Essential endocrinology

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Preface

Textbooks of endocrinology are usually written to accommodate the requirements of clinical students. This book is an attempt to provide sufficient information for medical students not only in their clinical but also in their preclinical years.

While it is appreciated that physiological and clinical aspects of endocrinology are closely related, they are considered separately when possible. This approach allows for the concise presentation of information and leaves integration to the student. It is our hope that this book will be used as a basis upon which a true understanding of the subject can be achieved.

Chapter 11, entitled 'common endocrine emergencies', has been written primarily for use on the wards and may be particularly helpful at times when advice from senior colleagues is not readily available. The final chapter, on tests of endocrine function, is presented in a form which is intended to give easy reference to the appropriate tests, and is illustrated by examples which we hope will allow for an appreciation of the importance of their correct interpretation.

Students, past and present, have maintained our interest in endocrinology by their persistent questioning. This has encouraged us to extend our knowledge and to try to stay 'one step ahead'; in return, we dedicate this book to them.

It is a pleasure to record our thanks to those past and present members of the Endocrine Unit at Charing Cross Hospital who have contributed towards the various chapters: in particular, Dr. P. Dorrington Ward (Chapter 4); Mr. M. Pawson, Dr. Janet Lambley (née Booth), and Dr. T. Greenwood (Chapter 5); Dr. K. Waters (Chapters 6 and 7); Dr. A. L. Wyman (Chapter 8); Professor J. Daly and Mr. R. W. Hoile for material on ectopic secretion and the Zollinger–Ellison syndrome respectively (Chapter 9); Dr. A. Khaleeli (Chapter 11); and Dr. J. Alaghband-Zadeh (Chapter 12).

Clinical colleagues have read many of the chapters and attempted to correct errors and point out omissions. Among these are Professor Reginald Hall, who read and commented on several chapters, Dr. Jean Ginsberg (Royal Free Hospital), and Dr. Jean Ross, who read and commented on the draft of Chapter 5. Any remaining errors and omissions are entirely our own responsibility.

The clinical photographs form part of the endocrine unit collection

and are presented with the consent of Professor Lee's consultant colleagues. We should like to express our gratitude to the patients for their kind permission to use the photographs and to the Department of Medical Illustration for the reproductions.

Finally our thanks are extended to secretaries Miss Amanda Watkins, Mrs. Hilary Dance, and Miss Alison Castledine, all of whom have patiently typed the various stages of the manuscript.

September 1977 J.L., J.F.L.

Professor Lee died without having the satisfaction of seeing this book in print. *Essential endocrinology* is a testimony to his dedicated work in the two fields of his special choosing, the science of endocrinology and the art of teaching.

November 1977 J.F.L.

Contents

1 Introduction

Plan of this book

The sequence of this book has been deliberately selected. The hypothalamus is considered first (in Chapter 2) because this is an important example of a nervous tissue which secretes hormones; furthermore this structure is essential for the normal activity of the hypophysis (pituitary gland) which is discussed in the same chapter. It may appear strange that the chapter on adrenal medulla is interposed between this chapter and those three chapters which consider the endocrine glands which are dependent upon the adenohypophysis (anterior pituitary). By adopting this particular order however, we enable the reader to consider first those endocrine glands which are mainly controlled by the nervous system and subsequently those endocrine glands which are influenced by the adenohypophysis. The parathyroids and the islets of Langerhans have to be discussed separately since their hormones are controlled mainly by the concentrations of those particular chemical substances which they themselves regulate.

We have included a variety of aspects in Chapter 9 ('miscellaneous subjects'), such as the concept of 'amine precursor uptake decarboxylation' cells (APUD cells), ectopic secretion, multiple endocrine adenomatosis, tumours of the (δ) islet cells, and consideration of two important substances: 5 hydroxytryptamine (including carcinoid) and prostaglandins, which are not easily classified but which are of importance to the clinical student. Chapter 10 has been devoted to a brief consideration of some common intracellular mechanisms through which many hormones are now believed to act. Chapter 11 is intended principally for the newly qualified graduate. The final Chapter (12) provides not only immediate reference to the appropriate tests of endocrine function, but also to the essential technical problems involved in some of these measurements, enabling the reader to assess their relative importance.

Certain tissues which can be considered to have an endocrine function have been excluded. While it is difficult to defend the exclusion of the upper part of the alimentary canal, this together with the spleen, the kidney, the thymus and the pineal gland have been omitted in accordance with many other textbooks. It is of interest to note that the thymus has now become a prized possession of the immunologist.

Each chapter concerned with a particular endocrine gland (Chapters 2–8 inclusive) has been written in two parts: the basic physiology of the gland is considered first (including a brief section on its general anatomy, histology, and development), followed by consideration of the clinical disorders associated with that gland. Naturally there is some interchange between the physiological and clinical components where necessary allowing both the preclinical and clinical student to appreciate the importance of physiology in medicine.

History

In 1905 Starling first applied the word 'hormone' to secretin, a chemical secreted into the blood-stream which stimulated the flow of pancreatic fluid. Subsequently a hormone was defined as 'any substance normally produced in the cells of some part of the body and carried by the blood-stream to distant parts which it affects for the good of the body as a whole'. Thus an endocrine gland was defined as a normal tissue which is ductless, and which secretes chemical messengers—the hormones—directly into the blood. Some tissues which secrete hormones, for instance the alimentary canal, are frequently omitted from textbooks of endocrinology, possibly because of their lack of interest to the clinical endocrinologist. This has resulted in confusion about the definition of an endocrine gland.

The belief that endocrine glands are secretors of chemical messengers which enter the blood-stream to affect the activity of other tissues provoked adverse criticism until the beginning of the twentieth century. However, evidence for this concept was rapidly accumulated from the scientific field aided and indeed stimulated by clinical observations, some of which had been made in the nineteenth century.

The appreciation of such a system, then, stimulated various disciplines. To the evolutionist the endocrine system could be accepted as a natural auxillary to the central nervous system (CNS). As the complexity of the organism developed (to include a cardiovascular system), it became essential that the response to a stimulus could be prolonged. In these circumstances the CNS, which in general evokes a rapid response, would be inefficient, whereas chemical messengers in the blood-stream could prolong a response, enabling better adaptation to changes in the external environment. To the biologist the endocrine system represents a mechanism for controlling growth, maturation, metabolism, and reproduction in an organism. To the clinical endocrinologist a certain pattern of symptoms and signs elicited on examination could now be shown to be the result of a disorder of a particular endocrine gland. Endocrinology should encompass all these aspects; furthermore the endocrinologist should try to extend his knowledge to include, for example, the biochemistry of the intracellular actions of hormones.

In the early days of neurophysiology the function of the nervous system was regarded simply as conveying and modifying action potentials. In the invertebrates (e.g. insects) many hormones are released from 'neurohaemal' organs, which anatomically consist of nerve fibres in close contact with blood, enabling the nerve endings to release chemical substances which may then pervade the whole insect. It was then realized that vertebrate nerve cells similarly release chemical substances and if these cells are in close association with a capillary these substances can also be released directly into the blood-stream to act as hormones (neurosecretion). Neurosecretions which are not released into the blood-stream, but act locally, are called neurotransmitters.

Control of hormonal secretion

1. Feedback mechanisms

Some basic knowledge of feedback mechanisms is required in order to understand individual control systems in endocrinology, and they are therefore briefly considered here. This section may appear complex, but an early discussion on the importance of feedback mechanisms will prove useful to the reader who should, whenever necessary, refer back to this chapter.

The basic function of a hormone is to regulate the metabolic activity of its target cells in a specific direction. To maintain this function it is essential that the endocrine gland receives constant rapid information (feedback) on the state of those systems regulated. A simple feedback as described may be insufficient and usually an endocrine gland continually receives signals from a variety of different sources and the rate of hormonal secretion from the gland is therefore determined by the integration of these different afferent signals.

(a) Direct negative feedback

Probably the most simple feedback to an endocrine gland is the direct negative feedback system which relates the rate of release of the hormone to the blood concentration of that chemical substance which it controls (or to a chemical product of the metabolic process which it regulates). An example of this type of feedback mechanism is the relationship between the hormone insulin and the variable which it controls, the blood glucose concentration. Insulin acts upon its target cells ultimately to decrease blood glucose levels; a change in these levels in turn alters the rate of secretion of insulin. Thus a rise in blood glucose levels increases the rate of secretion of the hormone which then acts on its target to restore the blood glucose to normal levels (simple direct negative feedback mechanism).

Some hormones from the adenohypophysis (anterior pituitary) act primarily to regulate the secretions of other endocrine glands. For example hormone X′ from the adenohypophysis acts upon an endocrine gland to stimulate the release of hormone X. This hormone can then influence its own release by direct negative feedback on the secretion of hormone X′ from the adenohypophysis (see Fig. 1.1). An increase in the secretion of X′ results in an increased release of X. Hormone X then acts on the adenohypophysis to inhibit the release of X′ which, in turn, results in a decreased secretion of X. The blood level of X is thus regulated within narrow limits.

(b) Indirect negative feedback

This term is used when the central nervous system, in particular the hypothalamus, is indirectly involved in the regulation of hormone secretion from an endocrine gland by controlling the release of the appropriate adenohypophysial hormones. In such a system, hormone X from the target endocrine gland can have a direct negative feedback on the release of the adenohypophysial hormone X′ (see previous section) and an indirect negative feedback on the release of the hypothalamic hormone X″ (see Fig. 1.2).

This indirect involvement of the hypothalamus is particularly important in the control of thyroidal, adrenocortical, and gonadal secretions (see relevant chapters).

Fig.1.1
Diagram illustrating the direct negative (−ve) feedback which can exist between the target endocrine gland hormone X and the release of the adenohypophysial hormone X′.

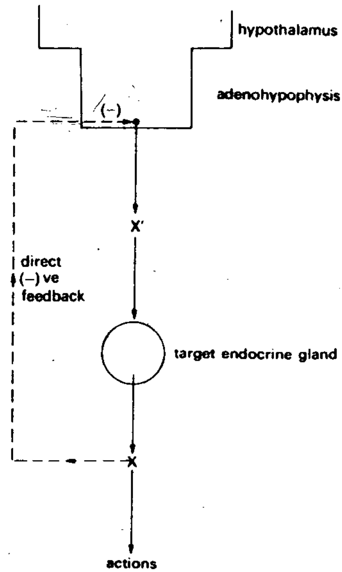
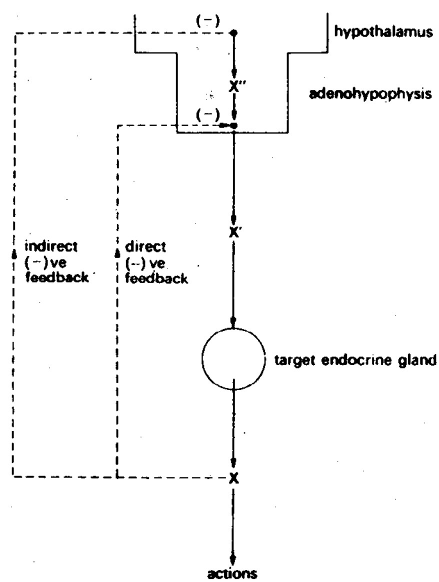


Fig.1.2
Diagram illustrating the direct negative (−ve) feedback loop which can exist between hormone X from the target endocrine gland and the release of the adenohypophysial hormone X′, and the indirect negative (−ve) feedback between X and the hypothalamic hormone X″.



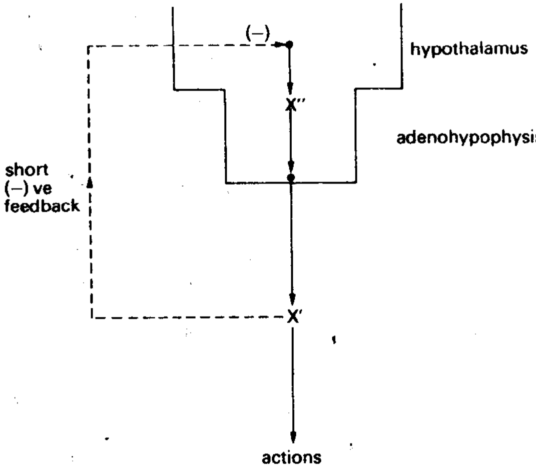


Fig.1.3 Diagram illustrating the short negative (–ve) feedback which can exist between the adenohypophysial hormone X' and the release of the hypothalamic hormone X''.

(c) Short feedback

As mentioned previously, the hypothalamus controls the release of adenohypophysial hormones by secreting releasing (or release-inhibiting) substances. Some of the adenohypophysial hormones are believed to have a feedback effect on the release of the hypothalamic hormones and this type of regulating system is called a short feedback loop (see Fig. 1.3).

(d) Positive feedback

In addition to the various negative feedback mechanisms discussed, positive feedback systems exist in which the change elicited by the action of the hormone alters the rate of release of that hormone (or some other hormone) so that its effect is further enhanced. This type of feedback could rapidly become uncontrollable if there were no other control mechanisms involved in the system. One example of such a positive feedback mechanism is the release of oestrogens (the generic name for a group of female sex hormones) from the ovarian follicle, controlled by the adenohypophysial hormone follicle-stimulating hormone (FSH). At a particular plasma concentration oestrogen stimulates the release of more FSH and luteinizing hormone (LH) from the adenohypophysis, so that a positive feedback between oestrogens and FSH occurs which would be unstable if no other factors were involved (see Fig. 1.4). This positive feedback mechanism is also probably mediated partly through the hypothalamus (see Chapter 5).

2. The influence of the CNS

Some endocrine glands are controlled primarily by the nervous system: these are the neurohypophysis and the adrenal medulla. The adrenal medulla is an endocrine gland which is directly controlled by nerve impulses propagated

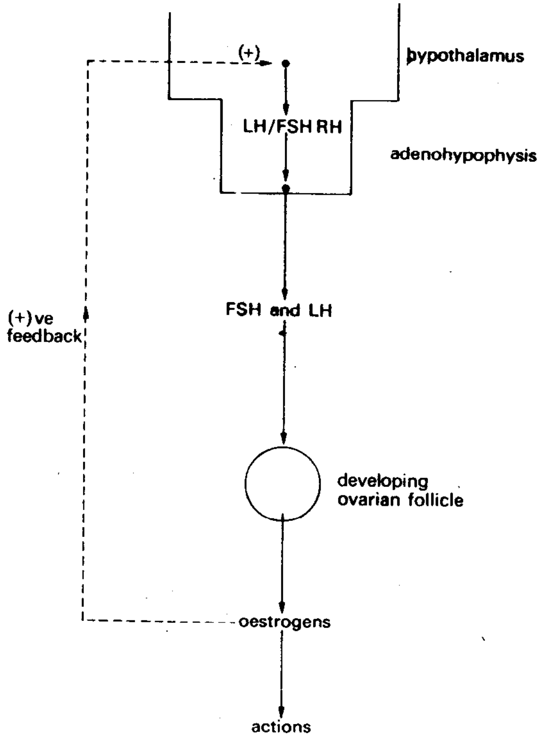


Fig.1.4 Diagram illustrating the positive feedback (+ve) which can exist between the plasma oestrogen concentration (at low levels) and the release of the adenohypophysial hormones FSH and LH.

along sympathetic preganglionic fibres originating in the hypothalamic region, with the ultimate mediation of a neurotransmitter (in this case acetylcholine) at the nerve terminals. Feedback in this case is integrated with the general autonomic reflexes which originate in the hypothalamus. In this system, an increase in sympathetic activity results in an excitation of the cells of the adrenal medulla which then release adrenalin.

One mechanism controlling the release of the neurohypophysial hormone vasopressin involves changes in the frequency of nervous impulses along specific nerve pathways from blood volume receptors. This feedback mechanism involves a neurotransmitter acting on the cell bodies of those neurones originating mainly in the supra-optic nucleus of the hypothalamus (see Chapter 2) which synthesize, store, and release vasopressin (Fig. 1.5). When the volume receptors are stimulated (by volume expansion for instance) the tonic inhibition exerted by this feedback system is increased, and therefore vasopressin secretion is decreased.

The importance of the relationship between the nervous system and endo-

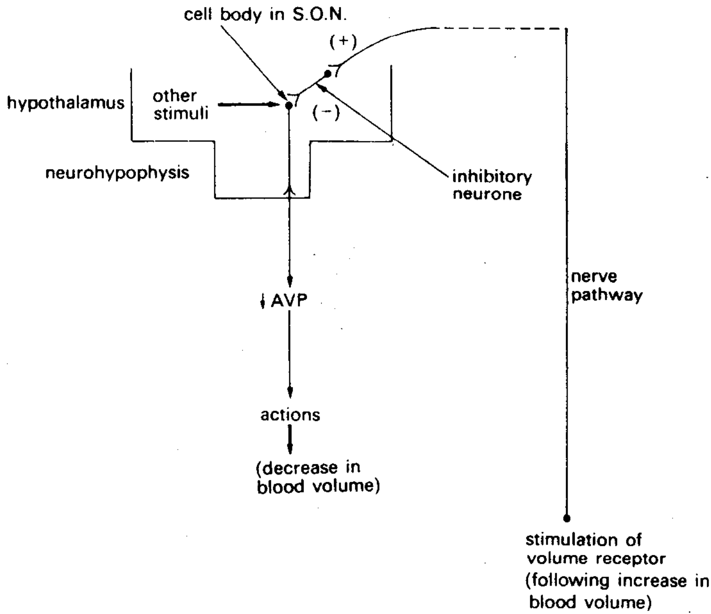


Fig.1.5 Diagram illustrating the decreased release of arginine-vasopressin (↓AVP) which results from increased stimulation of volume receptors following blood volume expansion (see text). S.O.N. = Supra-optic nucleus.

crine system is also emphasized through the various feedback control mechanisms which involve the hypothalamus. Since the hypothalamic nuclei also receive signals from other ('higher') centres in the brain, one special feature of the regulation of hypophysial hormone release is the ability of the brain to 'over-ride', or to finely adjust, all other control mechanisms. This type of control by the 'higher' centres of the brain is sometimes called 'an open-loop control system'.

Summary

The control of an endocrine gland's secretion is often complex and can involve not only nervous control loops but also chemical substances in the blood; these may be the actual concentrations of the hormones themselves. The close integration between nervous and endocrine systems is essential for the maintenance of a constant internal environment in the face of continually changing external conditions.

2 The hypothalamo-hypophysial system

PHYSIOLOGY

The hypothalamus and neurosecretions

The fundamental importance of the hypothalamus within the endocrine system was only appreciated following a series of experiments in the 1950s. This region of the brain is now considered as an endocrine gland in addition to its previously accepted functions, such as the regulation of autonomic nervous reflexes and temperature control.

Anatomy

The hypothalamus consists of nervous tissue below the thalamus. It virtually surrounds part of the third ventricle, with efferent and afferent fibres connecting it to the rest of the central nervous system. There are numerous groups of nerve cells (nuclei), but it is not yet possible to designate a specific function to the majority of these nuclei.

The hypothalamus is supplied with blood from the circle of Willis and, although most of the venous blood drains into the vein of Galen, a proportion flows through the capillary plexus in the median eminence to enter a sinusoidal network in the adenohypophysis (the anterior pituitary gland). The latter is an example of a venous portal system and is called the hypothalamo-hypophysial portal system (see Fig. 2.1).

The neurosecretions

Synthesis, storage, and release

The description now given is restricted to that part of the hypothalamus whose nerve cells have axons extending to the median eminence and the hypophysis

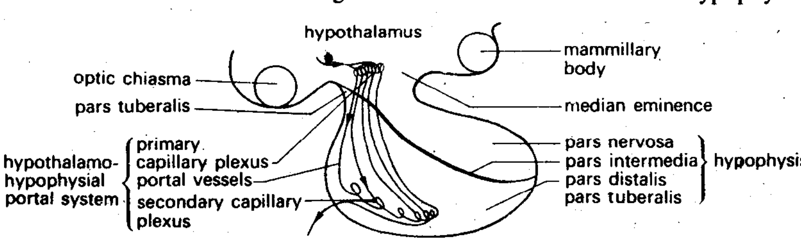


Fig.2.1 Diagram illustrating a cross-section of the hypothalamo-hypophysial system.

(pituitary gland). It is now accepted that synthesis and storage of chemical substances takes place within specific hypothalamic nerve cells; furthermore the release of these chemicals occurs from nerve terminals in close association with blood-vessels. As these substances originate from nerve cells the term neurosecretion is employed, and these neurosecretions satisfy the criteria for classification as hormones. However, we shall apply the term 'hormone' only if the chemical structure is known, otherwise reference is made to hypothalamic factors. This arbitrary classification has found universal acceptance.

Of the various hypothalamic nuclei, most have all their nerve endings in the region of the median eminence, but two have the majority of their axons terminating in the posterior pituitary gland with relatively few fibres ending in the median eminence and pituitary stalk. This hypothalamic/posterior pituitary system is called the neurohypophysis, and its two neurosecretions are octapeptide hormones (see page 16).

The neurosecretions in the median eminence are released into the portal system to the adenohypophysis and so far three have been identified as small polypeptides. Little is known about the actual processes involved in the synthesis of many of these substances, although it is probable that this occurs in the cell bodies. Similarly, the storage of these substances may occur in the respective nerve terminals. It is not yet known whether they are stored as a bound complex, perhaps involving a larger protein molecule, or whether storage is in the free (unbound) form, in vesicles.

Each median eminence neurosecretion acts on particular adenohypophysial cells to influence the release of a specific adenohypophysial hormone. Only three of these neurosecretions have so far been identified: these are (1) thyrotrophin releasing hormone (TRH) which stimulates the release of thyrotrophin (thyroid stimulating hormone, TSH); (2) luteinizing hormone-releasing hormone (LHRH) which (see later) also appears to influence FSH release, and (3) somatostatin which is somatotrophin-inhibiting hormone.

The remaining adenohypophysial hormones are also influenced by releasing factors, and in some instances also by inhibiting factors. Corticotrophin (or adrenocorticotrophic hormone, ACTH) and melanocyte-stimulating hormone (MSH) are under the control of their respective releasing factors, while somatotrophin (growth hormone, GH) and prolactin appear to be controlled by both releasing and release-inhibiting factors, the latter being the dominating influence on prolactin release. With reference to follicle-stimulating hormone (FSH) there is some uncertainty as to whether control is by a specific releasing factor or whether luteinizing hormone-releasing hormone (LHRH) also controls its release, and reference is often made to FSH/LHRH. The release of any one of the releasing (or release-inhibiting) -hormones or factors from its particular hypothalamic nucleus is probably controlled in part by nervous impulses from other parts of the central nervous system. This would account for the important influence of external stimuli such as environmental changes, emotion, and stress on the release of certain adenohypophysial hormones. In addition hypothalamic endocrine activity is controlled by hormone feedback mechanisms (see Chapter 1) and to some degree influenced by the concentration of particular chemical substances in the blood.