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Central Nervous System and Peripheral Effects of ACTH, MSH, and Related Neuropeptides

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BECKWITH, B. E. AND C. A. SANDMAN. *Central nervous system and peripheral effects of ACTH, MSH, and related neuropeptides*. PEPTIDES 3(3) 411–420, 1982.—Adrenocorticotropic Hormone (ACTH), Melanocyte-Stimulating Hormone (MSH), and related peptides have been shown to have several neurogenic effects: alteration of cerebral protein synthesis, RNA synthesis, protein phosphorylation, and neurotransmitter turnover. Furthermore, there appears to be an ACTH containing circuit in the CNS which originates in the arcuate nucleus. Changes in concentration of the peptides in this family have been shown to alter electrophysiology, neuromuscular function, and behavior (e.g., grooming, learning) in infrahuman subjects. These findings suggest that the neuropeptides MSH and ACTH influence the capacity of an organism to efficiently evaluate information and influence the affective functioning of humans.

ACTH Affect Attention Depression Electrophysiology MSH Neuropeptides

ADRENOCORTICOTROPIC hormone (ACTH) is a linear nonatriacontapeptide, i.e. a peptide consisting of 39 amino acid residues, which can be derived from a larger 31,000 dalton glycoprotein [77] and is but one member of a chemically and biogenetically related family of polypeptides which also includes melanocyte-stimulating hormone (MSH). It is also of considerable interest that endorphin and the enkephalins are members of this "family of peptides." Current beliefs indicate that a large glycoprotein, pro-opiomelanocortin, serves as a prohormone which is enzymatically reduced to smaller peptide chains (e.g., ACTH, MSH) based upon either site-specific processing and degradation [67] or other as yet unspecified processes. Furthermore, recent discoveries have indicated that ACTH and MSH share a core heptapeptide, Met-Glu-His-Phe-Arg-Try-Gly, which is important in many of the actions of these neuropeptides upon behavior [54,72].

Classical views postulate a role for ACTH in induction of steriodogenesis in the adrenal cortex and a role for MSH in regulation of pigmentary changes (e.g., skin darkening in amphibians) in lower vertebrates [130]. However, during the past two decades several "extraendocrine" functions have been attributed to these peptides. This new view of endocrinology also was stimulated by at least two main bodies of findings: (1) The discovery of pituitary hormones in the brain and (2) the discovery of behavioral altering consequences of these hormones and their fragments and analogues (see reviews [6, 11, 65]). The present paper reviews the major effects of these two hormones on CNS and peripheral functions.

ORIGIN AND NEUROCHEMICAL ACTIONS

A great deal of evidence indicates multiple sources of MSH/ACTH-like peptides. Of course, the pituitary remains the central site for production of these peptides, at least in terms of relative volume and variety (indeed, a recent study has identified 13 different peptides related to ACTH and lipotropin in the rat anterior and intermediate lobes [59]) of neuropeptides identified. However, several studies have identified MSH/ACTH-like peptides also in the hypothalamus, limbic system, midbrain, pons, medulla, striatum, cortex, and cerebellum [66,95]. In fact, it appears that the origin of this extrapituitary ACTH is the arcuate nucleus of the hypothalamus [92, 94, 95]. Furthermore, MSH/ACTH-like peptides have also been discovered in the gut and pancreas [69, 70, 71]. That the MSH/ACTH-like immunoreactivity in

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the CNS is of extra-pituitary origin has been demonstrated clearly by the continued presence of these peptides in the brain after hypophysectomy [65]. Thus, there appear to be two independent sources of CNS MSH/ACTH-like neuropeptides: The anterior/intermediate lobes of the pituitary and the arcuate nucleus.

Other studies have indicated that MSH/ACTH-like peptides induce numerous changes in neurochemistry. For example, MSH/ACTH alters cerebral protein synthesis, RNA synthesis, protein phosphorylation, cyclic nucleotide metabolism, and catecholamine and indolamine neurotransmitter turnover [36, 48, 137]. Additionally, MSH/ACTH-like peptides were found to reduce bloodflow to all CNS regions except the occipital cortex [50,51]. Overall, these actions suggest that the brain acts as a target organ for MSH/ACTH peptides which may be distributed via vascular systems [65] and/or cerebrospinal fluid routes [91]. Additionally, there appears to be a distinct MSH/ACTH system which originates in the arcuate nucleus and influences many CNS areas in a manner similar to that of more classical neurotransmitter systems.

ELECTROPHYSIOLOGICAL EFFECTS

Another mode of investigation of CNS physiological effects of MSH/ACTH fragments is the recording of electrical activity in the brain. The two most popular electrophysiological techniques are the electroencephalogram (EEG) and event related potentials (ERP) [122]. Both techniques are powerful noninvasive methods for elaborating upon the neurological alterations caused by these peptides.

Treatment with MSH/ACTH fragments has been shown to alter EEG frequencies in frogs [6], rats [110], and humans [38,87]. Spectral analysis of the EEG in humans [87] indicated that a 30 mg dose of MSH/ACTH 4–10 produced a decrease in power output of the 3–7 Hz frequency concomitant with an increase in the 8–12 Hz and 12+ Hz frequencies. Furthermore, the results of this study demonstrated that MSH/ACTH 4–10 delayed the alpha-blocking EEG response to repetitive stimulation (i.e., peptide treatment attenuated habituation of the alpha-blocking response). However, this effect was not found with a 60 mg dose of MSH/ACTH 4–10 [118] nor was it found in response to treatment with MSH/ACTH 4–10 (30 mg) in elderly subjects (mostly female whereas the former studies used mainly male subjects) [12]. Overall, it appears as if some dose levels of MSH/ACTH fragments do produce an alteration in EEG phenomena. Sandman and Kastin [114] have concluded that these changes in characteristics of the EEG are responsible for extending the impact of stimulation over a significantly long time course and Bohus and DeWied [11] have suggested that changes in EEG are the result of the influence of these peptides upon limbic-midbrain systems.

The other electrophysiological technique, the ERP, offers a more potentially elegant means of assessing the effects of peptides on electrophysiological activity [114]. The ERP is a temporally structured response of the brain to peripheral stimulation (e.g., somatosensory, auditory, or visual) which can be detected by averaging EEG recordings by a computer. This response consists of several components which are believed to be related to the various components of CNS activity related to information-processing [114]. Kastin *et al.* [61] were the first to indicate that MSH/ACTH fragments influence the ERP triggered by somatosensory stimulation. They found an increased amplitude of the P200 component during both relaxation and attention as a result of treatment with this peptide. In another study Miller, Harris, Kastin and Van Riezen [86] measured the visual ERP while subjects engaged in a continuous performance task. Results indicated that treatment with MSH/ACTH 4–10 decreased the amplitude of the P200 component whereas it augmented the negative peak about 350 msec after stimulation. Finally, Sandman, Berka, Walker and Veith-Flanigan [109] measured the effects of 0, 5, 10, and 20 mg of an orally active MSH/ACTH analog on the visual ERP. They found an interaction between dose, sex, and hemisphere resulting from treatment. The major effect on males was an enhanced P100 component of the right hemisphere and on females was enhancement of the P200 component of both hemispheres with the greatest effect on the left hemisphere. These responses were found to peak at about 60 minutes. Taken together, these results suggested both a provocative influence of MSH/ACTH fragments on dynamic measures of brain physiology and a sexually dimorphic response to treatment with this neuropeptide. Neither Miller nor Sandman [88,111] have reported changes in peripheral basal autonomic responding as a result of treatment with MSH/ACTH fragments. However, MSH/ACTH 4–10 produced significant heart rate deceleration to a novel stimulus [111]. This response is a reliable index of the orienting response and is consistent with the attenuation of alpha-blocking reported earlier since both responses reflect increased awareness to the environment.

EFFECTS ON NEUROMUSCULAR FUNCTION

Strand and Smith [128] have reviewed yet another function of MSH/ACTH fragments: modulation of neuromuscular function. These peptides increase the amplitude of muscle action potentials, increase contraction amplitudes, and delay the onset of fatigue in adrenalectomized and hypophysectomized animals [52,126]. MSH/ACTH fragments also have been shown to enhance regeneration of axons subsequent to crushing peripheral nerve connections in the motorneuron [127]. Further studies intended to localize these actions have indicated increased miniature endplate potential frequencies which suggests that the effect of these peptides is not on muscle directly but rather they alter presynaptic events in motorneurons [52,128].

This modulatory effect of MSH/ACTH fragments is not localized in the skeletal neuromuscular complex but also extends to the alteration of cardiac excitability, contractility, and sensitivity to norepinephrine [126]. Furthermore, MSH/ACTH 4–10 facilitates neuromuscular function in immature rats (9–40 days of age) by increasing muscle contraction amplitude and decreasing fatigue [123]. Finally, infusion of ACTH 4–10 has been shown to prevent the pathological decline in amplitude of a series of evoked muscle action potentials in patients suffering from pathology of motorneuron (e.g., multiple sclerosis, progressive spinal muscular atrophy, and carpal tunnel syndrome) [126,128].

Strand [126] indicates that these actions suggest that these peptides function to raise a depressed excitatory state to normal but that they have little or no influence in the modulation of normal states of excitation [126]. Moreover, Strand [123,126] believes that this influence on skeletal muscle function is a neurotropic action mediated by spinal motorneurons.

To this point this review has focused upon the diversity of neurogenic actions of MSH/ACTH peptides. The extraordi-

nary diversity of these effects makes it clear that these peptides have the potential to profoundly influence an organism independent of their classical endocrine actions. Now let us turn to an even more exciting area of peptide research, the effects of MSH/ACTH peptides on behavior.

ACTH-INDUCED EXCESSIVE GROOMING

Intracerebroventricular administration of MSH/ACTH fragments has long been known to induce both excessive grooming and the stretching and yawning syndrome [40, 41, 47]. It appears as if this action is most potently initiated by ACTH 1–24 or ACTH 1–16 with other fragments producing much smaller effects.

ACTH-induced grooming is similar in composition to naturally released grooming behavior with central administration of the peptide lengthening the duration of grooming bouts rather than producing an increased number of grooming episodes [47]. This behavior is independent of both the pituitary gland [60] and endocrine activity [41]. MSH/ACTH modulation of grooming seems to be mediated by hippocampal [28] and substantia nigral systems [47]. Interestingly, this response is organized by different neural circuits than is the stretching and yawning syndrome (a cholinergically mediated septal-hippocampal response) [78] and the extinction of conditioned avoidance responses (parafascicular and rostral septal responses) [134]. Therefore, it appears that these neuropeptides modulate independently different neural systems in producing their various effects on behavior.

Gispen and Isaacson [47] concluded that excessive grooming is most typically found after the termination of stressors and therefore that it may be part of a restorative neural and chemical process. They further suggest that ACTH is an initiating factor in the mobilization to meet emergency situations as well as an initiating factor in the reestablishment of equilibrium. This latter function is consistent with viewing grooming behavior as playing a deactivating role in animal behavior.

ROLE OF MSH/ACTH FRAGMENTS ON ATTENTIONAL PROCESSES

Early studies with hypophysectomized rats indicated that the pituitary gland exerted an influence upon behavior [16,98]. This conclusion was generated by results obtained from injecting animals with pituitary hormones or by selectively lesioning the pituitary. Both strategies indicated that peptides of pituitary origin exert effects which are independent of target organ activity. Miller [88,90] demonstrated a specific extraadrenal influence of ACTH upon behavior by showing that ACTH injections to normal and adrenalectomized rats resulted in prolonged extinction of an active avoidance response. DeWied [30] found similar results in adenohypophysectomized rats. More recent work has confirmed and extended this finding to include both several MSH/ACTH fragments for both active [31, 32, 34] and passive [29, 55, 115] avoidance responses.

Initial attempts to explain these findings produced arousal-stress explanations of ACTH actions. This was probably due to both the use of aversive conditioning paradigms for behavioral testing and the connections made between ACTH and the stress response by Selye [121]. However, these explanations may be only partially accurate. Data gathered from experiments using appetitive paradigms also suggested that MSH/ACTH inhibited extinction. Furthermore, in a direct test of the arousal hypothesis, Beckwith, Sandman, Alexander, Gerald and Goldman [7] demonstrated that pharmacological induction of arousal via d-amphetamine produced opposite results to those found with MSH/ACTH on a discrimination task. Finally, Beckwith, Sandman, Hothersall and Kastin [8] showed that neonatal injections of MSH/ACTH 4–10 influenced later performance of juvenile and adult rats on an appetitive task.

The first departure from an arousal-stress construct was presented by DeWied and Bohus [33]. They found that both MSH and pitressin have, respectively, short and long term effects on shuttlebox avoidance. This suggested to DeWied that brief peptide influences (i.e., MSH/ACTH-like influences) were due to actions upon short-term memory (i.e., "memorization from trail to trial"). Subsequent tests of the memory construct [62, 63, 99] have suggested that MSH/ACTH may not directly influence storage in any of the memory systems but rather that these neuropeptides may influence memory by interacting with memory control processes (e.g., retrieval, attention) [6,49].

Attention has been formulated as a third explanatory construct for the influence of these neuropeptides on behavior. The initial study generating this construct was actually undertaken as a test of the memory hypothesis. Sandman, Miller, Kastin and Schally [116] reasoned that if ACTH works by establishing more enduring short-term memory, then exogenous administration of MSH/ACTH analogues should retard the learning of a reversal discrimination because injection of the neuropeptide would make the original discrimination more difficult to give up. First, they trained albino rats on a simultaneous two-choice visual discrimination (e.g., White+, Black−). After the animals performed the response to a preselected criterion, the solution to the problem was reversed (e.g., White−, Black+). Pretreatment with MSH had no influence on acquisition of the discrimination but it did facilitate reversal of the discrimination. Drawing from the model developed by Mackintosh [74, 75, 129]. Sandman *et al.* [116], argued that these neuropeptides influence attentional processes.

According to this attentional analysis of discrimination learning there are two requirements for mastery of a discrimination problem. Subjects must first learn to attend to relevant stimulus dimensions via the strengthening of appropriate sensory analyzers. Then they must learn appropriate response attachments based upon reinforcement contingencies. Sutherland and Mackintosh [129] postulate that these two processes are strengthened somewhat independently; thus analyzer strength accumulates at a different rate than does response strength. Therefore, certain treatments such as overtraining or treatment with MSH/ACTH analogues and/or fragments increases the strength of the attending response to a level greater than the strength of the choice response to that cue. Subsequently, animals so treated have only to extinguish choice responses in order to again efficiently learn about the correlation between the relevant cue and reward; whereas, nontreated animals must extinguish both attentional and response components in the same situation. Several subsequent studies [9, 106, 107, 108] have supported the appropriateness of this interpretation of neuropeptide influence upon behavior.

Sandman, George, Nolan, Van Riezen and Kastin [112] used the human analogue of the animal discrimination task described above to test the attentional hypothesis of MSH/ACTH action in human male subjects. They used a discrimination task involving four two-choice problems: original learning (e.g., Red+, Black−), reversal learning (e.g., Red−, Black+), intradimensional shift (e.g., Blue+,

White−), and extradimensional shift (e.g., Square+, Circle−). The results confirmed the prediction that MSH/ACTH would enhance performance on shift problems. In a later study, Sandman, George, McCanne, Nolan, Kaswan and Kastin [111] replicated this finding. Furthermore, Ward, Sandman, George and Shulman [139] used the Sternberg Item Recognition Task [125] to assess the influence of MSH/ACTH 4–10 independently on attention and memory. They also included female subjects in their study. As would be consistent with the attentional hypothesis, the results indicated that this neuropeptide induced constant decreases in reaction time for each set size (i.e., 1, 2, 3, 4 items). There were no differences in performance between males and females. These findings may be interpreted as evidence that ACTH 4–10 influences attentional processes rather than memory processes involved in this task.

In yet another test of the attentional model Sandman *et al.* [111] divided attentional processes into two components: detection and discrimination. Detection was assessed by means of tachistoscopic stimulus presentation at varying luminance levels. Discrimination was tested by asking subjects to report the spatial configuration of a series of dots that were tachistoscopically presented for various durations. Male college students were used as subjects and were treated with either MSH/ACTH 4–10 or the vehicle solution in a double-blind study. The results again support an attentional interpretation: Subjects treated with the neuropeptide showed impaired simple stimulus intake but improved discrimination. The authors concluded that MSH/ACTH 4–10 may be involved in processes which reduce "perceptual noise" in the information processing system.

There are also several electrophysiological studies (reviewed earlier) which support the attentional interpretation of the actions of MSH/ACTH-like neuropeptides. For instance, these peptides have been found to increase average somatosensory potentials [61], improve performance on the Rod and Frame Test [111,112], alter occipital EEG patterns in a manner indicative of increased attention [87] and augment heart-rate responses during an orienting task [111]. Taken together the above reviewed evidence provides strong and convergent support for an attentional interpretation of MSH/ACTH-like peptide actions, although the specific nature of the attentional processes remains to be elaborated.

A final and highly suggestive piece of evidence for this model of neuropeptide action comes from recent attempts to reverse "attentional deficits" in a clinical population by means of neuropeptide treatment [113,138]. These projects again used the concept discrimination task described above to test the attentional hypothesis. They chose a population of retarded adult males as subjects based upon the rationale that this population displays attentionally deficient behavior [143]. Again results were highly consistent with those of studies reported above i.e., treatment with MSH/ACTH-like neuropeptides significantly improved performance of concept shifts. Furthermore, the results of these studies suggest that heretofore assumed irreversible deficits may be reversed by treatment with fragments of the neuropeptides MSH and ACTH.

In an interesting and independent series of studies Henkin [56,57] has provided additional support for the position that hormones from the pituitary-adrenocortical axis influence information-processing capacities in human beings. In an elegantly executed series of studies he demonstrated that glucocorticoid hormones from the adrenocortex facilitate the detection of sensory signals (i.e., decrease sensory thresholds) in the modalities of taste, olfaction, audition and proprioception but impair recognition and discrimination within these same sensory modalities. Furthermore, these changes in sensory detection occur during physiological as well as pathological and pharmacological changes.

The next step in trying to understand how these neuropeptides, perhaps in balance with corticosteroids, influence attention is to gain some understanding of where these hormones act on the brain and where the brain acts on the neuroendocrine system. A great deal of evidence indicates that the place to look for an interface between the neuropeptide-steroid and neural systems is in the limbic-hypothalamic areas of the brain. For instance, there is evidence that the hippocampus [2], and the amygdala [17] modulate basal concentrations of ACTH in the general circulation. Also, a large number of studies (reviewed by [82,83]) suggest that there are corticosteroid receptors in many areas of the limbic system. Together these findings indicate that limbic system circuits may be an important first place to look if one wants to find the neuroendocrine regulatory mechanism for attention. Specific evidence for this conclusion has been provided by DeWied's studies on the anatomical locus of neuropeptide action which were reviewed earlier [134].

Indeed, Pribram and McGuinness in two important review papers [84,97] have postulated that the control of attention is largely directed by major limbic circuitry. Briefly, it appears as if there are three major limbic circuits that regulate three components of attention: arousal, activation, and effort. First, there are reciprocally acting forebrain systems, dorsolateral frontoamygdaloid, and orbitofrontoamygdaloid circuits, that mediate arousal processes, i.e., the phasic reactions to stimulus input. Second, output from the basal ganglia mediates activation, i.e., the tonic readiness to respond which is important in maintaining attention. Third, hippocampal circuits in reciprocation with the median raphe nucleus and the locus coeruleous match stimuli with neuronal models and execute responses, i.e., effort. Furthermore, McGuiness and Pribram [84] have suggested the neurochemical systems which mediate these processes. They indicate that arousal may be modulated by means of noradrenergic/serotonergic balance (tied to amygdaloid activity) and activation may be regulated by means of dopaminergic/cholinergic balance (tied to the nigrostriatal system). Finally, they present the intriguing postulation that MSH/ACTH-related peptides modulate effort (via hippocampal circuits).

ROLE OF ACTH IN THE MODULATION OF AFFECT

There are converging data that also implicate limbohypothalamic neuroendocrine mechanisms in affective states. First, the limbic system is intimately involved in the control of hypothalamic neuroendocrine regulatory processes. Electrical stimulation of the amygdala produces marked elevations in plasma 17-hydroxycorticosteroids [79] whereas hippocampal stimulation decreases plasma corticosteroids [79]. Other evidence, reviewed earlier, indicates that lesions in major limbic structures both produce noteworthy alterations in plasma ACTH and mediate the effects of MSH/ACTH upon behavior [81]. Additionally, Bohus [10] and McEwen, Gerlack and Micco [81] demonstrated that the hippocampal circuit is the site most active in the uptake of adrenocorticoids. Finally, the classical theories of Papez [93] and Maclean [76] also provided strong support for the limbic system in affective states and more current views [20,100]

have implicated the limbic system in primary affective disturbances.

Second, the symptomatology of depression in man includes the so-called "vegetative and physical manifestations" which include anorexia, sleep disturbance, loss of libido, fatigability, and mood disturbance [3]. This list of symptoms is highly suggestive of autonomic disturbances which implies that hypothalamic controls are dysfunctional during depressive illness [3,102]. Considering, in addition, the direct relationship between hypothalamic and limbic circuits [45,93] it would appear reasonable to hypothesize that endogenous depression reflects a disturbance in normal limbic-hypothalamic coordination. Similar relationships have been expounded by Rubin and Mandell [100], Sachar [101,102] and Carroll [20].

Third, there is growing evidence that central monoamines are important regulators of ACTH-cortisol release [43, 64, 132]. It appears that norepinephrine exerts a tonic inhibitory influence over ACTH release throughout the circadian rhythm. Serotonin also appears to exert an inhibitory role over ACTH secretion but the evidence is mixed [25,105]. Furthermore, much circumstantial evidence suggests that these same biogenic amines are important factors in endogenous depressions. In short, the biogenic amine theory of depression postulates a deficiency of norepinephrine and serotonin as a controlling influence in depressive affect. Interestingly, this hypothesized reduction of central amines would indicate that there should be dysregulation of neuroendocrine systems, which indeed there is.

Increased cortisol and its metabolic by-products have been recognized as a marker for depression for many years [85, 100, 102]. During primary depressive states there is a substantial increase in cortisol secretion over a 24-hour period. This hypersecretion occurs primarily in the afternoon, evening, and early morning hours [104]. This pattern appears not to be associated with a non-specific stress response in that depressed patients feel worse in the morning, the hypersecretion occurs during sleeping hours, anxiolytic drugs do not affect this hypersecretion, and normal subjects under stress do not demonstrate hypersecretion [103]. Based on these data it appears that the biological basis for some depressions is based upon either a dysfunction of central neuroendocrine control mechanisms or at least that peripheral measures of corticosteroids provide an index of central monoaminergic processes. If this hypothesis is accurate then one would expect to find depression as part of the symptomatology characteristic of endocrinopathies of the pituitary-adrenocortical system such as Cushing's Disease.

Current textbooks of endocrinology do list depression as an important symptom of Cushing's Disease [78, 80, 141]. Also, several reviews have indicated that depression is frequently observed, suicide risk is high, euphoria is rare, and alleviation of hypercorticolism produces marked improvements in Cushing's Disease [13, 21, 85, 100]. Furthermore, Carroll [13] implicates hypersecretion of ACTH and corticotropin releasing factor (CRF) as responsible for the depressive affect found in Cushing's Disease. In a review of 78 cases of Cushing's Syndrome and Cushing's Disease he found about 63% of the patients with pituitary-ACTH disturbances (Cushing's Disease) showed symptoms of depression whereas only about 24% of those patients with predominately adrenal tumors (Cushing's Syndrome) showed symptoms of depression. A more recent study [124] conducted psychiatric evaluations of patients with Cushing's Syndrome/Disease. Additionally, plasma concentrations of both ACTH and cortisol were assessed. The results indicated patients with low or normal ACTH levels had mild rather than pronounced depressed moods while patients with moderate to high ACTH levels showed mild or pronounced depressed mood (with an equal likelihood). Further, these investigators reported an inverse relationship between depressed mood and cortisol to ACTH ratio. Together these studies provide support for a relationship between ACTH and depressed mood. However, it should be pointed out that another recent review has suggested that ACTH is "euphorigenic" [96]. This discrepency is accounted for by the fact that the studies reviewed by Pigache and Richter are predominantly dominated by exogenous treatment with MSH/ACTH-like neuropeptides for relatively short durations whereas the present review has focused upon chronic, endogeneous changes in these neuropeptides, as well as cortisol and corticotropin releasing factor.

There are several tests available for evaluation of hypothalamic-pituitary-adrenocortical function. Probably the simplest to perform and least likely to induce side effects is the dexamethasone suppression test. To perform this test one administers small doses of exogenous glucocorticoids (i.e., dexamethasone) at bedtime and then measures the concentration of plasma or urinary cortisol during the next day. Normal responses to this test include dramatic reduction in cortisol during the next 28 hours due to activation of the negative feedback control over ACTH release. Failure to show this suppression of plasma cortisol is considered a hallmark of Cushing's Disease [53,73]. Several studies have been undertaken to determine the response of severely depressed psychiatric patients to an overnight dexamethasone suppression test.

Early studies [18, 24, 39] consistently demonstrated that there was a subgroup of severely depressed psychiatric inpatients who failed to suppress cortisol release in response to dexamethasone administered the day before testing. Although there were contradictory findings (e.g., [46]) subsequent studies conducted in different laboratories have confirmed this finding. Recent estimates indicate that 40% [15], 65% [22], and up to about 85% [120] of severely depressed patients (the percent varies according to diagnostic criteria used to define subtypes of depressive disorder) manifest this endocrine abnormality.

Additionally, this endocrine dysfunction has been found to be unrelated to age [23], sex [23,24] and treatment [23]. Also, this condition is independent of the nonspecific stress response and ego disintegration [20] and is specific to depressive disorders [14,20]. Interestingly, it has also been shown that upon clinical judgments of remission of depressive symptomatology there is a return to normal pituitary-adrenocortical suppression in those patients who were non-suppressors upon admission for treatment [20]. It is clear, therefore, that resistance to suppression by dexamethasone is a specific endocrine disorder characteristic of a substantial subpopulation of severe, endogenous depressions and that this endocrine response is both a valuable diagnostic tool [22, 119, 120] and a potential biological index of outcome and response to various treatment regimes.

The next important strategy to pursue is delineation of the source of this failure of depressives to suppress or demonstrate early release from suppression after small doses of dexamethasone [26]. Several clinical tests exist which allow evaluation of individual components of the pituitary-adrenocortical system to determine if the problem occurs in the pituitary (i.e., inadequate release of ACTH) or in the

adrenal gland (i.e., inadequate regulation of cortisol synthesis and release). One such test involves infusion of ACTH to evaluate the response of the adrenal gland. Studies using this test have indicated that cortisol release in response to ACTH is within normal limits in non-suppressors [19,37]. Another test, the metyrapone test, inhibits cortisol synthesis and therefore allows determination of the pituitary's ability to release ACTH. This response also appears to be intact in nonsuppressors [37]. Therefore, it seems reasonable to assume, as have others (e.g., [21,26]), that the resistance to suppression by dexamethasone is a reflection of limbic-hypothalamic regulatory dysfunction.

In light of the findings reviewed above it appears reasonable to hypothesize that non-suppressors provide a naturally occurring group of humans who have altered concentrations of both ACTH and cortisol, moreover, suppressors provide a naturally occurring control group to assess the effects of chronic exposure to increased ACTH and cortisol. Furthermore, considering the growing evidence for cognitive disturbances in depression [35, 89, 140] and in view of the evidence reviewed earlier regarding the influence of this neuroendocrine system on cognitive processing it may be fruitful to use the same test systems that were found effective in describing the behavioral effects of ACTH to assess cognitive alterations occurring as a result of failure to suppress plasma cortisol in response to dexamethasone. Beckwith [4] has conducted such a study. The results suggested that non-suppressors demonstrate equivalent performance on reversal and extradimensional shift problems, which is contrary to the pattern where the extradimensional shift is more difficult than reversal shift for nonretarded adults. Also, non-suppressors showed improved learning of the extra-dimensional shift when compared with suppressors. These results are in general agreement with the expectations based upon the literature on concept learning performance under the influence of ACTH.

ORGANIZATIONAL ACTIONS OF MSH/ACTH

A final approach to investigations of the effects of MSH/ACTH peptides on CNS activity involves the treatment of immature animals with peptide fragments. The rationale behind these studies lies in the fact that the brain and endocrine system are not yet fully developed in these animals and are therefore uniquely prone to structural modification which may be later manifested behaviorally.

Beckwith, Sandman, Hothersall and Kastin [8] injected rats with MSH or a control solution from days 2 through 7 and tested these animals later on several behavioral tasks. In the first experiment they trained 33 day old rat pups to press a lever to receive food reinforcement. The pups were then trained to delay responses at least 20 seconds (DRL-20 schedule of reinforcement) in order to obtain reinforcement. The efficiency (reinforcement/responses) of animals treated with MSH was initially poorer than that of control animals. But, at 70% of total training time on this schedule the animals that received peptides as neonates demonstrated superior performance compared to the control animals. In a second experiment these investigators evaluated the performance of 90 day old rats who had again received peptide treatment at 2–7 days of age in an automated shuttlebox. Animals treated with MSH acquired and extinguished the avoidance more quickly than did animals injected with the control solution. Finally, a group of animals exposed to the same treatment regime were tested at 90 days of age with the same discrimination procedure that was described above. Animals who had received MSH treatments as neonates learned all discrimination problems; acquisition, reversal, and extradimensional shift (i.e., shift from black-white discrimination to a position habit); faster than did control animals. Both male and female rats were tested in the last experiment but the peptide treatment influenced only male animals. A subsequent study [22] essentially replicated these sexually dimorphic actions of the peptides. It is also interesting to note that human females who received treatments with this peptide at the time of testing do not show the same learning pattern as males [135].

A similar neonatal treatment procedure was used to assess the effects of MSH on social behavior [5]. These animals were then observed in an open-field apparatus when they were 45 and 120 days of age. Pairs of rats were placed in the open-field for 5 minutes and the time they were in contact with each other was measured. Females treated with MSH demonstrated greater time in contact than saline injected animals at 45 days of age but not at 120 days of age. On the other hand, males treated with MSH demonstrated an increased time in contact at 45 days of age which was also apparent at 120 days of age. In a recent study of the effects of an ACTH analogue on the behavior of male retardates in a sheltered workshop, Sandman, Walker and Lawton [117] demonstrated that both patient-patient and patient-supervisor contact increased during treatment with the neuropeptide. This result is the first evidence that the social behavior of humans may also be affected by MSH/ACTH-like neuropeptides.

Although few studies have examined the effects of MSH/ACTH on organization the results of these studies provide impressive evidence that neonatal exposure (the critical period has not yet been determined) to these peptides produces effects which re-organize the CNS substrates of learning and social behaviors. Moreover, these studies have also suggested a sexual dimophism in response to treatment with MSH/ACTH which has been replicated in more recent studies designed to evaluate the activational effect of these neuropeptides.

CONCLUSIONS

The main conclusion to be drawn from the evidence reviewed above is that MSH/ACTH-like neuropeptides modulate CNS, limbic-hypothalamic systems, and peripheral, neuromuscular systems networks involved in information-processing and mood. This is accomplished by two major systems: the hypothalamic-pituitary and arcuate nuclear-CNS routes. The interrelationships between these two systems and especially the specific functioning of the arcuate nuclear system remain obscure. In attempting to develop an explicit model of the adaptive significance of these neuropeptides, Sandman and Kastin [114] made the intriguing suggestion that there is a reciprocal relationship between MSH/ACTH and endorphin neuropeptidergic systems. This suggestion fits well within modern pharmacologic views which postulate reciprocal relationships between classical neurotransmitter systems in determining effects (e.g., [84]).

However, the MSH/ACTH-endorphin reciprocity is not the only modulating influence upon this neuroendocrine/neuropedidergic network. Several reviews (e.g., [11,58]) have also postulated a reciprocal relationship between glucocorticoids and neuropeptides: glucocorticoids suppressing excitation, ACTH increasing excitation. Hennessey and Levine [58] suggest that glucocorticoid-peptide feedback

regulates general arousal. Glucocorticoids may act upon the arousing and activating components of the Pribram-McGuinness [84,97] model of attention whereas the neuropeptides act more upon effort mechanisms which serve to fine-tune the attentional circuits to selectively attend to relevant components of a given stimulus situation.

Adding to the complexity of these relationships is the interaction between the pineal and pituitary which also appears to be reciprocal [6]. Furthermore, a recent study [108] demonstrated that different learning processes are subject to divergent structure-activity relationships with various MSH/ACTH neuropeptides. Interestingly, the speed of original learning was linearly related to molecular weight of the particular neuropeptide used; whereas, molecular weight of neuropeptide showed a "U"-shaped function for reversal learning and an inverted "U"-shaped function for extinction. These complexities of neuroendocrine interactions and neuropeptide-receptor interactions may help explain the range of action possible within attentional and affective behaviors. After all, to be an adaptive system there must be range for flexibility and this flexibility is probably established via complex feedback from many sources.

Finally, we would like to close by mentioning two recent studies which dramatically underscore the significance of our search for understanding of MSH/ACTH-like neuropeptides. First, Veith-Flanigan [136] studied the effects of endogenous changes in ACTH on attention in individuals with congenital hyperplasia, a genetically encoded defecit in enzymes necessary to produce cortisol. By testing subjects at different phases of treatment she was able to assess cognitive functioning during times when plasma levels of ACTH were either suppressed or elevated. Her results indicated a correlation between the slope of the item recognition function on a Sternberg Item Recognition Task [125] and plasma concentration of ACTH. This is the first direct evidence that plasma levels of ACTH predict enhanced performance on an attentional-memorial task. Second, Landfield, Buskin and Pitler [68] demonstrated that long-term treatment, 9 to 10 months, with ACTH 4–9 retarded the development of both neuromorphologic and behavioral correlates of aging in rats. Interestingly, these authors used the same reversal discrimination task as described above as one of their behavioral tasks. They found that treatment with the MSH/ACTH analogue improved reversal learning without influencing original learning. These authors concluded that endogenous peptides may exert long-term trophic effects on brain structure and functions which may influence aging. This finding becomes even more potentially significant when taken in the context of a recent study which demonstrated that ACTH declined with aging in the hypothalamus and corpus striatum of rats [44].

In brief, it appears that MSH/ACTH-like neuropeptides mediate attentional-affective processes in normal and clinical populations. Furthermore, these effects appear to be not just pharmacologic but rather due also to endogenous changes in neuropeptide concentrations. Finally, these neuropeptides may have an antagonistic action to certain processes that normally occur in aging.

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