

# The HPA axis and the genesis of chronic fatigue syndrome

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**Many studies of patients with long-standing chronic fatigue syndrome (CFS) have found alterations to the hypothalamo–pituitary–adrenal (HPA) axis, including mild hypocortisolism, heightened negative feedback and blunted responses to challenge. However, recent prospective studies of high-risk cohorts suggest that there are no HPA axis changes present during the early stages of the genesis of fatiguing illnesses. Moreover, HPA axis changes can be reversed by modifying behavioural features of the illness, such as inactivity, deconditioning and sleep disturbance. Nevertheless, raising levels of cortisol pharmacologically can temporarily alleviate symptoms of fatigue. This article presents the case that there is no specific change to the HPA axis in CFS and that the observed changes are of multifactorial aetiology, with some factors occurring as a consequence of the illness. Nevertheless, the HPA axis might play a role in exacerbating or perpetuating symptoms late on in the course of the illness.**

Chronic fatigue syndrome (CFS) continues to stimulate debate as to its nature, its aetiology and even its very existence. Extremes on both sides of this debate exist – on the one hand, that CFS is tantamount to a non-illness, and on the other that CFS is a progressive, incurable, organic condition in which stress or psychological factors have no part [1,2]. Most professionals recognize the reality of the symptoms and disability that patients suffer, and that CFS represents a multifactorial illness with a biopsychosocial aetiology [2–4]. An international consensus has been reached on the research criteria for the condition, which is essentially defined as chronic, disabling fatigue of six months or more duration; the fatigue is not the result of excessive ongoing activity, is unresponsive to rest, is associated with other symptoms (such as sleep changes, poor concentration, muscle and joint pains) and is not caused by any detectable underlying medical or severe psychiatric condition [5].

A heavily researched area in terms of potential biological aetiological factors has been the hypothalamo–pituitary–adrenal (HPA) axis (Box 1). Indeed, sufficient evidence of HPA axis changes has accumulated for some to call for the incorporation of neuroendocrine disturbance as part of the illness definition, or even to change the name of the illness itself: one recent suggestion being considered by the US Government Department of Health and Human

Services is ‘neuroendocrine-immune dysfunction syndrome’ (<http://www.cfids.org/archives/2003/2003-1-news.asp>). Here, I review briefly the evidence for HPA axis dysfunction in CFS, and argue that current evidence suggests that neuroendocrine changes are not a central core of the condition, but instead occur late in the history of the illness, at least partly as a response to certain features of the illness, such as sleep disturbance and physical deconditioning. Nevertheless, there is evidence that, once established, HPA axis changes might play a role in perpetuating the illness.

## Is there alteration of HPA axis function in CFS?

Some patients presenting with symptoms of CFS might not have CFS at all. Instead, they might have an underlying disorder of the HPA axis: known conditions, such as Addison’s disease, need to be excluded. Newly described conditions have also emerged, and might continue to do so. For example, a rare mutation of the cortisol-binding globulin was recently discovered in a pedigree: there were high rates of idiopathic chronic fatigue in both homozygotes and heterozygotes (14/17 subjects), many of whom would also have met the criteria for CFS [6]. However, in practice, underlying organic conditions are rarely found in those with chronic fatigue [7,8].

### Box 1. Assessing the HPA axis

The physiology of the hypothalamo–pituitary–adrenal (HPA) axis is complex and is reviewed in detail elsewhere [26,27]. Essentially, a combination of central neurotransmitters controls the release of hypothalamic corticotrophin-releasing hormone and arginine vasopressin, which then act synergistically on the pituitary to release corticotrophin (ACTH). ACTH controls the release of cortisol from the adrenal cortex, whereas cortisol exerts negative feedback at several levels, including hippocampus, hypothalamus and pituitary, via both glucocorticoid receptors and mineralocorticoid receptors. This negative feedback is related both to absolute cortisol level and to the rate of rise of cortisol, and might depend differentially on glucocorticoid and mineralocorticoid receptors, and vary depending on the stage of the circadian rhythm. Furthermore, additional feedback pathways exist, such as those via cytokines produced by immunocompetent cells. Cortisol has many biological effects, and it is through these that any effect that the HPA axis might have on fatigue is thought to be mediated. However, these biological effects depend on many factors other than plasma levels, such as the level of cortisol-binding globulin or sensitivity of receptors. Finally, the HPA axis does not exist in isolation and interacts with many other bodily systems. Most tests of the HPA axis assess only part of the system in isolation, and the assessment of the significance of results of such tests needs to be seen in this context.

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Is there an alteration of the HPA axis in those with CFS in whom known endocrine conditions have been excluded? On the surface, such a question appears simple to answer: if we look at patients defined according to the internationally accepted consensus criteria for this condition, do we find evidence of changes to the HPA axis? Many people have indeed applied this approach, using a variety of experimental methodologies to assess the HPA axis. The results of these studies have been extensively reviewed recently [9] and are briefly touched on here. Essentially, both *in vivo* and *in vitro* tests of negative feedback using dexamethasone support hypersuppression of cortisol and enhanced negative feedback. Other results are summarized in Table 1; the evidence is firmly against any increases in basal plasma cortisol levels or HPA responses to challenge, with over half of the studies suggesting lowered basal cortisol and/or blunted HPA axis responses.

In summary, it appears that there is a change to the HPA axis detectable in CFS. This could be interpreted either dimensionally, in that there is a downward shift in the observed distribution of cortisol levels or HPA axis responses, or categorically, in that a proportion of patients with CFS show abnormal HPA axis function.

### Confounding factors

However, there are significant problems in interpreting these data. First, it is clear that although there is a consensus operationalized definition [5], this still includes

a heterogeneous group of patients. One of the largest sources of heterogeneity is that of psychiatric comorbidity, which is in the order of 50–75%, most commonly depression and anxiety disorders [2]. This is clearly important because of the association of these conditions with HPA axis changes themselves [10,11]. Very few studies have adequately assessed psychiatric comorbidity, or controlled for it in terms of detecting whether there are any endocrine changes that specifically occur in CFS independent of comorbidity [9]. Second, it is surprising that many studies have not been thorough in excluding the effects of medication that patients might be taking, including that of over-the-counter, alternative or illicit medications, which have the potential to affect the HPA axis.

But the strongest criticisms of the type of research outlined above relate to the possibility that the observed endocrine changes are a consequence rather than a cause of being ill. Patients in most studies have been unwell for five years or more [9]. Given that CFS is associated with neurobehavioural changes, such as changes in sleep duration and pattern, levels of habitual physical activity, secondary physical deconditioning and alterations in the circadian pattern of activity and sleep, some or all of these factors could be exerting profound effects on the HPA axis (e.g. [12–14]). If one argues that the endocrine changes are causal to the illness – producing the neurobehavioural symptoms rather than being the result of them – then clearly this cannot be elucidated by studying patients who

**Table 1. Assessment of the HPA axis in CFS: summary of results<sup>a</sup>**

Test	Number of published studies (+ abstracts)	Summary results of studies <sup>f</sup>		
		Significantly lower basal values, blunted response to challenge or smaller size in CFS	No significant differences between CFS and controls	Significantly higher basal values, enhanced response to challenge or larger size in CFS
<b>CRH and/or AVP release from hypothalamus</b>				
AVP challenge <sup>b</sup>	1	1		
DDAVP + CRH challenge <sup>c</sup>	1	1		
AVP response to water deprivation	1	1		
<b>Pituitary response to CRH</b>				
CRH test	4	2	2	
<b>Adrenal cortex response to ACTH</b>				
Direct (ACTH test) <sup>d</sup>	3	2	1	1
Indirect (CRH test)	4	2	2	
<b>Adrenal gland size</b>				
CT adrenals <sup>e</sup>	1	1		
<b>HPA response to generalized stressor</b>				
Response to awakening	1 (+1)	1	1	
Response to exercise	2	2	3	
Response to social stress	1	1		
Response to naloxone	1	1		
Response to insulin	4	1		
<b>Basal cortisol</b>				
Serial blood samples	6	3	3	
24 h urine	6	4	2	
Serial saliva samples	4 (+1)	2	2	1

<sup>a</sup>Abbreviations: ACTH, corticotrophin; AVP, arginine vasopressin; CFS, chronic fatigue syndrome; CRH, corticotrophin-releasing hormone; CT, computerized tomography; DDAVP, desmopressin; HPA, hypothalamo-pituitary-adrenal.

<sup>b</sup>ACTH response to AVP blunted in CFS, which authors attributed to low ambient CRH.

<sup>c</sup>Co-administration of DDAVP and CRH normalized the blunted ACTH response to CRH alone, which authors attributed to low ambient AVP levels and upregulated AVP receptors.

<sup>d</sup>One study showed enhanced responses at low dose ACTH and blunted responses at high dose ACTH challenge.

<sup>e</sup>Patients selected on the basis of having a blunted cortisol response to ACTH challenge.

<sup>f</sup>For further details of studies summarized in this table see [9].

have been unwell for several years and who are attending specialist clinics. Studies of patients at the onset of the illness are required. Therefore, I discuss those prospective studies that have been more able to evaluate the evidence to support the HPA axis as instrumental to the genesis of CFS.

### Prospective cohort studies

Even if one takes a relatively conservative estimate of the prevalence of CFS (0.5–1%), it is clear that most patients are not seen in specialist care settings [2]. Thus, in trying to understand the aetiology of CFS independent of referral biases that might exist in the pathways to specialist care, it is important to study community or general practitioner samples where possible. Incidence rates of CFS are lower still, making it very difficult to study the incidence of CFS on a general population basis. However, there are now several identified groups of people that are at high risk for developing CFS, representing an ideal opportunity to study subjects at the very beginning of illness, rather than several years down the line.

One of the major risk factors that has been studied is that of severe viral illness [2]. For example, about six months after an episode of Epstein-Barr virus infection, ~22% of sufferers will have chronic fatigue and 9% more strictly defined CFS [15], in contrast to common and minor viral infections, where the rates of CFS are not higher than normal [16]. A recent study obtained salivary cortisol day curves to assess the HPA axis during an acute Epstein-Barr virus infection and at three- and six-month follow up [17]. Based on previous theories regarding the HPA axis and CFS [18,19], it was hypothesized that those who went on to develop CFS might show a more pronounced HPA axis reaction to the initial (viral) stressor. Furthermore, it was hypothesized that those who remained chronically fatigued at six months would show evidence of hypocortisolism if this were an important factor at that stage. The results showed that neither hypothesis could be supported: there was no difference in cortisol levels between those with chronic fatigue six months after the infection and those without. Similarly, the cortisol levels at the time of infection did not predict who remained fatigued six months later. Unfortunately, numbers were too small to test specifically whether those with strictly defined CFS, as opposed to chronic fatigue, at six months showed any HPA axis changes.

Another suggestion is that there may be some form of pre-existing risk factor or trait abnormality in the HPA axis that predisposes individuals to develop CFS, perhaps related to childhood abuse or chronic stress [20]. Studying individuals during an acute infection does not allow this to be assessed and other high-risk cohorts are needed where measures can be taken before and after a predictable trigger for fatigue. One example is operative stress [21]. One currently unpublished study from our group measured a daytime salivary cortisol profile one week preoperatively and on three occasions in the post-operative period up to six months later (G. James Rubin, PhD Thesis, University of London, 2003). We found no evidence of low cortisol either before surgery, or six months

later, in those who were chronically fatigued six months postoperatively.

In summary, results from these two cohorts provide the first good prospective evidence that becoming fatigued during the first six months after an acute precipitant is not linked to underactivity of the HPA axis. In addition, there is no evidence that an abnormal initial stress response is implicated. As it stands, the evidence suggests that during the early stages of fatigue genesis, the HPA axis is not an important factor. Instead, HPA axis changes probably develop somewhat later in the natural history of the illness. Clearly, longer-term follow up of such cohorts, and larger samples to enable the identification of any possible subgroups of patients, are needed to confirm this suggestion.

### Is the HPA axis implicated in the genesis of symptoms in established CFS?

Given the links in other conditions (such as Addison's disease and steroid withdrawal states) between low cortisol and symptoms similar to those seen in CFS, it might be argued that even if HPA axis changes are secondary to other factors in the illness, low levels of cortisol in CFS could be a factor relevant in symptom experience or symptom propagation. Studies examining this are discussed in [Box 2](#). In summary, there is evidence that some patients experience an alleviation of symptoms when hypocortisolism is reversed. Therefore, it is possible that, whatever its cause, this hypocortisolism could be one of the factors linked to maintenance of symptoms in CFS and to illness chronicity.

If one accepts that HPA axis abnormalities come on later in the illness and that this might be a consequence of certain symptoms or changes that the illness produces, such as sleep disturbance, physical inactivity and physical deconditioning, then one might also hypothesize that modification of these factors would lead to a reversal of the HPA axis changes in CFS. Indeed, the main evidence base for effective treatments in CFS at present comprises two therapeutic strategies that do just that; namely, graded exercise therapy and cognitive behaviour therapy (CBT) [22–24].

In cognitive behaviour therapy, the emphasis is on modification of those cognitive and behavioural factors that are felt to be important in perpetuating the illness; these include persistent or inconsistent levels of inactivity, alterations to the daily circadian cycle of activity and sleep disturbance. Few attempts have been made to investigate whether this leads to any alteration of the HPA axis changes that, as already noted, are present in those who have been ill with CFS for several years. In a recent study, the HPA axis was assessed in a cohort of 60 subjects with CFS before treatment and six months later, after the main treatment sessions had been concluded. Preliminary results have shown that, as expected, there were improvements in fatigue and functional capacity. Associated with this, there was an increase in mean salivary cortisol level after treatment and an increase in the HPA axis responses to corticotrophin-releasing hormone [25]. No studies have investigated the effects of graded exercise therapy on the HPA axis.

### Box 2. Hydrocortisone as a treatment for CFS?

There have been two randomized controlled trials testing specifically the hypothesis that low dose hydrocortisone in replacement doses might be therapeutic in chronic fatigue syndrome (CFS). The first prescribed full replacement doses of hydrocortisone [ $13 \text{ mg m}^{-2}$  ( $\sim 20\text{--}30 \text{ mg}$ ) at 8 am, and  $3 \text{ mg m}^{-2}$  ( $\sim 5 \text{ mg}$ ) at 2 pm, daily] [28]. Seventy patients were randomized to receive either active or placebo treatment for three months. There was a moderate but significant benefit of hydrocortisone on a global health scale, although not on other more specific measures of fatigue or disability. A second study used much lower doses of 5–10 mg, chosen to represent a dose that would probably replace the observed reductions in basal cortisol values [29]. Thirty-two subjects entered a placebo-controlled crossover study, with 28 days on each treatment. A full response (end of treatment fatigue scores at or below the population median) was seen in 28% on hydrocortisone and 9% on placebo, with 34% and 13%, respectively, showing a clinically meaningful response.

The mechanism of this response remains uncertain. Pretreatment endocrine status was not related directly to treatment response, although treatment responders did show a normalization of the pretreatment blunted cortisol response to corticotrophin-releasing hormone [30]. Similarly, there were other measurable physiological effects of hydrocortisone (such as increased leptin levels) that differentiated responders from non-responders [31], suggesting that those who responded might have had upregulated glucocorticoid receptors. However, it might also represent a nonspecific energizing response to being given a steroid, although there are no studies of such low doses of hydrocortisone in normal controls with which to compare these results. Studies using other steroids alone [32,33] or in combination with hydrocortisone [34] have shown no beneficial effects.

The rapid loss of efficacy upon discontinuation [29] and high rates of adrenal suppression [28] suggest that hydrocortisone cannot be recommended as a treatment for CFS. However, the results suggest that, in some patients, aspects of subjective fatigue perception, and its effects on functional capacity, can be temporarily improved by raising cortisol levels.

### The relevance and aetiology of HPA axis changes in CFS

In summary, evidence suggests that, although there is HPA axis disturbance present in subjects with operationally defined CFS, it is not present before the onset of CFS or during the early phases of illness, but develops once the illness has taken a more chronic course. Furthermore, when certain maintaining factors of the illness are targeted, the HPA axis changes can be reversed. How, then, can we fit this all together into a coherent theory of the HPA axis and the genesis of CFS?

My first contention is that there is no specific change to the HPA axis in CFS. There is reduced cortisol output in at least some patients, heightened negative feedback and glucocorticoid receptor function, and impaired corticotrophin and cortisol responses to a variety of challenges. However, one cannot locate a level of disturbance (e.g. hypothalamic, pituitary or adrenal) from the evidence to date.

I propose that the nonspecificity of HPA axis changes supports my second contention, which is that the aetiology of any HPA axis disturbance is multifactorial and relates to the many factors that might impinge on the HPA axis in CFS, such as inactivity, sleep disturbance, psychiatric comorbidity, medication, pre-existing trait abnormalities in the HPA axis and ongoing stress. A reversed direction of causation (i.e. that the illness leads to HPA axis change rather than the other way around) is supported by the

### Box 3. Outstanding questions

When do hypothalamo-pituitary-adrenal (HPA) axis changes begin in chronic fatigue syndrome (CFS)? Larger prospective cohorts with longer follow up are required.

Are HPA axis changes implicated in the genesis of CFS following other acute precipitants?

Does insidious onset CFS differ endocrinologically from acute onset CFS?

Is there a small subgroup of CFS patients with HPA changes that has been missed in the illness cohorts chosen to date?

findings that there is an apparent absence of HPA axis changes early in the genesis of chronic fatigue states, and that modifying cognitive behavioural components of the illness leads to a normalization of the HPA axis. However, reduced levels of cortisol can potentially have marked symptomatic effects themselves. Although this is clearly true in diseases with more dramatic cortisol deficiency, such as Addison's disease, even in CFS, small replacement doses of cortisol can lead to a temporary but significant improvement in symptoms. I suggest that a vicious cycle is set up in the later stages of CFS, in which certain features of the illness can precipitate HPA axis changes, which can in turn lead to propagation and maintenance of fatigue and other symptoms. Thus, low cortisol, along with several biological, psychological and social factors [4], can act as a maintaining factor in CFS.

These perpetuating HPA axis changes do seem to be responsive to CBT, which appears to be the most appropriate means of addressing them at present, given the much more favourable evidence base for graded exercise and CBT in CFS, the evidence of long-term benefit, the relative absence of side effects in published trials and the poorer evidence base for any direct attempts to alter the HPA axis.

Finally, I propose that the chain of events suggested here should be tested further in future studies. Clearly, work remains in its infancy, and some outstanding questions are listed in Box 3. Researchers wishing to unravel the aetiology of HPA axis changes in CFS more fully are encouraged to use a multidimensional assessment of the various components of CFS and the various confounding factors, where possible using prospective designs to assess varying stages of the illness phase – acute, subacute and chronic fatigue. I believe that it is imperative to use such an approach to define the many predisposing, precipitating and perpetuating features of CFS along a biopsychosocial continuum; this represents the most probable means by which we can improve our understanding of this challenging and enigmatic illness and, ultimately, benefit our patients.

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