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CENTRAL MEDIATION OF HORMONAL INFLUENCES ON INSTRUMENTAL AVOIDANCE CONDITIONING

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Abstract. Two behaviorally active hormones of the pituitary-adrenal system are adrenocorticotropic hormones (ACTH) and corticosterone, and their behavioral effects are facilitation and inhibition of performance of previously learned avoidance responses, respectively. Their uptake, distribution and effects on central nervous system are reviewed. Hypothalamic neurotransmitter control of corticotropin releasing hormone (CRH) is described together with hypothalamic and extra-hypothalamic (hippocampal) regulation of pituitary-adrenal activity. Extra-hypothalamic mediation of the behavioral effects of ACTH is evaluated. Recent isotopic mappings of the efferents of the hippocampal formation have identified pathways from hippocampal subiculum to hypothalamus and posterior lateral and anterior thalamic nuclei. The evidence reviewed suggests a complex circuit involving hippocampal subiculum, thalamus and hypothalamus may be involved both in regulating pituitary-adrenal responses to stress and in mediating the effects of ACTH on avoidance behavior.

INTRODUCTION

Instrumental avoidance behavior is complexly influenced by a number of structures in the central nervous system (CNS) and by some of the hormones of the pituitary-adrenal axis. These hormones, in turn, are regulated by hypothalamic and possibly extra-hypothalamic regions of

the CNS. In general, most of the extra-hypothalamic structures that have been implicated in pituitary-adrenal regulation lie within the Papez circuit (69, 70), now identified as the limbic midbrain area (65), which has long been known to have significant effects on avoidance behavior (60). Thus, the brain regions important for avoidance behavior are also important for pituitary-adrenal regulation. In this paper we wish to examine the possibility that the same structures are involved in mediating the effects of pituitary-adrenal hormones on avoidance behavior.

HORMONAL EFFECTS ON AVOIDANCE BEHAVIOR AND THE CNS

When addressing the role of the CNS in mediating the effects of pituitary-adrenal hormones on avoidance behavior the following questions arise: 1) are there demonstrable and reliable effects of the hormones on avoidance behavior, 2) to what extent and where are these hormones found in the CNS and 3) what neural events are modulated or changed as a result? These issues will be taken up in turn.

Effects of pituitary-adrenal hormones on avoidance behavior

Two pituitary-adrenal hormones that are important for avoidance behavior are adrenocorticotropic hormone (ACTH), a 39-amino-acid peptide from the anterior pituitary gland, and corticosterone (B), a glucocorticosteroid from the adrenal cortex. The first (N-terminal) 24 amino acids of ACTH ($ACTH_{1-24}$) are required for full steroidogenic action in the adrenal cortex, whereas there is little or no steroidogenic effect from α-MSH (melanocyte stimulating hormone) which is identical to $ACTH_{1-13}$. By comparing the behavioral effects of purified $ACTH_{1-39}$ or synthetic $ACTH_{1-24}$, both of which stimulate the adrenal, with those of α-MSH, which does not, it is possible to separate the behavioral effects of the pituitary peptide, ACTH, from those of the glucocorticoid, B.

The most notable effect of ACTH on avoidance behavior is to improve performance of previously learned avoidance responses, an effect which has been demonstrated in numerous experiments involving various conditions and treatments. For example, Bohus and Endroczi (7) found that exogenous ACTH improved avoidance performance early in training and reduced intertrial responding both early and late in training in both intact and adrenalectomized rats. DeWied showed that hypophysectomized and adenohypophysectomized rats were grossly deficient in learning two-way shuttle and pole-jump avoidance responses and that this deficiency could be reversed, in a dose-related fashion, by exogenous administration of ACTH (17, 19). All of the behavioral effects of ACTH appear

to be independent of its steroidogenic action because essentially identical behavioral effects are seen with $ACTH_{1-13}$, $ACTH_{1-10}$, and $ACTH_{4-10}$ (35). In general, the adrenocorticosteroids are either without effect or have an effect opposite to that of ACTH, i.e., B tends to inhibit performance of previously learned avoidance responses (18).

Uptake and distribution of pituitary-adrenal hormones in rat brain

It is obvious that in order for these hormones to influence behavior they must be available to the CNS, and since thay are secreted into the systemic circulation, they must bridge the blood-brain barrier in order to be effective. In the case of the corticoids, McEwen et al. (58) have shown that tritiated B, injected either intraperitoneally or intravenously, is selectively concentrated in various brain structures and that brain concentrations reach their maximum about 20–30 min after administration. In general, concentration of B in brain areas, relative to that found in cortex, is best described by the following rank order: Hippocampus > pituitary > septum > amygdala > hypothalamus (2, 45, 56). In brain areas other than hippocampus clearance of the hormone parallels the decline in plasma. Thus, there appears to be a free exchange of the hormone between the brain and blood (57, 59). In contrast to the other areas, B is retained by cell nuclei in the hippocampus and septum for at least 2 hr after administration (58), but hippocampal binding sites saturate at physiological doses of B, whereas septal binding sites, for example, do not. McEwen et al. (58) found evidence of a dorsal-ventral gradient of concentration of labelled B in the hippocampus, the concentration being highest in dorsal and lowest in ventral areas. Concentration of B also tended to be highest in the cells of the CA1 and CA2 fields and lowest in the cells of the CA3 field (56).

The distribution of ACTH in the CNS is a matter of controversy, in part because of measurement difficulties. However, van Riezen et al. (85) intravenously injected labelled analogues of behaviorally active ACTH fragments and were able to recover 1×10^{-4} of the administered dose in brain tissue 15 min later. Other investigators have found evidence of endogenous ACTH in brain (37, 47, 53), although the route of entry is under discussion (3, 62) and is thought by some to be the result of leakage from the sella turcica (62) whereas others argue that brain tissues may be capable of ACTH synthesis (36, 37, 53).

CNS modulation by pituitary-adrenal hormones

ACTH or its absence has a number of dramatic and reliable effects on CNS activity. For example, $ACTH_{4-10}$ has been found to increase protein metabolism and the incorporation of amino acid precursors into brain

protein (74), and hypopsysectomy alters brain protein chemistry in complex ways (33). Effects of ACTH or fragments of ACTH can be seen at the level of reflex activity in the spinal cord (49, 50) and at the level of whole brain EEG where, for example, it has been shown to disinhibit the final (synchronized EEG) stage of habituation (25). In contrast to these effects, corticosteroids such as cortisone and cortisol have been shown to increase the amplitude of sciatic nerve evoked response in brain stem and hypothalamus in rats (26, 28) and to produce sedation and inhibition, but these effects can be complexly related to dose (38). In some instances, hippocampal and hypothalamic recordings suggest that ACTH and B may have opposite effects on single unit activity (71, 79, 80). The safest inference may be that the electrophysiological effects of these hormones, which include increased amplitude of evoked potentials (30) and EEG activation (29), are dependent on the species and the specific structures being studied.

Conclusion

It seems, in view of these findings, that pituitary-adrenal hormones significantly influence avoidance behavior, that they are present in CNS, ACTH in hypothalamus and perhaps elsewhere and B in extra-hypothalamic areas, and that they can significantly modify the electrophysiological activity of these structures. We now turn to the question of the regulation of the pituitary-adrenal system by hypothalamic and extra-hypothalamic regions of the CNS.

CNS REGULATION OF PITUITARY-ADRENAL ACTIVITY

There are two aspect of CNS regulation of pituitary-adrenal activity that we wish to discuss: 1) neurotransmitter control of the hypothalamic releasing hormone for ACTH, i.e., corticotropin releasing hormon (CRH) and 2) feedback regulation by corticosteroids of ACTH release in stress. These will be taken up in turn.

Neurotransmitter control of CRH

It is generally accepted that CRH is secreted by neurons whose cell bodies are diffusely distributed in the hypothalamus from supra-chiasmatic, paraventricular and arcuate neuclei to posterior hypothalamic sites as caudal as the mammillary bodies (39*a*, 40, 68). The CRH secreting neurons are presumed to terminate adjacent to portal vessels in the median eminence. Excitatory and inhibitory inputs that control the CRH neurons are integrated in the hypothalamus, and in vitro analyses of the

hypothalamus of the rat have shown that CRH secretion is stimulated by acetylcholine (Ach) and serotonin (5-HT), the action of 5-HT being dependent on a cholinergic interneuron (40, 41). Inhibitory control is exerted by norepinephrine (NE), gamma aminobutyric acid (GABA) and melatonin (40, 41). In general, these stimulatory and inhibitory effects have been confirmed by others using both in vivo and other in vitro techniques (1, 9, 10, 48). The CRH is carried, via the portal circulation, to the anterior pituitary where it stimulates release, and synthesis, of ACTH, which, in turn, stimulates synthesis and subsequent release of B from the adrenal cortex. Free (unbound) plasma B then stimulates negative feedback mechanisms which regulate further secretion of CRH and ACTH.

Feedback regulation of CRH and ACTH by corticoids

Hypothalamic regulation. There are two temporally distinct negative feedback mechanisms that control pituitary-adrenal activity. Both operate at both the hypothalamic and the pituitary levels (38, 41, 42), although the hypothalamic feedback tends to override the effects seen at the lower pituitary level. The first of these mechanisms is called fast feedback, and it operates over a period of minutes. It is characterized by rate sensitivity and saturation. Rate sensitivity is shown by the fact that inhibition of ACTH release is induced by a rapid increase in the plasma concentration of exogenous or endogenous B. Rates of increase in excess of 1.3 μg/100 ml/min will block further release of ACTH in response to most stressors. Rates of increase below that value are ineffective (39). Initially, fast feedback is independent of the absolute level of plasma B. However, after a sustained, but moderate, elevation of plasma B, there is no rate of increase of plasma steroid concentration that will contemporaneously inhibit ACTH release. This is the saturation phenomenon (39). This fast feedback mechanism, then, is one that can respond quickly to the dynamic changes in hormone concentration during acute stress (rate sensitivity) and that can shut itself off and allow continued ACTH secretion during prolonged stress (saturation). There is evidence to suggest that the fast feedback effect in the hypothalamus works by inhibition of CRH release which may be a surface membrane, receptor binding phenomenon (40, 41).

The second negative feedback mechanism is called slow or delayed fedback, and it operates over a period of hours or days. Exogenous administration of B can induce a period of inhibition of ACTH release one or more hours after injection, by which time the plasma B concentration has returned to basal or near basal levels. The larger the dose of exogenous B the longer delayed is the period of maximal inhibition. Thus slow

feedback shows neither rate sensitivity nor saturation. The adaptive significance of this mechanism may be that it permits modulation of the overall excitability of the pituitary-adrenal axis. Slow feedback may require intracellular binding of B and probably reflects influences on CRH synthesis as well as release (39*a*, 40, 41, 55).

Extra-hypothalamic regulation. Although the hypothalamus may be the final common path for control of the pituitary-adrenal system, recent analyses suggest that the concept of a hypophysiotropic region of the hypothalamus is no longer viable. It is now thought that many remote brain regions may communicate chemically with the hypothalamus via the cerebrospinal fluid of the ventricles (75, 81, 82), and a number of structures within the Papez–Nauta limbic brain have been assumed to exert direct or indirect neural control of the pituitary-adrenal axis. One such structure, the hippocampus, has been thought to have predominantly inhibitiory control over pituitary-adrenal activity (31, 54, 88, 89).

Afferent inputs to the hippocampus arise principally in midbrain, septum and entorhinal cortex. 5-HT and NE mediated inputs to the hippocampus originate in the midbrain raphe nuclei and locus coeruleus, respectively (63, 77, 78), and projections from medial septal nuclei to the hippocampus provide Ach mediated inputs via the fornix (67). Afferents from cingulate cortex to hippocampus originate in part in the mammillary bodies and anterior thalamus.

There are three efferent pathways from hippocampus to hypothalamus: 1) From hippocampus proper, precommissural efferents traverse the septal area and reach the anterior and lateral hypothalamus via the medial forebrain bundle (MFB). Since this multisynaptic tract contains ascending and descending fibers from various limbic regions, it probably also serves to interconnect many other limbic regions (15). 2) From the ventral subiculum adjacent to the hippocampal CA1 field, efferents join the medial corticohypothalamic tract and terminate in the ventromedial hypothalamus and medial mammillary region (61, 72, 83, 84). 3) From dorsal and ventral subiculum and from pre- and para-subiculum efferents in the fimbria, fornix and posterior thalamic radiation terminate extensively in the mammillary bodies and in dorsolateral and posterolateral thalamic nuclei (61, 72, 83, 84). Thus efferents from the hippocampal formation project throughout the rostral-caudal extent of the hypothalamus. CRH secreting neurones are distributed throughout the same hypothalamic regions, so it appears that there is sufficient hippocampal input to the appropriate hypothalamic areas to support the hypothesis that the hippocampus exerts some control over pituitary-adrenal activity. Furthermore, a number of investigators have found that hippocampal units are responsive to a variety of sensory inputs that normally activate

the pituitary-adrenal axis (73, 76), and stimulation of dorsal hippocampus and fornix influences unit activity in the median eminence and mammillary bodies (46, 52).

Electrical stimulation of the hippocampus has resulted in both increased and decreased pituitary-adrenal activity. The predominant effects, however, seem to be decreases. For example, early work by Endroczi and colleagues (23, 24) showed that reduced ACTH secretion resulted from low (12 Hz) frequency stimulation. And low frequency stimulation has been shown to inhibit the pituitary-adrenal response to pain or cold stress (22) or to presentation of a Pavlovian conditioned aversive stimulu (66). On the other hand, increased pituitary-adrenal activity was induced by high (120 and 250 Hz) frequency stimulation (11, 23, 24), and in one case even low (25 Hz) frequency stimulation during the a.m. trough of the circadian rhythm of plasma B concentration resulted in increased pituitary-adrenal activity (11).

As we have seen, endogenous steroids are selectively bound by hippocampal cell nuclei, and electrical stimulation, presumably some of those same cells that bind corticoids, frequently results in inhibition of pituitary-adrenal activity. Implantation of steroids might therefore be expected to activate these cells and inhibit ACTH release. In accordance with this hypothesis, Davidson and Feldman (14) found that implants of dexamethasone in posterior and lateral hippocampus and in hippocampal commissure and precommissural fornix inhibited the compensatory adrenal hypertrophy that normally follows unilateral adrenalectomy. Others found no effects of dorsal implants of cortisol (8, 27), although it should be noted that the hippocampus does not preferentially bind cortisol, so it might be expected that such implants would be ineffective (56).

The effects of electrical stimulation and steroid implants seem relatively consistent and suggest a predominantly inhibitory role for hippocampus in regulating pituitary-adrenal activity. Lesions of the hippocampus would thus be expected to release these inhibitory effects and permit supra-normal responses to stress. However, a number of studies of lesions of the hippocampus, dorsal or ventral or both, failed to find effects of these lesions on pituitary-adrenal responses to stress (15, 43, 44, 51). However, Conforti and Feldman (12) found that dorsal hippocampal ablations resulted in a significant reduction in the magnitude of the pituitary-adrenal response to sciatic nerve stimulation (under barbiturate anesthesia). There were no effects of dorsal hippocampal damage on the magnitude of the responses to flashing light or ether stress. On the other hand, Murphy et al. (64) inflicted massive ablations of dorsal and lateral hippocampus and found increased plasma concentrations in response to stress (immobilization or immobilization plus electric shock to the feet).

In contrast to the above results, Fraley (32) studied the effects of small radio frequency lesions or more extensive aspiration lesions of the dorsal hippocampus and found neither a change in the pituitary-adrenal response to foot shock nor a change in slow feedback inhibition of the pituitary-adrenal response to the same stressor. She also failed to find any evidence of dorsal hippocampal function in mediation of or slow feedback inhibition of the pituitary-adrenal response to light or ether.

Conclusion

On the basis of these results we can safely conclude that the hypothalamus is the final common pathway for efferent control of pituitary-adrenal activity by the CNS. Fast and slow feedback mechanisms have been observed there in the in vitro preparation of Jones (40). Although the evidence is hardly consistent, the hypothesis that extra-hypothalamic limbic structures such as hippocampus may exert some control over pituitary-adrenal activity cannot be ruled out. The anatomy and physiology of the hippocampus seem appropriate to support such a role for that structure. Certainly the neural interconnections between hippocampus and hypothalamus and selective uptake of corticosteroids in the hippocampus are adequate for the role. Electrical stimulation of dorsal hippocampus often, though not always, results in inhibition of pituitary-adrenal activation, and implantation of the appropriate steroids can induce inhibitory effects. The conflicting results of the ablation studies may be resolvable on two accounts: 1) Many of the experiments employ systemic stressors that can act directly on the pituitary and/or median eminence, so that not even hypothalamic release of CRH is required for a normal elevation of plasma B (21). 2) There may be important differences among experiments as to which tissues were destroyed and which spared. Fraley's careful analysis of her lesions and reports of some others (12, 64) suggest that a critical structure may be the subiculum and its projections via the fimbria. In Fraley's experiments these structures were spared. In Conforti and Feldman and in Murphy et al., they were not. Since the response a shock stress was not altered in Fraley's experiments but was modified in the other two, further research to identify the functional role of the subiculum and its projections seems warranted.

HIPPOCAMPUS AS MEDIATOR OF THE BEHAVIORAL EFFECTS OF PITUITARY-ADRENAL HORMONES

There can be little doubt that hippocampal structures significantly influence avoidance learning and performance. Black et al. (4) have recently reviewed the extensive literature on this topic so we will not do

so here. However, a number of recent studies have found some interesting effects of ACTH or ACTH fragments on hippocampal theta activity (20, 34) which led Bohus (5) to conclude that ACTH stimulated or increased the excitability of the theta-generating network, thus providing a possible mechanism for behavioral facilitation by ACTH. Even more recently, vanWimersma Greidanus and deWied (87) were able to eliminate the effects of $ACTH_{4-10}$ on avoidance performance in extinction with relatively discrete lesions in the dorsal hippocampus. Unfortunately, detailed histological reconstructions were not provided in that report.

After a thorough review of the existing literature, Bohus (5) in 1975 suggested that the behavioral and endocrine functions of the hippocampus might be spatially separated, the behavioral elements being dorsal, the endocrine elements ventral. Recent isotopic mappings of the efferent projections of the hippocampal formation by Swanson and Cowan (83, 84) and by Meibach and Siegel (61) provide some anatomical basis for such functional differentiation. Earlier degeneration studies indicated that the postcommissural fornix projection to the mammillary bodies was composed of axons from cell bodies located primarily in the CA1 field of the hippocampus and that the medial corticohypothalamic tract to the medial basal hypothalamus was composed of axons originating in the ventral subicular portion of the hippocampal formation. The recent data suggest, however, that the postcommissural axons that enter the mammillary region of the hypothalamus also originate in the subicular areas, either only in the dorsal (84) or in both posterior dorsal and ventral portions (61). Furthermore, there is some topographical organization of the hippocampal efferent target sites in the mammillary region and in the septum.

These efferent projections of the various levels of the hippocampal formation may provide the anatomical substrate for differential control of behavior and endocrine function. From Fraley's analysis of the lesion studies, it was suggested that whether hippocampal lesions produced a significant endocrine effect depended on whether the subiculum was destroyed or its projections disrupted. If damage to that system occurred, changes in pituitary-adrenal activity were observed, despite significant variation in the extent of damage elsewhere. Conversely, if that system were spared, no alteration of pituitary-adrenal function was found. Whether the lesions involving the subicular system increased or decreased pituitary-adrenal responses to stress probably depends on the precise locus of the lesion within that system and on the kind of stress used. This suggests that the hippocampal subiculum, with its projections to the hypothalamus may be a system that normally provides an input to regulate the pituitary-adrenal response to some neurogenic stressors. The input

to the hypothalamus is mixed, both inhibitory and excitatory elements being present. But the inhibitory elements probably predominate. Lesions that destroy essential subicular elements or transect key projections to the mammillary bodies or ventral medial hypothalamus would be expected to alter the pituitary-adrenal response, most often by increasing the response, but on occasions decreasing it.

These results suggest that the hippocampal subiculum and its projections may be important in controlling avoidance behavior and pituitary-adrenal activity and in mediating the effects of hormones of that system on avoidance behavior. However, other brain areas have also been implicated in the hormone-behavior interactions. Earlier studies found that the parafascicular area of the posterior thalamus is a primary region where pituitary-adrenal hormones were exerting their effects on avoidance performance (6, 16, 86). The recent isotopic mappings, however, reported evidence of hippocampal subicular projections only to posterior lateral and anterior thalamic nuclei, not to parafascicular nuclei (83, 84). Further analyses may reveal such projections from hippocampal subiculum or intrathalamic connections between posterior lateral and parafascicular nuclei. If found, such projections or interconnections would provide the needed substrate for a complex circuit involving hippocampal subiculum, thalamus and hypothalamus that may be important both in regulating the pituitary-adrenal responses to stress and in mediating the effects of ACTH on avoidance behavior. Further research on this seems warranted by the data.

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