HYPOTHALAMIC-HYPOPHYSIAL INTERRELATIONSHIPS

A Symposium
Third Annual Scientific
Meeting of the Houston
Neurological Society
Texas Medical Center
Houston, Texas

Chairman
HEBBEL E. HOFF

Compiled and Edited by

WILLIAM S. FIELDS
Professor of Neurology
Baylor University
College of Medicine

ROGER GUILLEMIN
Assistant Professor of Physiology
Baylor University
College of Medicine

CHARLES A. CARTON
Assistant Professor of
Neurological Surgery
Baylor University
College of Medicine

Contributors
W. K. Clark
Pierre Gloor
John Green
James Greenwood, Jr.
Roger Guillemin
Geoffry Harris
Walther Hild
Hebbel E. Hoff
P. B. Hudson
L. Arthur Mirsky
M. E. Lombardo
J. Lawrence Pool
Charles L. Spurr
Marvin Stein

This topic was chosen because of the increasing interest in the relationship of Neurology and Neurophysiology to Endocrinology. So this book is of special interest to endocrinologists, internists, neurologists, neurophysiologists and psychiatrists, as well as to basic science research workers.

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FOREWORD

THE Houston Neurological Society was founded in 1951 by a group interested in fostering a closer relationship between those working in clinical and basic science disciplines allied to Neurology. It was our hope that the Society would create the stimulus needed for interest in both teaching and research in this field. Each year, since 1952, the Society has sponsored an Annual Scientific Meeting including a symposium on some subject of broad current interest.

For the 1955 meeting the topic "Hypothalamic-Hypophysial Interrelationships" was selected because of the increasing interest in the relationship of neurology and neurophysiology to endocrinology. The literature in this field has been rapidly expanding and it was considered that a critical appraisal of the current status of our knowledge would be timely.

In large measure the successful grouping of the presentations and the freedom of the ensuing discussions were directly attributable to the guidance of Dr. Hebbel E. Hoff in his capacity as chairman.

The symposium could not have taken place without the many contributions, both financial and otherwise, made by the following:

Baylor University College of Medicine.
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We wish also to express our appreciation for the great amount of time and effort expended by Drs. Charles A. Carton, William S. Fields, and Roger Guillemin in assisting in the planning of the program and editing of these proceedings.

JAMES GREENWOOD, JR., M.D.
President, Houston Neurological Society

CONTRIBUTORS

DR. WILLIAM K. CLARK: *Assistant Resident in Neurological Surgery, Neurological Institute of New York, New York City.*

DR. PIERRE GLOOR: *Research Associate, Montreal Neurological Institute, Montreal, Canada.*

DR. JOHN GREEN: *Associate Professor of Anatomy, U.C.L.A. Medical School, Los Angeles, California.*

DR. ROGER GUILLEMIN: *Assistant Professor of Physiology, Baylor University College of Medicine, Houston, Texas; Scholar of the John & Mary R. Markle Foundation.*

DR. GEOFFRY HARRIS: *Professor of Physiology; Director of Laboratory of Neurophysiology, Maudsley Hospital, University of London, England.*

DR. WALTHER HILD: *Research Associate, Tissue Culture Laboratory, University of Texas Medical Branch, Galveston, Texas.*

DR. HEBBEL E. HOFF, *Chairman: Professor of Physiology, Baylor University College of Medicine, Houston, Texas.*

DR. PERRY B. HUDSON: *Assistant Professor of Urology, College of Physicians and Surgeons, Columbia University, New York City.*

DR. MICHAEL E. LOMBARDO: *Research Associate in Biochemistry (Urology), College of Physicians and Surgeons, Columbia University, New York City.*

DR. I. ARTHUR MIRSKY: *Professor and Chairman, Department of Clinical Science, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.*

DR. J. LAWRENCE POOL: *Professor of Neurosurgery, College of Physicians and Surgeons, Columbia University; Director of Neurosurgery, Neurological Institute, Columbia—Presbyterian Medical Center, New York, New York.*

DR. CHARLES L. SPURR: *Associate Professor of Medicine, Baylor University College of Medicine, Chief, Research Laboratory, Veterans Administration Hospital, Houston, Texas.*

DR. MARVIN STEIN: *Research Associate in Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.*

DR. SAMUEL H. STRIBLING: *Clinical Instructor in Medicine, Baylor University College of Medicine; Ward Physician, Veterans Administration Hospital, Houston, Texas.*

A Symposium — March 18, 1955

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HYPOTHALAMIC-HYPOPHYSIAL INTERRELATIONSHIPS

A Symposium

NEURAL PATHWAYS TO THE HYPOPHYSIS*

JOHN D. GREEN

Department of Anatomy, School of Medicine
University of California at Los Angeles
and
Investigative Medicine Service
Veterans Administration Hospital
Long Beach, California

THE MECHANISM of nervous control of the pituitary gland presented a difficult problem for many years. On the one hand the neurohypophysis was known to contain abundant nerve fibers, but seemed to lack secretory cells, and on the other, although the pars distalis of the adenohypophysis was known to contain a variety of secretory cells, most histologists agreed that nerve fibers were scanty or absent. Ranson and his collaborators (Fisher, Ingram and Ranson, 1936) in this country and Verney (1926) in England clearly demonstrated that the neurohypophysis was capable of secretion and was controlled by the supraoptic and paraventricular nuclei. Harris (1947) showed that direct stimulation of the neural lobe or neural stalk caused the liberation of posterior pituitary hormones and to some (Fulton, 1949) the problem of the neurohypophysis appeared solved by the work of Gersh (1939) on pituicytes. This latter did not go unchallenged on anatomical (Rasmussen, 1938; Green, 1947a) and experimental grounds (deRobertis and Primavesi, 1942), and the alternative hypothesis that the abundant nerve fibers were responsible for the secretions of the neural lobe was advanced (Rasmussen, 1938). This gained impetus with the discoveries of Bargmann and his collaborators who observed sharp staining of the neurohypophysis by chrome alum hematoxylin. They proposed that the curious colloid described in the hypothalamic nuclei and elsewhere by the Scharrers was identical with the substance so stained

* This work was supported in part by Grant B-610 from the United States Public Health Service.

and was in fact the hormone or a hormone 'carrier.' The work of many authors now leaves little doubt that a relationship exists between the so-called Gomori substance and the antidiuretic hormone, though some points of an equivocal nature still remain (Green and Van Breemen, 1955).

The control of the pars distalis represents another problem. Various authors proposed a humoral transmitter from the tuberal region or neurohypophysis as a possible controlling mechanism for the pars distalis (Hinsey and Markee, 1933; Harris, 1944). The hypothesis was put forward on the basis of anatomical studies and various data collected from the literature that the hypophysial portal circulation served to carry a transmitter, liberated by nervous action in the median eminence, to the pars distalis there to influence the activity of this part of the gland (Green and Harris, 1947). Subsequently, experimental evidence (Harris, 1949; Harris and Jacobsohn, 1952) showed that this was apparently true for gonadotrophins. Harris (1955) indicates that some but not all phases of ACTH and TSH secretion are also controlled through the portal vessels.

Anatomical studies (Green, 1951a) indicated that the hypophysial portal circulation or a functionally similar system of vessels is constant in some 80 representative species of vertebrates from cyclostomes to man. Furthermore, in some species, for example, the pigeon, known to be particularly sensitive to nervous influences on the pituitary the only apparent link between the hypothalamus and the pars distalis is via a leash of blood vessels penetrating a dural septum between adeno- and neurohypophysis (Green, 1951a). Using phase contrast illumination and media of different refractive indices, strong evidence was obtained to show that the pericellular nets of so-called nerve fibers in the pars distalis were, in fact, reticular connective tissue (Green, 1951b).

The portal vessels have recently received particular attention in man (Green, 1948; Xuereb, Prichard and Daniel, 1954a, b) and the latter authors have published beautiful photographs of latex injections giving the clearest of all demonstrations of their anastomoses. This system is constant from the caudata to man and below the caudata is slightly modified in aquatic vertebrates which lack a neural lobe, but are often provided with a large median eminence and neural stalk. The neural lobe appears to have developed *pari passu* with the acquisition of a land habitat (Green, 1951a). Possibly this may be correlated with a new need to stabilize the tonicity of the body fluids associated with life on dry land.

The hypothalamus as such has no direct vascular connection with the pituitary, as was first shown by Wislocki and King (1936). Though certain regions, notably the supraoptic and paraventricular nuclei, receive an extraordinarily rich blood supply, possibly associated with osmo-reception, this has no anastomoses with the hypophysial system of vessels. The blood supply of the neural lobe is quite independent of that of any other part of the pituitary gland also.

Many environmental factors as well as psychic phenomena affect the activity of the hypophysis cerebri and both the neurohypophysis and adenohypophysis are affected by influences mediated through a wide variety of receptors. These exteroceptive factors have been reviewed repeatedly (Marshall, 1936, 1942; Green, 1946, 1947b; Harris, 1948). Although little is known about olfactory or proprioceptive influences affecting the anterior pituitary, it seems very likely that they may play some role in controlling its production of hormones, and it is clear that in one species or another all other modalities of afferent stimulation can affect this part of the gland.

Marshall (1936, 1942) suggested that courtship and sex display played a role in pituitary stimulation, and since this time many examples of psychic influences on the hypophysis have been reported. Perhaps the most dramatic of these is the narcissistic behavior of the female pigeon with a mirror (Matthews, 1939), but ancient clinical observations on emotion and the menstrual cycle must be placed in the same category as well as the many recent studies on emotional stress.

While the list for the neurohypophysis is less impressive, it is growing, and it is clear that emotional responses occur and that exercise, suckling, for, changes in blood tonicity and stress all affect the output of its hormones.

Since the evidence for direct sympathetic or parasympathetic control of the pars distalis is inconclusive (Harris, 1948) and evidence for neurohypophysial control by this route even more equivocal, it is clear that the main burden of pituitary control must be carried via the hypothalamus and the hypophysial stalk linking it to the pituitary.

Thus, there is abundant evidence for a truly amazing convergence of nervous influences in this area. We know that the neural stalk contains a variety of fibers derived from the hypothalamus. In the rhesus monkey and the cat the following main categories can be recognized (Green, 1951a): (1) fibers derived from the supraoptic and paraventricular nuclei; (2) fibers from the general area of the medial forebrain bundle, and (3) fibers from the lateral tuberal nuclei. In addition, small contributions from the periventricular system and the nucleus suprachiasmaticus may be observed, but no direct connections with the mammillary body.

While the demonstration by Ranson and his colleagues that the supraoptic and paraventricular nuclei control neurohypophysial secretion and the studies of Bargmann, Scharrer, Ortmann, Hild and others (Scharrer and Scharrer, 1954) indicate that these nuclei may also produce the hormones, the precise groups of cells involved in anterior pituitary control are not well understood, despite innumerable descriptions of dysfunction following clinical and experimental lesions and many examples of altered function following hypothalamic stimulation. It may well be that in the case of the pars distalis we are dealing with hypothalamic fibers rather than cells. Thus the position is that we know the peripheral receptors, but are very ignorant of pathways within the nervous system between these receptors and the final common neural path in the tractus hypophysius prior to the hypophysio-portal circulation.

Admitting from the start that these connections are not known, it may be appropriate to speculate about some of the neural pathways which may play a role in linking the anterior pituitary with peripheral receptors and the outside world. To try to clarify this discussion, Figure 1 illustrates certain possible connections. Within the system of cells and fibers concerned in the regulation of anterior pituitary activity, the following characteristics might

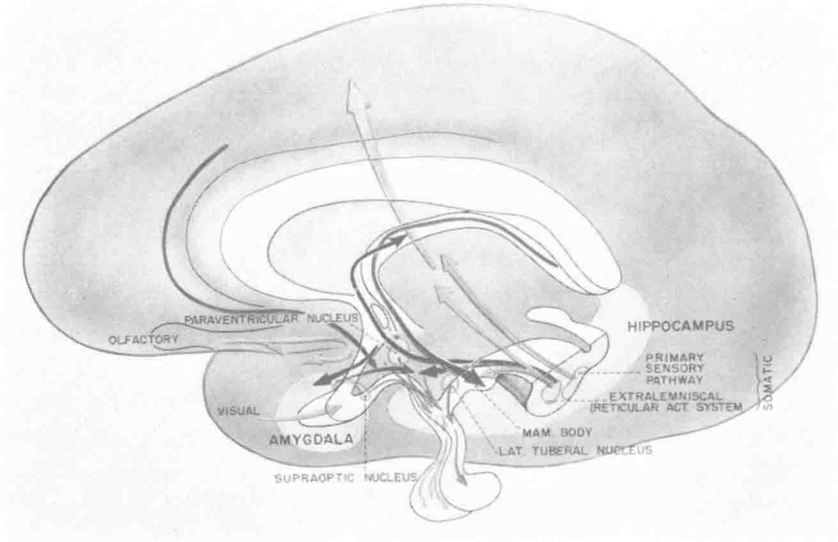

Figure 1. Ilustration of pathways discussed in text to account for convergence of afferents onto the tuberal region. The primary sensory pathways are indicated light gray as is the hypophysio-portal system. Proposed pathways under discussion, dark gray. Possible convergent pathways, medium gray. Amygdala, hippocampus and hypothalamic nuclei, stippled gray.

be expected: (1) They should be phylogenetically old. (2) Many modalities of impulses must converge upon them. (3) They must be related to "higher" functions also since, for example, adaptation to psychic stress occurs and emotional influences play an important role as indicated above. (4) They must have properties of discrimination (for example, the stimuli of a rectal thermometer and coitus evoke different anterior pituitary responses). (5) Finally, prolonged hypothalamic stimulation is required to evoke anterior pituitary effects suggesting that prolonged after-discharges must be produced by afferents reaching the hypothetical system of neurons.

Perhaps the most obvious point of departure would be to consider the primary lemniscal pathway. While this might conceivably relay in the thalamus and cerebral cortex and then influence the hypothalamus from some cortical area, perhaps the frontal cortex, there are several reasons for thinking that this is not likely despite the observations of Beach (1948). Phylogenetically the neocortex is a recent acquisition and together with its associated thalamic nuclei is a mere parvenu compared with the pituitary and ventral diencephalon. Furthermore, this pathway could not account for the effects of visual stimuli, for even the analogous path is not involved. LeGros Clark, *et al.* (1939) showed that in the ferret neither the visual cortex nor the bulk of the lateral geniculate were necessary for the estrus reaction of the ferret to constant illumination. They proposed that either the ventral nucleus of the lateral geniculate or the accessory optic tracts (by way of the subthalamus) relayed the stimulus to the hypothalamus. Since section of the optic nerve abolishes the response while almost complete destruction of the geniculate does not, their results certainly suggest that the impulse must leave the optic tract at some point before it arrives at the lateral geniculate.

The recent trend in neurophysiology has been to refer many adaptive and correlative mechanisms to subcortical areas in the brain stem, notably to the reticular activating system and to the non-specific thalamic nuclei. Through these structures course afferent neurons which are derived from many sources and, at the same time, appear more complex in their connections than those of the direct lemniscal pathway. Phylogenetically this is an ancient collection of neurons, for it was present long before the neo-cortex developed. It is attractive to consider since it is prolonged rostrally into the posterior hypothalamic nuclei On the other hand, it appears that lesions in the anterior hypothalamus and preoptic region may affect certain anterior pituitary responses, a finding which would suggest either that these impulses would have to pursue a recurrent course or that in these particular cases they were not involved. Very long after-discharges have not been recorded from these neurons in spite of their complex connections and behavior.

Recently we have obtained evidence (Green and Arduini, 1954; Green and Machne, 1954; Green and Adey, 1955) that afferent impulses reach the hippocampus in the rabbit, cat, and monkey and that in the rabbit and cat this is probably through the route: extralemniscal afferents→lateral hypothalamus→septum →pre-commissural fornix→hippocampus→post-commissural fornix→mammillary body→mammillo-thalamic tract→anterothalamus→cingulum. This also would be an attractive alternative, but against it must be set the absence of evidence for direct connections between the mammillary body and the pituitary and the suggestion implied by this lack of evidence is that the impulses sweep through the hypothalamus into the anterior thalamus. On the other hand, it has been shown (Green and Arduini, 1954) that the hippocampal responses show adaptation analogous to that of the neo-cortex and the hippocampus is, of course, an ancient and distinguished part of the cerebral hemisphere which might qualify as the dean of cortical areas. Indeed, Herrick (1933) suggested that its role was to correlate visceral and somatic activities.

Another region of the forebrain which plays an undoubted role in visceral activity is the amygdala. Bilateral removal of the region of the temporal lobes, especially the regions of the hippocampus and amygdala, produced hypersexuality and abnormal sexual behavior (Klüver and Bucy, 1939; Gastaut, 1952; Schreiner and Kling, 1953, 1954; see also Klüver, 1952). Although this never has been directly correlated with hypothalamic and pituitary activity, Klüver and Bartelmez (1951) found changes in the ovaries and endometrium strongly suggestive of such a relationship, and Schreiner and Kling (1954) find that castration prevents the hypersexuality seen after lesions of the amygdala, but that it may be restored with testosterone. The wealth of connections between the amygdala and diencephalon makes such a role a very attractive one to consider. Sawyer (1955) has recently found that changes in blood sugar produced by intravenous injection or by administration of insulin produce marked changes in the electrical activity of this structure. The main obstacle to this concept might appear to be the lack of evidence of afferents to the amygdala. Koikegami *et al.* (1954) produced ovulation in the rabbit by stimulation of the amygdala.

Using single shock stimulation and the after-discharge technique, Arana *et al.* (1955) were unable to locate afferent pathways from the midbrain to the amygdala although, on the other hand, Machne and Segundo (1955) using microelectrodes have found evidence of profound and long-lasting changes in neuronal activity in the amygdala following peripheral stimulation. Their preliminary results also suggest that primary responses are difficult or impossible to record by the macroelectrode method. Thus it might be suggested that the amygdala does not receive impulses directly, but only after considerable elaboration so that the effects of the initial volley are broadened into diffuse neuronal responses.

A possible mechanism whereby the amygdala might receive afferents is suggested by Figure 2. Single shock stimuli of the ipsilateral hippocampus evoke short-latency responses in the amygdala, particularly in the areas of the anterior, central and basolateral nuclei (Green and Adey, 1955), and this has been confirmed by strychnine neuronography (Clemente, Green and Sutin, 1955). Similar responses on the contralateral side have not been seen. Figure 2 illustrates some of these responses and responses in adjacent areas.

The suggestion is made, therefore, that the rather complex pathway: peripheral afferents→extralemniscal afferent paths in the reticular activating system*→lateral hypothalamus→septum →hippocampal formation→amygdala→hypothalamus (by way of the stria and medial forebrain bundle) fulfills all the requirements for a system of neurons controlling the anterior pituitary, and possibly the posterior pituitary also. A second possibility is that direct relays from the septum to the amygdala may occur. Responses in this area to afferent stimulation have been described (Green and Arduini, 1954; Hernández-Peón, Gunn and Eliasson, 1955).

All parts of the amygdala-hippocampal system are phylogenetically ancient. Within it, many different afferents are correlated and an important role in emotional and visceral reactions is undoubtedly played by it. It is capable of sustained after-discharges (Kaada, 1951; Green and Morin, 1953; Green and Shimamoto,

* It may be noted that the area from tegmental reticular activating system to septum may be regarded as a rostral extension of the reticular activating system of Moruzzi and Magoun (1949), since stimulation of this region produces the same neocortical "arousal" response (Green and Arduini, 1954) and lateral hypothalamic lesions produce sleep (Ranson, 1939).