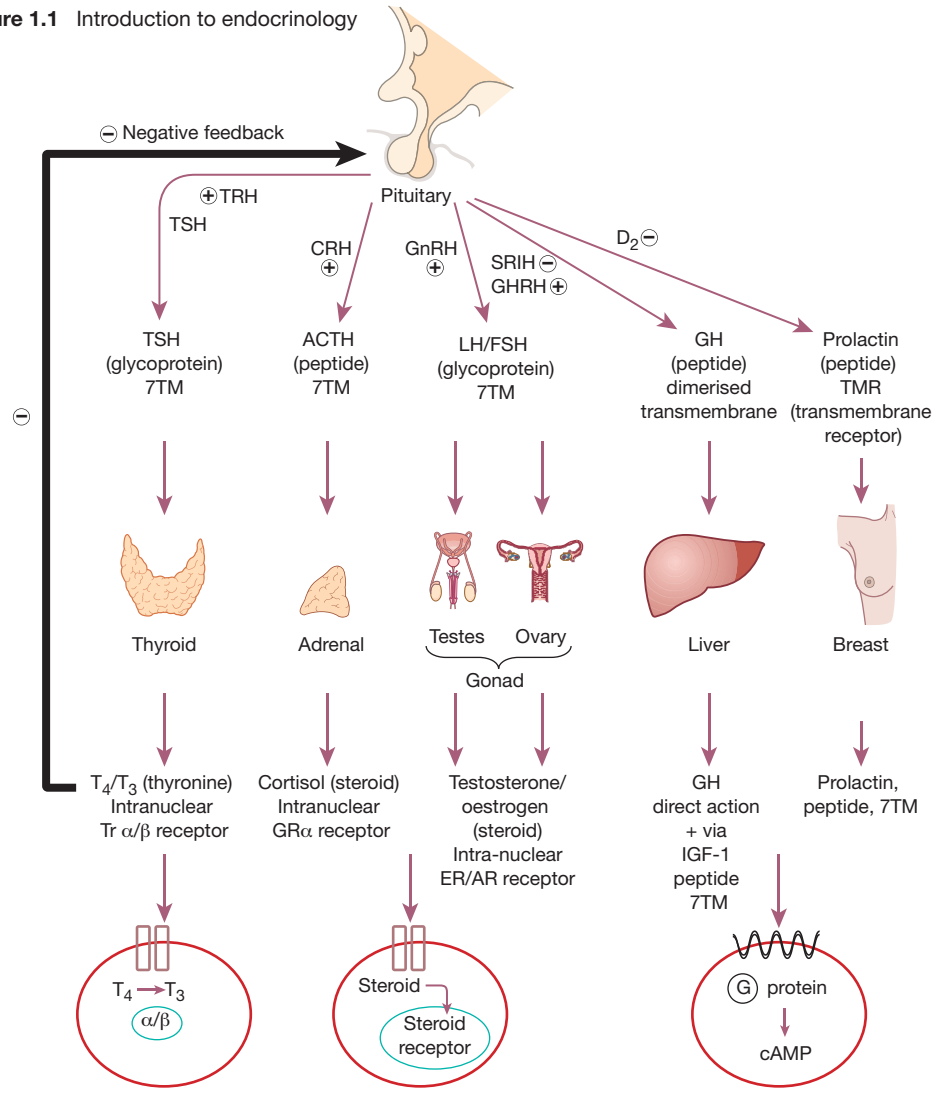
Introduction

Part 1

Chapter

1 Introduction to endocrinology

Figure 1.1 Introduction to endocrinology



Abbreviations: 7TM, 7-trans-membrane; ACTH, adrenocorticotrophic hormone; CRH, corticotrophin releasing hormone; cAMP, cyclic adenosine monophosphate; GH, growth hormone; GHRH, growth hormone releasing hormone; GnRH, gonadotropin-releasing hormone; SRIH, somatostatin; TRH, thyrotrophin releasing hormone; TSH, thyroid stimulating hormone; TSH, trophic hormone.

Clinical Endocrinology and Diabetes at a Glance, First Edition. Aled Rees, Miles Levy and Andrew Lansdown.

The endocrine system consists of glands, which secrete hormones that circulate and act at distant sites in the body. The key endocrine glands are the pituitary, thyroid, parathyroids, adrenals, pancreas and gonads. Endocrine disease can lead to hypo- or hypersecretion of hormones. Endocrine diseases include tumours, which are commonly benign, autoimmune diseases, enzyme defects and hormone receptor abnormalities.

Synthesis, release and transport

The chemical structure of hormones includes steroids, polypeptides, glycoproteins and amines (Figure 1.1). Hormones are secreted by the hypothalamus at low concentration, acting locally on the anterior pituitary, which in turn secretes trophic hormones to the relevant target gland. Hormones are secreted directly into the circulation either in their final form or as a larger precursor molecule, such as proopiomelanocortin (POMC), which is cleaved to adrenocorticotrophic hormone (ACTH), melanocyte stimulating hormone (MSH) and other smaller peptides. Many hormones are transported in the circulation by binding proteins, but only the free hormone acts on the receptor. Examples of binding proteins are sex hormone binding globulin (SHBG), which binds testosterone, and cortisol binding globulin (CBG), which binds cortisol.

Mechanisms of hormone action

Cell-surface receptors

Peptide hormones act on cell-surface receptors and exert their effect by activating cyclic adenosine monophosphate (cAMP). Most peptide hormones act via G-protein coupled receptors, most commonly a 7-trans-membrane (7TM) receptor (Figure 1.1). Examples of peptide hormones are growth hormone (GH), thyroid stimulating hormone (TSH), prolactin and ACTH.

Intranuclear receptors

Lipid-soluble hormones such as steroids and thyroid hormones pass through the cell membrane and act on intranuclear receptors, causing altered gene transcription (Figure 1.1).

Control and feedback

Hormones are usually controlled by a negative feedback mechanism (Figure 1.1). Using the thyroid axis as an example, the hypothalamus secretes its thyrotrophin releasing hormone (TRH), which travels down the portal tract to act on the anterior pituitary. The pituitary releases its trophic hormone (TSH) into the circulation, which acts on the target gland, stimulating the production of the relevant hormone (thyroxine). If the target gland hormone is too low, there is loss of negative feedback and a compensatory increase in the pituitary hormone (low T4, high TSH). If the target gland hormone is too high, there is increased negative feedback and suppression of the pituitary hormone (high T4, low TSH). All pituitary hormones are under predominantly stimulatory control by the hypothalamus apart from prolactin, which is under tonic inhibition by dopamine.

Patterns of hormone secretion

Some hormones are produced in a stable pattern with little circadian rhythmicity, for example thyroxine and prolactin. Other hormones have a significant diurnal variation. For example, cortisol is highest in the morning and lowest at midnight. Minor circadian rhythms can be seen with certain hormones such as testosterone, which is slightly higher in the morning than the afternoon. It is important to measure hormones at the appropriate time of day when assessing for deficiency or excess. Female hormones have a monthly cyclical variation and must be interpreted according to the time of the menstrual cycle.

Measurement of hormones

Hormones are usually measured by immunoassay, which uses specific labelled antibodies that give a signal according to the concentration of hormone. Interfering antibodies can affect blood results, so some results are not reflective of the true concentration of hormone. Assay interference should be suspected in any blood result that does match the clinical picture. Mass spectrometry is a newer technique that provides a more specific measure, and is increasingly being adopted in endocrine laboratories.

Dynamic endocrine tests

When basal investigations are difficult to interpret because of diurnal variation or equivocal results, 24-hour urine collection or dynamic blood tests can be helpful. If hormone deficiency is suspected, a stimulation test is used. This involves administration of a hormone that stimulates the target gland to increase its hormone secretion. Examples are the Synacthen test (to stimulate cortisol in suspected primary adrenal failure) and the insulin tolerance test (to stimulate GH and ACTH in suspected hypopituitarism). If hormone excess is suspected, a suppression test is used. Examples are the dexamethasone suppression test (to suppress cortisol in suspected Cushing's syndrome) and the oral glucose tolerance test (to suppress GH in suspected acromegaly).

Disorders of the hypothalamic–pituitary axis

Part 2

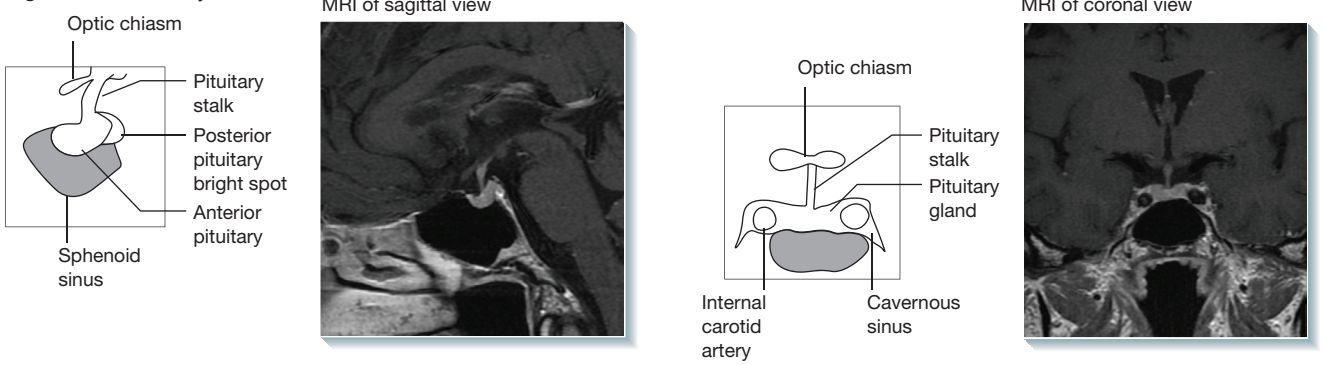
Chapters

2 The hypothalamic–pituitary axis and its assessment

Table 2.1 Endocrine tests used to assess hormone levels

Pituitary hormone	Pattern of secretion	Basal test	Dynamic test if deficiency suspected	Dynamic test if excess suspected
GH	Pulsatile release	IGF-1 Random GH	Insulin tolerance test Glucagon test GHRH–arginine	Glucose tolerance test
ACTH	Circadian rhythm (peak am; nadir midnight)	09.00 Cortisol (suspected deficiency) Midnight cortisol (suspected excess)	Insulin tolerance test Synacthen test (not in acute situation)	Dexamethasone Suppression test
LH/FSH	Stable in men Cyclical in women	Any time Follicular phase in female (day 1–5 of period)	N/A	N/A
TSH	Stable secretion	Any time	N/A	N/A
Prolactin	Stable secretion	Any time	N/A	N/A

Figure 2.1 Anatomy



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The pituitary gland is the 'conductor of the endocrine orchestra', controlling all peripheral glands via trophic hormones. It is approximately the size of a pea and sits in the pituitary fossa at the base of the brain (Figure 2.1). The anterior pituitary is derived embryologically from Rathke's pouch, derived from primitive gut tissue. The posterior pituitary is derived from a down-growth of primitive brain tissue. The optic chiasm lies superior to the pituitary gland. Lateral is the cavernous sinus, which contains cranial nerves III, IV and Va and the internal carotid artery (Figure 2.1).

Physiology

Hypothalamic releasing and inhibiting factors are transported along the hypophyseal portal tract to the anterior pituitary. There are five pituitary axes: GH, ACTH, gonadotrophins (FSH and LH), TSH and prolactin (Table 2.1).

Growth hormone

GH is secreted in a pulsatile manner with peak pulses during REM sleep. GH acts on the liver to produce IGF-1, which is used as a marker of GH activity. GH exerts its action both by direct effects of GH and via IGF-1. GH causes musculoskeletal growth in children and has an important role in adults. Growth hormone releasing hormone (GHRH) stimulates GH, while somatostatin inhibits it.

ACTH

ACTH has a circadian rhythm, with peak pulses early in the morning and lowest activity at midnight. ACTH stimulates cortisol release, and is itself stimulated by corticotrophin releasing hormone (CRH). Cortisol is the only hormone that inhibits ACTH.

Gonadotrophins (FSH and LH)

FSH leads to ovarian follicle development in women and spermatogenesis in men. In women, LH causes mid-cycle ovulation during the LH surge and formation of the corpus luteum. In men, LH drives testosterone secretion from testicular Leydig cells. Gonadotrophin releasing hormone (GnRH) stimulates LH and FSH release. Testosterone and oestrogen inhibit LH and FSH, while prolactin also has a direct inhibitory effect.

TSH

TSH drives thyroxine release via stimulation of TSH receptors in the thyroid gland. TRH stimulates TSH secretion and is a weak stimulator of prolactin secretion. Thyroxine directly inhibits TSH.

Prolactin

Prolactin causes lactation and inhibits LH and FSH. It is under predominantly negative control by dopamine and weak stimulatory control by TRH. Anything that inhibits dopamine leads to an elevation in prolactin level.

Assessment of the pituitary gland

Pituitary tumours develop as a result of compression of local structures and/or the effects of endocrine hypo- or hypersecretion. Compression of the optic chiasm classically leads to a bi-temporal hemianopia. Assessment of visual fields with a red pin is a mandatory part of the clinical examination of patients with pituitary tumours. Automated visual field assessment has superseded Goldmann perimetry as the formal way of documenting visual field defects.

Basal tests

Prolactin and TSH do not have major circadian rhythms so can be checked at any time of day. Both free T4 (fT4) and TSH should be checked in pituitary disease because TSH is often normal in secondary hypothyroidism. In women, LH and FSH should be measured within the first 5 days of the menstrual cycle (follicular phase). In men, LH, FSH and basal testosterone should be checked at 09.00 in the fasting state. Basal cortisol should be checked at 09.00 to exclude deficiency, although a stimulatory (Synacthen) test is usually needed to confirm this. IGF-1 is a marker of GH activity: low or low–normal levels suggesting GH deficiency; high levels suggesting GH excess.

Dynamic pituitary tests

Dynamic endocrine tests are used to assess hormones that have a pulsatile secretion or circadian rhythm. If an endocrine deficiency is suspected, a stimulation test is used; if endocrine excess is suspected, a suppression test is used (Table 2.1). All endocrine tests should be interpreted in the clinical context.

Synacthen test

This is predominantly used to assess primary adrenal failure, but also to assess pituitary ACTH reserve. After 2 weeks of ACTH deficiency, atrophy of the adrenal cortex leads to an inadequate response to synthetic ACTH (Synacthen). This test should not be used in the acute situation, such as pituitary apoplexy, or immediately post-pituitary surgery.

Insulin tolerance test

The insulin tolerance test (ITT) is the gold standard test of ACTH and GH reserve. Insulin-induced hypoglycaemia (glucose <2.5 mmol/L) causes physiological stress, leading to a rise in ACTH and GH. A normal cortisol response to hypoglycaemia is >550 nmol/L whereas a GH value >3 μg/dL after hypoglycaemia excludes severe GH deficiency in adults. The ITT is contraindicated in patients with ischaemic heart disease and epilepsy.

Other tests of GH reserve

The ITT is the gold standard assessment of GH reserve, but is an invasive and unpleasant test to undergo. Glucagon can be used instead of the ITT, although it is a less robust test of GH reserve; nausea is a common side effect. The GHRH–arginine test has particular use in patients who have had pituitary radiotherapy. Common side effects of this are flushing, nausea and an unpleasant taste in the mouth.

Imaging

Magnetic resonance imaging (MRI) is the imaging modality of choice for the pituitary gland (Figure 2.1). Dedicated pituitary views with injection of contrast highlight the difference between tumour and normal gland. Pituitary tumours >1 cm are termed macro-adenomas, while lesions <1 cm are called micro-adenomas. Computed tomography (CT) may be adequate in patients who are unable to undergo MRI. There is increasing interest in newer imaging modalities, including ^{11}C-methionine positron emission tomography (PET).