REPRODUCTIVE ENDOCRINOLOGY

Physiology, Pathophysiology and Clinical Management

SECOND EDITION

Samuel S.C. Yen, M.D., D.Sc. Robert B. Jaffe, M.D.

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PREFACE TO THE SECOND EDITION

At no time has information concerning the basic and clinical aspects of reproductive endocrinology, particularly in the molecular and neuroendocrine spheres, accumulated at a more rapid rate than at the present. The outstanding clinicians and scientists who have contributed to this second edition of *Reproductive Endocrinology* have attempted to incorporate the seminal advances in the field into their respective chapters. We have added additional chapters integrating advances in clinical and basic reproductive endocrinology and neuroendocrine control mechanisms, particularly in the areas of clinical neuroendocrinology, abnormal prolactin secretion, male reproductive disorders, and the endocrinology of pregnancy.

We were very gratified by the reception accorded the first edition of this book. We hope that this second edition continues to fulfill our original aims: "... to assist the clinician, excite and teach the student and investigator, and lend deeper understanding of the control of reproductive processes."

S. S. C. YEN

R. B. JAFFE

PREFACE TO THE FIRST EDITION

Among those biomedical fields in which a virtual explosion of new knowledge and understanding has occurred over the past decade, the physiology and pathophysiology of reproductive processes are prime examples. The neural and endocrine regulation of reproduction has been explored with new and sophisticated methods and with increasing comprehension of the important factors involved in the control of this important function. By extrapolation from animal models, as well as by direct investigation involving humans, new light has been shed on the operation of the human reproductive system in both health and disease.

The planning of a book embodying these advances began in July, 1976, when the author-editors were Visiting Scholars at the Villa Serbelloni, an elegant conference and study center operated under the auspices of the Rockefeller Foundation in the picturesque environment of Lake Como, Italy. An outline of this book was completed there, contributing authors were identified, and the writing of several chapters was begun.

Our overall purpose is to provide contemporary factual information and new understanding of human reproductive processes. We attempted to keep in mind the needs of students and investigators in reproductive endocrinology and biology, as well as the needs of clinicians who face the problem of diagnosing and treating reproductive dysfunction. To accomplish these purposes, our authors' expert knowledge ranges from the clinical and systemic to the cellular and molecular. Thus, whenever possible, cellular or molecular mechanisms for normal or disturbed function are presented.

The elements of the reproductive system with which we deal most extensively are various parts of the brain, the pituitary gland, and the gonads. Each of these obviously is a separate and distinguishable component of the system. However, not only are they intimately associated to form an integrated system for periodically releasing germ cells and hormones but, in addition, they have a number of common mechanistic features. We hope that these similarities and integrated modes of action will impress the reader as they have impressed us, and that some readers will be provoked into continued, deeper study of this intriguing field.

The contributing authors were chosen for recognized authority in their respective areas and for their ability to transmit information in a manner we think is lucid and interesting. The lists of references are not intended to be exhaustive but do include key articles and reviews.

Our task as editors was greatly facilitated by the help and cooperation of the contributing authors. We also wish to express our appreciation to Marcia

Finkle, Leslie Muga, Alana Schilling, and Rae Feinstein, our secretaries, whose capable assistance helped overcome the few trying problems we met. My (S.Y.) special thanks to Dr. Allen Lein for his critical review of and suggestions for several of my chapters. The editors are grateful to the staff of the W. B. Saunders Company, particularly John Hanley for his confidence, encouragement, and courtesies, which made the preparation of this book a satisfying experience.

The information in this book is at the cutting edge of contemporary reproductive endocrinology. If the book assists the clinician, excites and teaches the student and investigator, and lends deeper understanding of the control of reproductive processes, it will have served its purpose.

S. S. C. YEN

R. B. JAFFE

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PART I

ENDOCRINE REGULATION OF THE REPRODUCTIVE SYSTEM

1

NEUROENDOCRINE MECHANISMS: CELLS and SYSTEMS

ROBERT Y. MOORE

STRUCTURE OF THE NEURON

FUNCTION OF THE NEURON

THE HYPOTHALAMUS AND NEUROENDOCRINE REGULATION
Organization of Hypothalamic Nuclei
Neural Connections of Hypothalamic Nuclei
Magnocellular Neurosecretory System
Parvicellular Neurosecretory System
GnRH Neuron System
Tuberohypophyseal Dopamine System

VENTRICULAR SYSTEM AND CIRCUMVENTRICULAR ORGANS
Anatomy
Circumventricular Organs

HYPOTHALAMIC NEUROVASCULAR SYSTEM (THE PORTAL CIRCULATION)

CEREBROSPINAL FLUID AND BLOOD-BRAIN BARRIER

LOCALIZATION OF STEROID HORMONE RECEPTORS IN THE BRAIN
Estrogens
Androgens
Progesterone
Adrenal Glucocorticoids

ONTOGENY AND THE ORGANIZATION OF SEXUAL BEHAVIOR

REPRODUCTIVE CYCLES

CIRCADIAN RHYTHMS

CONCLUSION

During the early part of this century, the sciences of endocrinology and neurobiology developed rapidly but largely independently. In endocrinology, the unifying concept is that of the hormone: a substance secreted by an endocrine organ into the blood to have effects upon a distant tissue or tissues. The major unifying concept in neurobiology is the neuron doctrine: the view that the nervous system is composed of individual functional units—nerve cells—that are distinct and separate cellular entities. Early functional research on the neuron emphasized the unique capacity of these cells to transmit information rapidly and reliably over long distances by the mechanism termed the action potential, or nerve impulse.

Since neurons are morphologically separate entities, it was evident that some further mechanism must exist to accomplish the necessary transfer of information from one neuron to another or from a neuron to an effector cell. For some time it was assumed that this process, like the nerve im-

pulse, is essentially a bioelectric phenomenon. Over a number of years, however, it was established that the transmission of information from nerve cell to nerve cell or from nerve cell to effector cell requires release of a chemical at the point of functional contact, termed the synapse. The process is known as chemical transmission at the synapse.

It is now evident that nearly all synapses in the mammalian peripheral and central nervous systems use chemical transmission. Thus, one of the major advances in neurobiology has been the demonstration that nerve cells have two basic functions: one to transfer information rapidly along cell processes using a bioelectric phenomenon, and the second to transmit information to other nerve cells and effector cells by the secretion of a specific chemical.

During the period in which the concept of chemical transmission was developed and established, another neuronal function was discovered that brought neurobiology and endocrinology inextricably together and led to the development of the burgeoning field now called neuroendocrinology. This function is the process of neurosecretion, in which the neuron secretes a substance into the blood stream rather than at a synaptic junction. Neurosecretion was first demonstrated in fish by E. Scharrer (see Scharrer and Scharrer[1] for a review) but was not shown clearly in mammals until the late 1940s. Then the work of Bargmann and Scharrer provided the essential evidence that the posterior, or neural, lobe of the pituitary did not function as a self-contained, hormone-producing gland but instead stored and released neurohypophyseal hormones produced by the neurons of the supraoptic and paraventricular hypothalamic nuclei of the hypothalamus and transported along their axons in the supraopticohypophyseal tract to the neural lobe.[2]

These discoveries occurred during a period in which it was becoming increasingly apparent that the regulation of pituitary function, and, therefore, the function of target endocrine hormones involved both in feedback influences on the pituitary and in a variety of environmental and hormonal influences, is mediated by the central nervous system (CNS). Thus, the concept of feedback regulation of pituitary function became much more complex because of the introduction of the CNS into the regulatory mechanisms (Fig. 1–1). The importance of recognizing the contribution of the CNS to pituitary regulation was definitively established by Harris and his colleagues.[3] These studies demonstrated the necessity of portal

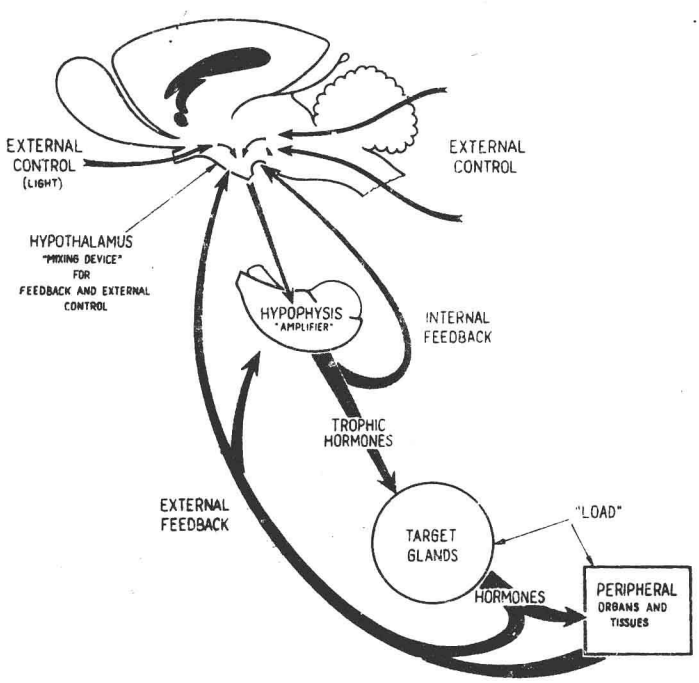

Figure 1–1. General principles of feedback control in the endocrine system. (Reproduced from Szentagothai, J., B. Flerko, B. Mess; and B. Halasz, Hypothalamic Control of the Anterior Pituitary, 3rd ed. Akademiai Kiado, Budapest, 1968. Used by permission.)

blood flow for pituitary function, and this concept has been further elucidated in great detail over the last 20 years. The medial hypothalamus has been identified as an area that is critical to the regulation of pituitary function,[4, 5] and in recent years neuroendocrinology has grown immensely with identification and characterization of releasing hormones, identification and localization of neurons producing releasing hormones, and elucidation of neural regulatory mechanisms participating in control of pituitary function. The remainder of this chapter will review current knowledge of the neural mechanisms that regulate hypothalamic-pituitary function, particularly in the control of reproduction.

STRUCTURE OF THE NEURON

The neuron, or nerve cell, represents a highly differentiated cell with distinctive cytologic features. Virtually all neurons in the CNS have a cell body, often with a centrally placed nucelus, cytoplasm surrounding the nucleus, and a number of cytoplasmic extensions called processes. Because of the multiple processes, the neurons are termed multipolar. A typical multipolar neuron is diagrammed in Figure 1–2. There are two types of neuronal processes. The first, termed the dendrite, comprises two or more processes extending from the cell body. These processes contain the same organelles found in the cell body cytoplasm.

The second neuronal process, called the axon, is always a single process. It may be short, terminating in the vicinity of the cell body, or it may be extremely long. An example of a long axon in the human is one arising from a neuron in the motor cortex and terminating in the gray matter of the spinal cord, a distance that may be as long as a meter. In such instances, the proportion of cellular cytoplasm is much greater in the process than in the cell body. A similar situation occurs if the axon has a very extensive terminal arborization. The axon differs from dendrites in not containing rough endoplasmic reticulum and in producing axon terminals. Examples of axon terminals and their types of contact with other neuronal elements are shown in Figure 1–3. This drawing illustrates the variety of potential synaptic and other cellular contacts that occur in the CNS and emphasizes the potential complexity of the cellular organization of the brain at the synaptic level.

FUNCTION OF THE NEURON

Although neuronal function includes events such as conduction of the action potential, its expression nearly always requires release of a chemical that affects other nerve cells or effector cells. This process is termed chemical transmission at the synapse. The conventional view of chemical synaptic transmission is that the neurotransmitter, stored in vesicles in the presynaptic axon (see Fig. 1–3), is released by exocytosis, traverses the synaptic cleft, and interacts with a postsynaptic receptor. This process has been studied most extensively in neurons that produce small-molecule neurotransmitters, such as acetylcholine, the catecholamines, serotonin, and GABA (Table 1–1). In most nerve cells, the transmitter is produced in the nerve terminal, with very little synthesized in the cell body, and transported along the axon to its terminals. Axoplasmic transport is an extremely active and important phenomenon, however, and is now recognized as one of the major cellular events in neuronal function. Axoplasmic transport from the cell body occurs

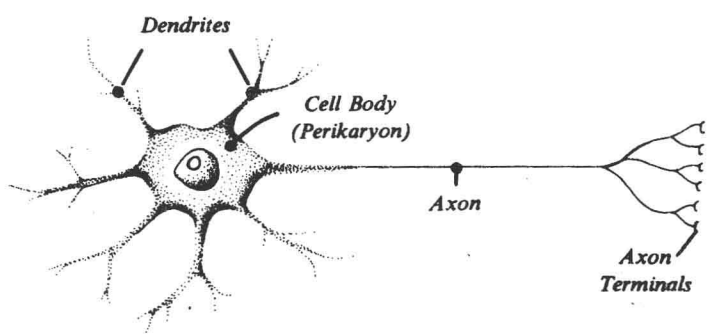

Figure 1–2. A nerve cell, or neuron. Multiple branching processes extending from the cytoplasm of the neuron cell body are termed *dendrites*. A single axon also extends from the cell body, and this may terminate at a distance from the cell body in numerous axon terminals.