

**PROGRESS
IN BRAIN RESEARCH**

Volume 32

**PITUITARY, ADRENAL AND
THE BRAIN**

PROGRESS IN BRAIN RESEARCH
VOLUME 32

PITUITARY, ADRENAL
AND THE BRAIN

EDITED BY

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AND

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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.

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SESSION I

Effects of the Nervous System on Pituitary-Adrenal Activity

Chairman: G. W. HARRIS

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The Limbic System and the Pituitary-Adrenal Axis

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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.

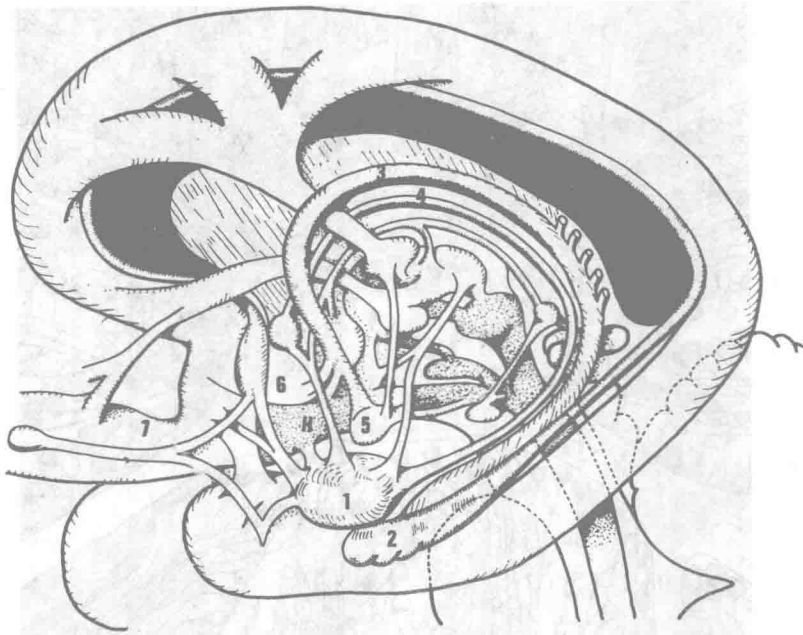


Fig. 1. Some limbic structures mentioned in the text. (Scheme after Needham and Dila, 1968)

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

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

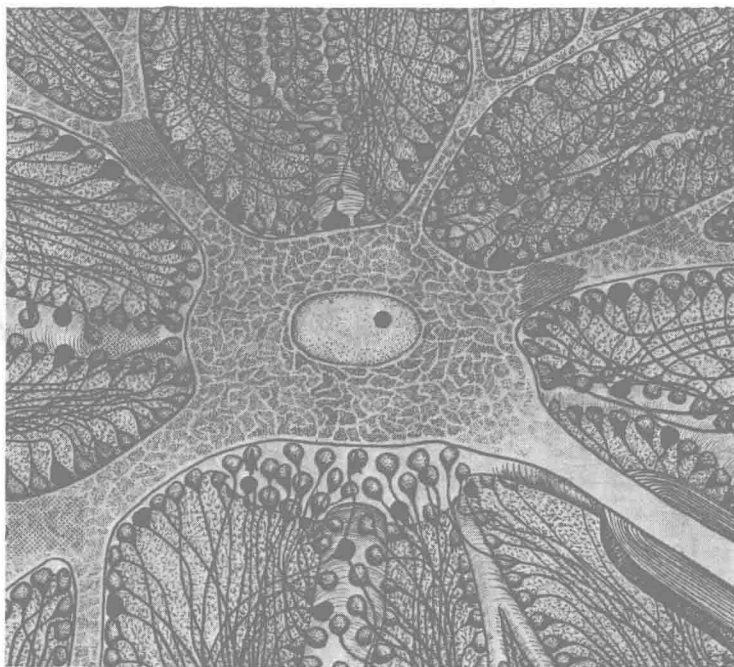


Fig. 2. Schematic model of the CRF-neuron (excitatory synapses: black; inhibitory synapses: arrow). The stippled and striped areas indicate parts of the receptive surface of the neuron which is sensitive to circulating factors.

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 antero-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

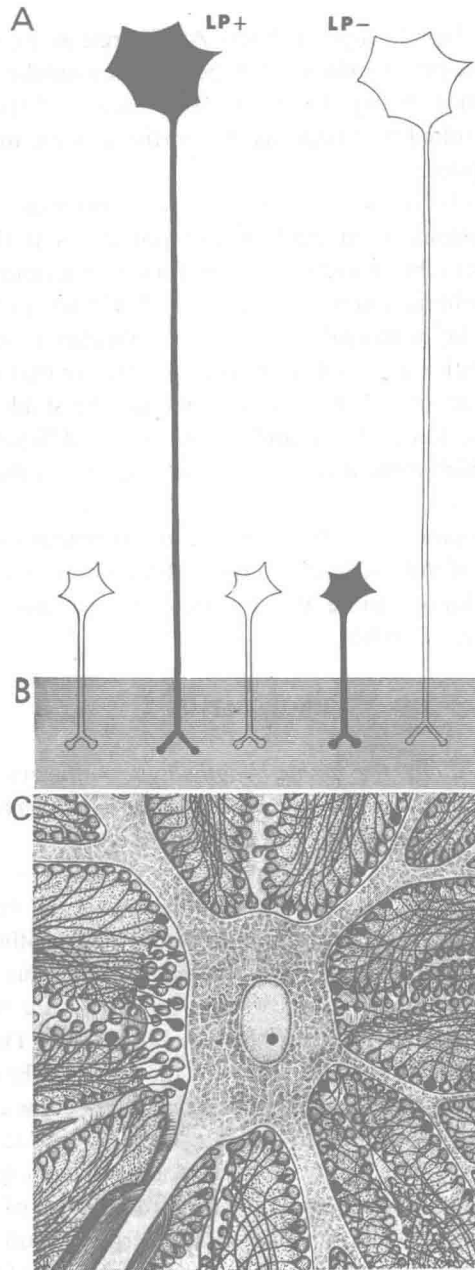


Fig. 3. Model of limbic and extralimbic influences on the CRF-neuron pool. A: limbic pyramidal system; LP+ fibers (e.g. from amygdala): limbic pyramidal system which excites CRF-neuron pool; LP- fibers (e.g. dorsal hippocampus): limbic pyramidal system which inhibits CRF-neuron pool; B: limbic extrapyramidal 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.