Clinical Endocrinology and Diabetes

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Foreword

During the thirteen years I spent as Professor of Medicine in Birmingham, I was fortunate enough to have in my department a series of bright and enthusiastic young lecturers who specialised in various branches of endocrinology and whose contributions form the major part of this volume. To them, and to the other authors who are in senior posts in Birmingham, I express my gratitude for their part in having made my stay so enjoyable. The regular endocrine meetings were always lively and challenging, and one was seldom able to get away with a loose or uncritical comment. Not surprisingly, they were all good teachers and this book gives tangible expression to their eagerness to impart their knowledge.

It is often argued that we already have enough books on enough topics. Why another? In this case, justification is to be found in the rapidly changing character of endocrinology. Not only has the basic science of endocrinology developed greatly over the past decade or so, but new clinical applications have emerged, as well as new clinical syndromes. A further justification exists in the kinship of the authors. In Birmingham the emphasis was always on clinical aspects of endocrinology, but understanding the scientific basis of the subject was regarded as essential. I believe this philosophy emerges from the book. I am delighted to see it in print.

Birmingham, 1988 Sir Raymond Hoffenberg

Preface

For a number of years the practice of clinical endocrinology and diabetes has thrived and expanded in Birmingham, with expertise being gained in many different aspects of both subjects. Colleagues with specialist experience in various branches of endocrinology and diabetes remain in Birmingham, or have moved on after a period of postgraduate training. It seemed logical therefore to bring together these colleagues, with their broad range of clinical skills and experience, to write a new textbook of endocrinology and diabetes, a textbook in which each chapter has been written by an author actively pursuing the specialist interest he describes.

It has been our aim to create a book which is up-to-date, easy to read and of practical use. It is a text which covers a broad range of topics, providing an insight into all aspects of the clinical practice of endocrinology and diabetes, and, we hope, is not to be used simply for reference purposes. We anticipate the book will be read by both undergraduate and postgraduate students, and may in general be of use to practising clinicians who do not have a specialist endocrine or diabetes interest.

We acknowledge gratefully the role of Sir Raymond Hoffenberg in providing the stimulus for the growth of endocrinology in Birmingham and we are indebted to him for his enthusiasm, guidance and support, and for bringing together the authors of this text. We also thank Professor David London for his lively and critical review of our clinical practice.

Birmingham, 1988

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1 *J. A. Franklyn*

Hormone physiology and clinical presentation of endocrine disease

Endocrinology is the study of the actions of hormones and of the organs in which hormones are synthesised. A hormone is traditionally defined as a chemical messenger which is released into the circulation and which acts at a site distant from its site of production. The limit of the boundary of endocrinology has become blurred, however, by the recognition that such chemical messengers can be produced and released by endocrine and neural as well as other tissues, and may act as either circulating hormones, local regulators or neurotransmitters, or all of these. There is no sharp distinction between the endocrine and nervous systems and intimate links at the level of the hypothalamus serve to integrate the two systems which act together to maintain the function of the intact organism.

The majority of hormones are peptides or amino acid derivatives. These include the glycoprotein hormones, thyrotrophin and luteinising hormone, the small peptide, thyrotrophin releasing hormone, and the amino acid derivatives, thyroxine and dopamine. The remaining hormones are steroid molecules derived from the precursor cholesterol. These include gonadal and adrenal steroids, as well as vitamin D and its derivatives.

Hormone synthesis, processing and release

The major sites of hormone synthesis are the endocrine organs, although many peptide hormones are synthesised in the central nervous system and gastrointestinal tract. Transcription of the hormone gene is the first step in the synthetic pathway which is illustrated in Figure 1.1. Messenger (m)RNA is processed within the cell nucleus and transported into the cytoplasm where translation of the mRNA occurs at the site of the ribosome. The first product of synthesis is often a large precursor molecule or prohormone which is progressively cleaved or processed to form the active molecule. An example of the importance of processing is pro-opiomelanocortin, which is efficiently converted to corticotrophin (ACTH) in the anterior pituitary gland. In the case of steroid hormones, the parent molecule cholesterol is modified by sequential cleavage and hydroxylation to form its varied products. After processing is complete, the hormone is packaged so that it is available for release into the circulation. In general there is a rapid turnover of synthesised hormone, stores being depleted within hours, or days if synthesis is inhibited. Exceptions to this rule are thyroglobulin which acts as a major reservoir for the hormones thyroxine and triiodothyronine, and vitamin D_3 or cholecalciferol which acts as a reservoir for the active hormone 1,25 dihydroxy vitamin D.

Hormone transport

Water soluble hormones are transported in the circulation in solution. Most hormones are insoluble in water and require specific transport proteins. Proteins such as albumin and prealbumin have a large number of low-affinity binding sites and act as transporters for a variety of hormones. Specific transport proteins are larger molecules with a smaller number of high-affinity binding sites. These include thyroxine-binding globulin, sex hormone-binding globulin and cortisol-binding

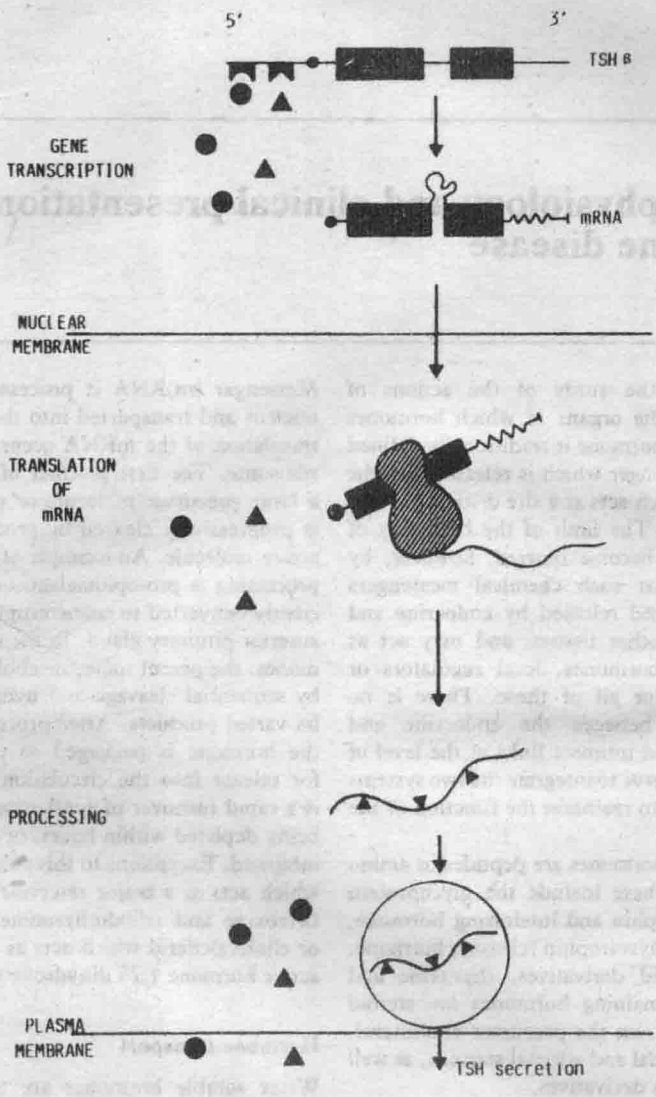

Fig. 1.1 Outline of thyrotrophin β subunit synthetic pathway.

globulin. In general, it is only the free or unbound hormone which enters the target cell and exerts its effect, so that protein bound hormone provides a large reservoir within the circulation. The small amount of free hormone in the plasma is in dynamic equilibrium with bound hormone. Increases or decreases in the amounts of specific transport protein have no effect on the function of the hormone but may cause diagnostic confusion by altering the total concentrations of hormone in the plasma.

Target organ effects

Hormones enter the target cell by a variety of processes. Many hormones are lipid soluble and

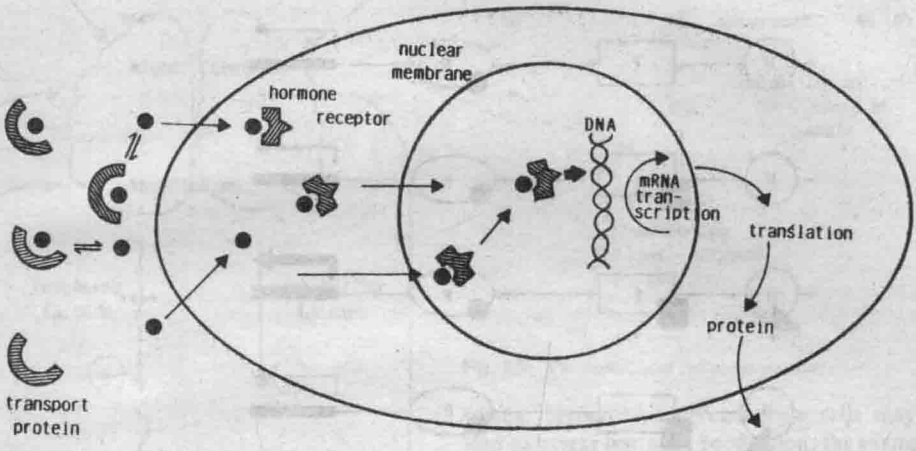

Fig. 1.2 Mechanism of action of steroid or thyroid hormones. 'Free' or unbound hormone enters the target cell and binds to specific receptors which may themselves bind to chromatin and hence modulate gene transcription.

enter by passive diffusion. Active uptake systems have also been described and in the case of peptide hormones that bind to cell surface receptors, the hormone-receptor complex may be internalised by endocytosis. This process of internalisation may be important in determining the rate of degradation of the hormone or the number of surface receptors available, but peptide hormone effects on the cell are mediated largely by activation of a complex system of intracellular second messengers including cyclic AMP and protein kinases. Steroid and thyroid hormones, on the other hand, have specific high-affinity intracellular binding sites — such sites or receptors being found in close association with nuclear chromatin (Fig. 1.2).

Another mechanism which targets the action of specific hormones is that of delivery into a defined circulation, such as the hypophyseal portal system or hepatic portal system. Because of dilution and rapid clearance, concentrations of hypothalamic and gastrointestinal hormones are much lower or even unmeasurable in the peripheral circulation. Local production of hormone from circulating precursors is another important mechanism which determines the site of hormone action, for example the production of dihydrotestosterone from testosterone in androgenic target tissues like the prostate.

The effects of hormones on the tissues are complex. A single hormone can exert different effects on a variety of tissues but a single tissue or metabolic process is often regulated by more than one hormone. Thyroid hormones, for example, exert diverse effects on the growth, development and function of most tissues of the body but the process of growth is regulated by complex interactions between thyroid, steroid and peptide hormones. The final common pathway through which hormones exert their cellular effects is not fully defined but interaction of hormone receptor complexes or intracellular messengers with specific regulatory sequences of DNA is known to promote or inhibit the transcription of genes and production of mRNA (Fig. 1.3).

Regulatory mechanisms

The most important regulatory mechanism is feedback control, a system in which the concentration of hormone determines the need for increased or

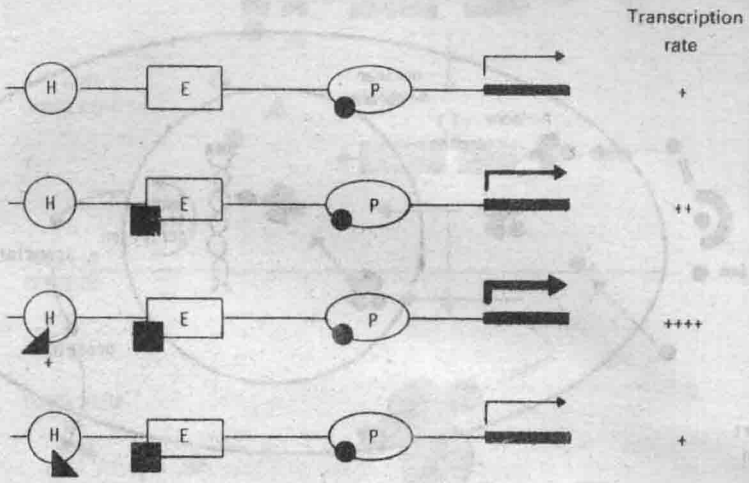

Fig. 1.3 Regulation of gene transcription. RNA polymerase links to the promoter (P) to initiate gene transcription. Binding of transacting factors to enhancer sequences (E) and hormone regulatory elements (H) further stimulates or inhibits the rate of transcription.

decreased synthesis and release. The best example of feedback regulation is the interaction of the anterior pituitary with the thyroid, adrenal and gonads.

Hormones produced from the target tissues feed back on the pituitary, and to a lesser extent the hypothalamus, and inhibit the production of the pituitary trophic hormones (Fig. 1.4).

Endocrine disorders can be divided into syndromes of hormone deficiency or excess.

HORMONE DEFICIENCY

Hormone deficiency may be due to diminished or absent secretion. The cause may be developmental as in thyroid or gonadal dysgenesis. Congenital enzyme deficiency may prevent hormone synthesis, such as 21-hydroxylase deficiency leading to congenital adrenal hyperplasia. More commonly, hormone deficiency results from damage or destruction of a normal endocrine gland. The destructive process may be one of infarction as in Sheehan's syndrome or pituitary necrosis, or may result from direct trauma due to surgery or radiotherapy. Infiltrative processes, such as granulomatous infiltration of the pituitary in sarcoidosis or malignant infiltration of the adrenals, form another category. Infections such as tuberculosis also lead to destruction of endocrine tissues. A common category is that of autoimmune destruction which may involve a variety of organs including the thyroid, gonads, adrenals and rarely the pituitary.

The syndrome of hormone deficiency may result not only from a reduction in hormone production, but also from production of abnormal hormone or resistance to hormone action. For example, diabetes results rarely from a single gene mutation leading to production of an abnormal insulin molecule which binds ineffectively to the insulin receptor. In general, hormone resistance results from abnormality of the hormone receptor, from blocking of the hormone receptor by an abnormal ligand or reflects abnormality of postreceptor events. For example, pseudohypoparathyroidism results from an herditary abnormality of the guanosine triphosphate binding protein in cell membranes which normally activates adenylate cyclase after binding of parathyroid hormone to its

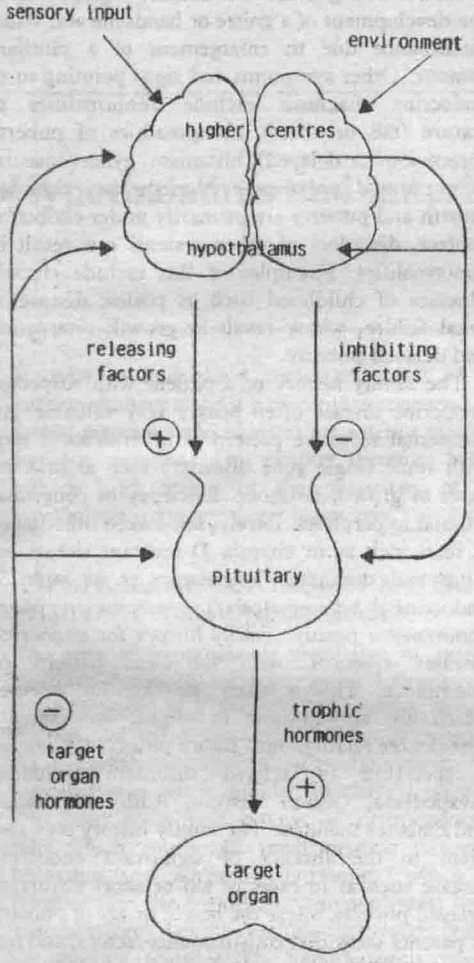

Fig. 1.4 Feedback regulation of the hypothalamic—pituitary—target organ axes.

cell surface receptor. Hormone resistance may be hereditary, as in testicular feminisation syndrome, or acquired, as in the insulin resistance of obesity.

HORMONE EXCESS

Syndromes of hormone excess similarly have a variety of causes. Tumours, either benign or malignant, can affect endocrine glands, for example adenoma or carcinoma of the adrenal

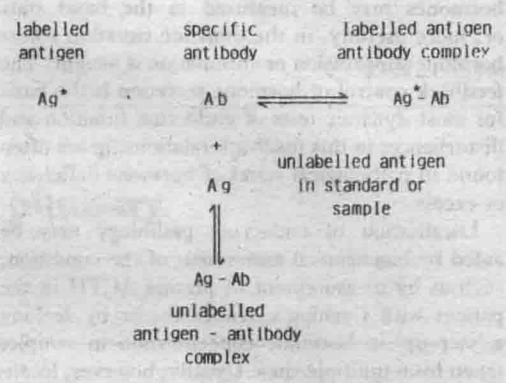

Fig. 1.5 The principle of radioimmunoassay.

cortex. Hyperplasia of endocrine cells may also lead to excess hormone production, for example in the parathyroids or adrenals, and may in turn result from excess secretion of the trophic hormone, such as adrenocorticotrophic hormone (ACTH) from the anterior pituitary. Tumours of non-endocrine tissues may assume an endocrine function and secrete hormones 'ectopically', such as production of ACTH and arginine vasopressin from bronchial carcinomas. Occasionally immunoglobulins function as hormones, for example thyroid-stimulating immunoglobulins which interact with the thyrotrophin receptor on the thyroid follicular cell, leading to stimulation of thyroid hormone synthesis and release.

Investigation of endocrine disorders

The principles of investigation of endocrine disorders are, firstly, definition of hormone deficiency or excess by measurement of circulating concentrations of specific hormones and, secondly, localisation of the abnormality. Measurement of circulating hormone concentrations in serum or plasma has been revolutionised by the progression from cumbersome and non-specific bioassays to the development of specific and sensitive radioimmunoassays. The basis of radioimmunoassay (Fig. 1.5) is the competitive inhibition of binding of radioactively-labelled hormone to antibody by unlabelled hormone contained in standards or in unknown samples. Circulating concentrations of

hormones may be measured in the basal state or, more usefully, in the dynamic situation where hormone suppression or stimulation is sought. The feedback control of hormone secretion is the basis for most dynamic tests of endocrine function and disturbances in this feedback relationship are often found in pathological states of hormone deficiency or excess.

Localisation of endocrine pathology may be aided by biochemical assessment of the condition, such as by measurement of plasma ACTH in the patient with Cushing's syndrome, or by seeking a 'step-up' in hormone concentration in samples taken from multiple sites. Usually, however, localisation and assessment of the extent of pathology requires radiological investigation with either plain X-ray or often by computerised tomography.

CLINICAL PRESENTATION OF ENDOCRINE DISORDERS

The modes of presentation of endocrine diseases are many and varied. Symptoms and signs may be non-specific, such as changes in weight, anorexia, lethargy, weakness, sweating, muscle aches and so on. Features of the history may point to an organic cause for the symptoms described. For example, loss of weight occurring over a short period may be the presenting symptom of diabetes mellitus or hyperthyroidism. Associated features such as thirst and polyuria, or palpitations and enlargement of the neck may lead to the diagnosis. Obesity on the other hand is a common problem and rarely has a specific endocrine cause. Hypothyroidism may lead to weight gain, but by the time it is pronounced, more characteristic features of myxoedema are present. Cushing's syndrome is another uncommon cause of obesity, but rarely presents without other more obvious features. The occurrence of 'funny turns' is another non-specific complaint, but one which may again result from endocrine disorders such as hypoglycaemia due to an insulinoma or from arrhythmias and hypertension due to a phaeochromocytoma.

In addition to some of the non-specific symptoms mentioned above, endocrine disease may present with symptoms and signs which more readily prompt investigation of the endocrine system. These include local symptoms and signs related to enlargement of endocrine organs, such as the development of a goitre or headache and visual disturbance due to enlargement of a pituitary tumour. Other symptoms and signs pointing to an endocrine diagnosis include abnormalities of stature (tall or short), abnormalities of puberty (precocious or delayed), hirsutism, gynaecomastia, polyuria and polydipsia. Nonetheless, although growth and puberty are primarily under endocrine control, disorders of other systems can result in abnormalities. Examples of this include chronic illnesses of childhood such as coeliac disease or renal failure, which result in growth retardation and delayed puberty.

The family history of a patient with suspected endocrine disease often proves very valuable. An autosomal recessive pattern of inheritance is seen with some single gene disorders such as in some cases of growth hormone deficiency or congenital adrenal hyperplasia. Rarely, sex-linked inheritance is seen such as in vitamin D-resistant rickets, or autosomal dominant inheritance as in multiple endocrine adenomatosis syndromes. More commonly a positive family history for endocrine diseases emerges, with no clear pattern of inheritance. This is often the case for diseases which are autoimmune in origin, for example first-degree relatives may have a positive history for a spectrum of related disorders including myxoedema, Graves' disease, Addison's disease and diabetes mellitus. The family history may also point to the absence of significant endocrine disease such as in cases of tall or short stature or delayed puberty where the height or age of puberty of parents show that constitutional factors, and not specific pathological processes, are responsible.

The past medical history is often of importance too in establishing an endocrine diagnosis. Previous infertility, surgery or radiotherapy, for example to the central nervous system in childhood leukaemia, may all suggest a later diagnosis of endocrine dysfunction.

It must be remembered that with few exceptions endocrine disorders present with a wide spectrum of symptoms and signs and delay in diagnosis may result from failure to suspect the underlying cause. Diagnosis is, however, usually worthwhile since most of the conditions to be described are readily amenable to treatment.

Hypothalamus and anterior pituitary

In order to understand clinical disorders of the anterior pituitary gland it is essential to appreciate the normal regulatory mechanisms for anterior pituitary hormone secretion. This chapter therefore begins with a brief review of the physiology of the hypothalamic-pituitary-target organ axes.

HYPOTHALAMIC CONTROL OF ANTERIOR PITUITARY HORMONE RELEASE

The idea of hypothalamic regulation of anterior pituitary hormone secretion arose following the demonstration of a vascular connection between the base of the brain and the adenohypophysis, the hypothalamo-hypophyseal portal system. The hypothalamus is a highly specialised area of the brain containing groups of neuroendocrine cells which synthesise small peptide molecules (releasing and inhibiting hormones) which are released into the hypothalamo-hypophyseal portal venous system thereby reaching their target cells in the anterior pituitary. The hypothalamus receives neural inputs, largely from catecholaminergic and serotoninergic neurones, from many brain areas which act as signals for the release (and synthesis) of releasing and inhibiting hormones. Accordingly, the hypothalamus is a final integrator, for both neural and hormonal feedback messages and provides the essential basic regulation (through releasing and inhibiting hormones) of the adenohypophysis. A schematic representation of the neural control of anterior pituitary hormone secretion is shown in Figure 2.1.

In recent years, major releasing and inhibiting hormones for all the anterior pituitary hormones have been isolated from the hypothalamus, their structure determined, and the peptides chemically synthesised in pure form suitable for clinical use. The structure and actions of the releasing and inhibiting hormones are depicted in Table 2.1.

Table 2.1 Structure and function of hypothalamic releasing hormones

Hypothalamic hormone	Peptide length (no. of amino acids)	Releases/Inhibits
TRH (thyrotrophin releasing hormone	3	TSH (thyrotrophin) PRL (prolactin)
GnRH (gonadotrophin releasing hormone)	10	LH (luteinising hormone FSH (follicle stimulating hormone)
CRF (corticotrophin releasing factor)	41	ACTH (adreno-corticotrophic hormone + related peptides
GRF (growth hormone releasing factor)	40–44	GH (growth hormone)
GRIH (somatostatin) (growth hormone release inhibiting hormone)	41	GH TSH
PIF (dopamine) (prolactin inhibiting factor)	—	PRL

These structures have been highly conserved during evolution, with only very minor changes between fishes, birds, reptiles and mammals. It should be noted that releasing hormones not only stimulate anterior pituitary hormone

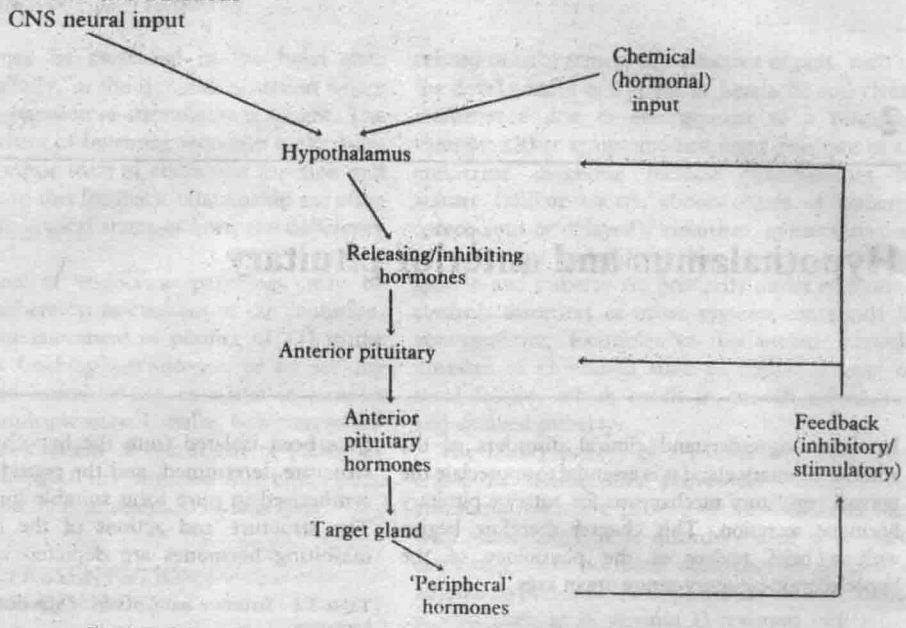

Fig. 2.1 Schematic representation of anterior pituitary hormone regulation.

release, but also their synthesis, and as such are trophic hormones. All the anterior pituitary hormones are under stimulatory control by releasing peptides with the exception of prolactin (PRL) which is under tonic inhibition by dopamine. Although exogeneous thyrotrophin-releasing hormone (TRH) will release PRL, the role of TRH as a physiological prolactin-releasing factor has not been established.

Somatostatin, named because of its ability to specifically suppress growth hormone (GH) secretion, was first isolated from the hypothalamus but has subsequently been found in a variety of extrahypothalamic tissues (see Ch. 8). In addition to its suppressive effect on GH secretion, somatostatin inhibits the release of a number of other hormones, including insulin and glucagon from the pancreas. The demonstration of somatostatin in axon terminals within the central nervous system suggests a neurotransmitter function. Many other small peptide hormones, originally isolated from the gastrointestinal tract have been found in the hypothalamus and extrahypothalamic brain tissue, e.g. cholecystokinin, vasoactive intestinal polypeptide (VIP), gastric inhibitory polypeptide. This has led to the concept of peptidergic, in addition to classical cholinergic and catecholaminergic, neurotransmission. VIP is also a potent stimulator of GH and PRL release, though its physiological role in this regard is not known.

In general, endogenous hypothalamic releasing hormones are not detectable in the peripheral circulation because of their very low concentration and rapid degradation. Thus, there is no readily available direct test of hypothalamic function. When measured at very frequent intervals (10 min or less), however, the serum levels of many anterior pituitary hormones (LH, FSH, GH, ACTH and PRL) show distinct peaks (pulses) and troughs. This has been best described for the gonadotrophins (LH and FSH) where periodicity or frequency of pulses is approximately 1 per 2 h. Since each LH pulse presumably occurs in response to a preceding pulse of gonadotrophin releasing hormone (GnRH), hypothalamic activity can be inferred indirectly from measurement of the peripheral gonadotrophin hormone levels, therefore GnRH is released from the hypothalamus in a pulsatile manner. The hypothalamus acts as a pulse generator, with an intrinsic frequency which can

be modulated by neural input. This same principle may also hold for corticotrophin-releasing factor (CRF), growth hormone releasing factor (GRF) and dopamine. The pulsatile nature of releasing hormone secretion has important therapeutic implications (see below).

Clinical application of hypothalamic hormones

Synthetic hypothalamic releasing hormones are used in the biochemical assessment of anterior pituitary hormone secretion (see below).

Gonadotrophin releasing hormone, in addition to its role in the assessment of gonadotroph function, may be used clinically for induction of ovulation, and sometimes spermatogenesis, in hypogonadotrophic hypogonadism (see Ch. 6). In contrast to its use in the treatment of infertility, long-acting agonist analogues of GnRH may be used to induce a medical gonadectomy. This therapeutic approach depends upon the phenomenon of 'desensitisation' of LH secretion, which occurs when large doses of GnRH or its synthetic analogues are administered. This form of treatment has the advantage that it is fully reversible when stopped.

GnRH is the first hypothalamic hormone for which a therapeutic role has been defined (Table 2.2). It is likely that a similar therapeutic role for GRF may emerge in the treatment of children with isolated GH deficiency (see below). The role of the hypothalamic hormone somatostatin is also being explored. Its greatest clinical impact has been in the control of gastrointestinal bleeding. Theoretically somatostatin is ideal to use in this situation because of its effects of reducing gastric acid secretion, splanchnic blood flow and portal vein pressure, but the results of clinical trials of its efficacy in the management of haematemesis and variceal bleeding have been conflicting. Other reported benefits of somatostatin include inhibition of symptoms of the dumping syndrome, and inhibition of abnormal hormone secretion in patients with acromegaly, insulinoma, glucagonoma, VIPoma and carcinoid syndrome.

Feedback regulation of pituitary hormone secretion by peripheral hormones

The preceding section described the primary regulation of anterior pituitary hormone secretion by hypothalamic hormones (Fig. 2.1). This section deals briefly with some aspects of end-organ hormone modulation of pituitary responsiveness to releasing hormones. In general, end organ hormones exert inhibitory feedback on secretion and synthesis of anterior pituitary hormones, feedback operating largely at the pituitary level. Though there is probably also an inhibitory effect on secretion of hypothalamic-releasing hormones, this is minor. The one important exception to the general principle of negative feedback occurs in the hypothalamic-pituitary-ovarian axis. While this is described in detail in Chapter 6, it is worth emphasising that rising serum oestradiol concentrations exert stimulatory feedback effects on gonadotrophin secretion at the mid-point of the menstrual cycle, and are responsible for the preovulatory LH surge essential for normal female reproductive function. Thus, oestradiol is both inhibitory and stimulatory to pituitary gonadotrophin release, a unique feature of this hormone in females, with no male counterpart.

HYPOPITUITARISM

Hypopituitarism may be classified as partial when the deficiency is limited to one or two of the anterior pituitary hormones or complete, when

Table 2.2 Therapeutic uses of gonadotrophin releasing hormone and agonist analogues

Stimulation of fertility	Inhibition of gonadal function
Pulsatile low-doses of GnRH	1. Hormone dependent cancer — prostate/breast
1. females with hypothalamic amenorrhoea and hypogonadotrophic hypogonadism	2. True precocious puberty
2. males with isolated gonadotrophin deficiency	3. Endometriosis
	4. ? Contraceptive for males
	5. ? Premenstrual tension

all anterior pituitary hormone secretion is absent. Thus, the clinical picture will depend upon which hormone is absent or deficient. Additionally, the age of onset of hormone deficiency will determine the clinical presentation. Thus, GH deficiency is of little consequence in adults, but a major cause of delayed growth when occurring during infancy and childhood. In general the hypothalamo-pituitary axis is more susceptible to damage in infancy and childhood and the consequences are correspondingly more severe. This has become particularly apparent with the widespread use of combination chemotherapy and craniospinal irradiation for treatment of childhood leukaemia, lymphomas and intracranial tumours.

Causes of hypopituitarism

These may be classified as primary when the cause is within the pituitary, or secondary when hypothalamic releasing hormone secretion is impaired. Occasionally, secondary partial hypopituitarism may be reversible. This applies specifically to the reduction in gonadotrophin secretion (secondary to decreased GnRH output) accompanying severe loss of weight (with or without anorexia nervosa). Upon gaining weight gonadotrophin secretion is restored. Some of the less common causes of primary hypopituitarism, e.g. granulomatous conditions, may also involve the hypothalamus and vice versa. The causes of hypopituitarism are listed in Table 2.3 with the commonest listed first. With progressively enlarging pituitary tumours, normal pituitary tissue is gradually destroyed. This may give sequential hormone deficiencies of gonadotrophins, GH, TSH and ACTH. This sequence of hormone loss is not invariably followed. When the pituitary stalk is involved, the interruption of dopamine supply to the anterior pituitary results in modest hyperprolactinaemia (see section on prolactinoma). Hypoprolactinaemia has no clinical sequelae in the non-pregnant individual, its only consequence being failure to lactate postpartum.

Clinical features of hypopituitarism

These are discussed with respect to each pituitary hormone deficiency; complete hypopituitarism will

Table 2.3 Causes of hypopituitarism

Primary	Secondary
Post-treatment of pituitary tumours Hypophysectomy Radiotherapy	Tumours Craniopharygiomas meningiomas/gliomas Pinealomas Metastases
Pituitary tumours Non-functional adenomas (non-hormone secreting) Functional adenomas (hormone secreting) Metastatic deposits (v. rare)	Irradiation/chemotherapy Craniospinal Combination chemotherapy
Pituitary infarction With pituitary tumours (either functional or non-functional) Post-partum necrosis (Sheehan's syndrome)	Developmental Hypothalamic GRF deficiency Hypothalamic GnRH deficiency (Kallman's syndrome when anosmia and colour blindness) With cerebellar ataxia and retinitis pigmentosa Congenital rubella
Chemotherapy	Trauma Head injury with pituitary stalk transection
Granulomas sarcoidosis Tuberculosis Syphilis Histiocytosis	Granulomas As primary
Autoimmune	