DUNCAN'S

Diseases of Metaboli

Endocrinology

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Endocrinology

Seventh Edition

Edited by

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Preface

The decision to bring out a new edition of *Diseases of Metabolism* after an interval of only four years may seem to require some justification. Readers familiar with the rate of progress in the field will not, however, be surprised to learn that most of the authors were satisfied that their contributions required quite extensive revision. In addition, experience with the previous edition of this work had shown ways in which the organization of the material could be improved. As a result, we feel that we can provide a better organized and more useful book than before. The degree to which we have been successful will be determined by the reader.

The largest burden of this revision has fallen on our authors, to whom we are most grateful. Science moves so rapidly that even a thoroughly up-to-date presentation may be somewhat outmoded by the time it has passed through the processes of publication. To minimize the importance of the necessary delay following submission of the chapters, each author has been offered an opportunity to write an addendum to his chapter, to make it as current as possible. These addenda appear at the ends of the chapters for which they were written.

We have been greatly helped in this work by the advice and support of Mr. John L. Dusseau of the W. B. Saunders Company, whose experience and knowledge were essential to the completion of this task. Sally E. Bondy and Marilyn E. Feldman provided invaluable secretarial and editorial assistance, and Mrs. Virginia Simon was of great help in preparing much of the art work.

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LEON E. ROSENBERG

Contents

III
Endocrinology

III

Endocrinology

15 Neuroendocrine Interrelations

ROGER GUILLEMIN

A generation ago we were taught that the anterior pituitary gland commands all other peripheral endocrine glands (with the unhappy exception of the parathyroids and perhaps the pancreas) and that a subtle reciprocal equilibrium between concentrations of circulating "peripheral" hormones and quantities of the corresponding pituitary hormones maintained endocrine homeostasis (feedback or push-pull theory). Thus were explained the experimental compensatory hypertrophy of peripheral endocrines following unilateral ablation, the development of goiter, the atrophy of the contralateral adrenal in the presence of a unilateral adrenal tumor, and so forth. Then followed a twilight period in which more and more aspects of this elegant construction lost their appealing clarity and heuristic value as it was realized that there were circumstances in which the simple pituitary-target organ relationship was not exclusively operative. For instance, an explanation was needed for the excretion in the urine of large quantities of corticoids during prolonged stress or exercise, an observation which was incompatible with the eucorticoidism theory postulated by the feedback system between pituitary and adrenal cortex secretion. Similarly, the extreme rapidity of the changes in pituitary ACTH secretion was realized, with increases in plasma concentration of pituitary hormones taking place in a few minutes with no evidence of preceding fall in plasma concentration of the peripheral hormones, which could have triggered the feedback system. Then clinicians and experimentators reported more and more evidence that lesions in certain areas of the base of the brain (in the hypothalamus) would produce various syndromes of pituitary dysfunctions such as inhibition of stress-induced release of ACTH, permanent diestrus, permanent estrus with an ovarian picture reminiscent of the Stein-Leventhal syndrome and testicular atrophy.

Today we teach our students that, for the most part, the center of control of the adenohypophysial functions is to be found in the hypothalamus, that the feedback relationships between peripheral hormone levels and adenohypophysial secretions are for the most part transhypothalamic, and that the hypothalamic control over the pituitary functions is exerted through the secretion of hypothalamic hormones or releasing factors, which may be called hypophysiotropic substances or hormones.

The purpose of this short review will be to describe briefly the principal tenets of the current concepts in neuroendocrinology without going into any of the techniques that were involved in acquiring the pertinent knowledge. Key references to several reviews or specific articles will be given for the reader who might want to go into the mechanisms of how these were obtained.

This review will discuss first the relationships between the hypothalamus and the adenohypophysis; we will then outline a more generalized concept of neuroendocrine relationships involving other parts of the central nervous system and describe some of the neurohormonal reverberating circuits which are one of the fundamental aspects of neuroendocrinology.*

*There will be no discussion here of control of the secretion of antidiuretic hormone, oxytocin and aldosterone since this will be covered in Chapters 21 and 22.

HYPOTHALAMUS AND ADENOHYPOPHYSIS

Methods of Study

Our current information about the endocrinology of the hypothalamus was acquired through the simple intellectual and experimental processes which have led to all basic knowledge in endocrinology: The deficiency syndrome produced by the classic surgical removal of the suspected endocrine tissue was achieved here by localized destruction of various parts of the hypothalamus through stereotaxically placed electrical coagulations, removing the hypothalamic influence from the pituitary connections by isolating the pituitary gland in peripheral grafts or by in vitro explantation or incubation. Replacement therapy was achieved by injecting hypothalamic extracts into the animals with hypothalamic destruction and studying the functions of the anterior pituitary or simply by adding these extracts to the isolated pituitary and studying its release of hormones. Recently it has become possible to measure with some degree of reliability variations in the concentration of the hypothalamic hormones in hypothalamic portal blood sampled under various experimental conditions. A unique feature of neuroendocrinology has been the study of the electrical activity of hypothalamic nuclei as modified by the levels of circulating hormones and also the induction of the release of a specific pituitary hormone by the electrical stimulation of the pertinent hypothalamic areas.

Hypothalamic-Hypophysial Portal System

There is general agreement[10,11] that connections between the hypothalamus and the anterior pituitary are not provided through tracts of nerve fibers (as in the case of hypothalamus to posterior pituitary), but rather through a vascular link in the form of a system of portal vessels. The primary plexus of this system of vessels is to be found in a contact area between ventral hypothalamus and pituitary stalk called the median eminence. Axon terminals from the cells of hypothalamic nuclei come into close contact with the capillaries of this primary plexus, and presumably there is passage of the hypothalamic releasing factors into the blood stream of these capillaries. The substances are distributed through collecting veins in the pituitary stalk into the adenohypophysial parenchyma by the secondary plexus of capillaries of this hypothalamo-hypophysial portal system (Fig. 15–1). Precise localization of the origin of a given releasing factor cannot be given in terms of specific hypothalamic nuclei as they have been described by the neuroanatomists. Rather, the neuroendocrine areas in the hypothalamus appear to be somewhat diffuse if we consider the considerable overlapping of hypophysiotropic activities related to one area or another (Fig. 15–2). This point of the exact hypothalamic origin of specific releasing factors requires further investigation; in its present and perhaps final state of affairs, the question is reminiscent of the conclusions reached by the neurophysiologists not many years ago regarding the absence of specific localizations in the hypothalamus, for instance, for sympathetic and parasympathetic integration. The nature of the cells in the hypothalamus that manufacture and secrete the hypophysiotropic hormones is not known.

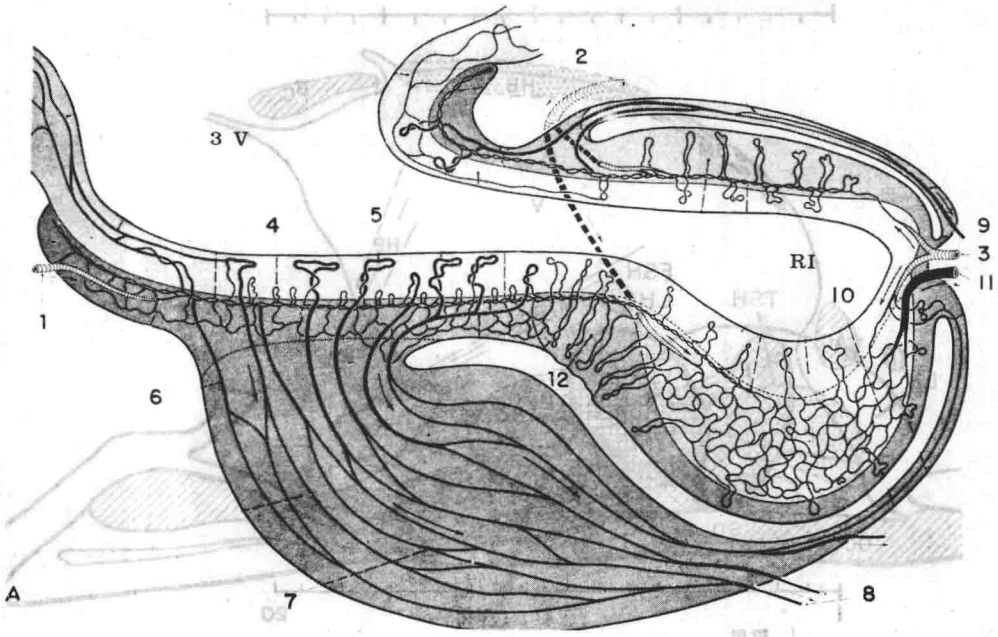
Localization of Hypophysial Control Centers

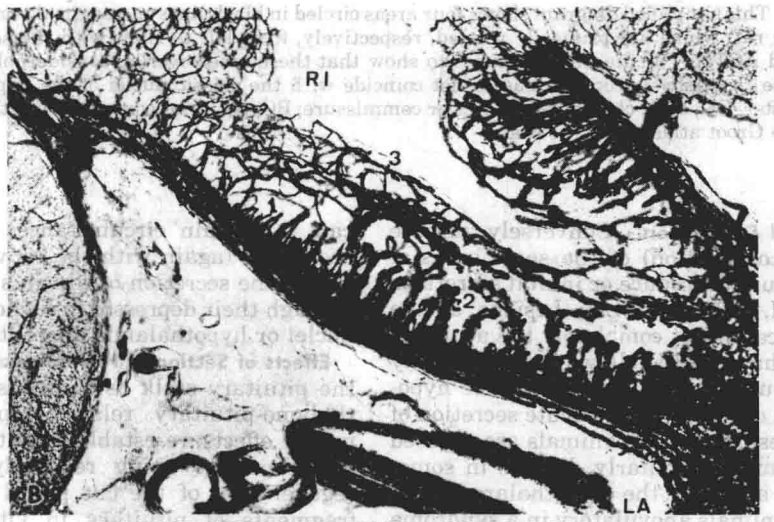
Effects of Stimulation. Electrical stimulation of various regions of the hypothalamus by implanted electrodes produces secretion of various pituitary hormones. Stimulation of the posterior hypothalamus is followed by secretion of ACTH, whereas stimulation of more anterior areas will trigger secretion of TSH. Somewhere in between is an area which upon stimulation will produce ovulation in suitably prepared animals, hence is related to secretion of gonadotropins (LH and FSH). Possibly this midhypothalamus area is under the command of a somewhat more anterior area, the interplay between the two areas regulating basal secretion of gonadotropins as opposed to "spurt" secretion as in the triggering of ovulation.[3,11,14]

FIGURE 15–1 *A*, Diagrammatic representation of the pituitary vascularization on a sagittal section (anatomy of the cat). Principal landmarks of the diagram relating to the portal circulation: 1, 2, 3 – hypophysial arteries resolving into (4) short loops, and (5) long loops of the primary plexus of the portal system. The primary plexus is in intimate contact with nerve fibers and terminals (not shown on diagram) of hypothalamic origin. The primary plexus collects in veins (6), spreading into capillaries (7) throughout the parenchyma of the adenohypophysis, constituting the secondary plexus of the portal system. This is eventually drained into veins (8, 9) leaving the pituitary. 10, Capillary net of posterior pituitary draining into posterior hypophysial vein (11); 12, intermediate lobe; RI, infundibular recess of the third ventricle. Arrows indicate direction of blood flow.

B, Sagittal section of median eminence (pituitary of the pig) after intracarotid injection of India ink. Three types of capillary loops of the primary plexus may be seen: 1, short loop; 2, medium size loops; 3, long loops. The latter extend in a rich network immediately below the ependyma. RI, Infundibular recess, LA, anterior lobe. (× 50.)

C, Sagittal section of median eminence (pituitary of the dog) after intracarotid injection of India ink. AC, long loops of the primary plexus with (a) ascending part, (b) subependymal part, and (c) descending part. (× 150.) (All figures courtesy of Professor H. Duvernoy, Department of Anatomy, School of Medicine of Besançon, France.)





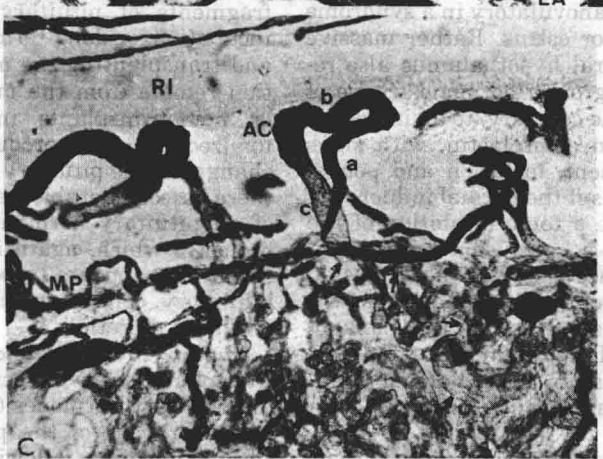


FIGURE 15–1 See opposite page for legend.