Evidence for and Pathophysiologic Implications of Hypothalamic–Pituitary–Adrenal Axis Dysregulation in Fibromyalgia and Chronic Fatigue Syndrome

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ABSTRACT: Chronic fatigue syndrome (CFS) is characterized by profound fatigue anad an array of diffuse somatic symptoms. Our group has established that impaired activation of the hypothalamic–pituitary–adrenal (HPA) axis is an essential neuroendocrine feature of this condition. The relevance of this finding to the pathophysiology of CFS is supported by the observation that the onset and course of this illness is excerbated by physical and emotional stressors. It is also notable that this HPA dysregulation differs from that seen in melancholic depression, but shares features with other clinical syndromes (e.g., fibromyalgia). How the HPA axis dysfunction develops is unclear, though recent work suggests disturbances in serotonergic neurotransmission and alterations in the activity of AVP, an important co-secretagogue that, along with CRH, influences HPA axis function. In order to provide a more refined view of the nature of the HPA dusturbance in patients with CFS, we have studied the detailed, pulsatile characteristics of the HPA axis in a group of patients meeting the 1994 CDC case criteria for CFS. Results of that work are consistent with the view that patients with CFS have a reduction of HPA axis activity due, in part, to impaired central nervous system drive. These observations provide an important clue to the development of more effective treatment to this disabling condition.

Clinical syndromes associated with fatigue, often accompanied by diffuse musculoskeletal pains and aggravated by physical or emotional stressors, have a lengthy history in medical literature. As early as the 1700s, Sir Richard Manningham reported the existence of the "febricula" or "little fever."[1] In this illness, the patient presented with a profound sense of lassitude, along with a bewildering array of constitutional complaints, but with few objective clinical findings: ". . .the symptoms of the febricula, or little, low, continued fever, are these. . .transient chilliness . . . a mist before the eyes . . . listlessness, with great lassitude and weariness all over the body . . . little flying pains . . . and sometimes the patient is a little delirious and forgetful. . . ."

Manningham remarked on the association of this condition with stressful life circumstance, and observed its preponderant incidence in females, particularly of

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the upper social classes. Probably the most well-known description of this condition is contained the work of the American neurologist George Beard, who coined the term, "neurasthenia" in the latter half of the 19th century.[2] On nearly the same historical timeline, a similar clinical syndrome initially termed "fibrositis," was described over 150 years ago by Valleix with his report of patients with widespread, and anatomically discrete, tender points, many of which the patient was not even aware.[3]

Beginning in the early 1970s, there has been a resurgence of interest in these clinical conditions. In a major advance, Smythe and colleagues suggested that a tender point examination provided diagnostic utility in distinguishing fibromyalgia (FM) from other conditions.[4] In 1981, Yunus and associates reported that chronic, diffuse pain and other constitutional symptoms, along with a tender point examination, could differentiate patients with FM from normal subjects.[5] Incorporating the results of a prospective, multicenter evaluation of proposed definitions for FM, in 1990 the American College of Rheumatology published operational criteria for the classification of the syndrome based on a history of widespread pain and the identification of pain in defined tender point sites (see TABLE 1)[6] Beginning in the late 1980s, the Centers for Disease Control and Prevention proposed, and again recently refined, a working case definition for the chronic fatigue syndrome (CFS) (see TABLE 2)[7] Patients meeting criteria for CFS must have persistent or relapsing, debilitating fatigue for at least six months in the absence of any medical diagnosis that would explain the clinical presentation. Symptom criteria used to identify this syndrome also include impaired memory or concentration, sore throat, polyarthralgias, myalgias, painful adenopathy, postexertional malaise, and unrefreshing sleep. This definition is the currently accepted standard to define a case of the syndrome and has served as a first attempt to bring coherence to a confusing array of names and diagnostic criteria.

It is now recognized that these syndromes lead to significant physical and psychological debility in a large segment of the population. In the United States alone, the prevalence of FM in general medical clinics ranges from 2 to 6%, while in

TABLE 1. Fibromyalgia—The American College of Rheumatology 1990 Criteria[6]

1. History of widespread pain, defined as pain present in all of the following sites: left and right sides of the body, above and below the waist. Additionally, axial pain must be present.

AND

2. The presence of pain in 11 of the following 18 bilateral tender point sites upon digital palpation (approximate force of 4 kg; must elicit the subjective sensation of pain from the subject):

   - Occiput, at the suboccipital muscle insertions
   - Low cervical, at the anterior aspects of the intertranverse spaces at C5–C7
   - Trapezius, at the midpoint of the upper border
   - Supraspinatus, at origins, above the scapula spine near the medial border
   - Second rib, at the second costochondral junctions, just lateral to the junctions on upper surfaces
   - Lateral epicondyle, 2 cm distal to the epicondyles
   - Gluteal, in upper outer quadrants of buttocks in anterior fold of muscle
   - Greater trochanter, posterior to the trochanteric prominence
   - Knee, at the medial fat pad proximal to the joint line

TABLE 2. Centers for Disease Control and Prevention Revision of the Chronic Fatigue Syndrome Definition, 1994[7]

Chronic Fatigue Syndrome

a. Clinically evaluated* unexplained, persistent or relapsing chronic fatigue (≥ 6 months duration) that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.

b. Four or more of the following symptoms are concurrently present for > 6 months:

1. Impaired memory or concentration
2. Sore throat
3. Tender cervical or axillary lymph nodes
4. Muscle pain
5. Multi-joint pain
6. New headaches
7. Unrefreshing sleep
8. Post-exertion malaise

Idiopathic Chronic Fatigue

Clinically evaluated, unexplained chronic fatigue (≥ 6 months duration) that fails to meet the definition for chronic fatigue syndrome.

***Recommended Clinical Evaluation**

- Medical history and physical examination
- Mental status examination
- Laboratory screening battery to include: complete blood count with leukocyte differential, erythrocyte sedimentation rate, serum levels of alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes and creatinine, thyroid-stimulating hormone, urinalysis

Exclusionary Clinical Diagnoses

- Any active medical condition that could explain the chronic fatigue
- Any previously diagnosed medical condition whose resolution has not been documented beyond reasonable clinical doubt and whose continued activity may explain the chronic fatiguing illness
- Psychotic major depression, bipolar affective disorder, schizophrenia, delusional disorders, dementias, anorexia nervosa, bulimia nervosa
- Alcohol or other substance abuse within 2 years before the onset of the chronic fatigue and at any time afterward

rheumatology clinics the prevalence may be as high as 20%.[8] In addition, recent population-based studies reveal a 1 to 3% prevalence rate of FM in the community. Longitudinal studies have confirmed the clinical observation that most FM

patients have persistent pain and fatigue that significantly impairs their quality of life.[9] A recent epidemiologic study of CFS in a community-based sample, employing the current case definition, reported a range of estimated point prevalence between 98 and 267 cases per 100,000.[10] The public health cost of these syndromes is not trivial. For example, it has been suggested that patients with CFS are overrepresented among the high utilizers of outpatient medical care.[11] A large database study of 260 fibromyalgia patients revealed that 15% were receiving disability compensation.[12] In Canada, FM was responsible for 9% of disability payments awarded by a single Canadian life insurance company.[13] It was estimated that if this proportion was representative of all disability awards in Canada, the financial burden would amount to $200 million per year.

As more detailed clinical information on these syndromes has emerged, interest has grown to determine whether these illnesses should more properly be considered as phenotypic variants of the same fundamental condition. Indeed, on descriptive measures alone, there are striking clinical and demographic similarities between FM and CFS. In an early report, Buchwald and colleagues[14] provided a detailed clinical and laboratory report on a series of 50 patients (46 women, 4 men) with primary FM. They were specifically interested in detailing in the FM patients the presence of symptoms characteristic of what was then referred to as the "chronic active Epstein-Barr virus infection syndrome," now nearly identical to the definition of CFS. They described a high prevalence of symptoms not previously thought to be characteristic of FM, such as recurrent sore throat, recurrent rashes, a history of allergies, chronic cough, recurrent adenopathy, and recurrent low-grade fevers. In many of the patients, the onset of illness was abrupt, in the aftermath of what appeared to the patient as an acute viral syndrome, quite similar to the most common pattern of onset in patients with CFS. These observations were extended by Goldenberg and coworkers,[15] who reported historical and physical examination data on a series of 27 patients with debilitating fatigue of greater than 6 months duration. Seventy percent of the sample described the presence of diffuse musculoskeletal pain. In addition, the tender point score in the fatigued patients was indistinguishable from the score in a concurrent group of patients with primary FM. Based on their own clinical anecdotal experience, they speculated that even the 70% reported in their study was an excessively conservative estimate of the degree of clinical overlap in the two illnesses. Of interest, the 1991 joint NIMH/NIAID workshop[16] on the medical outcome of CFS recommended a tender point examination as an essential part of the overall clinical assessment of patients with chronic fatigue. Finally, it is worth noting that even in the absence of establishing pure identity between FM and CFS, the presence of a discrete FM syndrome within the context of a syndrome of chronic, idiopathic fatigue may nevertheless be of particular clinical relevance since recent studies suggest that primary FM may bode much more poorly for long term clinical outcome than CFS alone.[9]

Unfortunately, despite these observations, there remains scant data that sheds light on the actual pathogenesis, common or otherwise, of these syndromes. We and others[17] have proposed that it may be useful to consider FM and CFS as falling into the spectrum of what might be termed "stress-related illnesses," by virtue of the increase in symptoms associated with physical or emotional stress and due to their apparent association with psychiatric illness. Indeed, dysregulation of the normal stress response can lead to abnormalities in both physical and behavioral adaptation that may mimic the clinical symptoms of FM and CFS. Moreover, we feel that placing an emphasis on the stress response as a central biological mediator of the symp-

toms of these conditions provides a more congenial fit with the majority of the credible contemporary formulations of these illnesses that reject a specific, unitary disease model, but rather acknowledge that a comprehensive, multifactorial pathway describing the development of either FM or CFS in a particular patient is much more consistent with clinical reality. Such multidimensional approaches usefully delineate among predisposing factors (e.g., pre-existing psychiatric illness or chronic life stress), precipitating events (e.g., physical trauma, infectious illness), and perpetuating factors (e.g., ongoing emotional distress, avoidance of physical activity, distortions in causal illness attribution) (TABLE 3). Finally, acknowledging the importance of the stress response apparatus in the development and course of FM and CFS is also consistent with the clinical observation that treatments that may affect these neurobiological systems (e.g., tricyclic antidepressants, cognitive–behavioral therapy) are often helpful in alleviating the symptomatic features of these disorders.

In this review, we will summarize data from our group, which has described perturbations of hypothalamic–pituitary–adrenal (HPA) axis function in both FM and CFS that may have relevance to the pathophysiology and clinical presentation of these syndromes.[18] We believe that these data hold considerable promise for providing a testable model for understanding the potential common pathophysiology of these illnesses, or their possible points of divergence, and may ultimately result in the more well-informed development of reasonable diagnostic approaches and treatment interventions.

THE HPA AXIS: AN OVERVIEW AND ROLE IN STRESS-ASSOCIATED DISEASES

Activation of the HPA axis is central to the individual's coordinated response to stress. Regulation of the HPA axis involves a complex array of biochemical

TABLE 3. A Multidimensional View of Fibromyalgia and Chronic Fatigue Syndrome

Predisposing Factors

- Life stress (early abuse, chronic life stress)
- Pre-existing psychiatric illness
- Familial/genetic factors
- Constitutional factors (atopic or allergic history)

Precipitating Factors

- Severe infectious illness
- Physical trauma
- Severe emotional distress

Perpetuating Factors

- Ongoing emotional distress
- Avoidance of physical activity
- Distortions in illness attribution in the face of conflicting empirical data (e.g., the fixed belief in an ongoing infectious cause)
- Disruption in normal work schedule

events occurring principally among the hypothalamus, anterior pituitary, and the cortex of the adrenal gland.[19] Key among these biochemical signals are corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), peptide hormones whose major concentrations in brain are localized in the medial parvocellular division of the paraventricular nucleus (PVN) of the hypothalamus. From there, neuronal projections transport CRH and AVP to the external layer of the median eminence. Both peptides are also widely distributed in other, extrahypothalamic locations, including the limbic system, cerebral cortex, midbrain areas, pons, and medulla. Acute stress results in the release of these peptides into the portal plexus, where they gain access to the hormone secreting cells of the anterior pituitary. 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 effecting glucocorticoid release from the adrenal cortex. CRH and AVP act synergistically, AVP causing a tremendous amplification of CRH-induced release of ACTH.[20] Indeed, evidence supports a role for AVP in sustaining the activation of the HPA axis during chronic stress. Complex short and long negative feedback circuits, primarily mediated by specific glucocorticoid receptors (the so-called Type I and Type II receptors), converge to terminate activation of the HPA axis.[21]

The particular supra-hypothalamic biochemical signals that effect activation of hypothalamic CRH and AVP in response to stress are complex, involving both peptide as well as monoamine-containing neural pathways.[22] Less well studied than these biochemical signals, but of equal importance, are several specific neural circuits that have regulatory effects on the HPA axis. These areas include the amygdala, hippocampus, septal area, cingulate cortex, and certain brainstem regions. Finally, in addition to its stress-dependent activation, it is well-known that the HPA axis exhibits a pronounced spontaneous basal circadian rhythm. In humans, this circadian rhythm is entrained to the sleep/wake cycle,[23] with the trough of activity occurring in the evening and early night, and the peak in activity occurring just before waking. Intrinsic rhythmic elements in the suprachiasmatic nucleus appear to be the principal drive for the basal rhythm of the HPA axis. Any stress effects are then superimposed on this basal circadian rhythm. There is also evidence that the stress responsiveness and negative feedback regulation of the HPA axis varies across the day, hence specific alterations in the timing, intensity, and duration of any stressor may result in widely varying patterns of HPA axis perturbation.

HYPOTHALAMIC–PITUITARY–ADRENAL AXIS FUNCTION IN CHRONIC FATIGUE SYNDROME

We have completed a series of studies assessing in the integrity of the HPA axis in 30 patients with CFS and in 72 normal healthy volunteers (for a discussion of the primary data, see Ref. 18). In these studies, basal functional activity of the axis was determined in several ways. We obtained multiple evening baseline samples for the measurement of total and free plasma cortisol concentrations. In addition, we collected serial 24-hour urine collections to assess urine free cortisol excretion. Finally, we determined the basal evening measurement of plasma cortisol-binding, globulin-binding capacity. This latter measure was of interest because it is known that levels of CBG are sensitive to the negative feedback

effect of circulating glucocorticoids,[24] and because we observed that CBG levels were significantly elevated in the patients with CFS. Overall, the results of this comprehensive basal assessment suggested a pattern of neuroendocrine dysfunction characterized by a significant reduction in both plasma and urinary glucocorticoid levels.

In order to more specifically characterize the locus of the disturbance in adrenal glucocorticoid secretion, we followed these measures of basal HPA axis activity with several specific challenge studies, which explored central nervous system, pituitary, and adrenal activity directly and indirectly. For instance, we used the plasma ACTH response to ovine CRH as a direct measure of corticotroph function, whereas adrenal functional activity was evaluated both indirectly by examining cortisol response to ovine CRH and directly by measuring cortisol response to graded, submaximal stimulatory doses of ACTH. We also assessed gross central nervous system activity of CRH by measuring its levels in the cerebrospinal fluid.

Given the evidence from our basal functional measures, which suggested a reduction in adrenocortical activity, we were interested in determining whether patients with CFS would demonstrate evidence of a primary disturbance in adrenal function upon direct stimulation. Such a functional defect would be expected to result in both a reduced responsiveness of the adrenal cortex to all dose ranges of ACTH and an exaggerated pituitary response to ovine CRH administration. In fact, CFS patients clearly did not demonstrate the latter response (i.e., the ACTH response to ovine CRH was reduced in comparison to healthy volunteers), and indeed appeared to *hyper-respond* to low doses of ACTH in three different instances: (a) patients with CFS showed significant net integrated cortisol responses beginning at the two lowest doses of ACTH employed (0.003 and 0.01 mg/kg ACTH); (b) compared to controls, patients with CFS showed a half-maximal cortisol response to a lower dose of ACTH (0.007 vs. 0.011 mg/kg ACTH); and (c) during evening challenge with ovine CRH, patients with CFS showed an exaggerated plasma cortisol response relative to the amount of ACTH released following ovine CRH administration. In this study, the peak levels of plasma ACTH during CRH stimulation testing were comparable to those obtained after the administration of the lowest doses of exogenous ACTH we used.

A further argument against a primary adrenal deficit as the source of the reduced glucocorticoid levels was the observation that the net integrated pituitary ACTH response to ovine CRH was reduced, a finding that is the antithesis of that expected in primary adrenal failure. A net reduction of ACTH in response to ovine CRH challenge has been reported in several other clinical conditions, including major depression[25,26] and the underweight phase of anorexia nervosa.[27] Both of these illnesses are associated with hypercortisolism, and it has been postulated that the attenuated ACTH response reflects a pituitary corticotroph cell appropriately restrained in its responsiveness by high levels of circulating glucocorticoids. It is clear that the blunted ACTH response to exogenous ovine CRH in patients with CFS is not analogous to what has previously been reported in major depression or anorexia nervosa, since patients with CFS show *reduced*, rather than *increased*, glucocorticoid levels. However, a third context in which an attenuated net integrated ACTH response to CRH has been noted is in the hypothalamic CRH-deficient state described during the early post-operative period after curative surgery in patients with Cushing's disease.[28,29] Several lines of evidence suggest that this post-operative adrenal insufficiency reflects, in large part, a state of prolonged suppression of hypothalamic CRH. First, these patients will demon-

strate measurable levels of plasma ACTH after the administration of CRH, indicating that if the patients' own hypothalamic CRH neurons were not suppressed by the long-standing hypercortisolism, one would expect to observe somewhat higher levels of basal plasma ACTH and cortisol. Second, it has been shown that patients with Cushing's disease show a marked reduction in cerebrospinal fluid levels of CRH.[30,31] Finally, although these post-operative subjects show an attenuated ACTH response to exogenous CRH, it can be normalized rapidly with repeated administration of CRH, but this response cannot be sustained after the withdrawal of CRH.[29] These data suggest that, in the post-operative period, the pituitary corticotroph of patients with Cushing's disease becomes hyporesponsive to exogenous CRH due to insufficient central priming by the long-standing, glucocorticoid-induced suppression of endogenous hypothalamic CRH. From these data we infer that the blunted ACTH response to CRH in patients with CFS may be more closely analogous to that seen in the context of post-operative Cushing's disease rather than to that of hypercortisolemic major depression or the underweight phase of anorexia nervosa.

The levels of cerebrospinal CRH and ACTH in patients with CFS were normal. Although these findings are difficult to interpret with confidence, we have considered such results to be *inappropriately* normal, given the magnitude of the putative reduction in glucocorticoid secretion in the periphery. Both CRH and ACTH in the cerebrospinal fluid are responsive to the negative feedback effects of circulating glucocorticoids[32,33] and hence a reduction in peripheral glucocorticoid levels might be expected to result in increased levels of cerebrospinal fluid CRH and ACTH due to a loss of this normal feedback inhibition, not the normal levels we have described. An important caveat to note is that the cerebrospinal fluid CRH and ACTH levels we reported were lumbar cerebrospinal fluid determinations, which may merely reflect cortical or spinal sources of CRH, and not direct functional CRH activity in the paraventricular nucleus (PVN). Indeed, there is no reason to presume that a functional deficit of CRH in the PVN is associated with similar reductions of CRH activity in limbic or cortical locations.

In conclusion, we have suggested that the findings of reduced adrenal glucocorticoid function in patients with CFS are most consistent with a central nervous system defect in the activation of this axis.

HYPOTHALAMIC–PITUITARY–ADRENAL AXIS FUNCTION IN FIBROMYALGIA

A principal rationale for the study of the HPA axis in FM includes clinical observations that patients with FM often have onset of their symptoms during periods of physical or psychological stress and exacerbation of symptoms during periods of stress. Studies of basal HPA axis function in patients with FM have demonstrated low 24-hour urine free cortisol levels as compared with normal subjects or patients with RA, similar to observations in CFS.[34,35] FM patients, however, exhibited normal morning (peak) and elevated evening (trough) cortisol levels, resulting in a loss of the normal diurnal cortisol fluctuation. Abnormal cortisol measurements were most prominent in patients with a longer duration (>2 years) of disease.[35] A In contrast to elevated CBG levels in patients with CFS, no differences were detected in FM patients.[34] A It is difficult to resolve the finding of low 24-hour urine free cortisol, which reflects the time-integrated plasma free cortisol concentrations over 24

hours, with higher cortisol levels in the evening, but no differences in morning cortisol levels compared with normal subjects. There are, however, possible explanations for these seemingly incongruous results. One possible explanation hinges on the pulsatility of cortisol secretion. There are normally eight to nine peaks of cortisol over a 24-hour period, presumably in response to basal surges of CRH and ACTH. The majority of cortisol secretion occurs during the nighttime circadian peak. In FM, the height of the cortisol peaks might be normal or even elevated, but the frequency of the peaks could be decreased, resulting in a low cortisol output when examined over 24 hours. Another possibility is altered regulation of CBG. Plasma free cortisol is filtered in the kidney, and no tubular reabsorption or secretion occurs, making a renal mechanism underlying low urine free cortisol unlikely. Further study of basal circadian HPA axis function in FM is clearly indicated.

The HPA axis response to administration of exogenous CRH is a measure of the stress-induced activation of the axis, whereas insulin-induced hypoglycemia tests the integrity of the stress-associated increase in hypothalamic CRH as a stimulus to pituitary–adrenal hormone secretion. Ovine CRH-stimulation tests performed in the evening, when FM patients exhibit elevated basal trough cortisol levels compared with control patients, revealed no statistically significant differences in CRH-stimulated ACTH levels between patients with FM and controls.[34] However, a non-significant trend toward elevated mean basal and CRH-stimulated ACTH levels was noted. Griep and colleagues performed stimulation testing of HPA axis function using exogenous CRH and insulin-induced hypoglycemia.[36] They demonstrated significantly elevated ACTH responses to both stimuli in patients with FM. Their studies were performed in the morning at the circadian peak, when there are no difference in basal cortisol levels compared with controls. Elevated trough cortisol levels in patients with FM as compared with normal subjects may have blunted the effect of CRH on ACTH in the evening by negative-feedback mechanisms. Both studies demonstrated a relatively blunted adrenal cortisol response to stimulated ACTH release A relatively hyporesponsive adrenal gland could be due to intrinsic hypoactivity of the adrenal cortex itself, or could develop in the context of chronic understimulation due to deficiencies of CRH or ACTH.

Although CRH is the dominant ACTH secretagogue during basal conditions, AVP may become more important during chronic stress.[37] Although plasma AVP represents release from the magnocellular portion of the paraventricular nucleus, increased magnocellular AVP may correlate with increased parvocellular production of AVP, which is released into the portal hypophyseal circulation and acts on pituitary corticotrophs.[38] We detected a trend towards increased release of AVP after postural change in patients with FM. In fact, 5 of 12 FM patients achieved AVP levels more than two standard deviations above the highest control value.[34] In contrast, Bakheit and coworkers evaluated a group of patients with postviral fatigue syndrome and demonstrated significantly lower basal AVP levels.[39] CFS patients also demonstrated a lack of correlation between serum and urine osmolality with plasma AVP. Differences in AVP, or other modulators, may underlie subtle differences in HPA axis function between patients with FM and CFS.

SUMMARY

As noted in the introduction to this review, there are several logical clinical and demographic justifications for considering FM and CFS as representing pheno-

typic variants of the same underlying pathophysiology. Indeed, our data would suggest that a unifying feature of the HPA axis dysregulation seen in both FM and CFS is a moderate basal hypocortisolism, as evidenced by a reduction in the 24-hour excretion of urine free cortisol. On its own, this observation is a striking finding, given the popular view that both of these conditions represent disguised variants of the well-known clinical syndrome of major depression. In fact, a majority of patients with classically described major depression are characterized by a pattern of glucocorticoid excess, the opposite finding we have described.[40] It should be cautioned though, that these biochemical observations nevertheless do not answer the nosologic question of whether FM and CFS represent a different, previously unrecognized subset of the admittedly heterogeneous class of patients who fall under the DSM-IV operational definition of major depression. Indeed, the clear excess of antecedent psychiatric illness in patients with FM or CFS in comparison to the general population speaks to the complexity of this problem. Despite these issues, it is worth noting that our observations are consistent with several early reports such as the reduced cortisol levels in chronic and acute fatigue states reported by Poteliakhoff,[41] and the relatively low incidence of dexamethasone nonsuppression in FM patients.[42,43] Moreover, our data is consistent with more recent work from independent groups in both FM36 and CFS.[44]

Although we have argued here and elsewhere that a centrally mediated mechanism of HPA axis inactivation represents one of the more parsimonious explanations for these observations, there are several reasonable hypothetical factors that may also be involved (see TABLE 4). Additional work is clearly necessary to determine the relative contribution of these, or other, factors. Furthermore, future work should also attempt to clarify apparent areas of divergence in the HPA axis disturbances present in FM and CFS. For instance, there appears to be more consistent evidence (e.g., enhanced ACTH response to either ovine CRH or to insulin-induced hypoglycemia) suggesting a relatively hypofunctional adrenal gland in patients with FM in contrast with the clear blunting of response to ovine CRH seen in patients with CFS. As previously discussed, differences in secretion of AVP or other modulators may explain divergence of HPA axis function in FM and CFS.[36,39] Whether these differences are real or merely represent differences in methodology or patient selection remains to be understood.

Finally, it should also be noted that, the vast majority of the studies described here have been conducted in patients who have been ill, on average, for several years. Hence, it is inappropriate to infer whether the observed HPA axis dysregulation represents a pre-existing, intrinsic defect in this system, or rather is acquired as a consequence of illness behaviors such as the profound reduction in physical activity or the distortions in habitual sleep–wake patterns. On the other

TABLE 4. Factors That May Contribute to the HPA Axis Dysregulation of Fibromyalgia and Chronic Fatigue Syndrome

- Alteration in sensitivity to glucocorticoid negative feedback
- Disruption in circadian organization
- Disturbance in suprahypothalamic influences on the axis (neural or biochemical)
- Primary alteration in hypothalamic drive
- Alteration in pituitary sensitivity
- Primary defect in adrenal responsiveness

hand, regardless of the temporal sequence of events, there are compelling circumstantial reasons to suspect that disruptions in the functional integrity of the HPA axis may still have important behavioral and biological consequences. Evidence to support such a view is drawn from the clinical resemblance of both FM and CFS to the symptoms seen in patients with glucocorticoid deficiency. Among the principal symptoms of glucocorticoid deficiency is debilitating fatigue. In many instances patients with glucocorticoid deficiency manifest an abrupt onset of clinically evident illness in response to a stressor, subsequently accompanied by arthralgias, myalgias, feverishness, adenopathy, post-exertional fatigue, exacerbation of allergic responses, and disturbances in mood and sleep. Because glucocorticoids represent the most potent endogenous immunosuppressive compounds, it is also intriguing to propose that some of the reported immunologic disturbances in patients with FM or CFS[45–53] may also reflect the immune activation that might be expected to accompany a mild or relative glucocorticoid deficiency. In animals, the relevance of this latter point is suggested by the observation that a defect in the responsiveness of the HPA axis to immune mediators has been shown to confer a risk for the development of inflammatory disease.[54,55] In humans, it has also been shown that withdrawal from hypercortisolemic states results in the exacerbation of autoimmune thyroiditis,[56] as well as the development of myalgias, arthralgias, muscle weakness,[57] and even severe FM.[58] Probably most provocative among the reasons to suspect that a centrally-mediated disruption in the HPA axis may result in a clinically evident fatigue state is the observation that CRH, in addition to its role as a central effector of the HPA axis, is itself a behaviorally active neuropeptide, whose central administration to animals induces signs of physiological and behavioral arousal.[59–61] Therefore, a reduction in the availability of central nervous system CRH could also contribute to the lethargy characteristic of both FM and CFS.

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