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REVIEW ARTICLE

The neuroendocrinology of chronic fatigue syndrome and fibromyalgia

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ABSTRACT

Background. Disturbance of the HPA axis may be important in the pathophysiology of chronic fatigue syndrome (CFS) and fibromyalgia. Symptoms may be due to: (1) low circulating cortisol; (2) disturbance of central neurotransmitters; or (3) disturbance of the relationship between cortisol and central neurotransmitter function. Accumulating evidence of the complex relationship between cortisol and 5-HT function, make some form of hypothesis (3) most likely. We review the methodology and results of studies of the HPA and other neuroendocrine axes in CFS.

Method. Medline, Embase and Psychlit were searched using the Cochrane Collaboration strategy. A search was also performed on the King's College CFS database, which includes over 3000 relevant references, and a citation analysis was run on the key paper (Demitrack *et al.* 1991).

Results. One-third of the studies reporting baseline cortisol found it to be significantly low, usually in one-third of patients. Methodological differences may account for some of the varying results. More consistent is the finding of reduced HPA function, and enhanced 5-HT function on neuroendocrine challenge tests. The opioid system, and arginine vasopressin (AVP) may also be abnormal, though the growth hormone (GH) axis appears to be intact, in CFS.

Conclusions. The significance of these changes, remains unclear. We have little understanding of how neuroendocrine changes relate to the experience of symptoms, and it is unclear whether these changes are primary, or secondary to behavioural changes in sleep or exercise. Longitudinal studies of populations at risk for CFS will help to resolve these issues.

INTRODUCTION

Chronic fatigue syndrome (CFS) is defined as medically unexplained, disabling fatigue of 6 months or more duration, often accompanied by several of a long list of physical complaints (Fukuda *et al.* 1994; Sharpe *et al.* 1991). It is relatively common, with a prevalence of around 0·5% in primary care (Wessely *et al.* 1998) and poor spontaneous recovery at 18 months follow-up (Vercoulen *et al.* 1996). Discussion of its nature and causes has initiated occasionally heated debate between sufferers, doctors and the media (Wessely *et al.* 1998). While psychiatrists have been keen to emphasize its close relation to psychiatric disorders – depression is present in about 50% (David, 199l) – sufferers often maintain that their fatigue has a solely physical cause, perhaps viral. Epstein–Barr virus has been shown to be a risk factor for CFS (White *et al.* 1998), though epidemiological studies suggest that viruses can not account for the majority of cases (Horwitz *et al.* 1985; Holmes *et al.* 1987; Buchwald *et al.* 1987). Findings from immunological studies have also been non-specific and inconsistent (Wessely *et al.* 1998).

A promising new line of enquiry into the nature of CFS is the hypothalamic–pituitary–

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adrenal axis (HPA). Interest led from observations that conditions of low circulating cortisol are characterized by debilitating fatigue, for example in Addison's disease, and following bilateral adrenalectomy (Riordain *et al*. 1994). These conditions also share other symptoms with CFS, such as arthralgias, myalgias and sleep and mood disorder (Baxter & Tyrell, 1981). It has therefore been suggested that the fatigue of CFS is mediated by low circulating levels of cortisol. This hypothesis has gained credence in the last decade or so, though a glance at history shows that it is not in fact new. From 1902 to 1925 the term hypoadrenia or 'a bit of Addison's disease' held sway as the diagnosis of the time for such symptoms, though without firm scientific grounding (Tattersall, 1999).

Recent interest in cortisol and the HPA axis in CFS has applied greater scrutiny to the hypotheses. Poteliakhoff was the first to demonstrate significantly lower baseline cortisol in patients with chronic fatigue, compared to controls (Poteliakhoff, 1981). However, since then, attempts to replicate and extend Poteliakhoff's findings have been far from straightforward. This review examines the current evidence for neuroendocrine disturbance in CFS, highlighting the methodological problems that have hampered consistency, but also led to greater appreciation of the complexity of the neuroendocrine/behavioural interplay.

OVERVIEW OF THE HPA

The HPA axis is the primary endocrine stress axis in man. Secretion of cortisol from the adrenal cortex is regulated by a complex system of long and short feedback loops. Corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP), released by the hypothalamus act synergistically to regulate the output of adrenocorticotrophic hormone (ACTH) from the anterior pituitary. In the systemic circulation ACTH acts at the adrenal cortex stimulating the release of cortisol, which has a negative feedback effect at hypothalamic and pituitary levels, decreasing the output of CRH, AVP and ACTH.

Control of the HPA axis is also achieved centrally via the hippocampus, partly through reciprocal interactions with the 5-HT (serotonin) system (Chaouloff, 1993). The HPA – 5-HT interactions are complex and not yet fully understood, though hippocampal 5-HT_{1A} receptors are thought to be of central importance and are involved in controlling CRH release from the hypothalamus (Lesch *et al*. 1990). 5-HT system modulation of the HPA probably extends beyond the hippocampus, as 5-HT is also thought to stimulate ACTH release at hypothalamic and pituitary levels. In turn, circulating cortisol, regulates central 5-HT system activity, as well as directly inhibiting the release of CRH and ACTH (Dinan, 1996). In depression, both 5-HT system down-regulation and HPA system up-regulation have been prominent neuroendocrine hypotheses over the last decade. Advances in the understanding of the relationship between these two systems allow a preliminary synthesis with implications for the treatment of depression (McAllister-Williams & Young, 1998).

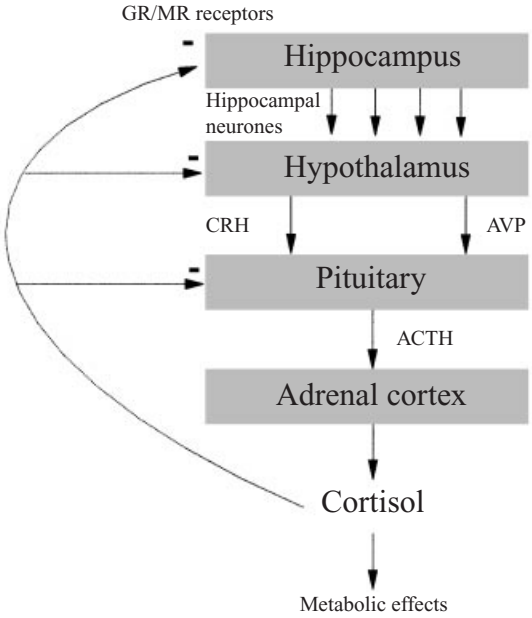

FIG. 1. The hypothalamic–pituitary–adrenal axis. (GR, Glucocorticoid; MR, mineralcorticoid; CRH, corticotrophin releasing hormone; AVP, arginine vasopressin; ACTH, adrenocorticotrophic hormone.)

METHOD

Medline, Embase and Psychlit were searched using the Cochrane Collaboration search strategy for CFS (available from authors), linked to

a key word search for relevant neuroendocrine variables (cortisol, ACTH, corticotrophin, CRH, synacthen, neuroendocrine, neuroendocrinology, hypothalamus, pituitary, adrenal, growth hormone, IGF), for the years 1966–1999. A second search was performed on the King's College CFS database, which has been maintained (by S.W.) since 1991 with over 3000 relevant references. Finally, a citation analysis was run on the key relevant paper (Demitrack *et al.* 1991).

SETTING THE SCENE: THE NIH RESEARCH

The most comprehensive study of the HPA axis in CFS remains that of Demitrack and colleagues at the National Institute of Health, USA – the NIH study (Demitrack *et al.* 1991). They studied 30 CFS patients and 72 normal controls, in a complex design that included baseline measures of cortisol, ACTH and cortisol-binding globulin (CBG). They also evaluated the response of the HPA axis to challenge tests, using ovine CRH and a range of doses of ACTH. Compared to controls, patients with CFS showed reductions of approximately 40% in evening basal plasma cortisol and 24 h urinary free cortisol (UFC) excretion. Since mean UFC was decreased, it was concluded that basal cortisol levels were low throughout the day, and not only in the evening as reflected in the low basal plasma sample. In addition, significantly higher levels of CBG were found in CFS subjects. This may relate to a decreased cortisol effect considering the evidence in rodents (Fleshner *et al.* 1995; Spencer *et al.* 1996) and in humans (Schlecte & Hamilton 1987; Gala & Westphal, l966), for a negative feedback of circulating glucocorticoids on CBG levels. Also significantly raised in CFS subjects were basal levels of ACTH, suggesting that the cortisol deficiency was not secondary to under-functioning pituitary corticotroph cells.

On challenge with ACTH, cortisol responses were proportional to the dose of ACTH in all subjects. However, at low doses of ACTH, only CFS subjects showed cortisol rises above placebo, suggesting a hypersensitivity of the adrenal cortex to ACTH compared with controls. This would be incompatible with a primary adrenal insufficiency. In contrast, at higher doses of ACTH, cortisol responses were significantly lower than controls, suggesting an overall reduced maximal secretory capacity of the adrenal cortex. On stimulation with ovine CRH, subjects with CFS had significantly attenuated ACTH responses, but cortisol responses were similar to controls, demonstrating proportionately higher cortisol secretion per unit of ACTH – further evidence for hypersensitivity of the adrenal cortex to ACTH. These findings led the NIH group to suggest that the hyperresponsiveness of the adrenal cortex in subjects with CFS was secondary to increased sensitivity of ACTH receptors due to chronically inadequate levels of ACTH. Further, they hypothesized that the decreased maximal cortisol response to high levels of ACTH was due to atrophy of the adrenal cortex itself, again consequent upon chronically inadequate levels of ACTH. They concluded that the mild hypocortisolism reflects a defect at or above the level of the hypothalamus resulting in a deficiency in CRH and/or other secretagogues that serve to activate the pituitary–adrenal axis. Their evidence was inconsistent with either a primary adrenal insufficiency or impairment of the pituitary corticotroph cell.

One finding which is not consistent with the NIH group's interpretation, though, is the raised evening ACTH – in contrast to the chronically low levels that they hypothesize. However, although three plasma samples were taken for ACTH measurement, they were all in the evening. This is undoubtedly inadequate for a hormone with a known diurnal variation, and a pulsatile nature of release (Pincus *et al.* 1999). The radio-immune assay employed is also likely to be less reliable than more recently developed assays for ACTH (Kertesz *et al.* 1998).

The evidence from the NIH group left two major hypotheses in need of further study. First, that in CFS, the experience of fatigue is mediated by inadequate levels of circulating cortisol, and a reduced ability to mount an adequate cortisol response to stress. This remains an appealing hypothesis considering the clinical correlation with medical conditions of low circulating cortisol. How the lack of cortisol exerts this effect warrants further study – is it centrally, peripherally, or a combination of both? The second hypothesis is that the fatigue is centrally mediated, not by low cortisol itself, but by

reduced CRH or other mediators controlling the HPA axis. Although central neurohormones/neurotransmitters cannot be measured directly in humans, indirect evidence suggests that these central mediators have an important part to play in CFS.

STUDIES OF BASAL HPA AXIS FUNCTION

The strength of the first hypothesis has been tested by several studies that measured basal cortisol in patients with CFS. These are summarized in Table 1. Despite the early finding of low basal cortisol by Poteliakhoff (1981) and the NIH group (Demitrack *et al.* 1991), the majority of further studies have failed to replicate this. Differences in methodology, and sample characteristics may explain the variety of results.

Methodology

Three basic methods of measuring baseline cortisol have been employed: plasma, urine – 24 h urinary free cortisol (UFC) excretion – and saliva. The majority of studies finding no significant difference in baseline cortisol in patients with CFS used plasma samples (Bearn *et al.* 1995; Yatham *et al.* 1995; Dinan *et al.* 1997; Scott *et al.* 1998*a*, *b*, *c*). Plasma samples entail intravenous cannulation in a hospital setting, both of which may induce a stress response, and a subsequent rise in circulating cortisol. In addition, plasma samples measure more than just the biologically active free cortisol (Kirschbaum & Hellhammer, 1994). Three groups have followed the NIH group and measured UFC – a non-invasive method. The Bart's group (Scott & Dinan, 1998) and the King's group (Cleare *et al.* 2001*a*) replicated the finding of low basal cortisol, but Young *et al.* (1998) found no significant difference. However, despite the wide usage of UFC in depression research (Murphy, 1968; Stokes *et al.* 1984), a controlled study of different cortisol measures found it to be an unreliable indicator of HPA activity (Thompson *et al.* 1992). Also, since free cortisol only represents 2–3% of the circulating cortisol metabolites (Raven & Taylor, 1996), a shift in the balance of cortisol metabolic pathways could potentially affect the measured UFC even in the presence of no change in total cortisol produced.

Salivary cortisol is arguably a better way to measure baseline cortisol, since as well as being non-invasive, it is thought to provide a more accurate and valid measure of biologically active free cortisol than plasma or serum (Kirschbaum & Hellhammer, 1994). If low levels of cortisol were to mediate the symptoms of CFS it would be the free, unbound fraction that is important. However, while Strickland *et al.* (1998) found significantly reduced cortisol from two morning saliva samples, Wood *et al.* (1998), who took 16 samples throughout the day, found significantly raised baseline cortisol, and Young *et al.* (1998) found no significant difference. Aside from the differences in the number and timing of saliva samples, characteristics of the study samples may help to explain the inconsistent results.

Sample confounds

One important confound is co-morbid depressive illness, present in approximately 50% of CFS patients. High circulating cortisol is a well replicated finding in major depression (Dinan, 1994) and so presence of depression makes the cortisol findings more difficul to interpret. Indeed, the subjects studied by Wood *et al.* (1998) included five out of 10 subjects with high Beck Depression Inventory scores (15–19). This may explain their unique finding of significantly raised baseline cortisol in their sample of CFS patients. Other studies have been inconsistent in their exclusion of co-morbid psychiatric illness, and several do not even report data (see Table 1). Length of illness is another potential confounding factor, not always reported on (Table 1). The original study by the NIH group used subjects with a particularly long illness (mean 7·2 years). Some groups who failed to replicate their finding used subjects with considerably shorter illness duration (Wood *et al.* 1998; Young *et al.* 1998). Few studies report on severity of the fatigue or disability, and there is reason to suggest that some behavioural consequences of fatigue may themselves cause the shift in adrenocortical functioning observed by the NIH group (Demitrack *et al.* 1991). For example Leese *et al.* (1996) found that short-term night-shift working mimics the HPA changes observed in patients with CFS. They conclude that the changes observed in CFS may

Table 1. *Summary of baseline studies of cortisol*

Study	Subjects	Fatigue duration	Co-morbid psychiatric illness	Method	Cortisol findings in CFS patients
Poteliakhoff, 1981	25 Fatigue 25 Healthy	> 1 month	No data	1 Plasma sample @ 9.00 h	Low
Demitrack *et al.* 1991	19 CFS (CDC) 18 Healthy	7·2 yr (mean)	No data	3 Plasma samples @ 8.00 h UFC over 4 days	Low – Plasma & UFC
Cleare *et al.* 1995	10 CFS (CDC + Oxford) 15 Depression 10 Healthy	Not given, but tertiary care referrals	Chronic fatigue patients free of depressive illness	1 Plasma sample @ 9.00 h	Low
Strickland *et al.* 1998	14 CFS (CDC + Oxford) 26 Depression 131 Healthy	Not given. Recruited from medical out-patient dept.	10 CFS had depression	2 morning saliva samples on consecutive days	Low
Scott & Dinan, 1998	21 CFS (CDC) 10 Depression 15 Healthy	Not given	5 CFS had depression	24 h UFC	Low No difference between depressed and non-depressed CFS
Cleare *et al.* 2001*a*	121 CFS (CDC) 64 Healthy	5·4 yr	32 CFS had co-morbid psychiatric illness	24 h UFC	Low No difference between depressed and non-depressed CFS
Bearn *et al.* 1995	9 CFS (Oxford) 10 Healthy	5·7 yr	Not given	1 Plasma sample @ 9.00 h	NS
Yatham *et al.* 1995	11 CFS (CDC) 11 Healthy	Not given	Depression not excluded	2 Plasma samples @ 9.00 h	NS
Dinan *et al.* 1997	14 CFS (CDC) 14 Healthy	Not given	Not given	1 Plasma sample @ 9.00 h	NS
MacHale *et al.* 1998	30 CFS (CDC) 15 Healthy	5·2 yr	Depression excluded	2 Plasma samples @ 8.00 h +22.00 h	NS
Racciatti *et al.* 1998	24 CFS (CDC) 5 Depression 16 Healthy	Not given	Not given	6 Plasma samples over 24 h	NS
Scott *et al.* 1998*a*	14 CFS (CDC) 14 Healthy	4·8 yr	Depression excluded	2 Plasma samples @ 12.30 and 13.00 h	NS
Scott *et al.* 1998*b*	20 CFS (CDC) 20 Healthy	Not given	3 CFS had major depression	1 Plasma sample @ 9.00 h	NS
Scott *et al.* 1998*c*	13 CFS (CDC) 13 Healthy	4·75 yr	Depression excluded	1 Plasma sample @ 13.00 h	NS
Young *et al.* 1998	22 CFS (CDC) 22 Healthy	2·5 yr	Depression excluded	4 Saliva samples +24 h UFC	NS
Wood *et al.* 1998	10 CFS (CDC + Oxford) 10 Healthy	3·75 yr	Depression excluded	16 hourly saliva samples from 7.00–22.00 h	High (significant)

CDC, Centers for Disease Control definition (Fukuda *et al.* 1994); NS = not significant; Oxford, Oxford definition (Sharpe *et al.* 1991); UFC, Urinary free cortisol.

be secondary to disrupted sleep and social routine, and thus an epiphenomenon in terms of fatigue causation.

Thus, the significance of basal cortisol levels in mediating fatigue is still not clarified. Furthermore, several authors have noted (Sharpe *et al.* 1996) that basal values may not be the most appropriate measure to determine HPA axis dysfunction, which leads us to consider the pharmacological challenge studies.

CHALLENGE STUDIES

CRH challenge

Measuring the response of the HPA axis to challenge – pharmacological, physiological or psychological, is arguably a better way to investigate HPA dysfunction, since the HPA's role is a dynamic one, in response to stress. The first pharmacological challenge test in CFS was by the NIH group, reported earlier. The Bart's group (Scott *et al.* 1998*a*) has recently repeated the CRH stimulation part of the NIH study, this time in a sample of CFS patients without co-morbid psychiatric disorder. They too found attenuated ACTH responses to exogenous ovine CRH. The NIH group had also found high basal levels of ACTH, and on that evidence ruled out underfunctioning pituitary corticotrophs being responsible for the poor ACTH response to CRH. However, basal ACTH was normal in the Bart's sample, and they suggest desensitization of CRH receptors on the pituitary corticotrophs as a possible explanation. Such an explanation would not be consistent with the theory of decreased hypothalamic CRH, since then up-regulation of CRH receptors would be expected, with exaggerated ACTH responses to exogenous CRH. To reconcile these contrasting theories, the Bart's group suggest that CFS is a stress-related disorder. They hypothesize first, that initial stress may cause an elevation in CRH with consequent down-regulation of CRH receptors on the pituitary corticotrophs. Secondly, they hypothesize that this down-regulation may fail to normalize following reduction in CRH levels. This would be an example of abnormal plasticity in the CRH receptor which could be investigated by studying pituitary–adrenal activation by CRH, during and following recovery from CFS. This would also provide evidence on whether the HPA axis abnormalities are a state- or trait-dependent phenomenon (Scott *et al.* 1998*a*). What might give rise to such abnormal functioning of the CRH receptor is far from clear. The differing basal levels of ACTH between the two groups may also be due to the inherent difficulties of measuring this pulsatile hormone, and the different assays used.

A further challenge test, which may help to clarify the state of the HPA in CFS, is the combined dexamethasone/CRH test pioneered by the Munich group (Heuser *et al.* 1994). This test is well validated and has been demonstrated to be of superior sensitivity compared to the traditional dexamethasone suppression test ($> 80\%$ *v.* 44%) for detecting HPA changes in depression (Deuschle *et al.* 1998).

ACTH challenge

The NIH group's study of the HPA axis suggested that there is up-regulation of ACTH receptors in the adrenal cortex of patients with CFS (Demitrack *et al.* 1991). Further evidence for this comes from the Bart's group (Scott *et al.* 1998*b*) who measured cortisol responses to a low dose ACTH challenge test (1 μg). They demonstrated an inverse relationship between the baseline cortisol and the incremental cortisol rise in response to ACTH, again suggesting hypersensitivity of the adrenal cortex to ACTH in CFS subjects with impaired HPA activity. They also found significantly attenuated cortisol responses overall, which they interpret as reflecting a diminished adrenocortical reserve secondary to reduced trophic output from ACTH, in line with the NIH group's interpretation of their data. The results from both groups would predict adrenal cortical atrophy, and a recent study from the Bart's group has found preliminary evidence for this in a group of eight CFS subjects, using computerized tomography (Scott *et al.* 1999*a*). 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.

Recent work from the King's group attempted to replicate the results of low dose ACTH challenge in 20 non-depressed, medication-free CFS subjects. The authors found no difference in cortisol response in comparison to a matched control group, though in males there was a trend towards a blunted response (Hudson & Cleare, 1999).

5-HT agonist challenge (see Table 2)

In the pathophysiology of depression, the relationship between the hypercortisolaemia and 5-HT may be important (Cleare *et al.* 1996; Dinan, 1996; McAllister-Williams & Young, 1998). Glucocorticoids have been demonstrated

Table 2. *Summary of studies of 5-HT agonist challenge*

Study	Subjects	Fatigue duration	Co-morbid psychiatric illness	5-HT agonist	Responses in CFS compared with controls	Authors' conclusions
Bakheit *et al.* 1992	15 PVFS 13 Depression 13 Healthy	Not given	Not given	Buspirone	Prolactin, significantly greater difference between peak and baseline measures	Up-regulation of hypothalamic 5-HT receptors
Bearn *et al.* 1995	9 CFS (Oxford) 10 Healthy	5·7 yr	Depression excluded	D-fenfluramine	ACTH, significantly raised Cortisol, no difference Prolactin, no difference	Possible altered adrenal cortical function
Cleare *et al.* 1995	10 CFS (CDC + Oxford) 15 Depression 10 Healthy	Not given, but tertiary care referrals	Depression excluded from CFS subjects	D-fenfluramine	Prolactin, significantly raised Inverse relationship between prolactin response and cortisol response	Increased 5-HT function related to reduced HPA axis function
Yatham *et al.* 1995	11 CFS (CDC) 11 Healthy	Not given	Many patients had past or current depression	D,L-fenfluramine	Prolactin, no difference Cortisol, no difference	No support for role of 5-HT in CFS
Sharpe *et al.* 1996	12 CFS (Oxford) 11 Healthy	3 yr	Excluded	Buspirone	Prolactin, significantly raised Growth hormone, no difference	Suggests that enhanced prolactin response may be secondary to changes in dopamine function, rather than 5-HT
Sharpe *et al.* 1997	10 CFS (Oxford) 10 Healthy	Not given	Depressive and anxiety disorders excluded	D-fenfluramine	Prolactin, significantly raised	Possible increased 5-HT function in CFS, may explain fatigue or be secondary to behavioural changes
Dinan *et al.* 1997	14 CFS (CDC) 14 Healthy	Not given	Not given	Ipsapirone	ACTH, significantly lower Cortisol, no difference	Role for 5-HT in the pathophysiology of CFS

CDC, Centers for Disease Control definition (Fukuda *et al.* 1994); PVFS, Post-viral fatigue syndrome; Oxford, Oxford definition (Sharpe *et al.* 1991).

to exert an inhibitory effect on central 5-HT neurotransmitter function (De Kloet *et al.* 1986; McAllister-Williams *et al.* 1998), while on the other hand, stress-induced CRH secretion is modulated by 5-HT (Delbende *et al.* 1992; Dinan, 1996). Accumulating evidence, from the use of 5-HT agonists, now suggests that 5-HT neurotransmission may be altered in CFS. 5-HT pathways from the dorsal raphe nuclei to the paraventricular nucleus of the hypothalamus are thought to bring about the secretion of hypothalamic–pituitary releasing peptides involved in the release of prolactin and ACTH from the anterior pituitary (Checkley, 1980). Therefore, measuring serial prolactin and cortisol responses to 5-HT agonist drugs are thought to reflect hypothalamic-5-HT neurotransmitter function.

Several different 5-HT agonists have been used. Bakheit *et al.* (1992) measured the prolactin response to the 5-HT_{1A} receptor agonist buspirone, and found it to be significantly raised in CFS subjects compared with controls, suggesting up-regulation of post-synaptic 5-HT_{1A} receptors in the hypothalamus. However, buspirone also binds to dopamine D2 receptors, and so its ability to increase prolactin may be mediated in part by D2 receptor blockade (Meltzer *et al.* 1991; Maskall *et al.* 1995). Sharpe *et al.* (1996) tested this by measuring growth hormone responses in addition to prolactin, since it is known that GH release is much more likely to be mediated via 5-HT_{1A} receptors (Cowen, 1993). While prolactin was significantly increased in CFS subjects, GH was not, suggesting that the enhanced prolactin response may be due to abnormalities in dopamine neurotransmission, rather than 5-HT.

Three further studies have used the more selective 5-HT-releasing agent D-fenfluramine. The King's group (Cleare *et al.* 1995) measured prolactin and cortisol responses to D-fenfluramine in CFS patients without depression, healthy controls, and patients with major depression. Relative to controls, prolactin responses were significantly higher in CFS patients, and significantly lower in those with major depression. In addition, prolactin responses were found to be inversely proportional to the baseline cortisol. Thus, CFS patients had low baseline cortisol and enhanced prolactin response to D-fenfluramine, and depressed subjects the converse. Not only does this study provide evidence for increased 5-HT function in CFS, it also suggests that HPA and 5-HT function may be pathologically altered in opposite directions in the two conditions. The King's group also note that in depression, the neurochemical changes are associated with insomnia, anorexia and agitation, whereas the opposite chemical changes in CFS are associated with the reverse of these vegetative behaviours.

While some have replicated the finding of enhanced prolactin response to D-fenfluramine (Sharpe *et al.* 1997), others have not (Bearn *et al.* 1995; Yatham *et al.* 1995). Methodological problems may well be to blame for these inconsistencies. Bearn *et al.*'s sample had poor age and gender matching, and Yatham *et al.*'s subjects had a heterogeneous psychiatric history. Also, Yatham *et al.* used D,L-fenfluramine instead of D-fenfluramine. The former includes both stereoisomers and has less specific neurochemical effects, including additional catecholaminergic effects.

Further evidence for disturbed functioning of the 5-HT and HPA axis relationship comes from a study by the Bart's group (Dinan *et al.* 1997), who used ipsapirone – a partial agonist of 5-HT_{1A} receptors, like buspirone, but without action at dopamine receptors. They were testing the hypothesis that in CFS, abnormalities of HPA function arise from disturbance in serotonergic (5-HT) inputs. In healthy controls ACTH and cortisol rise in a dose-dependent fashion on stimulation with ipsapirone, though in CFS patients they found significantly attenuated ACTH responses, but normal cortisol responses. This finding could be interpreted as evidence of decreased responsivity of 5-HT_{1A} receptors at the hypothalamic level. However, other interpretations such as either decreased responsivity of CRH receptors on the pituitary corticotrophs, or underactivity of the pituitary corticotrophs are possible which do not necessarily invoke abnormalities of the 5-HT system. As noted earlier, the Bart's group (Scott *et al.* 1998*a*) have already suggested decreased responsivity of CRH receptors on the pituitary corticotroph to explain the attenuated ACTH response to exogenous CRH stimulation, found by them and also by the NIH group. Thus although the Bart's group found significantly attenuated 5-HT_{1A} mediated ACTH responses to ipsapirone, the site of abnormality (5-HT_{1A}

receptor, CRH receptor or pituitary corticotroph) is not yet clear.

None of the current 5-HT neuroendocrine probes used in CFS are perfect. As well as the problems of selectivity for the 5-HT system and its many receptor subtypes, most studies do not measure plasma levels of the probes or take into account active metabolites. These problems could potentially account for the inconsistencies in the 5-HT challenge tests reported in CFS.

Naloxone challenge

Several other neurotransmitters are also being implicated in CFS, such as the opioidergic system, which unlike the stimulatory 5-HT system, exerts a predominantly inhibitory influence upon the HPA axis in man (Taylor *et al.* 1983). The Bart's group (Scott *et al.* 1998*c*) put forward the hypothesis that the documented down regulation of the HPA axis in CFS may be secondary to increased opioidergic tone. They stimulated CFS patients and controls with the opiate receptor antagonist, naloxone. In healthy subjects naloxone will decrease central opioidergic tone, thereby releasing the HPA axis from inhibitory control, and causing a rise in ACTH and cortisol. They found that in CFS patients compared to controls there was an attenuated ACTH response to naloxone. They conclude that this effectively rules out increased opioidergic tone as a cogent explanation for the abnormal HPA function in CFS – the opposite finding to that which they predicted. However, their conclusion may be inaccurate due to the difficulty of interpreting challenge tests using a receptor antagonist as the probe. The outcome will depend upon receptor affinities of the probe compared with endogenous opioids, and relative changes in receptor occupancies. The balance of these factors may theoretically determine quite different outcomes from the naloxone challenge. This issue warrants further detailed study.

If however, the Bart's group is correct in their interpretation of decreased opioidergic tone in CFS, then it is interesting considering that pain prone individuals have been found to have lower than normal concentrations of opiates in the CSF (Terenius & Wahlstrom, 1978). Thus, the Bart's group suggest that a reduction in endogenous opioid tone may explain the common pain symptoms which CFS patients experience, such as myalgia, arthralgia and headaches. Indeed, Conti *et al.* (1998) have found decreased β-endorphin levels in patients with CFS. Further investigation of the opioid system is now indicated, including measures of the other endogenous opioids, and investigation of the endogenous opioid receptor ligands. Future studies should include objective measures of physical activity, since activity levels may affect opioid tone (Inder *et al.* 1995).

Argenine vasopressin

Another hormone exerting control over the HPA is argenine vasopressin (AVP), which acts synergistically with CRH to promote ACTH release (Lamberts *et al.* 1984; Antoni, 1993). Therefore a deficit in endogenous AVP could contribute towards the attenuated ACTH response seen with exogenous CRH stimulation. Indeed, Bakheit *et al.* (1993) found basal levels of AVP to be significantly reduced in response to water deprivation challenge in CFS patients. The Bart's group (Scott *et al.* 1999*b*) found that desmopressin, a vasopressin analogue, was able to normalize the blunted ACTH response to CRH that they had previously found. They hypothesized that this was due to upregulated AVP receptors on the pituitary, again consistent with an AVP deficiency.

CIRCADIAN RHYTHMS

In contrast to the many studies observing neuroendocrine function at one time point, there have been relatively few studies of diurnal variation, or circadian rhythm. MacHale *et al.* (1998) demonstrated a significantly attenuated diurnal variation of serum cortisol in CFS, though the absolute concentrations at each time point were not significantly different compared to controls. However, the relevance of diurnal variation is highlighted by their additional observation of a significant relationship between the degree of diurnal variation in cortisol and measures of functional improvement over the past year and current social functioning. Loss of diurnal variation in cortisol has previously been demonstrated in fibromyalgia, pain syndromes and depressive illness (Lascelles *et al.* 1974; Carroll *et al.* 1976; McCain & Tilbe, 1989), all of which have significant symptom overlap with CFS. Supporting McHale *et al.* (1998), a significant decrease in the early morning surge

of cortisol has been demonstrated (Papadopoulos *et al.* 1997), although other studies have found no significant difference in the circadian rhythm of cortisol (Raciatti *et al.* 1998; Wood *et al.* 1998; Young *et al.* 1998).

FIBROMYALGIA

Fibromyalgia is a condition characterized by widespread muscle pain, fatigue and sleep disturbances. Most authors agree that the symptomatology of fibromyalgia overlaps with CFS, and some now believe that it is essentially the same condition (Wessely *et al.* 1999). Of particular interest are the findings from neuroendocrine studies, which on some, but not all, parameters show remarkable similarities to those in CFS. At least two groups have demonstrated reduced 24 h urinary free-cortisol in patients with fibromyalgia (McCain & Tilbe, 1989; Crofford *et al.* 1994). Furthermore, in response to exhaustive physical exercise, Van Denderen *et al.* (1992) reported reduced adrenocortical activation, and in response to exogenous CRH, Griep *et al.* (1993) demonstrated a blunted cortisol response. In contrast to CFS, both Crofford *et al.* (1994) and Griep *et al.* (1993, 1998) found exaggerated ACTH responses to CRH stimulation. The reason for this divergence is not clear, though Demitrack (1997) suggests that a clue may come from AVP levels. Whereas in CFS, AVP levels were found to be low (Bakheit *et al.* 1993), in fibromyalgia they were found to be high compared to controls, in response to postural challenge. Since AVP acts in synergy with CRH to release ACTH, a difference in AVP levels would be consistent with the differences demonstrated in ACTH responses for the two syndromes.

Thus, comparison of CFS with fibromyalgia highlights both similarities and differences in neuroendocrinology. It may be that the differences reflect distinct pathophysiologies for the two syndromes. However, the similarities, both in reduced HPA activation, symptomatology and abrupt stress-related onset suggest otherwise.

GROWTH HORMONE, CFS AND FIBROMYALGIA

The rationale for studying growth hormone in CFS and fibromyalgia comes from several directions. The HPA-stress axis and the growth hormone (GH) axis do interact with one another, as demonstrated, for example, by blunted growth following prolonged stress in childhood. However, a different observation led to the first GH study in fibromyalgia. In 1975 Moldofsky *et al.* demonstrated a distinct disturbance of stage-4, non-REM sleep in patients with fibromyalgia, characterized by alpha-wave intrusion into the delta rhythm. They also induced a transient syndrome similar to fibromyalgia by depriving healthy subjects of this stage of sleep. Stage-4 sleep is closely related to the pulsatile secretion of GH, and approximately 80% of the total daily production of GH is secreted during this stage. GH regulates the hepatic production and release of somatomedin C (IGF-1) which is an important mediator of muscle homeostasis and repair, a deficiency of which would predispose to muscle microtrauma and pain. This led Bennett *et al.* (1992) to hypothesize that disruption of stage-4 sleep in fibromyalgia would lead to low levels of IGF-1, and indeed their study confirmed this.

Similarly, low basal GH, IGF-1 and IGF-2 have been demonstrated in CFS by two groups (Allain *et al.* 1997; Berwaerts *et al.* 1998), although not by another (Bennett *et al.* 1997). The study by Allain *et al.* (1997) also demonstrated a reduced GH response to insulin-induced hypoglycaemia, though Berwaerts *et al.* (1998) failed to repeat this. In an attempt to clear away the confusion from inconsistent results, the King's group (Cleare *et al.* 2000) carried out the largest and most comprehensive study of the GH axis to date in patients with CFS closely matched to healthy controls. They failed to find any significant differences in either baseline or challenge tests of GH function, and concluded that there is no evidence for GH deficiency in CFS patients free from co-morbid psychiatric illness.

TREATMENT STUDIES

Several treatment studies have attempted to reverse the symptoms of CFS and fibromyalgia by artificially replacing hormones thought to be deficient in these conditions. Such studies serve the dual purposes of: (1) testing new logical

therapeutic strategies; and (2) further testing the hypothesis that symptoms are due to disordered neuroendocrine function.

In fibromyalgia, Bennett and colleagues followed up their earlier finding of low somatomedin C (IGF-1) levels in 30% of patients, by conducting a randomized, double-blind, controlled trial of growth hormone replacement (Bennett *et al*. 1998). They included only those patients who had low levels of the growth hormone surrogate marker, IGF-1 (somatomedin C). Daily subcutaneous GH injections resulted in a prompt and sustained increase in IGF-1 levels, and at 9 months, a significant overall improvement in symptomatology and number of tender points. The authors conclude that although the high cost-benefit ratio precludes its therapeutic use in fibromyalgia patients, the study provides further support for the theory that a secondary growth hormone deficiency is responsible for some of their symptoms.

Moorkens *et al*. (1998) carried out a similar, though smaller, randomized controlled trial of GH hormone replacement in CFS. They also selected patients with a demonstrated deficiency of GH, though their results were less marked. There was no improvement in quality of life, after 12 months, although 4 out of 17 patients were able to return to work after prolonged sick leave. The lack of any clear benefit in patients with CFS is perhaps not surprising following the extensive study of the GH axis by the King's group (Cleare *et al*. 2000), noted above.

Of interest to the hypothesis of low circulating glucocorticoids as the mediator of symptoms in CFS, are three recent randomized controlled trials of steroid replacement therapy. The first was by Peterson *et al*. (1998), who used low-doses (0·1–0·2 mg) of the mineralocorticoid fludrocortisone. They found no improvement on any symptom or test of function, over 6 weeks, between active drug and placebo groups. Their rationale for treating with fludrocortisone was unconnected with the neuroendocrine hypotheses presented here. Their study followed the demonstration by Bou-Holaigh *et al*. (1995) that CFS is associated with neurally mediated hypotension. Bou-Holaigh *et al*. also noted in an uncontrolled study, that some CFS patients (9/23) showed a marked improvement after treatment with fludrocortisone and an increase in dietary salt intake. The aim had been to suppress the supposed reflex underlying neurally mediated hypotension by increasing blood volume.

However, two further trials, this time using hydrocortisone, were able to show significant improvements in patients with CFS. McKenzie *et al*. (1998) used a dosing regime chosen to approximate the normal diurnal variation in cortisol (20–30 mg at 8 a.m., and 5 mg at 2 p.m., daily). They demonstrated a moderate but significant benefit on a global health scale, though not on other scales. The cost of this mild improvement was significant adrenal suppression in 12 out of 33 patients, which led the authors to advise against the use of hydrocortisone in clinical practice. The King's group (Cleare *et al*. 1999) also reported a randomized, controlled trial of hydrocortisone in CFS. However, they used much lower doses of 5–10 mg, which are consistent with replacement of the reduction in cortisol output of between 30–40% in CFS, reported in some studies (Demitrack *et al*. 1991; Scott & Dinan, 1998). In contrast to McKenzie *et al*. study, no significant adrenal suppression was seen, and there were no other serious adverse effects. There was a clinically significant fall in fatigue scores in 34% on active treatment, compared with 13% on placebo, and this benefit declined rapidly on crossover to placebo treatment. In those whose fatigue improved, physical role limitations were also significantly improved, as were mean disability scores. Although pre-treatment endocrine disturbance did not predict response to hydrocortisone, those that did respond showed normalization of the cortisol response to CRH challenge, whereas non-responders did not (Cleare, 2001*b*). Overall, this lends support to the suggestion that HPA axis disturbance may be one reversible factor contributing to fatigue in CFS. Despite this, the authors warn against simple acceptance that normalization of the HPA axis is a direct effect of hydrocortisone, as clinical improvement leads to a complex of changes in sleep, exercise, mood and circadian rhythms (above, and Cleare, 2001*b*). Clearly, further evaluation is needed of hydrocortisone as a possible treatment in some patients with CFS, and further study of the HPA axis in those responding to non-pharmacological treatments such as graded exercise or cognitive–behavioural

therapy, both of which are effective in CFS (Wessely *et al*. 1998).

Anti-depressants have also been tried in the treatment of CFS – the rationale being the overlap in symptoms between depressed, and chronic fatigue patients, and the suggestion that CFS may be a variant form of depression. However, the neuroendocrine studies of the HPA axis reviewed above, demonstrate marked differences between the two conditions, suggesting different pathophysiologies (Cleare *et al*. 1995; Scott & Dinan, 1998; Strickland *et al*. 1998). In further support of distinct pathologies, is the randomized controlled trial of fluoxetine in CFS reported by Vercoulen *et al*. (1996). On a range of measures, including subjective fatigue, depression, well-being, functional impairment and activity, they found no beneficial effect for fluoxetine. Even those CFS patients with comorbid depression showed no improvement in mood, suggesting that dysphoria in CFS may have a different basis to that in primary major depression. Three further trials using monoamine oxidase inhibitors (MAOIs) to treat CFS have been carried out. Natelson *et al*. (1996) used a low-dose of the non-specific MAOI, phenelzine, in a double-blind, randomized controlled trial. They found a very small, though statistically significant improvement, which was independent of any anti-depressant effect. They followed this up with a single-blind, placebo phase-in trial of the specific MAO B receptor inhibitor selegiline (Natelson *et al*. 1998), again finding a small, but significant benefit, in the absence of any anti-depressant effect. The most recent study found the strongest effect seen to date, comparing 450–600 mg of moclobemide to placebo over 6 weeks (Hickie *et al*. 2000). Significant subjective global improvement was reported in 24/47 patients on active treatment (51%) compared to 14/43 on placebo (33%). There was a significant and progressive improvement in ratings of 'vigour', though the reduction in disability over the short treatment period was not significantly greater than that seen with placebo. Interestingly, improvement was seen equally in those with and without comorbid depression, while the largest response sizes were seen in a subgroup with immunological changes. Once again, these studies suggest a rather different pattern of antidepressant response to that seen in classical depression.

SUMMARY AND CONCLUSIONS

The extensive study by the NIH group in 1991 suggested three related theories for the mediation of symptoms in CFS (Demitrack *et al*. 1991). First, that the fatigue is due directly to low circulating cortisol; secondly that it is due to abnormalities of central neurotransmitters involved in HPA axis function (e.g. CRH); and thirdly that symptoms are a result of a more complex disturbance of the relationship between the two. Support for all three hypotheses has been found, though it has been problematical providing consistent evidence, and attempts to make causal attributions require caution on the available evidence. On balance, there does appear to be down-regulation of the HPA axis in at least some patients with CFS, and that this is most apparent on challenge tests, rather than measures of baseline function. This would concur with patients' reports of symptoms worsening following physical or emotional stress (Wessely *et al*. 1998).

In keeping with the first hypothesis, reduced circulating cortisol may also explain the modest, non-specific activation of immune responses reported in CFS (Wessely *et al*. 1998), since glucocorticoids usually dampen immune activation. Several studies have supported the role for central neurotransmitter dysfunction (Bakheit *et al*. 1992; Demitrack *et al*. 1992; Cleare *et al*. 1995; Sharpe *et al*. 1996, 1997). In particular, a deficiency of hypothalamically derived CRH is an attractive hypothesis considering that central administration of this neurohormone to animals produces marked behavioural and locomotor activation (Britton *et al*. 1982; Sutton *et al*. 1982; Swerdlow *et al*. 1986). The possibility of the third, complex, but vaguer hypothesis serves to illustrate our current ignorance of how any such chemical changes may translate into subjective symptoms.

Although the HPA axis does appear to be dysregulated in CFS, it is far from clear how the two relate causally. Leese *et al*. (1996) provided evidence that the HPA changes may be secondary to behavioural change, whilst the King's group (Cleare *et al*. 2001*b*) have demonstrated that symptomatic improvement is associated with a reversal of the endocrine changes. Down-regulation of the HPA axis is still weak as an aetiological theory since no theoretical model

exists of how this may come about – from viruses, stress or other insult. This is in contrast to depression, where a robust model exists of how chronic psychological stress leads to up-regulation of the HPA axis, and may also explain changes in monoamine pathways (Checkley, 1996). The finding by White *et al.* (1998) that following glandular fever, 9–22% of subjects develop CFS, suggests that new cases of glandular fever may represent a useful starting point for future longitudinal studies of neuroendocrine function. Such an approach may help establish whether under-activity in the HPA axis is a trait/vulnerability factor or a state factor, and whether it is secondary to a change in behaviour, such as prolonged rest or altered sleep patterns. Correlating the development of HPA dysfunction over time with the development of CFS, would clearly lend support to a role for HPA dysfunction in the aetiological chain.

Although in depression, HPA axis overdrive is well established, no intervention directly targeting this dysfunction has yet proven to be clinically useful and safe. However, in CFS, where antidepressants have been disappointing (Vercoulen *et al.* 1996), direct manipulation of the HPA axis, with oral hydrocortisone, has shown promising results (Cleare *et al.* 1999). This requires further evaluation, particularly in larger, less selected samples to establish efficacy, tolerability and safety, before it can be recommended clinically.

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