PROGRESS IN BRAIN RESEARCH

Volume 32

PITUITARY, ADRENAL AND THE BRAIN

PROGRESS IN BRAIN RESEARCH
VOLUME 32

PITUITARY, ADRENAL AND THE BRAIN

EDITED BY

D. DE WIED

AND

J. A. W. M. WEIJNEN

Rudolf Magnus Institute for Pharmacology,
University of Utrecht, Medical Faculty
Vondellaan 6, Utrecht, The Netherlands

ELSEVIER PUBLISHING COMPANY
AMSTERDAM / LONDON / NEW YORK
1970

ELSEVIER PUBLISHING COMPANY
335 JAN VAN GALENSTRAAT,
P.O. BOX 211, AMSTERDAM, THE NETHERLANDS

ELSEVIER PUBLISHING CO. LTD.
BARKING, ESSEX, ENGLAND

AMERICAN ELSEVIER PUBLISHING COMPANY, INC.
52 VANDERBILT AVENUE, NEW YORK, N.Y. 10017

This volume contains the Proceedings of an International Conference on

THE PITUITARY–ADRENAL AXIS AND THE NERVOUS SYSTEM

*The Conference was organized by the Rudolf Magnus Institute for Pharmacology,
University of Utrecht, and held at Vierhouten,
The Netherlands, 22–24 July, 1969*

LIBRARY OF CONGRESS CATALOG CARD NUMBER 70–110965

STANDARD BOOK NUMBER: 444-40854-1

PRINTED IN THE NETHERLANDS

List of Contributors

A. N. Bhattacharya, Department of Physiology, School of Medicine, University of Pittsburgh, Pittsburgh, Penn., U.S.A.

B. Bohus, Institute of Physiology, University Medical School, Rákóczi út 80, Pécs, Hungary.

P. K. Bridges, Department of Psychological Medicine, Royal Free Hospital, London, W.C.1, England.

R. A. Cleghorn, Department of Psychiatry, Allan Memorial Institute, McGill University, 1025 Pine Avenue West, Montreal 112, Province Quebec, Canada.

A. J. Coppen, M.R.C. Neuropsychiatric Research Unit Carshalton, and West Park Hospital, Epsom, Surrey, England.

H. Corrodi, Biochemical Laboratory, AB Hässle, Fack, 402 20 Göteborg, Sweden.

N. Dafny, Department of Neurology, Hadassah University Hospital, Jerusalem, Israel.

J. Delacour, Centre d'Etudes de Physiologie Nerveuse, Département de Psychophysiologie du Comportement, 4, Avenue Gordon-Bennet, Paris 16 ème, France.

D. A. Denton, Howard Florey Laboratories of Experimental Physiology, Department of Physiology, University of Melbourne, Parkville, Victoria 3052, Australia.

D. De Wied, Rudolf Magnus Institute for Pharmacology, University of Utrecht, Medical Faculty, Vondellaan 6, Utrecht, The Netherlands.

E. Endröczi, Institute of Physiology, University Medical School, Rákóczi út 80, Pécs, Hungary.

T. Fekete, Institute of Physiology, University Medical School, Rákóczi út 80, Pécs, Hungary.

S. Feldman, Department of Neurology, Hadassah University Hospital, Jerusalem, Israel.

J. Frankel, Paediatric Metabolic and Endocrine Service and Rogoff-Wellcome Medical Research Institute, Division of Paediatrics, Beilinson Hospital, Tel Aviv University Medical School (and Psychology Department, Bar-Ilan University), Israel.

C. Franklin, Department of Physiology, Health Sciences Centre, The University of Western Ontario, London, Ontario, Canada.

K. Fuxe, Department of Histology, Karolinska Institutet, 104 01 Stockholm 60, Sweden.

W. H. Gispen, Rudolf Magnus Institute for Pharmacology, University of Utrecht, Medical Faculty, Vondellaan 6, Utrecht, The Netherlands.

E. Glassman, Department of Biochemistry and the Neurobiology Curriculum, University of North Carolina, Chapel Hill, N. C., U.S.A.

M. M. HALL, Department of Pharmacology, Ohio State University College of Medicine, Columbus, Ohio, U.S.A.

G. W. HARRIS, University of Oxford, Department of Human Anatomy, South Parks Road, Oxford, England.

R. I. HENKIN, Section of Neuroendocrinology, Experimental Therapeutics Branch, National Heart Institute, National Institutes of Health, Bethesda, Md20014, U.S.A.

J. R. HODGES, Department of Pharmacology, Royal Free Hospital School of Medicine, 8, Hunter Street, London W.C.I., England.

T. HÖKFELT, Department of Histology, Karolinska Institutet, 104 01 Stockholm 60, Sweden.

M. T. JONES, Sherrington School of Physiology, St. Thomas' Hospital, London S.E.I., England.

G. JONSSON, Department of Histology, Karolinska Institutet, 104 01 Stockholm 60, Sweden.

M. KARP, Paediatric Metabolic and Endocrine Service and Rogoff-Wellcome Medical Research Institute, Division of Paediatrics, Beilinson Hospital, Tel Aviv University Medical School, Israel.

R. KLEIN, Pediatric Clinical Center, Boston City Hospital, Boston, Mass. 02118, U.S.A.

L. KORÁNYI, Institute of Physiology, University Medical School, Rákóczi út 80, Pécs, Hungary.

W. A. KRIVOY, National Institute of Mental Health, Addiction Research Center, P.O. Box 2000, Lexington, Ky., U.S.A.

S. LANDE, Section of Dermatology, Department of Medicine, Yale University School of Medicine, New Haven, Conn., U.S.A.

Z. LARON, Paediatric Metabolic and Endocrine Service and Rogoff-Wellcome Medical Research Institute, Division of Paediatrics, Beilinson Hospital, Tel Aviv University Medical School, Israel.

D. LEAK, McGregor Clinic and St. Joseph's Hospital, Hamilton, Ontario, Canada.

S. LEVINE, Stanford University School of Medicine, Department of Psychiatry, Stanford, Calif. 94305, U.S.A.

K. LISSÁK, Institute of Physiology, University Medical School, Rákóczi út 80, Pécs, Hungary.

B. H. MARKS, Department of Pharmacology, Ohio State University College of Medicine, 1645 Neil Avenue, Columbus, Ohio 43210, U.S.A.

L. MARTINI, Institute of Pharmacology, University of Milan, 32, Via Vanvitelli, 20129, Milano, Italy

B. S. MCEWEN, Rockefeller University, 66th and York Avenue, New York, N.Y. 10021, U.S.A.

K. MILKOVIĆ, Institute of General Biology, Medical Faculty, University of Zagreb, Yugoslavia.

S. MILKOVIĆ, Laboratory for Experimental Medicine, General Hospital "Dr. Mladen Stojanović", Vinogradska c. 29, Zagreb, Yugoslavia.

I. A. MIRSKY, Laboratory of Clinical Sciences, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, Penn. 15213, U.S.A.

J. MONEY, Department of Psychiatry and Behavioral Sciences and Department of Pediatrics, The Johns Hopkins Hospital, Baltimore, Md. 21205, U.S.A.

M. MOTTA, Institute of Pharmacology, University of Milan, 32, Via Vanvitelli, 20129, Milano, Italy

A. H. MULDER, Rudolf Magnus Institute for Pharmacology, University of Utrecht, Medical Faculty, Vondellaan 6, Utrecht, The Netherlands.

J. F. NELSON, Howard Florey Laboratories of Experimental Physiology, Department of Physiology, University of Melbourne, Parkville, Victoria 3052, Australia.

J. PAUNOVIĆ, Institute of General Biology, Medical Faculty, University of Zagreb, Yugoslavia.

A. PERTZELAN, Paediatric Metabolic and Endocrine Service and Rogoff-Wellcome Medical Research Institute, Division of Paediatrics, Beilinson Hospital, Tel Aviv University Medical School, Israel.

F. PIVA, Institute of Pharmacology, University of Milan, 32, Via Vanvitelli, 20129, Milano, Italy.

E. J. SACHAR, Montefiore Hospital and Medical Center, 111 East 210th Street, Bronx, N.Y. 10467, U.S.A.

J. P. SCHADÉ, Netherlands Central Institute for Brain Research, IJdijk 28, Amsterdam-O, The Netherlands.

P. SCHOTMAN, Laboratory for Physiological Chemistry, Medical Faculty, University of Utrecht, Vondellaan 24a, Utrecht, The Netherlands.

I. SENČAR, Laboratory for Experimental Medicine, General Hospital "Dr. Mladen Stojanović", Vinogradska c. 29, Zagreb, Yugoslavia.

J. L. SLANGEN, Rudolf Magnus Institute for Pharmacology, University of Utrecht, Medical Faculty, Vondellaan 6, Utrecht, The Netherlands.

P. G. SMELIK, Department of Pharmacology, Free University, P.O. Box 7161, Amsterdam, The Netherlands.

F. A. STEINER, Department of Experimental Medicine, F. Hoffmann-La Roche & Co. Ltd., Basel, and Institute for Brain Research, University of Zurich, Switzerland.

J. A. F. STEVENSON, Department of Physiology, The University of Western Ontario, London, Ontario, Canada.

A. M. L. VAN DELFT, Rudolf Magnus Institute for Pharmacology, University of Utrecht, Medical Faculty, Vondellaan 6, Utrecht, The Netherlands.

TJ. B. VAN WIMERSMA GREIDANUS, Rudolf Magnus Institute for Pharmacology, University of Utrecht, Medical Faculty, Vondellaan 6, Utrecht, The Netherlands.

J. A. W. M. WEIJNEN, Rudolf Magnus Institute for Pharmacology, University of Utrecht, Medical Faculty, Vondellaan 6, Utrecht, The Netherlands.

J. M. WEISS, Rockefeller University, 66th and York Avenue, New York, 10021, N.Y., U.S.A.

J. E. WILSON, Department of Biochemistry and the Neurobiology Curriculum, University of North Carolina, Chapel Hill, N. C., U.S.A.

A. WITTER, Rudolf Magnus Institute for Pharmacology, University of Utrecht, Medical Faculty, Vondellaan 6, Utrecht, The Netherlands.

Other volumes in this series:

Volume 1: *Brain Mechanisms*
Specific and Unspecific Mechanisms of Sensory Motor Integration
Edited by G. Moruzzi, A. Fessard and H. H. Jasper

Volume 2: *Nerve, Brain and Memory Models*
Edited by Norbert Wiener† and J. P. Schadé

Volume 3: *The Rhinencephalon and Related Structures*
Edited by W. Bargmann and J. P. Schadé

Volume 4: *Growth and Maturation of the Brain*
Edited by D. P. Purpura and J. P. Schadé

Volume 5: *Lectures on the Diencephalon*
Edited by W. Bargmann and J. P. Schadé

Volume 6: *Topics in Basic Neurology*
Edited by W. Bargmann and J. P. Schadé

Volume 7: *Slow Electrical Processes in the Brain*
by N. A. Aladjalova

Volume 8: *Biogenic Amines*
Edited by Harold E. Himwich and Williamina A. Himwich

Volume 9: *The Developing Brain*
Edited by Williamina A. Himwich and Harold E. Himwich

Volume 10: *The Structure and Function of the Epiphysis Cerebri*
Edited by J. Ariëns Kappers and J. P. Schadé

Volume 11: *Organization of the Spinal Cord*
Edited by J. C. Eccles and J. P. Schadé

Volume 12: *Physiology of Spinal Neurons*
Edited by J. C. Eccles and J. P. Schadé

Volume 13: *Mechanisms of Neural Regeneration*
Edited by M. Singer and J. P. Schadé

Volume 14: *Degeneration Patterns in the Nervous System*
Edited by M. Singer and J. P. Schadé

Volume 15: *Biology of Neuroglia*
Edited by E. D. P. De Robertis and R. Carrea

Volume 16: *Horizons in Neuropsychopharmacology*
Edited by Williamina A. Himwich and J. P. Schadé

PROGRESS IN BRAIN RESEARCH

Volume 17: *Cybernetics of the Nervous System*
Edited by Norbert Wiener† and J. P. Schadé

Volume 18: *Sleep Mechanisms*
Edited by K. Akert, Ch. Bally and J. P. Schadé

Volume 19: *Experimental Epilepsy*
by A. Kreindler

Volume 20: *Pharmacology and Physiology of the Reticular Formation*
Edited by A. V. Valdman

Volume 21A: *Correlative Neurosciences. Part A: Fundamental Mechanisms*
Edited by T. Tokizane and J. P. Schadé

Volume 21B: *Correlative Neurosciences. Part B: Clinical Studies*
Edited by T. Tokizane and J. P. Schadé

Volume 22: *Brain Reflexes*
Edited by E. A. Asratyan

Volume 23: *Sensory Mechanisms*
Edited by Y. Zotterman

Volume 24: *Carbon Monoxide Poisoning*
Edited bij H. Bour and I. McA. Ledingham

Volume 25: *The Cerebellum*
Edited by C. A. Fox and R. S. Snider

Volume 26: *Developmental Neurology*
Edited by C. G. Bernhard

Volume 27: *Structure and Function of the Limbic System*
Edited by W. Ross Adey and T. Tokizane

Volume 28: *Anticholinergic Drugs*
Edited by P. B. Bradley and M. Fink

Volume 29: *Brain Barrier Systems*
Edited by A. Lajtha and D. H. Ford

Volume 30: *Cerebral Circulation*
Edited by W. Luyendijk

Volume 31: *Mechanisms of Synaptic Transmission*
Edited by K. Akert and P. G. Waser

Volume 33: *Computers and Brains*
Edited by J. P. Schadé and J. Smith

Preface

For several years we have felt that it would be appropriate to organize a meeting on the pituitary–adrenal axis and the nervous system. The present expansion of research in this area called for a survey of the field in order to gain insight into the significance of the interaction between the pituitary–adrenal axis and the brain and to set new goals for future research.

It was intended to examine the subject of the conference from different angles. The meeting started with a discussion on the influence of the nervous system on pituitary–adrenal activity, a topic which has been extensively studied during the last two decades. Subsequently, the action of the pituitary–adrenal axis on the nervous system was discussed, an area which has been recently expanding. The third aspect of the meeting was the relationship between the pituitary–adrenal system and animal behavior, which is an important topic in our own research. The conference ended with studies on the interaction between pituitary–adrenal system hormones and human behavior.

During the meeting, a magnificent accomplishment was made when the first human being set foot on the moon. This spectacular technological achievement hopefully is indicative of the speed with which knowledge on the living organism will be attained in the near future. One would wish that the achievements in this area of research would parallel the progress made in sounding the universe during the last decade. May this conference have contributed to the understanding of the organ essential for all our accomplishments: The Brain.

I am grateful to all who contributed to the success of the conference, to the chairmen Professors R. A. Cleghorn, G. W. Harris, K. Lissák and I. A. Mirsky, and to the speakers and the discussants who were so kind to accept my invitation to participate in the meeting. I would also like to mention the valuable assistance of the secretarial staff with special reference to Miss T. A. Baas, the technical staff, and in particular the organizing committee consisting of Drs. A. M. L. Van Delft, W. H. Gispen, J. L. Slangen, J. A. W. M. Weijnen and Tj. B. Van Wimersma Greidanus, who are all members of the Rudolf Magnus Institute.

D. de Wied
Professor of Pharmacology,
Head of the Rudolf Magnus Institute
for Pharmacology

Acknowledgements

The Organizing Committee expresses its special thanks for the generous support by the following organizations:

Dutch Government, Department of Education and Science, The Hague
Farbe Werke Hoechst A.G., Frankfurt
Hoffmann–La Roche N.V., Mijdrecht
Merck Sharp and Dohme Nederland N.V., Haarlem
N.V. Organon, Oss
N.V. Philips Duphar, Amsterdam
The Dr. Saal van Zwanenberg Foundation, Oss
Schering Co., Bloomfield, N.J.
Smith, Kline and French Labs., Philadelphia, Pa.
Specia, Paris
Syntex Corp., Palo Alto, Calif.
The University of Utrecht
The Van Wijck Stam Casper Foundation, Utrecht

Contents

SESSION I

Effects of the Nervous System on Pituitary–Adrenal Activity

Chairman: G. W. HARRIS

University of Oxford, Department of Human Anatomy, South Parks Road, Oxford (U.K.)

The Limbic System and the Pituitary–Adrenal Axis

J. P. SCHADÉ

Netherlands Central Institute for Brain Research, Amsterdam

INTRODUCTION

The limbic system appears to be involved in activating or inhibiting basic drives as well as their concomitant hormone release. The anterior and medial hypothalamic areas are regarded as integrating centers for regulation of pituitary function (Sawyer *et al.*, 1968; Smelik, 1969). These hypothalamic regions are embedded in a dense meshwork of fibers, originating not only from neurons in other hypothalamic areas, but also from limbic and extralimbic systems (Nauta, 1958; De Groot, 1966).

Of particular importance for the study of control of the pituitary-adrenocortical system are the intrahypothalamic and intralimbic pathways which converge upon the anteromedial region. In this area, groups of neurons are located which produce and release a corticotrophin-releasing factor (CRF) which is essential for the release of ACTH by the pituitary.

The pool of CFR neurons is accessible to neural and humoral stimuli of excitatory and inhibitory nature. Therefore, it has been suggested that this pool is an integrative part of the "steroidstat", a homeostatic mechanism for keeping the glucosteroid content at a constant level (Schadé, 1969; Steiner *et al.*, 1969).

In the past decade, the introduction of axon degeneration techniques for the mapping of poorly myelinated systems, and the use of micro-electrodes for the investigation of the sensitivity of hypothalamic neurons, has facilitated the analysis of the role played by the hypothalamus in pituitary adreno-cortical relations. The finding of reciprocal neural pathways linking limbic areas with hypothalamic nuclear masses as well as certain brain stem areas, has necessitated a reappraisal of the neuronal control mechanisms of pituitary function.

No regulatory system can be adequately assessed until we appreciate the nature of physiological integration between the systems. Since we are dealing with the influence of the limbic system upon the pituitary-adrenal axis, an attempt should be made to integrate the functional properties of the two systems involved. The first principle, in such an understanding, is to know the morphological substratum with which one is dealing and its physiological properties. Since a rectilinear relationship may be assumed to exist between the CRF-producing neurons, the ACTH-producing cells in the anterior pituitary, and the corticosteroid-producing cells in the adrenals, the analysis of the limbic influence upon the pituitary-adrenal axis boils down to the functional interaction between the limbic system and the CRF-neurons in the hypothalamus.

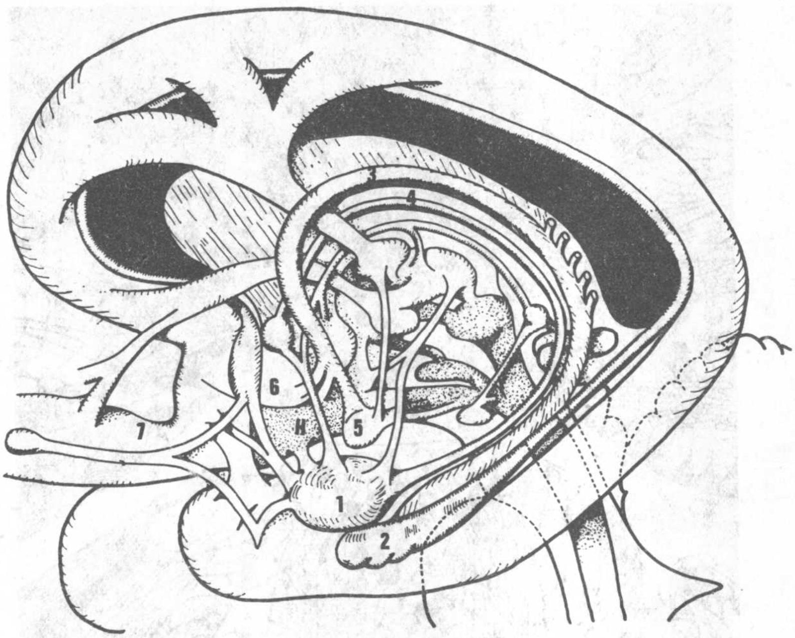

Fig. 1. Some limbic structures mentioned in the text. (Scheme after Needham and Dila, 1968)

1. amygdala
2. hippocampus
3. fornix system
4. stria terminalis
5. mammillary body
6. septum
7. medial forebrain bundle
H. hypothalamus.

For this discussion we would like to have available a detailed anatomical scheme of the afferent and efferent connections between the limbic system and hypothalamus, and also an insight into the intrahypothalamic and intralimbic circuitry. Unfortunately, this information is not yet available. Since we are dealing with a multiloop control system in which rigid one-to-one or linear relations do not hold, it is essential to provide a structural frame of reference in order to draw up a simplified model. Therefore an attempt at system analysis of the limbic CRF-neuronal trajectory is being made. In this respect we have to deal with the following aspects of the problem:

(a) the characteristics of the substratum of the limbic regulatory system;

(b) its neurophysiological properties;

(c) the nature of the CRF-neuron pool and the reciprocal interaction between limbic system and CRF-pool.

PROPOSITION 1

The substratum of the limbic-hypothalamic (CRF-neuron pool – pituitary-adrenal) regulation consists of two classes of pathways with different integration levels, both classes of pathways having excitatory and inhibitory properties

Using histological and physiological methods, a number of limbic-hypothalamic pathways have been clarified. Especially important are the well-developed neuronal

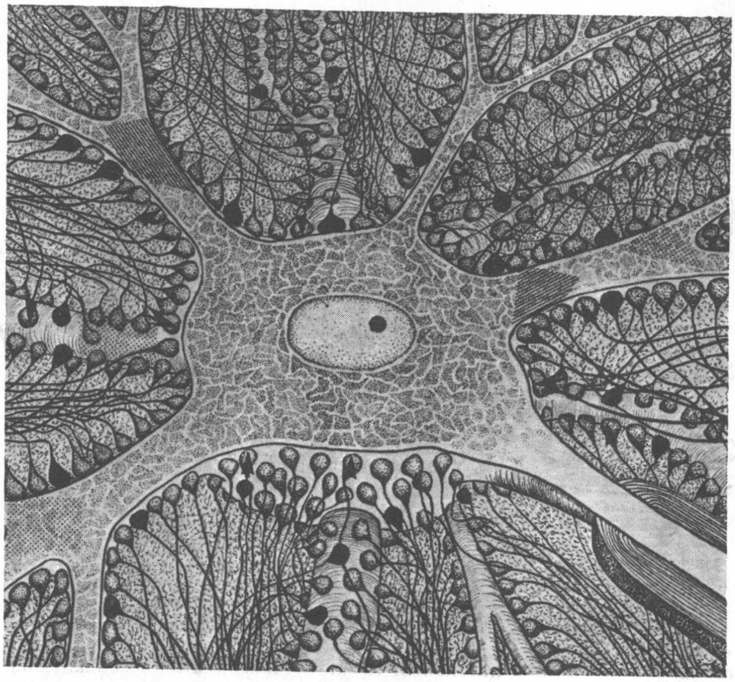

Fig. 2. Schematic model of the CRF-neuron (excitatory synapses: black; inhibitory synapses: arrow). The stippled and striped areas indicate parts of the receptive surface of the neuron which is sensitive to circulating factors.

trajectories between the amygdaloid complex and hippocampal formation on the one hand, and the neuronal pools of certain regions of the hypothalamus on the other hand (Bargmann and Schadé, 1963, 1964; Szentágothai *et al.*, 1968). The anterio-medial region: nodal area for the regulation of pituitary function and location of the CRF-neuron pool, receives afferent connections through the stria terminalis and the fimbria-fornix bundle. Furthermore, this hypothalamic area receives numerous short fiber bundles, a.o. from the periventricular system, mammillary bodies, medial fore-brain bundle, and the lateral and posterior hypothalamic regions.

On the basis of the functional properties, the pathways could be divided into two classes: the stria terminalis and fimbria-fornix bundle on the one hand, and all other connections on the other hand. In both classes fiber systems could be distinguished which either excite or inhibit the basic activity of the CRF-neuron pool (cf. Adey and Tokizane, 1967; Dallman and Yates, 1968).

The amygdaloid complex exerts an excitatory influence on the CRF-neuron pool, as illustrated by stimulation and ablation experiments (Mangili *et al.*, 1966; Gloor *et al.*, 1969). Stimulation of the amygdaloid nuclei activates ACTH-release; while bilateral destruction diminishes the activity of the pituitary adrenocortical axis.

The hippocampus and some other forebrain and rhinencephalic structures have been reported to inhibit the CRF-neuron pool. Stimulation within physiological

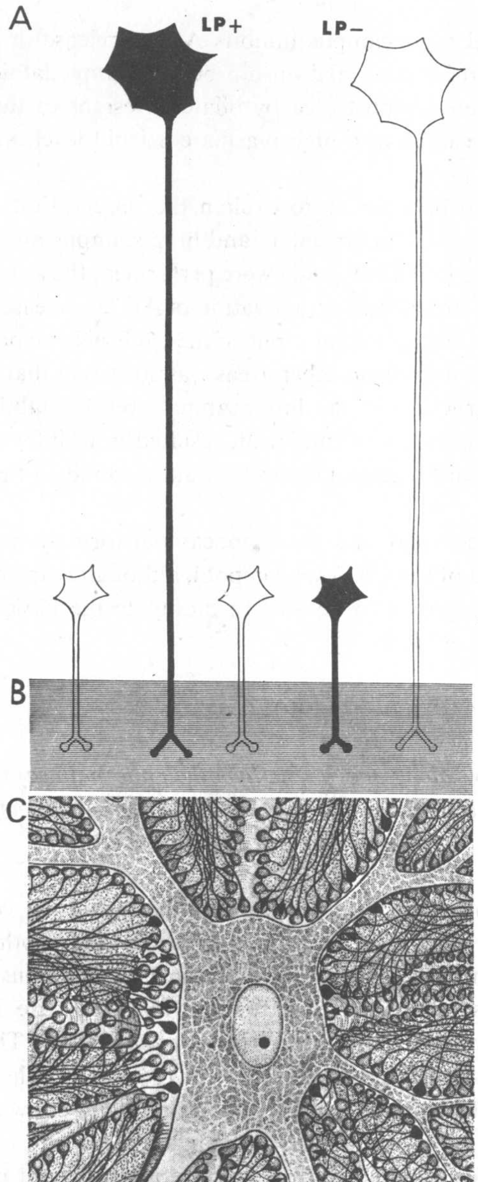

Fig. 3. Model of limbic and extralimbic influences on the CRF-neuron pool. A: limbic pyramidal system; LP+ fibers (e.g. from amygdala): limbic pyramidal system which excites CRF-neuron pool; LP− fibers (e.g. dorsal hippocampus): limbic pyramidal system which inhibits CRF-neuron pool; B: limbic extrapyramidal and other influences upon the CRF-neuron pool. The hierarchy of A is higher than that of B. The striped area of B indicates interneuron pools; C: CRF-neuron pool.

References pp. 9–10