Comprehensive Endocrinology

The Pituitary Gland

Editor

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Raven Press ■ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

Library of Congress Cataloging in Publication Data
Main entry under title:

The Pituitary gland.

(Comprehensive endocrinology)
Includes bibliographies and index.
1. Pituitary body—Diseases. 2. Pituitary body.
I. Imura, Hiroo. II. Series. [DNLM: 1. Hypothalamo-Hypophyseal System—anatomy & histology. 2. Pituitary Diseases—diagnosis. 3. Pituitary Diseases—therapy. 4. Pituitary Hormones—physiology. WK 500 P9618]
RC658.P58 1985 616.4'7 84-24975
ISBN 0-88167-058-8

The material contained in this volume was submitted as previously unpublished material, except in the instances in which credit has been given to the source from which some of the illustrative material was derived.

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Preface

Since it plays an important role not only as the "master gland" in the endocrine system but also as a center for regulating homeostasis, the hypothalamo–pituitary system has attracted the interest of endocrinologists for many years.

In the past decade, much progress has been made in this field. The discovery of hypothalamic hypophysiotropic hormones such as TRH, LHRH, somatostatin, CRF, and GRF, has opened doors in the research of the hypothalamo–hypophyseal system. Contributions have been made to the understanding of the physiology of this system, as well as to the diagnosis of various hypothalamo–pituitary diseases.

A variety of bioactive peptides, including hypothalamic hormones, have been isolated and identified. Most of these peptides, now called neuropeptides, exist in high concentrations in the hypothalamo–pituitary system, and play a role in regulating function of this system possibly as neurotransmitters or hormones. Among these, the opioid peptides and vasoactive intestinal polypeptide already are known to be of physiological significance. Nonpeptide transmitters, such as dopamine, norepinephrine, and serotonin, also play an important role in regulating the hypothalamo–pituitary system. Another important contribution has been made by the recombinant DNA technique, which has permitted the elucidation of not only the structure of precursors of pituitary or hypothalamic hormones but also of the organization of their genes. Studies on the regulation of expression of these genes are now in progress.

Clinical endocrinology as related to the hypothalamo–pituitary system has also seen major advances in the past decade due to the impact of hormone assays, computed tomography, surgical procedures, and medical treatment. The diagnosis and management of hypothalamo–pituitary diseases have become much simpler and more accurate.

This volume delineates our present knowledge of the hypothalamo–pituitary system as a basis of future development, at this time when information is explosively increasing. This book begins with a review of the morphology of the normal hypothalamo–pituitary system and human pituitary tumors. Subsequent chapters discuss the molecular endocrinology of pituitary hormones: organization and expression of genes, structure of hormone precursors, and posttranslational processings; regulation of secretion of pituitary hormones with special reference to the role of newly discovered hypothalamic hormones also are reviewed. The last section of this volume deals with hypothalamo–pituitary diseases. Advances in pathophysiology, diagnosis, and treatment are discussed in a light of recent progress in physiology of the hypothalamo–pituitary system.

The contributors are internationally recognized authorities in the field of en-

docrinology, and have been carefully chosen and freely express their personal prospects in their respective fields. Although research in the hypothalamo–pituitary system is continually progressing, this volume presents the most updated knowledge and promotes the understanding of modern endocrinology of the pituitary gland. This book is intended to meet the needs of a variety of readers, both basic and clinical investigators, and advanced medical and graduate students.

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The Pituitary Gland, edited by H. Imura.
Raven Press, New York © 1985.

Hypothalamo-Anterior Pituitary System and Pituitary Portal Vessels

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The fundamental idea of Harris (54) and Green and Harris (46) formulated nearly four decades ago—i.e., that the mechanism by which the central nervous system controls the anterior pituitary is neurohumoral—has been proved; the existence of neurons producing hypophysiotrophic neurohormones and the presence of these neurohormones in the pituitary portal vessels has been established.

This chapter summarizes the available information on the site of production of the chemically identified substances, i.e., thyrotrophin-releasing hormone (TRH) (19,26,87,108); luteinizing hormone-releasing hormone (LHRH) (6,9, 107); corticotropin-releasing factor (CRF) (119); growth hormone release-inhibiting hormone (GIH) or somatostatin (20,27,105); prolactin release-inhibiting factor, at least one of which is dopamine (DA) (see ref. 120); and the most recently isolated, human pancreatic growth hormone-releasing factor (hpGRF) (49). It discusses distribution of nerve cell bodies containing these neurohormones, the course of the fibers, and their terminations in the median eminence and pituitary stalk (for details there are excellent reviews in refs. 92, 110). Further, it describes briefly the portal vascular system.

LOCATION OF NEURONS SYNTHESIZING THE HYPOPHYSIOTROPHIC NEUROHORMONES AND PROJECTING TO THE EXTERNAL ZONE OF THE MEDIAN EMINENCE AND PITUITARY STALK

Since the first experimental observations on the existence of hypothalamic substances acting on pituitary trophic hormone secretion were published, several attempts have been made to localize the structures producing these substances. Various approaches were used, such as lesioning various hypothalamic regions and determining the troph hormone-releasing or hormone-release-inhibiting activity of the median eminence–pituitary stalk region (77,82), cutting the hypothalamus into small pieces and measuring troph hormone-releas-

ing activity of the pieces (71), implanting anterior pituitary tissue into the hypothalamus and investigating its structure and hormone secretion (52,53), completely or partially cutting around certain hypothalamic regions and testing pituitary trophic function in various ways (e.g., refs. 50,51,76), or trying to find the smallest hypothalamic region that can be cut around without the occurrence of degeneration of nerve fibers and terminals in the surface zone of the median eminence and pituitary stalk (103).

All of these investigations provided some information about the site of production of the hypophysiotrophic substances but did not clarify this question. In recent years, immunohistochemistry primarily, together with some other techniques, has furnished more direct evidence about the location of neurons synthesizing these neurohormones. Before summarizing the data it has to be pointed out that there are two factors that in most cases make the interpretation of the immunohistochemical picture difficult from our point of view.

1. Neurons containing the troph hormone-releasing and release-inhibiting neurohormones are widely distributed in the central nervous system, some of them are even present in other tissues (as will be evident in the following pages). Not all of these neurons terminate in the hypothalamic median eminence and in the pituitary stalk.

2. In many cases it is almost impossible to trace the axon from its origin to its terminal arborization. Therefore, immunohistochemistry has been combined by some authors (75,79) with hypothalamic deafferentations. If neurons projecting to the median eminence are outside the deafferented area, there is an accumulation of the immunoreactive material close to the cut line; and if a considerable number of fibers are cut, it results in a decrease of the immunoreactive material in the median eminence. But it has to be pointed out that a significant amount of material has to disappear in order to detect the decrease by immunohistochemistry. Radioimmunoassay is more sensitive, and therefore investigators (21,22,34) have used this technique instead of immunohistochemistry to measure the neurohormone content of the median eminence after various knife cuts.

Although fundamental information was obtained by immunohistochemistry, location of all the neurons producing the chemically identified and synthesized releasing hormones is still not known, mainly because of the two factors mentioned above.

TRH

So far only a few weakly fluorescent TRH cell bodies have been detected in the dorsomedial nucleus of the rat hypothalamus (56). Regarding TRH-positive fibers, the highest concentrations of such fibers can be seen in the medial part of the median eminence, with a decreasing density toward the lateral parts (Fig. 1c). There are rather few fibers in the most frontal part of the me-

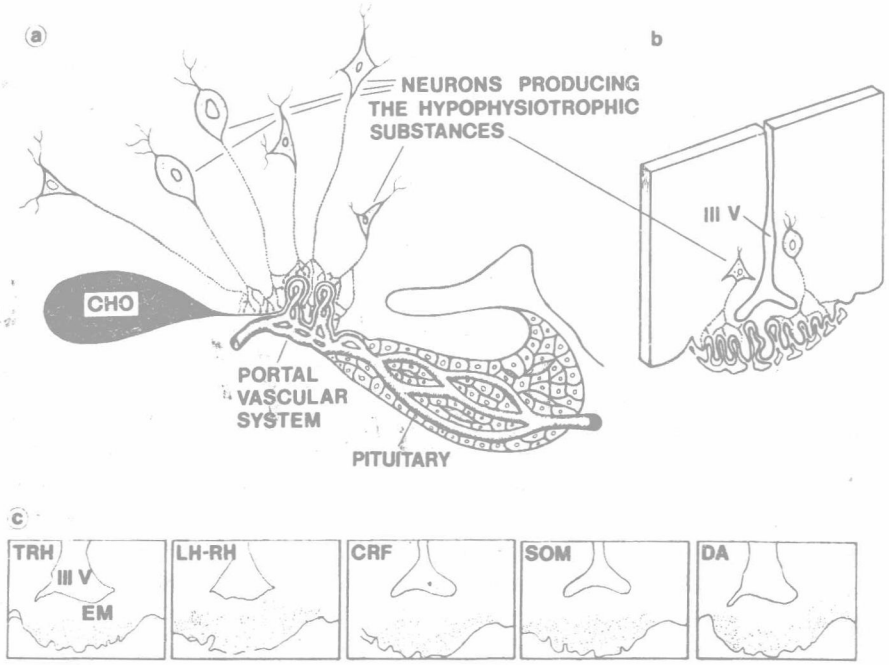

FIG. 1. Neurohumoral mechanism controlling the anterior pituitary as seen in mid-sagittal section of the hypothalamo-hypophyseal system (**a**) or in coronal section of the hypothalamus (**b**). (**c**): Distribution of TRH, LHRH, CRF, somatostatin (SOM), and dopamine (DA) fibers and terminals in the surface zone of the median eminence (EM). Coronal section of the median eminence region. CHO, optic chiasm; III V, third ventricle.

dian eminence, whereas a dense plexus exists in the external layer of the entire stalk (56). TRH-like immunoreactivity was observed in dense granular vesicles (90 to 140 nm in diameter) in TRH-like immunoreactive nerve fibers and terminals. The terminals are in direct contact with the perivascular basal lamina of the portal vessels (59,114). Besides the median eminence, TRH-containing nerve terminals were found in the dorsomedial nucleus, in the perifornical area, and in several extrahypothalamic nuclei, such as the nucleus accumbens, the lateral septal nucleus, and several motor nuclei of the brainstem and spinal cord of the rat (56). Radioimmunological determinations of TRH also indicate a wide distribution of this neurohormone in the central nervous system of both rat and monkey (23,58,64,65,70,86,88,121). It is unlikely that all TRH present in various regions of the central nervous system is synthesized by the few weakly fluorescent TRH cell bodies observed so far in the hypothalamic dorsomedial nucleus by Hökfelt et al. (56). That this is probably not the case is indicated by the recent findings of Palkovits et al. (93), who investigated by radioimmunoassay the topographical distribution of TRH fibers that run to the median eminence. They found that anterolateral or lateral cuts bilaterally transsecting fibers at the caudal edge of the optic chiasm diminish TRH levels

in the median eminence by 95 and 73%, respectively. Paramedian cuts were ineffective. These data suggest that TRH fibers reach the median eminence from the anterolateral direction. The origin of these fibers is at present unknown.

LHRH OR GONADOLIBERIN

In general, there are two areas that contain a significant amount of immunoreactive LHRH nerve cell bodies: (a) the septal-preoptic-suprachiasmatic region and (b) the mediobasal area of the tuber cinereum, especially the infundibular and premamillary nuclei. But there are great variations in the number of such cells in these two regions of various species. In humans they are mainly concentrated in the second region and in the medial preoptic area. Some neurons are also present in the septal region (11). In primates most LHRH perikarya are found in the mediobasal area of the tuber cinereum, and about 25% of the cells are located in the septal-preoptic region (12). In the cat most cells are located in the rostral area; in the dog about 40% of the cells are situated in the posterior region (13). In the rabbit the majority of the cells were found in the preoptic-suprachiasmatic areas (109). In the guinea pig most of the LHRH perikarya are located in the preoptic and septal areas, but such cells are present

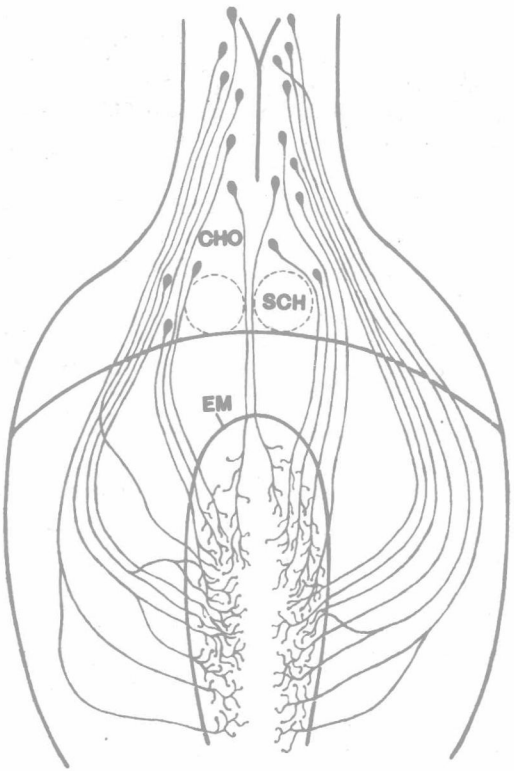

FIG. 2. Rat LHRH pathway terminating in the median eminence (EM) and pituitary stalk as seen from the base of the diencephalon. CHO, optic chiasm; SCH, suprachiasmatic nucleus. Drawing is based on the findings of Merchenthaler et al. (79) and Réthelyi et al. (104).

also in the tuberal region. In the rat many LHRH cells were observed in the periventricular medial preoptic area, the diagonal band of Broca, and the septal nuclei, and some cells in the anterior hypothalamic area (57,61,67,69,113,-125). Some special treatment (colchicine treatment, cutting the axons) is required in order to detect LHRH perikarya in the rat brain. Therefore, several investigators were unable to stain LHRH cells in the rat (e.g., refs. 10,72).

The septal-preoptic-suprachiasmatic and the tuberal region are not the only areas containing LHRH perikarya. Such elements were observed in several other structures of the brain, such as the olfactory bulb, the indusium griseum, the hippocampus, and others. (69,78,125).

The following LHRH fiber tracts projecting to the median eminence have been distinguished (Fig. 2) in the rat hypothalamus (104): close to the midline a small median, a medial, and a lateral bundle. One portion of these pathways arises from LHRH neurons in the preoptic-suprachiasmatic region. This has been named the preopticoinfundibular LHRH pathway (79). Our radioimmunoassay data (85) indicate that presumably less than 50% of the LHRH in the median eminence region is produced by neurons in the preoptic-suprachiasmatic region. The other 50% is probably synthesized by neurons sit-

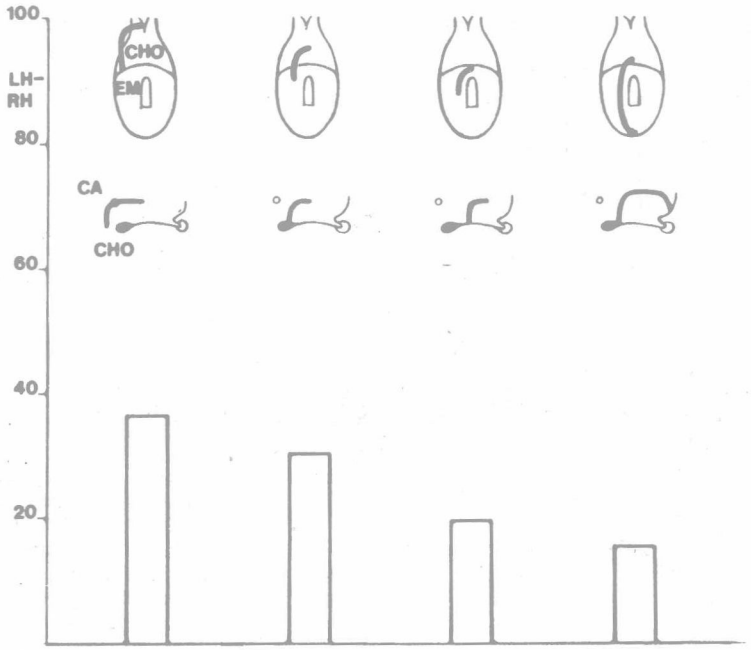

FIG. 3. Effect of different knife cuts on LHRH content (expressed as percentage of the control value) of the median eminence half on the side of the brain intervention. **Top:** knife cut (*thick line*) as seen from the base of the diencephalon. **Bottom:** knife cut as seen in midsagittal section of the hypothalamus. CA, anterior commissure; CHO, optic chiasm; EM, median eminence. (Data from Molnár et al., ref. 85; for details see their publication.)

uated rostral to and above the preoptic area, most probably mainly in the septum. We have made unilateral knife cuts in the preoptic area and in front of it and measured the LHRH content of the two halves of the median eminence region. A knife cut rostral and lateral to and above the preoptic area on one side resulted in a more than 50% reduction in the LHRH content of that half of the median eminence that was on the side of the brain intervention (Fig. 3). If one takes into account the above-mentioned LHRH pathways and makes various knife cuts in the supra- and retrochiasmatic region to study ovulation, as has been done by K. Köves of our department (*unpublished observations*), it appears (Fig. 4) that the majority of the known fiber tracts have to be interrupted in order to block ovulation. Constant estrus syndrome developed in those animals that did not ovulate after the knife cut. But it should be mentioned that there was a blockade of ovulation also in one group of animals (in at least half of them) in which the cut (labeled *1* on Fig. 4) did not transsect known LHRH pathways. We assume that in this latter case the knife cut interfered with the mechanism controlling the release of LHRH.

Regarding the distribution of LHRH fibers, in the most rostral part of the median eminence they accumulate in a flat superficial layer receiving numerous fibers from the anterior direction. More caudally, the fibers gather into two major bundles on both sides of the median eminence and pituitary stalk just

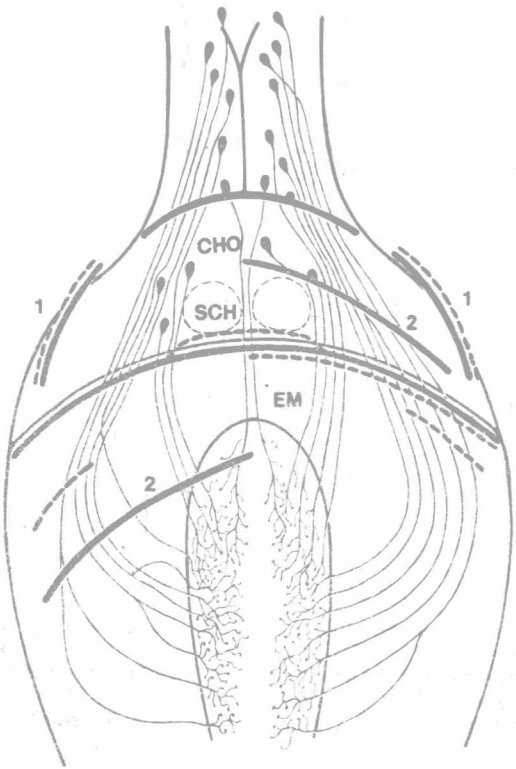

FIG. 4. Effect of various supra- and retrochiasmatic deafferentations on ovulation several weeks after the brain interventions. *Thick continuous line* indicates knife cuts, which blocked ovulation and induced constant estrus with polyfollicular ovaries; *broken line* indicates those cuts that did not interfere with ovulation. Half of the rats bearing cut labeled 1 ovulated and half of them did not. The two cuts labeled 2 were made in the same animals. Knife cuts are superimposed on the LHRH pathway shown in Fig. 2. CHO, optic chiasm; EM, median eminence; SCH, suprachiasmatic nucleus. (Data obtained by K. Köves of our department.)

above the hypothalamoinfundibular sulci (Fig. 1C). The axons form grape-like end arborizations with terminal boutons in the vicinity of the capillary loops of the portal vessels and in the surface zone of the median eminence and pituitary stalk (10,72,112). About 10 to 20% of the nerve terminals in the superficial layer of the median eminence is LHRH immunoreactive. In these endings the reaction product was observed over secretory granules that were 75 to 95 nm in diameter (45,97). But others' results indicate that probably more than one population of LHRH secretory granules exists (for details see ref. 110).

CRF OR CORTICOLIBERIN

The most prominent CRF-containing cell group of the hypothalamus is the paraventricular nucleus, mainly its parvicellular part (18,24,80,94), as postulated earlier by Makara et al. (74). The elegant immunohistochemical studies of Merchenthaler et al. (81) indicate that CRF-positive fibers from the paraventricular nucleus project to the median eminence, forming a medial, an intermediate, and a lateral fiber pathway (Fig. 5). The lateral and intermediate CRF tracts leave the dorsolateral part of the paraventricular nucleus and course laterally and medially of the fornix, respectively, then ventrally toward the optic tract. Just dorsal to the optic tract they turn in a caudal direction

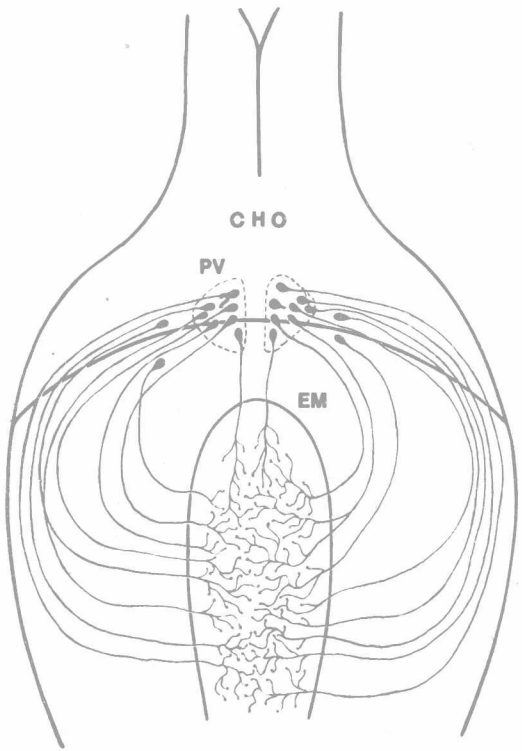

FIG. 5. Paraventricular-infundibular CRF pathway as seen from the base of the hypothalamus. CHO, optic chiasm; EM, median eminence; PV, paraventricular nucleus. (Based on the findings of Merchenthaler et al., ref. 81.)