Endocrine pharmacology

Physiological basis and therapeutic applications

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Preface

This book presents a view of endocrinology as seen by a pharmacologist. It is concerned with the actions and uses of hormones as drugs, and with the drugs that influence endocrine functions in the body. As the practical application of such substances arises in health and disease, the physiological background for both these situations is provided. No prior knowledge of endocrinology or pharmacology is assumed, so the material should be understandable at the undergraduate level. No attempt is made to provide a detailed protocol (for instance, dosages) for the clinical use of such drugs, but an account is provided of the preparations that are available, their administration, expected therapeutic responses, side effects, and interaction with other drugs. Special emphasis has been placed on the mechanisms of action of such drugs and hormones, and the relationship of their chemical structure to their biological activities and structural analogues. The emphasis is on the human situation, but clearly our understanding of the working of the endocrine system depends largely on experiments carried out on animals. An extrapolation between human and nonhuman species is, however, made with care, especially when considering the use of endocrine-active drugs.

The clinical application of drugs can be a highly controversial practice, and changes arising from advances in knowledge are continual. I am not a physician and so am reticent to describe clinical procedures. I have therefore tried to remain objective and dispassionate in such descriptions and have attempted to quote the most recent and best authorities of whom I am aware. The editorial advice given by such eminent publications as the *British Medical Journal*, *The Lancet*, and *The New England Journal of Medicine* has therefore been proffered especially often.

This book is quite a long one, so it is unlikely that many people will read it in its natural sequence. An attempt has therefore been made to make each section reasonably self-contained. A certain amount of repetition is thus inevitable but is limited by cross-referencing. When attempting to cover such a large scientific area, a problem inevitably arises regarding the quotation of references. For the earlier work in endocrinology, I have often sought refuge in reviews provided by others, but I have attempted to give original references to more recent papers. An especially useful source of basic material has been the endocrinology section of the *Handbook of Physiology*, prepared under the guidance of Drs. R. O. Greep and E. B. Astwood for the American Physiological Society. The background for many of the more clinically related aspects of the subject has been provided by numerous textbooks of medicine, but Dr. A. Labhart's excellent and comprehensive book, *Clinical Endocrinology: Theory and Practice* (Springer-Verlag, 1976), has been of special help. For more basic pharmacological information, I have often dipped into such volumes as *Drill's Pharmacology in Medicine* (edited by Dr. J. R. DiPalma; McGraw-Hill, 1971) and *The Pharmacological Basis of Therapeutics* (edited by Drs. L. S. Goodman and A. Gilman; Macmillan, 1975).

In these days, multiauthored scientific books are the rule rather than the exception, and they are considered by many to be a necessity. Some may therefore question my audacity and ability to overcome this prejudice; after writing this book I can certainly appreciate the problems that are involved. Nevertheless, I hope that the overall view of one person may provide some interest and cohesion, and a useful general background for what is a subject of quite general importance.

I am primarily indebted to the many basic and clinical scientists who have published their observations, and I apologize to the many authors who, because of my ignorance of their work or the necessity for literary continuity, remain anonymous. Some of the inspiration and information for

this book resulted from my listening to lectures in courses on pharmacology, endocrinology, and reproduction, which my institution provides for its medical students. A lot of people, and their publishers, have allowed me to quote their work, and in many instances this has involved active help in providing material suitable for reproduction and suggestions for modifications and changes. I would also like to thank all those who have helped me, over a period of about three years, in the more onerous tasks of collecting references and preparing the manuscript. The Mount Sinai School of Medicine and The City University of New York succored me during the writing of this book. Special thanks are due my Chairmen, Professor J. P. Green and Professor S. A. Podos, for their moral and practical support during a period when some may have considered that my time could have been better spent.

P. J. B.

New York
January 1980

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Introduction

1.1. Definition and scope

Endocrine pharmacology is a branch of both endocrinology and pharmacology. It is a happy marriage that has mutually benefited both of these important biological disciplines. *Endocrine pharmacology* may be defined as the study of hormones that are used as drugs, and drugs, including analogues of hormones, that are used as agonists and antagonists of endocrine functions. The scope of these studies includes an understanding of the various effects of these drugs and hormones as well as their metabolism, mechanism of action, and therapeutic use. (A *drug* is commonly defined as any substance used in the composition of medicine.)

The endocrine glands and the nervous system coordinate and control the multitude of bodily activities concerned with physiological homeostasis, growth, and reproduction. Their actions are mediated by chemical compounds which they can synthesize and release and which can influence the activity of other cells. Such substances are quite basic for the life of multicellular animals. Nerves and endocrine glands share the basic role of integrating the function and activity of the various types of cells and tissues in the body, although they act in somewhat different ways. Nerve transmission is relatively fast and generally can be directed more precisely for relatively short and specific periods of time. Endocrine glands, on the other hand, release their hormones into the circulation, so that the onset of their action is usually slower but their effects are often quite ubiquitous and of relatively prolonged duration. These properties are, however, only a broad generalization, and there are exceptions.

Hormones are especially well suited for the types of functions where chronic, relatively long-term stimulation of an organ or tissue may be necessary. As they are distributed widely by the circulation, they are also well designed for physiological situations in which stimulation at widespread and multiple types of sites is required.

The actions of hormones can be divided into four basic types, which usually reflect their special properties and propensities as described above (Figure 1.1):

a. Hormones regulate the various interconversions of nutrient fats, carbohydrates, and proteins, and the production of energy, which constitutes the body's *intermediary metabolism*.
b. Hormones can influence the *tone of smooth muscle* cells such as are present in the uterus, gut, and blood vessels.
c. Hormones also provide stimuli, which may arise as a result of changes in the external or internal environment, which *influence the activity of other endocrine glands*. Such tropic actions are especially important in regulating cyclical events such as reproduction, and in providing feedback control mechanisms for hormone secretion.
d. A quite general property of many hormones, which may also be related to the processes described above, is their ability to influence the *permeability* of biological membranes to such substances as water, ions, and metabolic solutes such as sugars and amino acids. Changes in the permeability of cells may be directly important for bodily homeostasis, as in promoting the conservation or excretion of salts, or they may contribute indirectly by providing signals, such as substrates and ions, that trigger metabolic mechanisms.

It should be emphasized that the nervous and endocrine systems cannot be considered as independent entities – they interact, support, and reinforce each other's actions in various ways. The present book, principally for practical reasons, is concerned with the functioning of the endocrine glands, but their many interactions with the nervous system will be emphasized.

Endocrinology has many practical applications in our everyday life. Apart from the treatment of human disease, it has provided methods for limit-

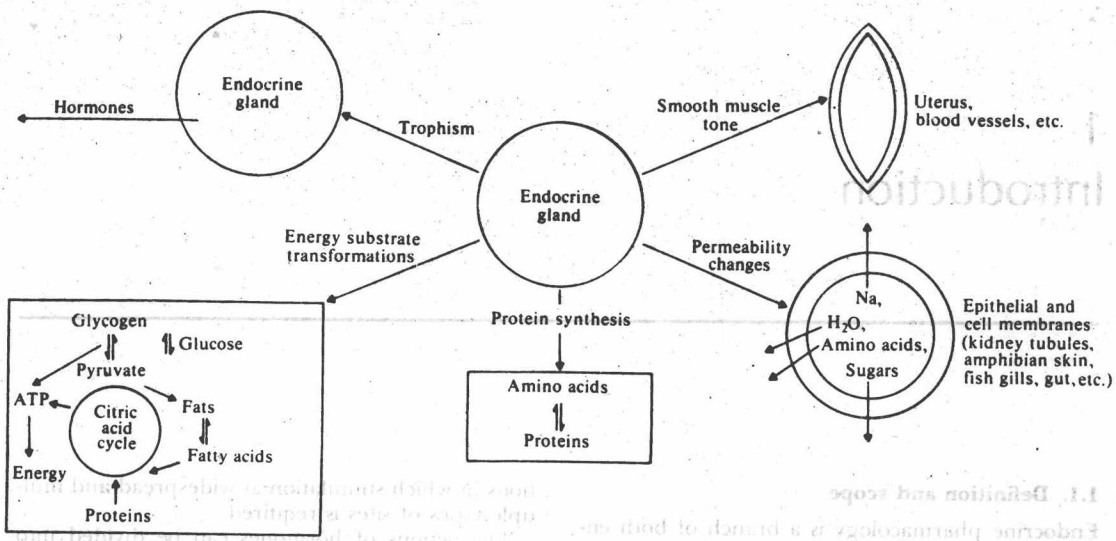

Fig. 1.1. Summary of the basic types of hormone actions. (From Bentley, 1976.)

ing the growth of the human population and promoting the supplies of food that are provided from animals. In 1967, the use of endocrine preparations in the United States amounted to $500 million, which was about 12 percent of the total value of all therapeutic drugs used.

Several pharmacological and therapeutic strategies are used to modify endocrine function in the body. In the instance of hyposecretion of hormones, replacement therapy may be instituted in several ways. Hormones from exogenous sources can be administered. These drugs may be the naturally occurring hormones that can be extracted from animal glands or may be made by chemical synthesis. In some instances, a surrogate compound can be provided which, although not identical to the endogenous hormones, may, nevertheless, exert a satisfactory effect. An early developed example of such a substance is diethylstilbestrol (DES), a synthetic compound with female sex hormone (estrogenic) activity but which, unlike the natural ovarian hormones, is not even a steroid. In some instances, a hypoactive endocrine gland can be stimulated to synthesize and/or release additional amounts of its secretion. Such an effect can be promoted by preparation of natural tropic hormones, such as corticotropin (ACTH), which stimulates the adrenal cortex, or even foreign chemical compounds such as tolbutamide, which stimulates the release of insulin. The action of some hormones can be potentiated by drugs and it seems likely that such an effect may account for the usefulness of chlorpropamide in the treatment of diabetes insipidus, which is due to insufficient antidiuretic hormone. Hyperfunction of endocrine glands can also be treated pharmacologically, although usually surgical, or sometimes radiological procedures are ultimately used. An overactive endocrine gland can be suppressed by the administration of a drug that inhibits hormone synthesis, such as the action of propylthiouracil on the thyroid, or release, for instance the effect of diazoxide on the pancreatic B-cells, or the action of the hormone at its effector site, such as the antagonism of aldosterone's effect by spironolactone.

There are other occasions apart from hypo- and hyperendocrine conditions when pharmacological interference with a normal endocrine gland may be desirable. Oral contraceptive drugs can be used to prevent pregnancy, insulin to produce psychotherapeutic convulsions or to lower plasma K levels, androgens to promote muscle growth in athletes, and estrogens to reduce the proliferation of certain tumors.

Endocrine preparations may also be used for medical diagnostic purposes. These methods need not necessarily be of direct endocrine significance; for instance, the hypothalamic releasing factors and pituitary tropic hormones can be used to diagnose and locate brain tumors.

Hormones may also be utilized for the treatment of certain nonendocrine diseases. The best known example of such use is that of adrenocorticosteroids to treat inflammatory diseases such as rheumatoid arthritis.

Of importance to human welfare is the use of endocrine preparations to promote the health, reproduction, and growth of farm animals that pro-

vide us with food. The veterinarian, like the physician, uses endocrine preparations to control and cure animal diseases. Probably of even greater significance, however, is the use of hormones to speed growth and enhance the efficiency with which animals convert feed into bodily tissues. The use of such drugs has, however, recently been questioned, owing to uncertainties about the effects of such hormone residues when they are consumed by man.

No drug is completely specific in its action, but produces side effects whose number, incidence, and importance differ widely. Many nonendocrine drugs may have adverse effects in the body which can be related to their interference with normal endocrine function. The recognition and understanding of such effects may play an important role in assessing the possible significance of a drug's side effects and possibly suggest ways of antagonizing it. For instance, diazoxide is a potent hypotensive drug which also has a hyperglycemic action due to an inhibition of the release of insulin. It is interesting that this side effect of diazoxide has been utilized to treat hypoglycemia, so that what is a side effect for one application of a drug can in turn be utilized for its desirable endocrine effect.

1.2. History and synopsis

The roots of endocrine pharmacology lie in the application of knowledge of the workings of the endocrine glands. The word "hormone" was not coined until 1902, when W. M. Bayliss and E. H. Starling used it to describe the properties of a chemical excitant, secretin, which they had extracted from the intestine. During the 10 years prior to this semantic beginning of endocrinology, the biological activities of extracts from the thyroid, adrenal medulla, and the posterior pituitary gland were demonstrated. Renin, the midwife of angiotensin, was also discovered during that period. Endocrinology was thus born less than 100 years ago. The pharmacological application of the new information was almost immediate. In 1891, G. R. Murray treated hypothyroid patients with preparations of thyroid gland. In 1909, W. Blair Bell injected posterior pituitary gland extract into women to prevent postpartum uterine bleeding, and in 1911, J. Hofbauer used the same material (which contains the hormone oxytocin) to stimulate labor. The pharmacological applications of new knowledge about endocrine function has indeed often been quite prompt. The use of nonhormonal types of drugs that influence endocrine functions has, however, usually been much slower to occur and has largely depended on empirical types of studies with a good deal of help in the form of serendipity – happy accidental observations.

Knowledge of the endocrine glands as anatomical, but not hormone-secreting structures, originated, in many instances, several hundreds of years ago. In some cases, however, their discovery was quite recent. For instance: the islets of Langerhans were first described in 1864, the parathyroids in 1880, and the thyroid C-cells in 1876. The association of human diseases with pathological changes in such glandular tissues is also relatively recent. These include the description of adrenocortical insufficiency by T. Addison in 1855, exophthalmic goiter by R. J. Graves in 1835, hypothyroidism by H. Gull in 1874, and acromegaly by P. Marie in 1886. At these times, however, the essential endocrine nature of these tissues, and hence the disease, was unknown, so that specific treatment was not possible. It is, however, interesting that iodide was first used empirically, to treat hyperthyroidism, more than 100 years ago, and there was much speculation about the possible use of testicular extracts to promote masculine sexual vigor.

Organotherapy or opotherapy is an ancient branch of medicine based on the assumption that one can correct the disease of an organ by ingesting an equivalent organ from an animal or even another human being. The practice of eating the heart of one's enemy, to gain courage, as formerly practiced in some societies, is probably in the nature of such therapy. The self-administration of testicular extracts to improve sexual vigor was described by C. E. Brown-Sequard in 1889 and is a type of organotherapy. He reported favorable results, although subsequent tests of extracts of the type he used showed them to be devoid of a rational basis for the effects he described, as they contained no male androgenic hormones. This valiant attempt at hormone replacement therapy is in fact an early example of endocrine pharmacology. In 1891, G. R. Murray successfully administered thyroid gland extracts for the treatment of hypothyroidism, probably the first valid example of therapeutic endocrine pharmacology. This event was, however, soon followed by the use of posterior pituitary gland extracts in obstetrical practice. In 1913, R. van den Welden and F. Farini separately discovered the use of such glandular extracts for the treatment of diabetes insipidus. The most famous discovery of a hormone preparation that could be used to treat a specific human disease was that of insulin. This hormone was isolated from animal pancreases by F. G. Banting and C. H. Best in 1921 and was used to save the life of a 14-year-old boy suffering from diabetes mellitus. The event was followed by popular acclaim which was important at a time when endocrinology was still treated with some suspicion and was assumed to be mainly concerned with nefarious sexual activities.

In the succeeding decade, the importance of the anterior lobe of the pituitary became apparent. Largely as a result of the studies of P. E. Smith,

H. M. Evans, S. Ascheim and B. Zondek, O. Riddle, and others, the presence and actions of such hormones as the gonadotropins, thyrotropin, growth hormone, prolactin, and corticotropin were demonstrated in the pituitary gland. These discoveries were of immense importance for elucidating the mechanisms of the control of endocrine functions and gave a basis for understanding the nature of diseases that affect the pituitary. What was probably the first diagnostic endocrine test was concurrently developed: the Ascheim–Zondek pregnancy test, which utilized urinary gonadotropins to stimulate ovulation in rabbits or mice. The use of such hormones to treat human disease was, however, not of practical significance for more than 20 years. In 1950, corticotropin was used to stimulate the adrenal cortex in inflammatory diseases, especially rheumatoid arthritis, and in 1958 human growth hormone was introduced for the treatment of hypopituitary dwarfism in children. The gonadotropins have been used sporadically for many years in attempts to treat infertility in women, by inducing ovulation, but it is only recently that this has become an accepted practice.

Advances in endocrine pharmacology have largely depended on the application of new chemical techniques. Procedures developed by both organic and physical chemists have made possible the isolation of hormones in a pure form. The elucidation of their structure and, subsequently, their chemical synthesis is then made possible. The provision of suitable hormone preparations for therapeutic use is also facilitated. In addition, it then becomes feasible to modify the chemical structures of such hormones in a manner that may change their properties. These include a prolongation of their actions and alterations in the spectrum of their different effects in the body. The provision of pure hormones and knowledge of their chemical nature also allows the development of more convenient and accurate methods for their measurement and identification.

In 1914, E. C. Kendall prepared crystalline thyroxine. C. R. Harrington, in 1926, described its structure and in the next year chemically synthesized this hormone. The structures of many of the steroidal sex hormones, from the ovaries and testes, were also described during the next decade and their synthesis was then undertaken. These important contributions involved such pioneers in steroid hormone biochemistry as A. Butenandt, E. A. Doisy, G. F. Marrian, and L. Ruzicka. Of particular interest to endocrine pharmacology was the demonstration by Butenandt in 1937 that esters of estrone and testosterone had prolonged activity. The potent orally active female sex steroid ethinyl estradiol was synthesized by H. H. Inhoffen and W. Hohlweg in 1939. Just prior to this, in 1937, the progestin ethisterone was synthesized by Ruzicka, but although, unlike progesterone, this was active orally, it had strong androgenic side effects that limited its use. Probably the most interesting contribution to endocrine pharmacology at the end of this decade was the synthesis of an artificial estrogen, diethylstilbestrol (DES), by E. C. Dodds in 1938. This chemical is not a steroid but has potent estrogenic properties, is active orally both in man, and of special interest, in farm animals. It is also cheap to produce. Dodds did not even take out a patent on this compound, an omission he bemoaned many years later, as it would have provided his laboratory with more liberal funds for research.

Such discoveries have provided hormone-like preparations which are useful for the treatment of endocrine disorders in man. They have also furnished drugs that are used to control fertility (oral contraceptives). The use of these compounds was developed by G. Pincus, starting in 1955, largely in response to prompting by Margaret Sanger. This application of estrogens and progestins has involved many millions of women throughout the world and has contributed in a major way to limiting human population. Estrogens are also of considerable direct economic importance as they have been used for more than 20 years to promote growth and improve the quality of meat in farm animals.

Research on the chemical nature of the steroid hormones produced by the adrenal cortex was also started in the 1930s. Deoxycorticosterone, an intermediate in the biosynthesis of these hormones, but which exhibits some activity, was synthesized by T. Reichstein in 1937. This compound had a limited use for replacement therapy in Addison's disease. However, the real impetus for the chemical study of the adrenocortical steroid hormones came during World War II, when it gained a priority associated with the Allies' war effort. It has been suggested that a rumor was spread that German pilots were taking these steroids in order to allow them to fly at high altitudes. If this is true, the efforts were misdirected but nevertheless had a productive outcome. In 1949 studies at the Mayo Clinic showed that cortisone had dramatic effects in the treatment of rheumatoid arthritis. This steroid was popularly called a "wonder drug" and ushered in the era of the antiinflammatory steroids. E. C. Kendall, T. Reichstein, and P. S. Hench jointly received a Nobel Prize in 1950 for their roles in this discovery. This was not the first such recognition for the work of endocrinologists, nor was it to be the last.

The determination of the structures and the chemical synthesis of the polypeptide hormones was ushered in 1951, when V. du Vigneaud described the structure of oxytocin. The structure of

vasopressin was described soon thereafter, and both compounds were then synthesized. Several hundred analogues of these octapeptide hormones have since been prepared. The structure of the larger hormones was more of a problem, but F. Sanger described the amino acid sequence of insulin in 1955. This was the first such description of the structure of a protein. Human insulin was chemically synthesized in 1964 by P. Katsoyannis. This synthetic product, however, is too expensive to make for commercial therapeutic use. The large pituitary hormones require even more herculean efforts; C. H. Li has been preeminent for many years in such research, including the determination of the sequences of the nearly 200 amino acids in growth hormone. He has also made such measurements on prolactin, β-lipotropin, and corticotropin. Future provision of therapeutic preparations of such large hormones appears to rest in the possible use of smaller active fragments and the artificial genetic programming of bacteria to form them by biosynthesis. In December 1977, K. Itakura and his colleagues described the successful implantation of a chemically synthesized gene for the hormone somatostatin into *Escherichia coli* and the separation of the resulting tetradecapeptide product that was synthesized by the bacteria.

In the last 20 years there have been major advances in the elucidation of the nature of the relationship between the nervous and endocrine systems, which is often described under the discipline of neuroendocrinology. The brain is now known to have a direct influence on many endocrine glands. These effects are conveyed from the hypothalamus, at the base of the brain, to the pituitary gland and then, via the pituitary tropic hormones, to the thyroid, adrenal cortex, testes, and ovaries. G. W. Harris was an originator and the most persistent proponent of the concept that hormones are formed in the hypothalamus and are conveyed in the small portal blood vessels to the pituitary gland. The related supporting observation that nerve cells can secrete hormones (the process of neurosecretion) was proposed many years earlier by E. and B. Scharrer. Several hormones have been identified in the hypothalamus which mediate this function, and the structures of three of these – thyrotropin-releasing hormone (TRH), somatostatin, and luteinizing/follicle-stimulating hormone releasing hormone (LH/FSH-RH) – were described between 1969 and 1971 by R. Guillemin and A. V. Schally. These are peptides that have been chemically synthesized.

Such investigations have often involved laborious or, perhaps more aptly described, "heroic" methods. Butenandt had to extract 15,000 liters of urine to obtain 15 mg of the testosterone metabolite androsterone. Guillemin used the hypothalami of 5 million sheep to prepare 1 mg of pure thyrotropin-releasing hormone. More recently, E. Rinderknecht and R. E. Humbel extracted 11,000 kg of the Cohn protein fraction of human plasma, representing nearly 1 million liters of blood, to obtain enough material for determination of the amino acid sequence of a somatomedin (insulin-like growth factor).

A considerable amount of information is now available regarding the basic mechanisms of hormone action. In 1958, E. W. Sutherland described the role of cyclic AMP as a "second messenger" in the functioning of glucagon and epinephrine. This mechanism has since been shown to apply to several other hormones, especially polypeptides. Steroid hormones, however, work differently and act on the cell nucleus to promote genetic transcription, the formation of mRNA, and the *de novo* synthesis of specific proteins which mediate their effects. The original hypothesis was proposed by U. Clever and P. Karlson in 1960. The development of this concept of the mechanism of action of a hormone is largely based on the theory of F. Jacob and J. Monod, which they conceived in 1959 to account for the genetic control of cell functions.

The hypothesis that drugs influence the functioning of cells by combining with specific components called "receptors" was first proposed by J. N. Langley in 1905 and was developed by A. J. Clark in the 1920s. This pharmacological concept has received considerable support with respect to the action of hormones. Macromolecules that specifically bind particular steroid and polypeptide hormones have been identified, described, and even isolated. This area of research is currently very active. Its recent advances depended largely on the technical ability to prepare radioactively labelled hormones that have a high ratio of label to biological activity. E. V. Jensen in 1961 provided suitable steroid hormone preparations while comparable labelling procedures for polypeptides were concurrently developed in several laboratories. The subject of hormone–receptor interactions is a special example of the happy marriage of endocrinology and pharmacology.

The binding of hormones to their receptors is a reversible process that involves a complementary association of fields of forces in their molecules. The arrangement and even existence of such properties depends on the three-dimensional structure or conformation of the molecules and the particular disposition of their reactive groups. Knowledge of the conformation of hormone molecules is thus of basic importance for understanding their function and may provide information that is of practical significance for the design of modified forms of hormones. In 1969, D. C. Hodgkin and her collaborators, using the technique of X-ray crystallographic analysis, provided a three-dimensional picture of insulin.