COMPARATIVE ENDOCRINOLOGY

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A WILEY-INTERSCIENCE PUBLICATION
JOHN WILEY & SONS
New York · Chichester · Brisbane · Toronto · Singapore

Library of Congress Cataloging in Publication Data:

Main entry under title:
Comparative endocrinology.

"A Wiley-Interscience publication."
Includes bibliographies and index.
1. Endocrinology, Comparative. I. Gorbman, Aubrey, 1914–

QP187.C5966 1982 596'.0142 82-13455
ISBN 0-471-06266-9

Printed in the United States of America

10 9 8 7 6

We dedicate this textbook to those of our teachers, associates, and friends—pioneers in the young science of comparative endocrinology—who have died in the past 20 years. It was they who inspired our interest and fascination with this remarkable field.

A. Elizabeth Adams
Herbert M. Evans
Irving I. Geschwind
Ernest Scharrer
Philip E. Smith
Emil Witschi

Preface

Comparative endocrinology, like all phases of comparative physiology, has experienced profound quantitative as well as qualitative development since *A Textbook of Comparative Endocrinology* was published nearly 20 years ago. In fact, we could not consider this book a revision of the 1963 version but rather a completely new text, retaining only a few of the original illustrations. Our basic orientation to endocrinology remains the same, however. We consider endocrine mechanisms adaptive systems that play a basic role in making each species fit into its environmental niche.

We have compromised this principle only in Chapter 13, which deals with reproduction. Most college courses in endocrinology or reproductive endocrinology focus on mammalian reproduction, for several good reasons. Mammalian and human reproduction are the most thoroughly understood of all. Endocrine mechanisms regulating reproduction in nonmammalian species are among the most specialized, most specific, and most complexly adapted; at the same time they are the least well understood. Thus we have chosen to emphasize the well-known mechanisms for reproductive regulation in mammals and man and to bring in comparative aspects secondarily.

For all other endocrine systems the comparative approach has been primary. The broad context of the basic biological principles of animal endocrine structure, function, and evolution have motivated the writing of this text. We hope that this orientation will be found as attractive in the future as it has been in the past.

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Seattle, Washington
November 1982

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Introduction

MECHANISMS FOR INTEGRATION

The animal body is, after all, a machine, a device that utilizes energy to produce or execute certain functions. It is no accident that physiologists, in speaking of these functions, refer to their "mechanisms." In the literary sense, a machine is "an apparatus for applying mechanical power, consisting of a number of parts, each having a definite function" (*Oxford Universal Dictionary*). The parts of simpler integrated machines generally are connected levers or interlocking geared wheels, or similar contrivances to produce visible motion. In the most complex machines the separate parts are most often integrated by electrical signals that may begin in sensors of various kinds and that are led through a conduction system to appropriate responsive parts of the machine; the signals may be stored in a memory bank, and they may be integrated or modulated in various ways before utilization to provide an element of adaptiveness to the machine.

In animal organisms most of the functions of the living machine are chemical in nature, whether we are dealing with the obvious processing and metabolism of energy-yielding fuels, or the conversion of metabolites into additional organized protoplasmic constituents (growth), or the "mechanism" whereby chemically encoded genetic information is used to regulate cellular processes. This being so, it is not surprising that one of the most effective kinds of agents for integrating the widely distributed chemical functions in the complex organism is itself a chemical rather than an electrical signal. These chemical integrating substances, the focus of this book, are the *hormones*, and typically they are distributed by the blood vascular system. In fact, it is interesting that even when an electric (nervous) signal is used for integrative purposes in the organism, it is transduced into a chemical one when it reaches the target cell (Fig. 1.1).

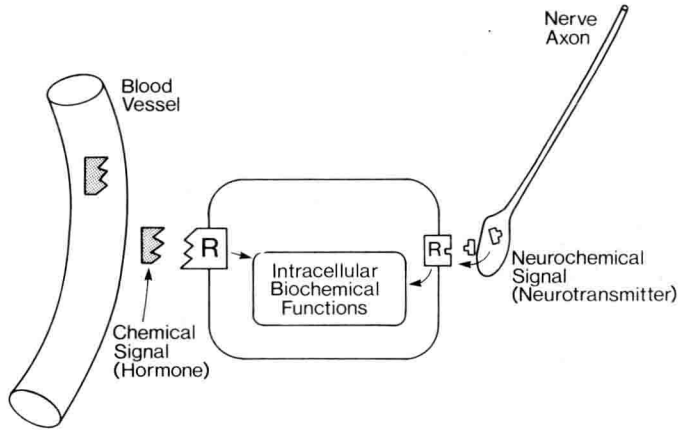

FIGURE 1.1. Comparison of the ways in which hormones and nervous signals interact with target cells to produce their typical actions. Hormones are chemical molecules that are distributed at large through the blood vascular system. When the hormone diffuses out of a blood vessel it may encounter a cell that contains or bears a receptor (R) chemical molecule. The two interact and their interaction sets off a series of intracellular chemical changes that are the "response" to the hormone. Only those cells will respond that have the specific receptor, shown in this diagram by the exact complementary external shapes of the hormonal and receptor molecules. A nervous signal is an electrical one that travels on a prescribed route or "pathway." At its end it causes the release of a chemical "transmitter" which diffuses toward and interacts with the receptor molecule at the target cell surface. The result of this interaction, as with the hormone, is to set off the intracellular chemical processes that comprise the response. The transmitter chemicals may be the same for many different kinds of cells. For nervous responses the specificity of the response depends upon the special route or pathway of the nervous signal.

The mechanism for engaging the chemical integrating signal to the responding intracellular processes involves a *receptor* molecule, whether the signal arrives via the blood or from the end of a nerve. Since hormones are distributed indiscriminately throughout the organism, wherever the blood vascular system extends, the hormone receptor is an important element in the machine because it provides *specificity* to the hormone–target cell relationship. That is, the hormones will be locked into the mechanisms of only those cells that display the receptor which, by virtue of its specific molecular shape, will interact with the hormone molecule. Receptors for neural chemical signals, like hormonal receptors, have the function of coupling the nervous signal to intracellular chemical processes. However, neurochemical receptors are relatively more common (less specific) in their tissue distribution than hormone receptors because their specificity is rendered by the special nervous pathways, as in a complex electrical circuit pattern.

The usefulness of the concept of the organism as a machine, and the hormones as chemical messengers within it, is limited. It is obvious that the organism is different from machines as we know them, being much more complex than any machines so far devised and displaying some properties

that no nonliving machine can duplicate. It is useful at this point to better define the nature of hormonal integration, to give some actual examples of physiological processes in which hormones have their typical integrative actions.

Homeostatic Regulation of the Level of Glucose in the Blood

The level of glucose in the blood is subject to considerable variation due to periodic sudden influxes after feeding, and more gradual effluxes due to tissue metabolism (storage in liver or muscle, or breakdown for energy). Yet, it is important that the concentration of glucose in the blood be kept within narrow limits, because the functions of some organs, as the brain, are quite sensitive to changes in glucose levels in their immediate fluid environment.

Several hormonal mechanisms are used to maintain constant blood plasma glucose levels. The insulin-secreting cells in the pancreas are directly sensitive to the plasma glucose concentration. In humans, when glucose levels rise to some value above 100 mg/100 ml, a release into the blood of the hormone insulin is evoked. Insulin is manufactured and stored in specialized (beta) cells in the pancreas (Fig. 1.2). The insulin interacts with receptors in the plasma membranes of muscle and liver cells. These receptors, when "activated" by combination with the insulin, initiate a chain of intracellular chemical processes whose net effect is the uptake of glucose from the blood

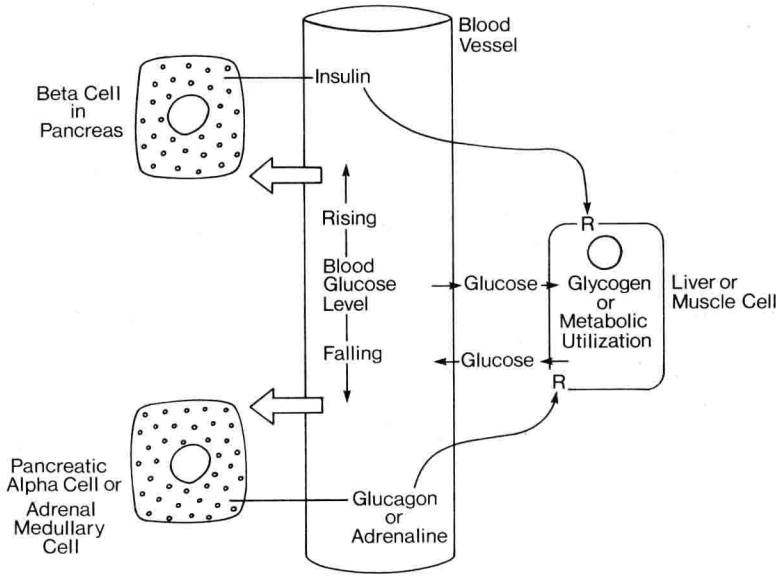

FIGURE 1.2. Diagrammatic representation of the mechanisms for regulating the level of blood glucose. See text for detailed explanation.

by the cells and storage of the glucose as glycogen. The consequent general result is a lowering of plasma glucose to appropriate levels that no longer provoke the beta cell to secrete insulin.

On the other hand, when plasma glucose levels fall significantly *below* the regulated level due to continued glucose utilization between meals (e.g., below 100 mg/100 ml in humans) other glucose-sensitive cells in the pancreas (the alpha cells) release glucagon, and cells in the adrenal gland release adrenaline into the blood. Receptors for these hormones may be found on the same glucose-storing cells that responded to insulin. However, the enzyme-driven chemical system with which glucagon or adrenaline are coupled leads to a release of glucose from glycogen storage. This glucose diffuses back into the blood to raise the plasma glucose level. By interplay of the glucose-lowering (hypoglycemic) and glucose-raising (hyperglycemic) hormones, the plasma glucose level is kept within well-specified limits. This is a simplified description of the blood glucose homeostatic mechanism. This mechanism will be described in greater detail in later parts of this book.

It should be mentioned that similar reciprocal mechanisms exist also for hormonal regulation of blood calcium and phosphate, as well as general ionic or specific ionic (K^+, Na^+) concentrations. In all of these instances the cells that secrete the regulating hormones appear to be directly sensitive to the changing blood plasma levels of the element whose concentration they regulate. The receptors for the hormones, then, are located on cells that, by their action, can appropriately correct the plasma level of the metabolite concerned.

Coordination of Gastric Function During the Digestive Process

When food reaches the stomach after a meal is eaten, the previously quiescent stomach begins to secrete peptic enzyme and hydrochloric acid, and an active phase of muscular activity is triggered. The observable secretory and contractile processes are all responses to a hormone—gastrin—that is secreted by cells in the mucosal layer of the stomach when the meal enters. The gastrin secretion is stimulated by the mechanical presence of the meal in the stomach, as well as by chemical constituents in the food (secretagogues). It is not clear how the mechanical or secretagogue-initiated stimuli are communicated to the gastrin cells. In this instance a hormone messenger is secreted into the blood and is distributed throughout the organism, though its target cells are in the same organ. The target gland and smooth muscle cells of the stomach have been shown to contain gastrin receptors.

It is interesting that the ultimobranchial gland cells also display gastrin receptor activity. This gland is far removed from the stomach and secretes a hormone—calcitonin—whose function, in short, is to reduce blood calcium level. Teleologically, we may suppose that this action of gastrin is in anticipation of the rise in blood calcium that is about to occur as a result of absorption of calcium in the digested meal.

Rapid Maturation of Tissues in Developing Frog Embryos

The metamorphosis of the aquatic tadpole into the terrestrial frog is a remarkable developmental event that appears to be under the control of the thyroid hormone. That is, tadpoles deprived of their thyroid glands fail to metamorphose for prolonged periods. However, if given synthetic thyroid hormone, they quickly resume development and metamorphosis. Although thyroid hormone receptors have been actually identified in relatively few tadpole tissues, it is fairly safe to assume that all of the many thyroid hormone–responsive tissues of the tadpole have such receptors. These tissues include skin, muscle, skeleton, the eye, the brain, the entire digestive tract, mouth parts, etc. In keeping with these facts, it has been found by use of sensitive measuring techniques that the metamorphic climax is preceded by a large surge of thyroid hormone levels in the blood of the tadpole.

How can we account for such a surge in thyroid hormone levels at the precise time when it must be coordinated with a normal developmental event? There is no complete explanation yet available, but we can assume that the hormonal surge is part of the genome-controlled sequence of changes in the developmental program of events. This program would have had to include synthesis of thyroid hormone receptor in time for all of the tadpole's tissues to become responsive to thyroid hormone. The same developmental program should dictate a later disappearance of thyroid hormone receptor in many of the same tissues, since they eventually lose their responsiveness to thyroid hormone.

SURVEY OF THE ENDOCRINE GLANDS

Figure 1.3 represents a summary of most, but not all, vertebrate hormone-secreting tissues. These endocrines are grouped, first of all, with respect to their relationship to the hypothalamus–pituitary–target organ system. Six glandular tissues, which secrete at least ten hormones, can be identified as having no primary or direct relationship to the hypothalamus–pituitary–target organ system. They are the parathyroids, ultimobranchials, gastrointestinal tract, pancreas, liver, and adrenal medulla. It is of interest that secretion of most of the ten hormones in this group is triggered by physical (osmotic pressure or hydrostatic pressure) signals or chemical (glucose or calcium concentrations) signals from the blood itself. The exceptions are the three gastrointestinal hormones whose secretion is triggered by the contents of the gut acting upon the gut wall more or less directly.

The hypothalamus–pituitary–target organ system is large and miscellaneous, but the three anatomical elements in it have a descending hierarchical relationship to each other. That is, the hypothalamus, which is part of the brain, regulates the pituitary by direct nervous connections or by secreting neurohormones whose receptors are located in the pituitary. The pituitary