Endocrine Physiology

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To H.R.N.

Preface

The central theme of this book is the application of molecular endocrinology principles to the understanding of whole animal physiology in mammals. Hormones performing common or related functions are grouped together in each of the subdivisions.

Human physiology is emphasized, and references to the clinical literature have been included. Since most basic research is conducted on laboratory animals, species variations and the relevance of the findings to human subjects are considered in some detail. Nonmammalian vertebrates and invertebrates solve some of their biological problems in different ways. They therefore can provide insights into differences between "what is" and "what must be so." Despite the advantages of limiting the text to manageable size, selected aspects of comparative endocrinology are presented in the chapters on calcium metabolism, water balance, reproduction, and pituitary gland functions.

The text's format was designed for versatility. The sections in large type cover all of the major topics. They should be easily comprehended by students who have completed elementary training in animal physiology and biochemistry, and they are therefore appropriate for use in graduate and advanced undergraduate courses. Some of the sections in small type demand more advanced knowledge of biochemistry. Others are concerned with unresolved controversies, or with details that will interest only limited numbers of readers. These sections can be omitted with no loss of continuity in the text.

Since the index is liberally supplied with subheadings and cross-references, the text can also serve as a convenient source of information for investigators, for graduate and medical students requiring supplements to shorter texts, and for physicians seeking background materials not generally available in clinical books and journals.

Certain chapters assume knowledge of material presented in the earlier ones. However, the index provides ready access to terminology and details that might be needed if the text is read in a different order.

Most of the references are taken from the recent literature. Each of the papers supplies additional citations, and some review articles have been included. I hope that authors whose works were omitted will recognize that it was not feasible to incorporate all of the important findings.

Preparation of this book was made possible by the scholarly approach and indulgence of Oxford University Press. The initial version of the manuscript was begun in 1977. Because of rapid advances in the field, earlier chapters were revised each time a new one was completed. Changes and additions were also made when a new journal arrived hours after a section had been rewritten, during copy editing and examination of the galley proofs, and even after preparation of the page proofs. Needless to say, this has taxed the patience and endurance of many editors. I am especially grateful to Dr. William F. Curtis, who good-naturedly bore the brunt of burden. I also wish to thank Mr. Jeffrey House, Mr. William Tilley, and the copy editors, Ms Susan Meigs and Ms Brenda Jones.

From the beginning, my husband, Henning Norbom, consistently provided inspiration and understanding. Without his support, encouragement, and sense of humor, the book could not have been completed.

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PART I

Introduction to the Endocrine Systems of Vertebrates

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1

What Are Hormones? What Do They Do?

Vertebrate hormones are highly potent, specialized organic molecules that serve as regulators and coordinators of the biological functions of the animals in which they are synthesized. They exert their actions on cells equipped with receptors that bind the hormones with high affinity and specificity and couple that binding to the initiation of characteristic responses.

Distinctions can be made between hormones and certain other regulators, such as *inorganic ions, enzymes* (acting on substrates rather than receptors), water-soluble *vitamins* (derived from the diet or from microorganisms residing in the digestive tract), *macronutrients* utilized in substantial quantities as either energy sources or protoplasmic building blocks), *parahormones* (ubiquitous substances produced by most cell types), and *pheromones* that act on other members of the species. Hormones, however, interact with all of the preceding.

CHANGING CONCEPTS OF THE NATURE AND FUNCTIONS OF HORMONES

Recently developed methods have brought new insights into the chemical natures of hormones and receptors; their sites of biosynthesis, activation and degradation; and their mechanisms of interaction at the molecular level. We now appreciate the wide distribution of target cells, the rapid changes in the hormone concentrations presented to them, and the factors that modify the receptor numbers and functions. These advances have changed our understanding of the endocrine system.

The "classical" concepts are nonetheless worth examining since they have been widely disseminated and are still being taught. According to the traditional view, each hormone is a *defined chemical entity* that is synthesized exclusively within, and released from, its own special, morphologically recognizable cell type. The secretory units are organized into distinct, circumscribed structures known as *endocrine glands* whose activities are regulated by blood-borne chemical signals. The hormone is discharged into the *circulatory system,* through which it travels to a single or limited number of *target organs* for the purpose of exerting "specific" stimulatory or inhibitory influences. The responses take time to develop and are of *longer duration* than those elicited by neurotransmitters.

Since each kind of endocrine gland serves as the unique source of its hormone, surgical ablation leads to the emergence of a characteristic deficiency syndrome that can be alleviated by administering the missing product.

This neat, orderly arrangement distinguishes the endocrine system (whose regulators are synthesized in glands and are released into the bloodstream) from the nervous system (which produces its messengers in neurons and releases them to synpases or neuromuscular junctions). It also implies that hormones differ from locally acting "autacoids" such as histamine and prostaglandins.

The picture presented in the preceding discussion was almost universally accepted until quite recently. When observations that diverged from it first began to emerge, attempts were made to preserve the dogma by suggesting that regulators failing to conform were unworthy of reccgnition as bona fide members of the endocrine system. In time, however, it became necessary to acknowledge that the classical views do not reflect biological reality.

The endocrine system is powerful, versatile, and self-regulating. However, it is decidedly *not neat;* and it has little respect for time-honored traditions. Its boundaries merge imperceptibly with those of other regulatory systems, as its influences extend to

all facets of biological function. Exceptions to all of the traditional beliefs are cited in this chapter, and additional examples will be found throughout the text.

Chemical Nature of the Hormones

Most hormones are "families" of related molecules. Two or more insulins and several kinds of glucagons can be made by a single species. Gastrins seem to be universally present in multiple forms. Human pituitaries contain many genes that direct the biosynthesis of growth-promoting regulators. Testosterone acts directly on some cell types, but it requires transformation to dihydrotestosterone, estradiol or other steroids before it affects different targets.

Sites of Hormone Biosynthesis

While it is true that parathyroid glands serve as the major sources of parathyroid hormones and that pancreatic beta cells make most of the insulins, most (and probably all) hormones are synthesized at multiple sites. Tumor cells unrelated to parathyroid glands can make parathyroid hormone, insulin-like molecules are synthesized in the brain, and biologically active somatostatin originates (among other places) in the brain, pancreatic islets, thyroid glands, and gastrointestinal tract.

Relatively few of the regulators are made in structures recognizable as endocrine glands. Most of the angiotensin I is formed extracellularly within the bloodstream, while most of the angiotensin II originates in the lungs. Some of the hormones that regulate digestive system functions are synthesized in cells widely scattered in small clusters throughout the gut. Neurons are important sources of oxytocin, vasopressin, and hypothalamic releasing hormones. The kidney provides us with hormones that play major roles in the control of erythropoiesis and of blood pressure, and the liver converts a variety of molecules into specialized products.

We are now recognizing that many different kinds of cells make substances chemically similar to (or identical with) the hormones traditionally associated with specific endocrine glands. Related molecules have been identified in worms, protozoa, and plants (59).

Mechanisms for Controlling Hormone Secretion

It is true that blood-borne signals make substantial contributions to the regulation of hormone secretion. For example, the various cell types of the endocrine pancreas respond to changes in the glucose concentration of the systemic blood, whereas parathyroid gland and calcitonin-secreting cells are affected by the levels of calcium ions. On the other hand, even the "typical" endocrine glands are richly innervated. Interrelationships between the endocrine and nervous systems permit the body to make adjustments that avert, rather than correct, imbalances; and they provide for interactions with environmental factors. The pineal gland, the endocrine components of the hypothalamus, and the adrenal medulla provide examples of hormone-secreting structures controlled primarily by neurons.

Hormone Transport

While many endocrine cells secrete into the systemic blood vessels, those residing in the hypothalamus and exerting their influences on the anterior portions of the pituitary gland pour most of their products into a restricted part of the circulatory system known as the hypothalamo-hypophysial portal system.

Hormones also gain access to the target cells in other ways. For example, glucagon released by the alpha cells of a pancreatic islet can travel directly to neighboring beta cells within the same islet (110). In addition, a hormone may act on the very cell that produces it.

The Specificities of the Target Organs

The target organ concept is easily applied to certain of the regulators. For example, thyroid stimulating hormone (TSH) acts mostly on the follicular cells of the thyroid gland, while adrenocorticotropic hormone (ACTH) stimulates the zona fasciculata of the adrenal cortex.

On the other hand, insulin regulates hepatocytes, adipocytes, skeletal muscle cells, and some hypothalamic neurons, while estrogens affect (among other things) the ovaries, fallopian tubes, uterus, vagina, mammary glands, bone, bone marrow, liver, thymus gland, pituitary gland, and brain. It is difficult to find a cell type that does not contain receptors for glucocorticoids (17), and even TSH and ACTH act at multiple sites.

Latent Periods and Durations of Hormone Actions

The belief that the responses to hormones take more time to develop and last longer than those elicited by neurotransmitters is not supported by the facts. Target cells cannot distinguish between norepinephrine

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released from sympathetic nerve endings (and therefore regarded as a neurotransmitter) and norepinephrine discharged into the bloodstream by cells of the adrenal medulla. Some of the hormonal actions of glucagon on the liver are detectable within seconds after that regulator reaches its receptors, and there are efficient mechanisms for termination of the responses when this becomes appropriate. Acetylcholine and other "classical" neurotransmitters exert long-range, trophic actions on cells equipped with receptors for those regulators (112).

Currently acceptable concepts of the endocrine system are like beautifully blurred versions of the simple, sharply drawn pictures made by yesterday's endocrinologists. Ideas have changed so rapidly within the past few years that there are controversies concerning which of the regulators should be included in the official list of "true" hormones. In this text, all molecules meeting the criteria set forth in the opening paragraph are regarded as components of the endocrine system.

THE FUNCTIONS OF VERTEBRATE HORMONES

Cell Specialization and Survival

Specializations permit each cell type to perform unique functions that contribute to the versatility and survival of the organism as a whole. Concomitantly, they limit the ability of individual units to maintain autonomous existences. In complex animals, the various cell types become highly dependent on each other and on the continuous presence of a closely regulated internal environment.

The endocrine system establishes the kinds of cell-to-cell communication that foster cooperation, and it thereby accounts for many of the differences between cell aggregates and integrated individuals. It monitors and maintains the compositions of the body fluids, and it favors specializations by commanding cells of one type to support the activities of another. Through influences on growth, differentiation, maturation, proliferation, and metabolism, it encourages each body component to realize its potential and to assume its appropriate role.

Hormones provide mechanisms whereby organisms as a whole can make adjustments to changing internal needs and external environments. They accomplish this in part by promoting maturation of the nervous system and by regulating the activities and sensitivities of neurons. Hormones also contribute in essential ways to perpetuation of the species, since they are needed for differentiation and maturation of the reproductive organs, for the production of gametes, and for the nurturing of conceptuses and neonates.

Nutrition, Metabolism, and Body Composition

Hormones affect the intake of foods and fluids via the influences they exert on olfactory and gustatory receptors, on the appreciation of and responses to hunger and thirst, and on the locomotor activities involved in the acquisition and ingestion of nutrients. They promote digestion and absorption, and they enhance the blood flow to the gut during times when no heavy demands are made upon the skeletal muscles. They regulate the distribution of essential materials, and they encourage both the storage of nutrients following meal ingestion and the recruitment of reserves during fasting or when there is increased need. They facilitate immediate and long-range adaptations to changes in the quality, quantity, and timing of food intake, favoring growth and repair when the supplies are abundant, as well as minimizing such processes when survival can be prolonged by shunting very limited resources into pathways that support vital functions.

Hormones regulate the conservation of water and electrolytes and the excretion of metabolic wastes. They modulate the generation, distribution, and dissipation of body heat and thereby contribute to the maintenance of optimal internal temperatures. They control the biosynthesis and degradation of structural and regulatory molecules and play important roles in the attainment of the body composition characteristic of the species.

Activity and Rest

Hormones provide mechanisms for initiating and sustaining skeletal muscle activity, for coping with stress, and for reversion to the resting state when this becomes appropriate. Influences are exerted on the cardiovascular and nervous systems, and also directly on the skeletal muscles. The hormones encourage the suspension of digestion and of nonessential anabolism during times of exertion and the resumption of such functions and the institution of repair during times of relaxation. They contribute in major ways to the regulation of circhoral, diurnal, and seasonal rhythms. Animals deprived of the regulators are incapable of sustained effort, and they readily succumb to conditions easily tolerated by individuals with healthy endocrine systems.

Reproduction and Care of the Young

The crucial roles of hormones in regulating the expression of phenotypic sex are perhaps best demonstrated by observations of the effects of hormone deprivation. Mammals with male-type sex chromosomes develop into sterile individuals with female-

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