Z Rheumatol 57: Suppl 2
67–71 (1998)

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The hypothalamic-pituitary-adrenal stress axis in fibromyalgia and chronic fatigue syndrome

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Die Achse Hypothaalmus-Hypophyse-Nebennierenrinde bei Fibromyalgie und Chronischem Ermüdungs-Syndrom

Summary HPA axis abnormalities in FM, CFS, and other stress-related disorders must be placed in a broad clinical context. We know that interventions providing symptomatic improvement in patients with FM and CFS can directly or indirectly affect the HPA axis. These interventions include exercise, tricyclic anti-depresssants, and serotonin reuptake inhibitors. There is little direct information as to how the specific HPA axis perturbations seen in FM can be related to the major symptomatic manifestations of pain, fatigue, sleep disturbance, and psychological distress. Since many of these somatic and psychological symptoms are present in other syndromes that exhibit HPA axis disturbances, it seems reasonable to suggest that there may be some relationship between basal and dynamic function of the HPA axis and clinical manifestations of FM and CFS.

Zusammenfassung Veränderungen der Achse Hypothalamus-Hypophyse-Nebennierenrinde (HPA) beim Fibromyalgie-(FM) und Chronischem-Müdigkeits-Syndrom (CFS) sowie anderen Erkrankungen, bei denen Streßeinflüsse eine große Rolle zu spielen scheinen, müssen in einem größeren klinischen Kontext gesehen werden. Wir wissen, daß therapeutische Interventionen, die eine symptomatische Besserung bei Patienten mit FM und CFS bewirken, direkt oder indirekt Auswirkungen auf die HPA-Achse haben. Diese Interventionen schließen Bewegungstherapie, trizyklische Antidepressiva und Serotonin-Wiederaufnahme-Hemmer mit ein. Es ist wenig über die genauen Beziehungen zwischen den spezifischen Regulationsänderungen der HPA-Achse bei FM und den Hauptsymptomen wie Schmerz, Schwäche, Schlaftstörungen und psychologischer Streß bekannt. Da viele dieser somatischen und psychologischen Symptome auch bei anderen Syndromen vorkommen, welche Störungen der HPA-Achse zeigen, scheint es folgerichtig anzunehmen, daß zwischen den klinischen Manifestationen von FM und CFS Beziehungen zu basalen und dynamischen Funktionen der HPA-Achse bestehen.

Key words Fibromyalgia – chronic fatigue syndrome – hypothalamic-pituitary-adrenal axis – neuroendocrine

Schlüsselwörter Fibromyalgie – Chronisches Ermüdungs-Syndrom – Hypothalamus-Hypophysen-Nebennierenrinden-Achse – Neuroendokrine

Introduction

Clinical syndromes characterized by diffuse musculoskeletal pains and fatigue precipitated or aggravated by physical or emotional stressors have a lengthy history in medical literature (12). However, it was not until recently that efforts to classify patients into more homogeneous clinical groups has made it possible to begin investigation of basic biochemical mechanisms underlying these syndromes. In 1990, the American College of Rheumatology formalized classification criteria for fibromyalgia (FM) based on the presence of widespread musculoskeletal pain and the presence of specific tender points (30). Similarly, the Centers for Disease Control and Prevention proposed a working case definition for chronic fatigue syndrome (CFS), based on persistent or

relapsing, debilitating fatigue in the absence of an alternate diagnosis explaining the clinical presentation (84, 85). Despite the magnitude of clinical and public health concerns associated with FM and CFS, little is known of the underlying pathophysiology of these syndromes. Analysis of neuroendocrine and circadian architecture has proven to be one of the most fruitful areas of resarch into the pathobiology of these disorders. This manuscript will review the function of the HPA axis and summarize disturbances of HPA axis function in FM, CFS, and related disorders.

A Stress Model of FM and CFS

It has been hypothesized that FM and CFS fall into the spectrum of what might be termed 'stress-related illnesses' because of the increase in symptoms associated with physical or emotional stress. Dysregulation of the normal stress response can lead to abnormalities in both physical and behavioral adaptation that may mimic some of the clinical symptoms of FM. Other conditions that share substantial symptomatic overlap with FM and CFS, such as irritable bowel syndrome, chronic headaches, irritable bladder syndrome, and temporomandibular disorders, are also thought to be associated with stress (8). The HPA axis is generally considered to play a pivotal role in the coordinated physiological response to physical and emotional stress.

HPA Axis Physiology

Regulation of the HPA axis involves a complex array of biochemical events occurring principally among the hypothalamus, anterior pituitary, and the cortex of the adrenal gland (Fig. 1) (5). Corticotropin-releasing hormone (CRH) and arginine vasopressing (AVP) are neurohormones with cell bodies in the medial parvocellular division of the paraventricular nucleus (PVN) of the hypothalamus. CRH is also widely distributed in other, extra-hypothalamic locations including the limbic system, cerebral cortex, mid-brain areas, pons, and medulla. Activation of the HPA axis results in the release of these peptides into the hypophyseal portal plexus. Stimulation of specific receptors for CRH and AVP on the corticotroph cells of the anterior pituitary results in the release of adrenocorticotropic hormone (ACTH) into the systemic circulation, primarily affecting glucocorticoid release from the adrenal cortex. CRH and AVP act synergistically, with AVP causing a tremendous amplification of CRH-induced release of ACTH. Indeed, evidence supports a role for AVP in sustaining the activation of the HPA axis during chronic stress (11, 21, 25). Complex short and long negative feedback circuits, primarily mediated by specific glucocorticoid receptors, converge to terminate activation of the HPA axis.

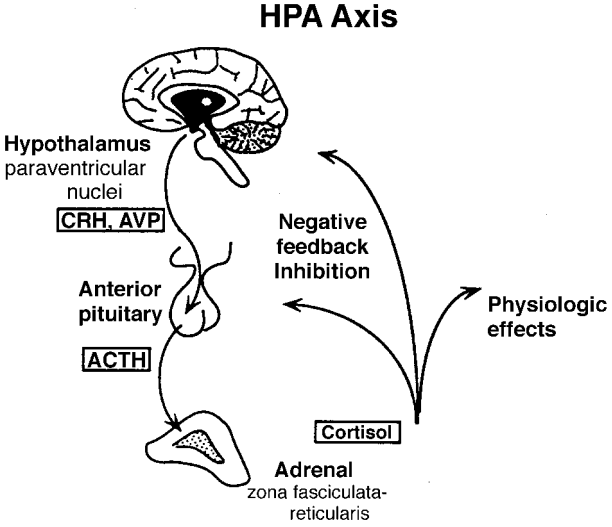

Fig. 1 The Hypothalamic-Pituitary-adrenal (HPA) Axis. Corticotropin releasing hormone (CRH), the principal activating hormone, and arginine vasopressin (AVP), an adjunctive secretagogue, are released from the paraventricular nucleus of the hypothalamus into the hypophyseal portal plexus. Stimulation of specific receptors for CRH and AVP on the corticotroph cells of the anterior pituitary results in the release of adrenocorticotropic hormone (ACTH) into the systemic circulation, primarily affecting glucocorticoid release from the adrenal cortex. Cortisol acts through multiple negative feedback mechanisms to inhibit HPA axis activation. Cortisol also has important physiologic functions that allow adaptation to stress

In addition to its stress-dependent activation, the HPA axis exhibits a pronounced spontaneous near 24 h, or circadian, rhythm. In humans, this circadian rhythm is entrained to the light-dark and sleep-wake cycles (10), with the trough of activity occurring in the evening and early night and the peak in activity occurring just before waking. Stress-induced secretion is superimposed on this basal circadian rhythm. There is evidence that the stress responsiveness and negative feedback regulation of the HPA axis varies throughout the day, hence specific alterations in the timing, intensity, and duration of any stressor may result in widely varying patterns of HPA axis perturbation. It is thought, however, that under normal conditions the HPA axis may be a 'closed loop' system, such that activation of cortisol secretion by stress will result in a compensatory decrease in circadian drive for cortisol secretion with maintenance of 24 h integrated cortisol levels in the 'normal' range.

HPA Axis Dysregulation in FM and Related Disorders

It has been proposed that the phenomenological overlap between FM, CFS, and a variety of 'stress-related' somatic and psychiatric syndromes reflects the involve-

ment of a shared final pathway, the HPA axis, which may be perturbed as the result of a disparate variety of antecedent events (7). The earliest studies of stress-response systems in human disease states led to the observation that patients with major depression demonstrated a characteristic disruption of the normal circadian rhythmicity of the pituitary-adrenal axis involving an elevation of adrenal glucocorticoid output, usually seen as an earlier onset of the morning surge of the axis, in conjunction with enhanced cortisol secretion in the late afternoon (24). Aberrant feedback regulation of the axis was suggested by studies employing the synthetic glucocorticoid, dexamethasone (4). A model of HPA axis dysregulation which suggests an excessive central release of CRH in some cases of major depression was developed.

The initial investigations of the neuroendocrine correlates of depression largely concerned the more classical, melancholic form of depression, characterized by increasing agitation, loss of sleep, loss of interest in all activities, persistent suicidal thoughts, and reduced appetite and libido. In recent years, however, it has become increasingly apparent that depression is a heterogeneous condition from both a psychological and a physiological perspective. Forms of depressive illness dominated by reduced energy, a reactive mood, and a reversal of the typical pattern of vegetative features seen in classical depression have been described (5). These depressive subtypes are of particular interest because of their overlap with the symptoms of FM and CFS. Recent evidence suggests a pattern of HPA function in some of these syndromes reflecting inappropriately normal or frankly reduced activation of the axis (17–19, 23, 29). It has been hypothesized that one of the principal features of the HPA axis disturbance in these conditions may be functional *deficit* in the release of hypothalamic CRH. This is of interest since CRH serves not only as a principal stimulus to the HPA axis, but also because it is a behaviorally active neurohormone whose central administration to animals and non-human primates induces signs of physiological and behavioral arousal, including activation of the sympathetic nervous system (3), hyper-responsiveness to sensory stimuli (27), and increased locomotion (26). It must be noted, however, that posttraumatic stress disorder (PTSD) is also characterized by low levels of cortisol that were shown to be due to enhanced glucocorticoid negative feedback rather that low levels of CRH (32).

The symptomatic overlap of FM and CFS with some forms of depression, and the increased lifetime incidence of psychiatric conditions, provoked further interest in examining the specific neuroendocrine characteristics of patient with FM and CFS (Table 1). Poteliakhoff reported in 1981 that subjects with both acute and chronic fatigue states showed reductions in plasma cortisol compared to non-fatigued individuals, along with altered circadian variation in capillary resistance and eosinophil counts (22). These results are of interest since they suggest that even quite mild decrements in circulating glucocorticoids may be associated with measurable physiologic changes. In a report of benign myalgic encephalomyelitis (an illness essentially identical to CFS), only 1 of 16 subjects showed evidence of glucocorticoid non-suppression after dexamethasone (28). Demitrack and co-workers, reported reduced urine free cortisol in association with inappropirately low concentrations of CRH and ACTH in the cerebrospinal fluid, low evening plasma cortisol, elevated evening plasma ACTH with blunted response to exogenous administration of ovine CRH, and altered responsiveness of the adrenal cortex to graded doses of ACTH (13). Bearn and colleagues reported that patients with CFS did not differ form controls in response to insulin challenge but displayed exaggerated ACTH, but not cortisol, response to d-fenfluramine, which causes pre-synaptic release of serotonin (2). In a related study, this group compared the response to d-fenfluramine in patients with CFS and major depressive disorder, demonstrating a reduced cortisol profile relative to depressed patients while healthy controls fell between the two patient groups (6). In contrast, Yatham and colleagues reported no difference in the cortisol response between CFS and normal subjects after administration of d/l-fenfluramine (31).

Table 1 Comparison of HPA Axis Parameters in FM and CFS

		FM	CFS
Brain	– Diurnal Rhythm	Blunted	–
	– CSF CRH	–	Reduced
	– Plasma AVP (Magnocellular)	Normal or Elevated	Reduced
	– Insulin-Induced Hypoglycemia (Acute)	Exaggerated ACTH, Blunted Cortisol	Normal
	– Hypoglycemic Clamp (Gradual)	Blunted ACT, Nl Cortisol	–
	– Serotonergic Challenge	–	Exaggerated ACTH, Blunted Cortisol
Pituitary	– Basal ACTH	Normal	Elevated PM
	– CRH Challenge	Exaggerated ACTH	Blunted ACTH
Adrenal	– Basal Cortisol	Normal AM, Elevated PM	Decreased PM
	– 24-h Urine Free Cortisol	Decreased	Decreased
	– ACTH Challenge	Normal	↑ Sensitivity, ↓ Capacity
	– CRH Challenge	Blunted Cortisol	Normal

In contrast to CFS, up to 35% of patients with FM showed abnormal suppression after dexamethasone (14, 16). McCain and Tilbe reported that patients with FM had reduced 24-hour urine free cortisol excretion, *but* a loss of the circadian fluctuation of glucocorticoid levels with elevated levels during the circadian nadir (20). Griep and colleagues reported exaggerated ACTH, but blunted cortisol response to exogenous administration of human CRH and to insulin-induced hypoglycemia (15). In our own studies, we also found a loss of circadian fluctuation of plasma cortisol in patients with FM due to elevated levels, with reduced overall 24-hour urine free cortisol excretion that could not be explained by excess cortisol binding globulin (9). On provocative challenge with ovine CRH, there was a trend towards increased ACTH, but blunted cortisol respone to exogenous CRH, similar to the findings of Griep (9). In a paradigm employing a different kind of hypoglycemic challenge where the rate of decline in blood glucose is carefully titrated or clamped, Adler and co-workers reported reudced ACTH secretion with a cortisol response no different from control subjects (1). It can be seen from these data that the pattern of HPA axis response appears to diverge between these conditions, with exaggerated activity (physiological hyperarousal) in FM and blunted activity in CFS.

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