Endocrine Physiology

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General preface to series

Student textbooks of medicine seek to present the subject of human diseases and their treatment in a manner that is not only informative, but interesting and readily assimilable. It is also important, in a field where knowledge advances rapidly, that the principles are emphasized rather than details, so that information remains valid for as long as possible.

These factors all favour an approach which concentrates on each disease as a disturbance of normal structure and function. Therapy, in principle, follows logically from a knowledge of the disturbance, though it is in this field that the most rapid changes in information occur.

A disturbance of normal structure without any disturbance of function is not important to the patient except for cosmetic or psychological considerations. Therefore, it is the disturbance in function which should be stressed. Preclinical students must get a firm grasp of physiology in a way that shows them how it is related to disease, while clinical students must be presented with descriptions of disease which stress the basic disturbance of function that is responsible for symptoms and signs. This approach should increase interest, reduce the burden on the student's memory and remain valid despite alterations in the details of treatment, so long as the fundamental physiological concepts remain unchallenged.

In the present Series, the major physiological systems are each covered by a pair of books, one preclinical and one clinical, in which the authors have attempted to meet the requirements discussed above. A particular feature is the provision of cross-references between the two members of a pair of books to facilitate the blending of basic science and clinical expertise that is the goal of this Series.

RNH
MH
KBS

Preface

This book is intended as an introduction to the study of endocrinology and has been written with the needs of preclinical medical students in mind. It therefore aims to provide a readable and up-to-date account of the endocrine system sufficient for candidates for the 2nd MB Examination or its equivalent. In addition, care has been taken to include (generally in smaller print) material beyond this level, notably in those parts of the subject which are advancing rapidly; for this reason it is hoped that the book will commend itself to honours students in physiology. The endocrinology of reproduction is not discussed in detail in this text but will be considered in the proposed two volumes on reproductive physiology in this Series.

Reference to endocrine disease has been restricted, since this topic forms the basis for the complementary book on clinical endocrinology in this Series and correspondingly, the clinical text will assume a basic knowledge of normal endocrine function.

I would like to express my thanks to Dr Peter Daggett, to my fellow General Editors and to my many colleagues in the Physiological Laboratory for their advice during the preparation of this text and in particular to Dr A. V. Edwards who was very largely responsible for writing Chapters 4 and 9. It would be invidious to single out any of the many secretaries in the Physiological Laboratory and Fitzwilliam College who have assisted with the typescript during the prolonged gestation of this book: I am extremely grateful to all of them for their patience and good humour. Finally, I am greatly indebted to Fiona Hake and Peter Starling for their skill in preparing the draft illustrations and to my publishers for their advice and encouragement.

Cambridge, 1981 RNH

Notes on the arrangement of this book

In a text of this length it is clearly impossible to describe the experimental basis of every assumption, but examples of evidence from a variety of experimental techniques have been included where appropriate. Liberal use has been made of figures and tables and, for ease of reference and, it is hoped, comprehension, each hormone/endocrine gland is discussed in the following standard sequence.

Anatomy and microstructure of the gland
Chemistry and metabolism of the hormone
Action of the hormone on the target cells
Effects of hormone deficiency
Effects of hormone excess
Control of hormone secretion.

The second section of the book contains a discussion of the coordinated behaviour of the components of the endocrine system in the control of energy metabolism and calcium homeostasis. Throughout the book it has been assumed that the reader has a working knowledge of basic biochemistry and, similarly, no attempt has been made to include detailed histological material.

Relation to Daggett: *Clinical Endocrinology*

This present book was written in conjunction with the corresponding clinical text, called *Clinical Endocrinology,* by Peter Daggett, and the two books have been planned to complement each other, as have other pairs of books in the *Physiological Principles in Medicine Series.* Thus, this book does not contain a detailed consideration of endocrine diseases and the clinical book assumes a knowledge of basic physiology.

Although each of the books will stand on its own, they are both designed to interdigitate with each other, and therefore each contains cross-referencing to the other. So, for example, if readers of this text wish to find out more about hyperparathyroidism (p.15), they will find a reference to the appropriate chapter in the clinical text, designated thus (Daggett: *Clinical Endocrinology,* Chapter 7). Similarly, references from the clinical book to this book will be designated (Hardy: *Endocrine Physiology,* Chapter 2).

References

Two types of references will be found in this book. First, at the end of this section, a list of General references, which are texts recommended for further general reading. Second, a list of Further reading as a general rule at the ends of the other chapters. Here reference will be made to recent reviews, monographs and occasionally original papers, to which the reader may refer in order to explore more deeply the material covered in that particular chapter.

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Valuable review articles can also be found in:
Recent Progress in Hormone Research
Annual Review of Physiology
Physiological Reviews

Contents

1

Introduction

Communication between cells

One of the more obvious advantages possessed by multicellular organisms is the ability to differentiate cells which can perform particular and disparate functions and thereby increase the versatility of the organism as a whole. However, the presence of a variety of functionally adapted cell types necessitates the development of an efficient means of internal communication in order to coordinate and regulate their many activities.

There are basically only four ways in which one cell can influence the activity of another. Perhaps the most obvious method by which cells communicate with other cells in distant parts of the body is by means of cellular information channels called nerves, along which a frequency-modulated series of electrical changes, called nerve impulses, is directed between particular cells along precisely defined nerve fibres. In this communication system the specificity of the message is determined by the way in which the 'wiring diagram' is laid down, consequently it is sometimes called an 'anatomically addressed' system.

The three remaining types of communication involve the release of chemicals and may be considered to be 'chemically addressed' systems. The first, and simplest of these systems functions by virtue of close proximity: all cells affect their immediate neighbours non-specifically by consuming oxygen or metabolites from the interstitial fluid and releasing carbon dioxide or other products into it; such changes are incidental to general metabolism and probably serve no regulatory function. However, in the second case, certain cells influence their neighbours by the release of specific chemicals into the surrounding interstitial fluid which have *local* effects restricted to cells within a very small radius—such effects are called **paracrine** actions. Paracrine control is probably particularly important in the alimentary tract but, because technical difficulties make it a difficult field to study, paracrine physiology is still in its infancy.

This book is concerned with the final type of intercellular communication, termed **endocrine**, in which cells influence other cells by releasing into the circulating body fluid particular chemicals called hormones, which, although carried into contact with every cell in the body, only affect those **target cells** which possess particular recognition features (hormone receptors).

Ignoring paracrine control, the two main executive control systems, nerves

and hormones, both appeared early in evolutionary development. To an extent this is not altogether surprising since, in general terms, each system subserves a different mode of control. Thus, nerves assume importance where a fast, rapidly modulated control channel is required, such as for example that which initiates and coordinates voluntary movement. Hormones, conversely, would seem best adapted for longer-term regulation, where speed of response and continuous rapid variation are of secondary importance to a stable, prolonged regulatory action. However, such a rigid segregation of nervous and endocrine control pathways as that above would now be considered naive, in view of the mass of evidence available to indicate the many ways in which the two systems can be seen to act *in concert;* research into aspects of **neuroendocrinology** accounts for the vast majority of current work on the endocrine system.

The concept of a hormone

What is a hormone? A simple question to which there is no simple, 'watertight' answer, for it is extremely difficult to devise a precise, succinct definition of a hormone which includes all those compounds generally held to be hormones while excluding all those which are not. Most working definitions are variations on the following general theme. 'A hormone is a substance secreted *directly into the blood* by discrete *specialized cells* (which may be grouped into an endocrine gland) in *response to a specific stimulus* (neural or bloodborne) and in amounts which *vary with the strength of the stimulus*. Hormones are present in only *minute concentrations* in blood and when carried to their *target cells* exert specific effects which always involve the *regulation of pre-existing cellular reactions* other than by the provision of metabolic energy.' This definition may seem unnecessarily cumbersome, but when you have read this book, try to do two things:

1. See if the definition fits all compounds assumed to be hormones;
2. See if it excludes all other possibilities, such as that CO_2 is a hormone produced by exercising muscle to stimulate respiration, or glucose is a hormone produced by the liver for the benefit of exercising muscle.

The history of endocrinology

The birth of endocrinology is generally accepted to be the classic paper by Bayliss and Starling (1902) in which they described secretin and analysed its actions on secretion from the denervated pancreas. They called secretin a 'chemical messenger' and it was left to a colleague, W. B. Hardy, to coin the word **hormone** from a greek verb meaning 'I excite to activity'. With the wisdom of hindsight, however, it is clear that many observations prior to 1902 can now be explained in endocrinological terms (Table 1.1).

As is almost always the case in science, advances in our understanding of the endocrine system have been largely secondary to improvements in experimental methodology. This is reflected in Table 1.1, which illustrates in chronological order some of the major landmarks in the development of the subject and should be studied with the content of Table 1.2 also in mind.

Table 1.1 The history of endocrinology

Early observations	
From antiquity	Effects of castration on man and animals
1849	Testis transplant prevents atrophy of cock's comb after castration
1850	Cretinism associated with congenital absence of thyroid
1855	Adrenal malfunction in man (Addison's disease)
1869	Discovery of pancreatic islets
1886	Acromegaly in man (overproduction of growth hormone)
Major landmarks by decades	
1890	Sheep thyroid grafts relieve myoedema in man
	Pressor agents extracted from posterior pituitary and adrenal
	Pancreatectomy produces diabetes in dog
	Parathyroidectomy produces tetany
1900	Isolation, purification and synthesis of adrenaline
	Action of secretin described
	First use of term 'hormone'
	Action of posterior pituitary extracts on kidney and uterus
1910	Effects of hypophysectomy described
	Diabetes insipidus controlled by posterior pituitary extracts
1920	Insulin prepared from pancreatic extracts
	Anterior pituitary hormones discovered
	Structure of thyroxine established; thyroxine synthesized
1930	Hypothalamo-pituitary portal system described
	Structure and synthesis of gonadal steroids and adrenal glucocorticoids
1940	Parathyroid secretion shown to be influenced by blood Ca^{2+}
	Mode of neural control of anterior pituitary analysed
1950	Amino acid sequence of insulin described
	Discovery of aldosterone
	Synthesis of oxytocin and vasopressin
1960	Competitive radio-immunoassays developed
	Calcitonin discovered
	Potency of vitamin D metabolites discovered
	Hypothalamic-releasing and -inhibiting hormones isolated
	TRH structure established and synthesis achieved
	Prostaglandin actions
	Role of cAMP in hormone action demonstrated
	Action of other hormones on genome defined
	Three -dimensional structure of insulin described
1970	Inter-relations of brain/gut peptides explored
	Endorphins and enkephalins discovered
	Endocrinology of fetus investigated
	Immunocytochemical localization of endocrine cells
	Role of calmodulin in intracellular regulation

The analysis of endocrine activity

In the case of most of the major endocrine glands, their identity has been uncovered by the appearance of a 'deficiency syndrome' as a result of decrease or failure in secretion of a particular hormone, brought about by disease or damage to the gland. Further analysis of the function of a newly discovered endocrine system usually follows the lines illustrated in Table 1.2. Needless to say, the complete 'dossier' envisaged in Table 1.2 is not yet available for every hormone and endocrine gland, but such comprehensive documentation is obviously the goal of endocrinological research.

Table 1.2 The experimental analysis of endocrine function

Basic evidence

1) Malfunction of gland leads to deficiency syndrome
   - → 2) Transplantation of healthy gland may correct deficiency syndrome
   - or
   - → 3) Extracts from gland correct deficiency syndrome

The hormone

1) Isolation and purification of active principle from gland and venous blood → 2) If pure hormone is antigenic, prepare antibodies
   - a) Radio-immunoassay
   - b) Immunocytochemistry
3) Establish structure of hormone and if possible synthesize it and its analogues → c) Examine relationship between structure and function

4) Define cellular action of hormone *in vivo* and *in vitro*

5) Assess effects of acute and chronic deficiency and excess of hormone and relate to human disease

6) Examine biosynthesis of hormone and subsequent secretion, metabolism and excretion. Is pharmacological alteration of these processes of value in the treatment of disease?

The endocrine gland

1) Macroscopic, microscopic and ultrastructural examination

2) Embryological origin and development of gland

3) Immunocytochemical localization of hormone and metabolites

4) Comparative study of gland in other mammalian species and phylogenetic analysis of structure and function if present in submammalian groups.

Table 1.2 continued

Analysis of possible control mechanisms

1) Control by nerves?
   a) Examine effect of denervation or transplantation to a remote site
   b) Look for nerves associated with secretory cells
   c) Assess effect of electrical stimulation of nerves
   d) Try pharmacological blockade

2) Control by bloodborne factors?
   a) Look for direct effects on the gland of blood parameters influenced by the hormone (e.g. glucose, Ca^{2+}, volume)
   b) Examine possible role of anterior pituitary by noting effects of hypophysectomy and pituitary extracts
   c) Look for feedback effects of the hormone or its metabolites

3) The central nervous system (CNS)

If 1) or 2b) above yield positive results it is likely the CNS is implicated in control of the gland

   a) Look for evidence for CNS involvement e.g. circadian pattern of secretion or relation to environmental factors such as stress, temperature or day length
   b) Attempt detailed localization of the neural areas involved (usually in the hypothalamus) using stereotactic methods to destroy, stimulate or record from precisely defined areas

The cellular basis of hormone action

The problem of the mode of action of hormones on cells is still largely unresolved; moreover, any comprehensive discussion must assume a knowledge of biochemistry and familiarity with those endocrine systems from which convenient examples can be cited. For these reasons the following account makes no claim to be comprehensive: it will not assume other than a superficial knowledge of biochemistry and will leave the reader to consult other texts to pursue this aspect. We will, however, draw upon examples of hormone action discussed later in *this* text: reference will be made to the appropriate page, but the reader may wish to defer reading this section until *after* having studied later chapters.

Before examining how hormones can influence *individual cells,* it is worth noting that hormones can affect the functioning of specific *groups* of cells (tissues) in more general ways. These include stimulation of growth of the tissues by promoting an increase in the number of cells (this is often called a **trophic** effect) and increase in blood flow through the tissue due to a vasodilator effect on local blood vessels (e.g. ACTH promotes adrenal blood flow, p.118).

At the level of individual cells, hormones influence activity basically by controlling one or more rate-limiting steps in the metabolism of the cell. Almost without exception, such control devolves ultimately upon the production or activation of specific proteins, usually with enzyme activity. How this is achieved depends upon the chemical nature of the hormone involved, as illustrated in Fig. 1.1. The following account should be read in conjunction with Fig. 1.1 by reference to the numerical sequence.

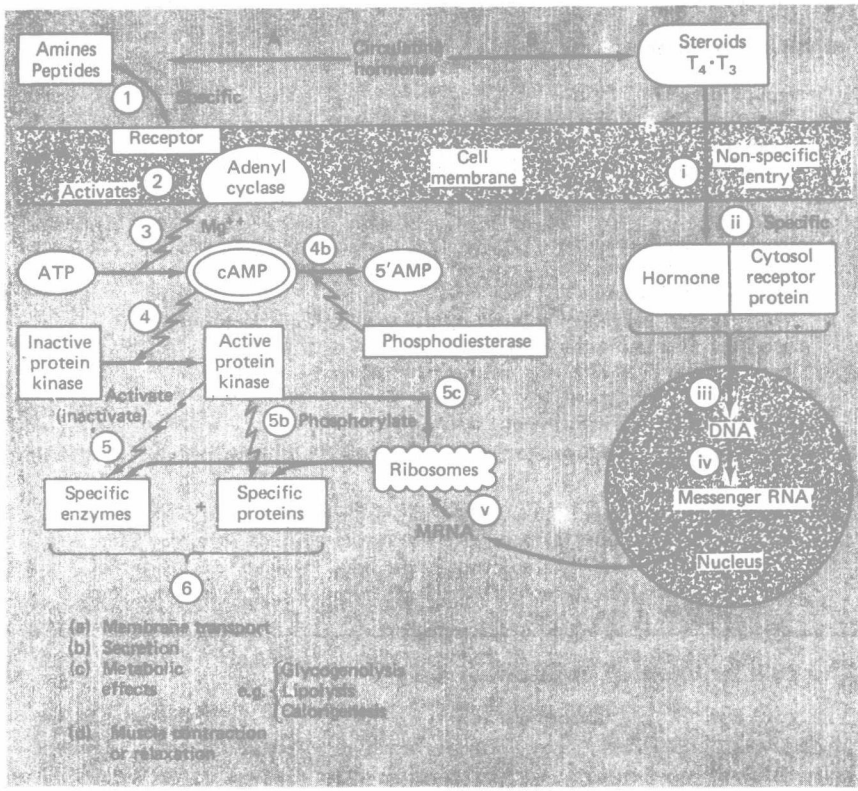

Fig. 1.1 Diagram to illustrate the basic pathways by which; A, amine and peptide hormones and B, steroid and thyroid hormones regulate the synthesis of specific proteins and thereby modulate cell function. For detailed explanation see text. ATP = adenosine triphosphate; AMP = adenosine monophosphate; cAMP = cyclic adenosine—3′, 5′—monophosphate ('cyclic AMP'); T_4 = thyroxine, T_3 = triiodothyronine.

A. Amine and peptide hormones

1. These hormones do not enter the cells, but each reacts with a specific receptor in the cell membrane.

2. Combination with the receptor activates membrane-bound adenyl (adenylate) cyclase.

3. This enzyme, in the presence of Mg^{2+}, induces the formation, from ATP, of cyclic AMP (cAMP).

4. This nucleotide activates one or more of the cAMP-dependent protein kinases with the cell.

4b. The cAMP is degraded by phosphodiesterase producing 5′AMP.

5. The active protein kinase promotes the phosphorylation of specific enzymes which may serve to activate, or sometimes deactivate, the enzyme.

5b. Phosphorylation may also alter the configuration and properties of other specific proteins (e.g. structural or membrane proteins).