

Glucocorticoids and glucocorticoid receptors: mediators of fatigue?

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Fatigue is a common problem; when chronic and disabling, subjects can be categorized as having chronic fatigue syndrome (CFS). Whilst it is most likely a multifactorial condition of biopsychosocial origin, the nature of the pathophysiological component remains unclear. There has been a wealth of interest in the possible hypothalamo–pituitary–adrenal (HPA) axis dysfunction in CFS, and whether such changes may mediate fatigue. On balance, there appears to be reduced cortisol output in a proportion of patients, together with heightened negative feedback and glucocorticoid receptor function. There is evidence for impaired adrenocorticotrophic hormone (ACTH) and cortisol responses to a variety of challenges. However, there is no evidence for a specific or uniform dysfunction of the HPA axis. Evidence that these changes may be related to symptom production comes from randomized controlled trials of glucocorticoid replacement therapy, which have shown improvements in fatigue and disability. Given the many factors that may impinge on the HPA axis in CFS, such as inactivity, sleep disturbance, psychiatric comorbidity, medication and ongoing stress, it seems likely that there is not a single or specific change to the HPA axis in CFS and that the observed HPA axis disturbances are of multifactorial etiology. This is further supported by a comparison of neuroendocrine findings in other conditions in which fatigue is prominent, showing both similarities and differences with the pattern in CFS.

Keywords: chronic fatigue syndrome; Cortisol; hydrocortisone; hypothalamo–pituitary–adrenal axis; neuroendocrine

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Introduction

Persistent fatigue is a common complaint; between 20 and 50% of the population report suffering from this problem, depending on the definition (1). Indeed, 10% of primary health care attenders have fatigue of 6 months or more duration (2). In a number of these cases, a clear medical explanation exists for the fatigue, but in many it does not. Many of these at the extreme end of the continuum of chronic fatigue suffer marked disability from their symptoms, and can be categorized as suffering from chronic fatigue syndrome (CFS). While sometimes regarded as a modern illness, in fact there are many parallels between CFS and the Victorian concept of neurasthenia (3).

Research criteria for CFS have been published by the Center for Diseases Control (CDC) (4), although the definition is currently under review

and a revised version likely (CDC, personal communication, 2003). Current criteria state that the fatigue must be severe enough to cause a significant loss of physical and social function for a minimum of 6 months, and four of the following symptoms must also be present: sleep disturbance (usually unrefreshing sleep or hypersomnia), concentration impairment, muscle pain, multiple joint pains, headaches, postexertional exacerbation of fatigue, sore throat and tender lymph nodes. Exclusions include a clear underlying organic cause, substance misuse and severe psychiatric disorder, such as psychotic depression. Less severe psychiatric disorders, such as major depression without DSM-IV-defined melancholic features or anxiety disorders, are not exclusionary diagnoses and are frequently comorbid with CFS. Recent estimates at

the prevalence of CFS in the community according to this definition vary from 0.5 to 1.5% (5).

HPA axis function in CFS

The exact etiology of CFS remains elusive, with evidence for and against the importance of virological, immune, endocrine, psychological and other factors(3). The suggestion that chronic fatigue or CFS might be related to HPA axis dysfunction has a long history. From 1902 to 1925 the term hypoadrenia, or ‘a bit of Addison’s disease’ was used, though without firm evidence of altered adrenal function (6). In more recent times, this theory has re-emerged. In particular, parallels have been drawn with Addison’s disease (7), glucocorticoid withdrawal (8) and bilateral adrenalectomy (9). All of these conditions are associated with fatigue, and with other symptoms also seen in CFS, such as arthralgia, myalgia, sleep disturbance and mood disorder (10).

This article will review the accumulated evidence linking glucocorticoids and glucocorticoid receptors to fatigue, concentrating on the example of CFS, but also referring to other conditions in which fatigue is a prominent symptom. Several key questions emerge from the literature and will be addressed in turn.

Are basal cortisol levels altered in CFS?

Cortisol represents the final output from the HPA axis (Fig. 1). There have been a large number of studies reporting the results of single unstimulated measures of plasma cortisol (11–26). As noted in Table 1, most of these failed to find any differences between patients and controls. There are several problems with these studies. First, many were not looking specifically at this question, the data having been extracted by this author from dynamic challenge studies for the purposes of this review; thus, they were probably underpowered. Furthermore, plasma samples involve intravenous cannulation and hospital attendance, which are both likely to induce a stress response on top of any baseline changes. Single samples are probably inadequate for detection of a pulsatile hormone such as cortisol. Finally, they also measure both the biologically active free cortisol and bound cortisol (27). Thus, few conclusions can be drawn from these studies.

More reliable information comes from studies where serial plasma or saliva cortisol samples are taken, or 24-h output of cortisol in the urine is measured. Six studies have measured serial plasma

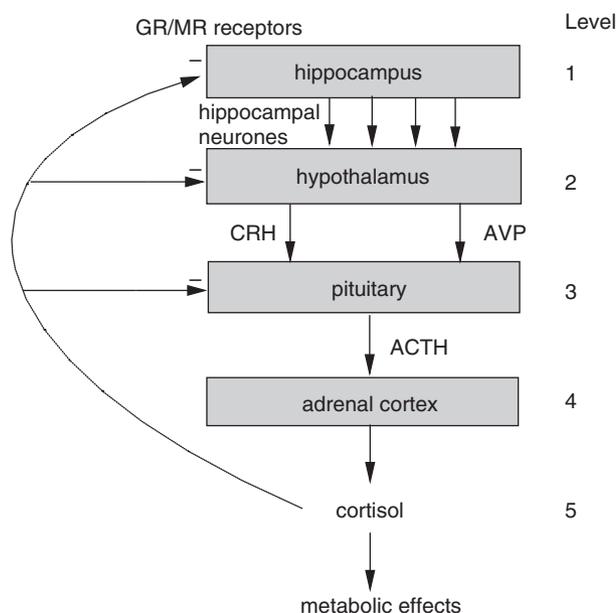


Fig. 1. Schematic representation of the hypothalamo-pituitary-adrenal (HPA) axis. Bold arrows represent stimulation, dotted arrows represent negative feedback at glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) level or hippocampus, hypothalamus and pituitary. Level of abnormality in chronic fatigue syndrome (CFS) relates to Table 1. AVP, arginine vasopressin; ACTH, adrenocorticotropic hormone (corticotropin).

Table 1. Sites of possible hypothalamo-pituitary-adrenal (HPA) axis abnormalities in chronic fatigue syndrome (CFS)

Level (Fig. 1)	Finding	Papers published (number)	Consistency (positive:negative studies)
1	Hippocampal atrophy	1	-
1	Impaired rate-sensitive negative feedback	1A	-
1	Reduced suprahypothalamic drive to HPA axis	H	-
2-3	Enhanced negative feedback		
	<i>In vivo</i> (dexamethasone suppression)	1 + 1A	2:0
	<i>In vitro</i>	3	2:1
2	Impaired CRH and/or AVP release from hypothalamus	2	2:0
3	Impaired pituitary response to CRH	4	2:2
4	Blunted adrenal cortex response to ACTH		
	Direct (ACTH test)	3	2:1
	Indirect (CRH test)	4	2:2
4	Adrenal gland atrophy (CT scan)	1	1:0
1-4	Impaired HPA response to stressor		
	Response to awakening	1 + 1U	1:1
	Response to exercise	2	2:0
	Response to social stress	1	1:0
	Response to naloxone	1	1:0
	Response to insulin	4	1:3
5	Low basal cortisol		
	Single blood sample	16	2:14
	Serial blood samples	6	3:3
	24-h urine	6	4:2
	Serial saliva samples	5 + 1U	2:4

A, abstract; U, unpublished data; H, hypothesis.

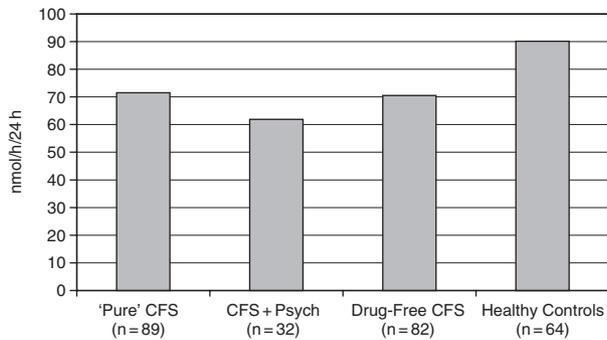


Fig. 2. Twenty-four hour urinary free cortisol (UFC) values in CFS patients without ('Pure CFS') or with ('CFS + Psych') psychiatric comorbidity, in CFS patients medication-free for 2 months or more ('Drug-free CFS') and in healthy controls. Data taken from Cleare et al. (35).

samples (28–33), six studies 24-h urinary free cortisol (UFC) (24,29,31,34–36) and five studies serial salivary cortisol (36–39).

Summarizing these studies, about half found evidence for lowered cortisol levels at some point in the day. The most consistent results have been found with the studies of UFC. This includes the largest study of the HPA axis to date, in which we found the mean cortisol output to be 66.6 ± 36.8 nmol/day in CFS patients compared with 97.0 ± 52.9 nmol/day in healthy controls (35). Importantly, this finding held whether or not subjects had comorbid psychiatric illness or whether they were taking any medication (Fig. 2). There was no apparent effect of disability or illness duration on cortisol output.

Despite these relatively consistent findings, it has been argued that 24-h UFC is an unreliable indicator of HPA activity, particularly at the lower end of the spectrum (40). It has also been proposed that commercially available kits for assessing UFC may systematically overestimate UFC in urine (41). Also, only 2–3% of circulating cortisol is excreted as free cortisol, the rest entering various metabolic pathways (42); shifts in these metabolic pathways could theoretically alter free cortisol output independently of circulating cortisol levels. There have been no published studies addressing this issue, although a preliminary study found no difference in urinary cortisol metabolites in CFS compared to healthy controls (N. Taylor, personal communication, Kings College London, 2002).

Nevertheless, there is some support from the studies using serial plasma or saliva measures. One would like therefore to see corroboration from other methods. Preliminary reports from a recent meta-analysis of all studies of 24-h UFC and morning and afternoon plasma cortisol levels found a moderate overall effect size for reduced

24-h UFC (-0.73) and morning cortisol (-0.35) but with substantial heterogeneity between studies, and larger effect sizes in samples recruited from tertiary compared with primary care (43). There were no differences in afternoon plasma cortisol levels.

Consistent with reduced basal adrenal activation is a computed tomography study reporting a significant reduction in adrenal gland size in a small group of CFS patients (44). However, since subjects were chosen specifically to have a blunted cortisol response to ACTH, the authors admit that this may not generalize to all CFS subjects; indeed, it is possible that normals selected for low cortisol responses would also show smaller adrenal glands.

Is the HPA axis circadian rhythm altered in CFS?

An alternative hypothesis about how the HPA axis may influence symptoms in CFS relates to the circadian rhythm. Rather as in jet lag, it is hypothesized that a broken circadian cycle may be responsible for some symptoms in CFS. Symptoms of jet lag include fatigue, myalgia, sleep rhythm disruption, appetite change and other somatic symptoms, paralleling many symptoms in CFS (45).

Relatively few studies have attempted to measure the circadian rhythms of the HPA axis in CFS. MacHale et al. (33) demonstrated a significantly attenuated diurnal variation of serum cortisol in CFS, although using just two samples. Notably, there was a significant relationship between the degree of diurnal variation in cortisol and measures of functional capacity. A similar finding of reduced diurnal variation was found in a small study by Hamilos et al. (31), mainly accounted for by a reduced peak cortisol level. Further support comes from the demonstration of a significant decrease in the early morning surge of ACTH and cortisol in a small group of CFS patients (46,47). However, there are also several studies that have not found significant changes in the diurnal variation in cortisol (32,36,37).

If circadian changes are present in CFS, it is not clear whether they are a primary abnormality, or are secondary to disrupted sleep patterns or other behavioral changes. Regardless of this, such circadian changes may well be contributing to some of the symptoms in CFS; as such, treatments aimed at resynchronizing rhythms may be helpful. It is clear that modifying unhelpful sleep patterns is an important component of cognitive behavioral

therapy, the most effective therapy found to date for CFS (3).

Is glucocorticoid receptor function altered in CFS?

One of the theories regarding the underlying cause of hypocortisolism in CFS is that of enhanced negative feedback of corticosteroid receptors on the hypothalamus or pituitary. Feedback to the HPA axis is provided via glucocorticoid and mineralocorticoid receptors in the hippocampus, hypothalamus and pituitary. Methods used to investigate this included *in vivo* and *in vitro* experiments.

In vivo studies

The standard way of assessing negative feedback and glucocorticoid receptor function *in vivo* is using a dexamethasone suppression test. One of the first studies *in vivo* did not specifically investigate CFS itself, but was a large study carried out in the community that administered a simple questionnaire measure of 'fatigue' and performed a standard 1 mg overnight dexamethasone suppression test in 266 subjects (48). Forty-one subjects scored positive for fatigue, but there was no relation between postdexamethasone cortisol levels and fatigue. As might be expected, there was a positive correlation between depression level and postdexamethasone cortisol levels.

Preliminary reports of studies in patients with CFS using dexamethasone (49) or hydrocortisone infusion (50) have suggested that more the severe fatigue of CFS may in fact be associated with heightened negative feedback. The most convincing evidence to date of an enhanced feedback sensitivity of glucocorticoid receptors comes from a carefully conducted study by Gaab et al. (39). They measured salivary cortisol before and after a low-dose (0.5 mg) dexamethasone suppression test, which is more sensitive to hypersuppression than the standard 1 mg test used in depression. There was reduced postdexamethasone salivary cortisol output seen in CFS patients compared with controls, thus providing evidence of heightened negative feedback. The authors note the similarity of this finding with other stress-related conditions such as burnout syndrome (51), post-traumatic stress disorder (52), adolescents exposed to earthquake-related trauma (53), women with histories of childhood sexual abuse (54) and chronic pelvic pain (55). They hypothesize that precipitating or chronic stress in CFS patients may underlie the finding.

In vivo studies

In vitro studies of feedback provide further support for enhanced glucocorticoid receptor sensitivity. Visser et al. (56) looked at CD4-positive T-cells from a small group of subjects with CFS. They found that a lower concentration of dexamethasone was needed to inhibit CD4 function, suggesting increased sensitivity to dexamethasone. The same group followed this finding up by measuring glucocorticoid receptor function directly on peripheral blood mononuclear cells (PBMCs) (57). Whilst there was no difference in glucocorticoid receptor affinity or number, or of glucocorticoid receptor m-RNA expression, the PBMCs from patients with CFS were again more sensitive to dexamethasone than those from controls. This suggested that the location of the hypersensitivity was somewhere in the postreceptor binding signal transduction. These findings are in keeping with the *in vivo* studies described above.

Not all studies have found increased glucocorticoid receptor function (22,58,59). However, there are problems with these studies. One specifically studied adolescents and found a reduced effect of dexamethasone on white cells, using T-cell proliferation as the marker (22). However, since the presentation of functional symptoms, the continuity with adulthood illness and the function of the endocrine system may differ in adolescence, the results may not apply more generally. Another used CFS subjects specifically chosen to be also suffering from depression (58). Finally, one study used the GH response to dexamethasone challenge, an unusual and unreplicated methodology that may have been susceptible to GH function changes in CFS (30) and also studied a polysymptomatic group also suffering from fibromyalgia and IBS (59).

On balance, then, the evidence for enhanced negative feedback and glucocorticoid receptor function is fairly consistent in the relatively small number of published studies to date.

Is there a specific dysfunction of the HPA axis in CFS?

There are a number of reasons for undertaking dynamic studies of the HPA axis in CFS: (i) given the likely presence of hypocortisolism in some patients, to attempt to detect where there may be abnormalities in the control of the HPA axis; (ii) to detect more subtle disturbances of the axis than may be evident by simply measuring basal levels of cortisol; (iii) to provide a more reliable and standardized indicator of HPA axis

disturbance, less susceptible to extraneous influences than unstimulated measures; and (iv) to allow hypotheses of etiology to be refined, such as how various stresses may exert effects on the disorder, or be implicated in the etiology. This has parallels in the investigation of the HPA axis in other stress-related disorders, such as major depression. Figure 1 shows an outline of the HPA axis, and Table 1 summarizes the evidence for and against dysfunction at various levels of the axis.

Attempts to assess the integrity of the HPA axis have utilized the physiological regulators – corticotropin-releasing hormone (CRH), arginine vasopressin (AVP) and adrenocorticotrophic hormone (ACTH). The CRH challenge test has been the most widely used in CFS. In the first study, Demitrack et al. (29) found blunted ACTH but normal cortisol responses in a chronically ill sample of patients (mean illness duration 7.2 years) who had high rates of psychiatric comorbidity. Of the attempts to replicate this, none has found this pattern. Thus, Scott et al. (17) found both ACTH and cortisol responses to be blunted; our group found normal ACTH but blunted cortisol responses (24); and a final study found both ACTH and cortisol responses to be normal (22). Even our group has struggled to replicate our original findings (from what was the largest of these studies) in a separate group of patients (Roberts et al., unpublished data). Some of the inconsistencies in the results of CRH challenges may result from the challenges being carried out at different times of the day, or by the use of both ovine and human CRH in differing doses. Once again, one of the studies was in adolescents, and may not be comparable to the others. Finally, a theme that will be returned to later is the differing nature of the samples of CFS subjects.

A similarly inconsistent pattern emerges from the studies using ACTH challenge. A placebo-controlled, dose–response study used four doses of ACTH (Cortrosyn 0.003, 0.01, 0.1 and 1.0 µg/kg) or placebo, administered on five separate days. Dose–response curves were significantly different in patients and controls: at low doses of ACTH, only CFS subjects showed cortisol rises above placebo, suggesting a hypersensitivity of the adrenal cortex to ACTH. However, at higher doses of ACTH, cortisol responses were significantly lower than controls, suggesting an overall reduced maximal secretory capacity of the adrenal cortex. Two further studies have administered a standard 1 µg low-dose ACTH test in CFS. The first (18) reported findings in keeping with those of Demitrack et al., including significantly attenuated cortisol responses overall.

However, our group (60) could detect no difference in cortisol responses between CFS and controls groups, though there was a trend towards a blunted response in males only.

The second main factor regulating the pituitary release of ACTH is AVP, which acts synergistically with CRH. The ACTH response to AVP is critically dependent on central levels of CRH, since this response is potentiated by CRH co-administration in a dose-dependent manner and also fluctuates alongside circadian changes in hypothalamic CRH (61,62). Altemus et al. (28) argued that the ACTH response to AVP acts as an indirect index of ambient hypothalamic CRH levels. Thus, when they found a reduced ACTH response to AVP in CFS, they felt this was evidence of lower hypothalamic CRH levels. However, another explanation is that there are abnormalities of AVP release or receptors. Supporting this, Bakheit et al. (63) found AVP levels to be significantly reduced during a water deprivation challenge in CFS patients. Additionally, Scott et al. (20) used desmopressin (DDAVP), an AVP analog, both alone and in co-administration with CRH. They found that, as in their original CRH test study (17), there were blunted ACTH and cortisol responses in CFS subjects. However, the co-administration of DDAVP was able to normalize the ACTH response in CFS subjects. They hypothesized that this was due to upregulated AVP receptors on the pituitary in CFS, consistent with a hypothesized hypothalamic AVP deficiency.

In conclusion, there is no clear pattern of a specific alteration in pituitary or adrenal function. However, there are many suggestions of non-specific impairments to the HPA axis, which will be expanded on in the next section.

Is there a generalized impairment in the response to activation of the HPA axis?

Several studies have used more generalized stressors or challenges to activate the HPA axis. One of the standardized challenges is the insulin stress test (IST), in which HPA axis responses to insulin-induced hypoglycemia are measured. Although a preliminary study of nine patients had suggested some abnormal responses during the insulin stress test (IST) (13), two more thoroughly undertaken studies from our group (24) and elsewhere (30) found no differences in ACTH or cortisol responses. However, a recent study did find a blunted ACTH response, but a normal cortisol response, to the IST (26). Since the IST remains the gold standard test for adrenal insufficiency, the above

results suggest that CFS is not associated with frank hypocortisolism.

Another challenge test reported in the literature is the maximal exercise, clearly of relevance given the exercise intolerance reported by CFS subjects. Two studies have been undertaken, both of which found an impaired ACTH response but normal cortisol responses (25,26). This latter group also found an impaired ACTH response to social stress, induced by the Trier Social Stress Test, which involves a public speaking task. Finally, Scott et al. (19) measured responses to naloxone, an opiate receptor antagonist that attenuates the physiological opioidergic inhibition of the HPA axis and hence leads to HPA axis activation. Once again, they found an attenuated ACTH response.

It seems therefore that there are several suggestions from a series of different challenge tests that there may be a trend for a general reduction in HPA axis responses in CFS. The next important question is whether any of these observed changes are related to symptoms, and in particular fatigue, in CFS.

Do any of the HPA axis changes mediate fatigue?

If low circulating cortisol mediates some or all of the symptoms in CFS, replacement of the hypothesized deficiency should lead to improvements in those symptoms. There have been two randomized controlled trials testing this hypothesis. In the first, 70 patients with CDC defined CFS (many with comorbid psychiatric diagnoses) were randomized to receive either active or placebo treatment for 3 months (64). Those in the active group received daily hydrocortisone according to their weight in a pattern approximating the normal diurnal variation in cortisol (20–30 mg at 08.00 h and 5 mg at 14.00 h). There was a moderate but significant benefit on a global health scale, though not on other more specific measures of fatigue or disability. However, testing with an ACTH challenge revealed a significant degree of adrenal suppression in 12 out of 33 patients on hydrocortisone. A study carried out by our group (65) used much lower doses of 5–10 mg, chosen to represent a dose likely to replace the observed reduction of approximately 30% in 24-h UFC seen in previous studies without causing significant adrenal suppression. Thirty-two subjects entered a randomized, placebo-controlled, crossover study, receiving 28 days of each treatment. There was a clinically significant (30%) fall in fatigue scores in

34% on active treatment compared with 13% on placebo. Furthermore, 28% of those receiving active treatment reported fatigue scores at or below the population median score, compared with 9% receiving placebo. There were concomitant large reductions in self-rated disability scores in those whose fatigue improved. Furthermore, on this dose of hydrocortisone, there was no significant adrenal suppression seen on an IST, and there were no serious adverse effects.

We went on to examine the possible mechanism through which this improvement in fatigue occurred. We administered CRH tests before and after patients received 28 days treatment with 5–10 mg hydrocortisone. Analysis showed that those patients who responded to treatment showed a normalization of their pretreatment blunted cortisol response to CRH (24). This did not occur in those who did not respond to the treatment. We also looked at other measurable physiological effects of hydrocortisone. It had previously been shown that hydrocortisone and other glucocorticoids can cause an increase in circulating leptin levels (66). We found that those who responded clinically to hydrocortisone showed larger increases in circulating leptin than the non-responders (67). This suggested that those who responded may have had upregulated glucocorticoid receptors before treatment, and a subsequently larger biological response to hydrocortisone therapy.

Overall, these findings support the contention that low cortisol levels may be one factor contributing to symptoms and disability in CFS. However, the studies were short-term only, and the positive effects wore off rapidly on the switch to placebo; thus, routine clinical use of this strategy as a treatment is not recommended without further evaluation.

All treatment studies in CFS have relied heavily on self-reported measures of fatigue and disability. This could be thought of as problematic, given that self-reporting may be biased and may not accurately represent illness severity. However, since one of the hypotheses about CFS is that there is a fundamental distortion of perception of the sense of effort (68), reversal of such a distortion would be apparent on self-report measures. Alternative measures of response such as actigraphy may be useful in future studies – such measures appear to represent independent aspects of the illness that do not correlate well with reported fatigue (69). Several patterns are apparent in CFS patients, such as being constantly underactive or showing a variable pattern of inactivity (70), and these patterns may be predictive of response to cognitive-behavioral therapy (71).

Are the HPA axis changes secondary to other factors?

From the above series of studies, then, it seems there is evidence for altered function of the HPA axis, in the direction of lowered cortisol levels and reduced general responsiveness of the axis, and that these abnormalities may at least contribute to some of the symptoms of CFS. However, an important question is whether the observed HPA axis changes are a primary feature of the illness, or occur secondary to other factors involved in the development of CFS.

Psychiatric comorbidity

Comorbid depressive illness is present in up to 50% of CFS patients (3). Since high circulating cortisol is a frequent occurrence in major depression (72), this may clearly affect the results of these studies. Similarly, in atypical major depression, in which fatigue is a prominent complaint along with hypersomnia, hyperphagia and rejection sensitivity, several studies have shown hypocortisolism and HPA axis disturbances (73). Other psychiatric disorders are also over-represented in CFS, and there is evidence that, for example, somatoform disorders (74) or panic disorder (75) are also associated with HPA axis changes. The degree to which psychiatric disorders are assessed or excluded in CFS studies has varied widely; few attempts have been made to compare those with or without psychiatric comorbidity.

Sleep

Disturbance in sleep can affect the HPA axis (76). Given that sleep is so frequently affected in CFS, and is one of the diagnostic features, surprisingly little work has been undertaken to see if this contributes to the endocrine dysfunction. No studies have attempted to study the link between detailed sleep assessments and/or polysomnography and HPA axis changes in CFS. On the other hand, prospectively disrupting sleep leads to alterations in the HPA that mimic some of those seen in CFS (77).

Functional capacity and deconditioning

Physical deconditioning and the stress of exercise can also have marked effects on the HPA axis (78). Although we reported that HPA axis change was not related to self-reported functional capacity (35), no studies have related objective measures of activity levels to HPA axis changes. Another group reported that lowered basal cortisol levels were correlated with a shorter time to

exhaustion on an exercise test (25). This was a cross-sectional finding, so it could be interpreted as showing either that those who were habitually less active had lower cortisol levels and lower fitness or that those with lower cortisol levels had less energy capacity. Not all patients with CFS may have physical deconditioning (79); again, differences between sample characteristics could be important.

Medication

It is clearly important to exclude the possibility that any HPA axis changes are an epiphenomenon of medication use. Not all studies have adequately controlled for past or current use of medication that might affect the HPA axis. In one of our studies, we reported that there was reduced 24-h UFC regardless of concomitant use of medication (35).

Length of illness

Another factor to be considered is length of illness; some studies finding impaired HPA axis function have used subjects with a particularly long illness duration [e.g. a mean of 7.2 years in the study by Demitrack et al. (29)], while other studies that did not find HPA axis changes used subjects with much shorter lengths of illness (36,37). It would clearly be of interest to know how any endocrine changes evolve as CFS develops; studies of high-risk cohorts will be useful to this end, and several such studies are ongoing. Preliminary results from one study, which measured salivary cortisol profiles in subjects with EBV infection, who have a subsequent rate of chronic fatigue of around 15%, suggest no link between the development of chronic fatigue and low cortisol within this time-frame (80).

Pre-morbid factors

It is also notable that there are factors that could lead to longstanding HPA axis changes prior to the illness onset. One example might be childhood abuse; this has strong effects on the HPA axis (81,82), and has also been linked to the etiology of patients with unexplained physical symptoms like fatigue. None of the endocrine studies has assessed this.

The HPA axis and other disorders

It has already been highlighted that there are a number of conditions in which fatigue is a prominent symptom, and which may overlap temporally

or in symptomatology with CFS. To what extent does data from these conditions support the notion that fatigue may be related to HPA axis changes?

Fibromyalgia

The hallmark of fibromyalgia is chronic, widespread pain and the presence of multiple tender points to light palpation (83). However, fatigue is an almost universal complaint in patients with fibromyalgia, and muscle pain is one of the items in the CFS diagnostic criteria. There is a large comorbidity between the conditions (3) and some authors argue that they are manifestations of essentially the same condition (84). There is a growing neuroendocrine literature in fibromyalgia, paralleling that of CFS. There are some similarities in the findings, such as reduced 24-h UFC (85–87) and blunted cortisol responses to a variety of challenges, including exhaustive physical exercise (88), CRH (86), ACTH (89) and the IST (89,90). A major difference is the demonstration of enhanced ACTH responses to CRH and/or IST stimulation (86,91,92). Similar methodological issues apply to the fibromyalgia literature as to the CFS one. Notably, none of these studies has linked symptoms of fatigue to the HPA axis changes.

Depression

It is well documented that there is HPA axis overactivity in a proportion of depressed patients, as well as changes in HPA axis function (72). Many differences exist in comparison to CFS, including: increased CSF CRH levels; enlarged adrenal glands and an enhanced response to exogenous ACTH; and impaired negative feedback measured by the dexamethasone suppression test (93). However, the picture appears markedly different in the atypical subtype of depression (94), in which two of the four defining symptoms (profound fatigue and unrefreshing hypersomnia) are also two of the defining features of CFS. The neuroendocrine profile of atypical depression has several similarities to CFS, including cortisol hypersuppression to dexamethasone (95), lowered plasma cortisol levels (96,97) and hypofunction of CRH neurons (73).

One hypothesis that may link the findings across these disorders is that there are common components that may be linked to the common HPA axis changes. Alternatively, common behavioral changes (altered sleep or reduced physical activity) that are common to the disorders may affect the HPA axis in similar ways. It might be possible to

tease out a possible symptom-specific link by focusing on subjects that have CFS but not muscle pain, fibromyalgia but not fatigue, atypical depression but not fatigue, etc. to determine this. Similarly, the presence of fatigue may be related to biological changes other than the HPA axis, and insight into this could be obtained from other fatiguing illnesses.

Genetic mutations

An recent paper has linked chronic fatigue to a specific genetic substrate. Torpy et al. (98) described a pedigree in which they identified a mutation in the gene controlling the production of corticosteroid-binding globulin (CBG) that was associated with a complete loss of function of CBG. Amongst 32 family members, three were homozygous for the mutation, and had no detectable CBG, while 19 were heterozygotes, who had levels reduced by approximately 50% from the normal reference range. While total cortisol levels varied according to the amount of CBG, being lowest in the homozygotes, free cortisol levels were similar in all members. The majority (86%) of the heterozygotes and two of the three homozygotes had troublesome chronic fatigue that met the CDC criteria for idiopathic chronic fatigue. Five cases met full criteria for CFS, and fibromyalgia and other pain disorders were common. Following these findings, it is suggested that CBG is measured and gene mutations sought in cases of idiopathic chronic fatigue. It may also be the case that those with identifiable CBG abnormalities may be the most likely to respond to hydrocortisone therapy (see above). Despite this, the one study reporting CBG levels in unselected CFS patients found raised levels (29), perhaps as a feedback response to lowered cortisol levels (99,100).

Does the HPA axis influence other biological systems implicated in fatigue?

One theory of how the HPA axis may effect changes in fatigue perception is via the serotonin system. There is a complex interaction between the HPA axis and serotonin systems in the brain. Many studies have demonstrated that glucocorticoids can have an inhibitory effect on central serotonin (5-HT) neurotransmitter function (101, 102), whilst on the other hand, stress-induced CRH secretion is modulated by 5-HT (72,103). There is some evidence from neuroendocrine challenge studies for heightened serotonin activity in CFS. Thus, there is an enhanced endocrine

response to the 5-HT_{1A} receptor partial agonist buspirone (104,105) and to the selective 5-HT-releasing agent d-fenfluramine (12,106). This is in contrast to the finding of impaired responses in major depression (12). Furthermore, serotonergic responses have been shown to be inversely related to the basal cortisol levels. Thus, CFS patients had low baseline cortisol and enhanced serotonergic responses, and depressed subjects the converse. We have suggested that HPA and 5-HT function may be pathologically altered in opposite directions in the two conditions, and also related to characteristic symptom profiles, such as insomnia, anorexia and agitation in depression, and the reverse of these in CFS. Which is the primary deficit remains unclear from these cross-sectional studies. It may also be that there is a disturbance of the relationship between 5-HT and the HPA axis, as found in another study using ipsapirone, a more specific 5-HT_{1A} partial agonist than buspirone (15).

Summary and implications

Chronic fatigue syndrome is most likely a heterogeneous condition with a multifactorial origin. One of these factors is likely to include disturbances to some neuroendocrine systems. The most studied to date has been the HPA axis; whilst the quality of some studies has been poor, balancing the quality of studies, number of replications and consistency of findings, this author believes that there does appear to be indications that in some samples of CFS there is:

1. a mild, relative hypocortisolism;
2. enhanced negative feedback with increased glucocorticoid receptor sensitivity;
3. impaired response of the HPA axis to activation.

Whilst there is not evidence supporting any specific change to the HPA axis, almost all reports of changes to a wide variety of challenges are in the direction of blunting of ACTH or cortisol responses. There is no convincing evidence that any HPA axis changes are specific to CFS or a primary cause of the disorder rather than being related to the many possible consequences or corollaries of the illness.

Reasons for the somewhat inconsistent in findings are clearly apparent, not least the heterogeneous nature of CFS itself; one international study found that samples differ on many parameters even when the international case definition is

used (107). The lack of assessment or control of the confounding factors may also contribute.

There is also a suggestion that low-dose hydrocortisone therapy can improve fatigue in a minority of subjects, though it is not known if this is a specific finding. Nevertheless, it suggests that, even if low cortisol levels are a secondary or epiphenomenal finding, they may be contributing to fatigue perception or prolongation in some patients. Whether the mechanism of this effect is directly via effects on glucocorticoid receptors or via alternative pathways such as serotonin requires more study.

It is also not yet known what happens to endocrine function in CFS patients upon recovery from the illness. It might be hypothesized that clinical recovery would be paralleled by alterations in endocrine status. Studies using hydrocortisone replacement have been described already, but the most effective treatments so far discovered for CFS are non-pharmacological, namely graded exercise and cognitive-behavioral therapies (108). Studies assessing the impact of these therapies on the HPA axis are awaited. Similarly, understanding the importance of endocrine disturbances at the onset of the illness, i.e. as risk factors or triggers, will necessitate prospective cohort studies in groups at high risk of CFS, such as after EBV infection (109), major surgery (110), cancer (111), and similar groups.

Multidimensional model of HPA axis changes

Thus, it seems unlikely that there is a specific or uniform change to the HPA axis in CFS. This author believes that the etiology of HPA axis changes in CFS is, like that of CFS itself, multifactorial. The presence of the many potential confounding factors makes it likely that a variety of alterations to the HPA axis may occur, depending on the presence of these various factors. In order to disentangle these changes, it is recommended that future studies in CFS include

Table 2. Methods for assessing multidimensional components to HPA axis dysfunction in CFS

Factor to be measured	Possible methods
Illness phase	Prospective studies; high-risk cohorts; assessment on recovery of CFS
Sleep	Questionnaire; actigraphy; polysomnography
Psychiatric illness	Structured interview; self-report questionnaires
Childhood abuse	Questionnaires
Medication use	Self-report; doctor report
Drug abuse	Self-report; urine testing
Psychosocial stress	Structured interviews; self-report questionnaires; prospective diaries
Physical activity	Actigraphy; self-report
Diet	Self-report; prospective diaries; weight charting

subjective and objective measures of these changes (Table 2). It is perhaps the heterogeneity of these features in CFS in the different studies that underlie the divergent findings seen to date.

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