Review Article

A Review of Hypothalamic-Pituitary-Adrenal Axis Function in Chronic Fatigue Syndrome

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1. Introduction

Chronic fatigue syndrome (CFS) is a debilitating illness which was classified as a neurological disease in 1993 by the World Health Organisation (WHO) [1]. Symptoms of CFS include persistent fatigue, difficulty with memory and concentration, a disturbed sleep pattern, and severe muscular-skeletal pain [2]. Post exertional exacerbation of symptoms is common but not invariable [3]. The symptoms displayed vary markedly from patient to patient; some patients remain bedridden for very long periods of time, while others are able to manage their fatigue by staying within their own energy boundaries [4]. Diagnostic reliability is enhanced by the use of operational criteria such the Centre for Disease Control and Prevention Criteria [5], the Oxford Criteria [6] or the International Consensus Criteria [7, 8]. However, the heterogeneous symptom profile and absence of clear biological markers militate against confidence in the validity of CFS as a unitary diagnosis. It is not known, for instance, whether there is a core set of biological processes which underlie all cases of CFS or whether there are multiple processes (and if so, whether or not these potentially disparate processes converge on a final common pathway) [9].

Dysregulation of the biological systems which mediate the response to stress potentially has an important role in the aetiopathogenesis of CFS [1, 4, 10]. The neurobiological stress system comprises a range of networks that form intricate pathways; an important part of this is the hypothalamic-pituitary-adrenal (HPA) axis [11–14] which is a self-regulated feedback system which contributes to the maintenance of homeostasis and which is impacted by multiple factors such as time of day and physical and psychological stressors [2, 15]. There are a number of structures within the HPA axis, including the paraventricular nucleus (PVN) of the hypothalamus which releases corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) which in turn stimulates the pituitary to secrete adrenocorticotropic hormone (ACTH) into the systemic circulation. The ACTH acts at the adrenal gland to stimulate the synthesis and secretion of cortisol. Cortisol is released in a pulsatile fashion and ensures strict regulation of both feedforward and feedback loops involving the HPA axis. Hence circulating cortisol activates mineralocorticoid and glucocorticoid receptors (MR and GR) and so decreases the secretion of CRH, AVP, and ACTH [16, 17]. This feedback mechanism is shown in Figure 1. Functional capacity of glucocorticoid receptors is considered, by some,
to be the determining factor in the regulation of the HPA axis [18]. The effects of cortisol are both potent and extensive; it affects numerous physiological functions, for instance, in the regulation of the neuroendocrine and sympathetic nervous systems, modulation of the inflammatory response, inhibition of secretion of multiple hormones, and induction of lymphocyte apoptosis [19, 20].

2. Schematic of the Hypothalamic-Pituitary-Adrenal Axis Feedback Loops

See Figure 1.

3. Adrenal Steroid Metabolic Pathways

See Figure 2.

4. HPA Axis Function in Patients with CFS

Basal hypocortisolism was first reported in CFS patients in 1981 [21]. Cortisol concentrations have since been measured in blood, saliva, and urine in a number of studies with rather varying results (reviewed in [8]), but the notion of a hypocortisolaemic picture in CFS is supported by a meta-analysis [22]. Reduced cortisol levels are more apparent in female patients and also tend to occur during the later stages of the illness [22]. These abnormal cortisol concentrations may reflect differences in the biological mediation of the stress response or may be consequent on the differential nature/magnitude of the stressor engendered by the experimental procedure (e.g., the hospital visit or the venepuncture) in patients with CFS compared to comparator subjects [8, 16, 23]. Further, basal studies have also shown an attenuated diurnal variation [8, 24] particularly with a loss of the morning peak of ACTH [8, 20, 21, 25, 26] or cortisol [8, 20, 27] while challenge studies often, but not invariably, show a diminished HPA axis responsivity. This has been assessed using the ACTH, cortisol, and/or 11-deoxycortisol response to pharmacological challenge using, for example, dexamethasone combined with corticotropin-releasing hormone (CRH) [28], insulin [29], inflammatory cytokines, and metyrapone [30]; to psychological challenge (e.g., using the Trier Social Stress Test [31]), and to physiological challenge (such as wakening) [32–34].

The hypocortisolaemia, attenuated diurnal variation, and reduced responsivity to challenge seen in these cross-sectional studies may be mediated by upregulation of GR and MR, reduced hormone synthesis, or increased metabolism [8, 35]. The enhanced suppression of cortisol during the dexamethasone [36, 37] and prednisolone suppression test [38] supports the notion that increased functional activity of GR and possibly MR may have pathophysiological significance in CFS. However, as dexamethasone is metabolised via cortisol metabolic pathways, the enhanced cortisol suppression during the DST may therefore be caused not by GR upregulation but by reduced dexamethasone metabolism (as a consequence of the enzyme inhibition secondary to persistent hypocortisolaemia [39]).

The thesis that the hypocortisolaemia is caused by a shift in the balance of the various metabolic pathways (Figure 2) in steroid synthesis is tentatively supported but by no means
proven by studies examining plasma concentrations of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS) and by those which calculate the cortisol:DHEA ratio. DHEA levels have been shown to be normal [29], numerically [40] or significantly [41] increased; DHEAS levels have been reported to be reduced [42, 43], and the cortisol:DHEA ratio has been shown to be normal [41, 44] or, in the larger study, reduced [40] in patients with CFS.

5. Cause of the HPA Axis Dysregulation in CFS

It is valuable to explore the mechanisms which may explain the HPA axis dysregulation seen in adults with CFS. Specific genes (acting on the HPA axis or otherwise) which confer an increased risk of CFS have not been identified. There is, however, evidence of a heritable component to the disorder [45]. In addition, the role of early adversity also warrants consideration, particularly given the evidence of an increased rate of childhood trauma in patients with CFS. Around 50% of patients report at least one type of childhood trauma [46, 47]. It has been estimated that childhood trauma increases the risk of CFS between 6- and 8-fold [33, 48] with a graded relationship between the severity of the trauma and the risk of developing CFS [33, 46, 48]. Furthermore, an increased severity of symptoms has been noted in those who report childhood trauma [48]. It is increasingly established in other disease areas that childhood trauma acting via the HPA axis impacts the risk of disorder in adulthood, but it must also be remembered that early adversity is a broad concept which encompasses much more than childhood physical, emotional, and sexual abuse and neglect.

Animal models of early-life stress reveal HPA axis changes which persist into, or became evident in, adulthood [49]. There are a number of potential mechanisms. Variations in maternal care in rodents [50, 51], early life neonatal stress [52, 53], and childhood trauma in man [54–56] have been shown to increase methylation in the CpG-rich regions of a broad range of candidate gene promoters and transcriptional and intragenic sequences [57, 58]. One of the better studied interactions is that ISOXIDATIVESTRESSANDADCREASEINANTIOXIDANCAPACITYresult in the presence of histone deacetylase (HDAC) [72]. Increased activity of HDAC 2 and 3 coincides with a decrease in plasma cortisol [14]. This theory has been cited as another possible cause of hypocortisolism found in patients.

6. Impact of HPA Axis Dysregulation

Having argued that altered HPA axis function may have an aetiopathological role in CFS, it remains necessary to consider the link between cortisol and the typical symptoms of CFS. This may be mediated by immune mechanisms as a dysregulated HPA axis, particularly if characterised by hypocortisolæmia, has the potential to reduce the capacity with which HPA axis hormones can restrain the immune system. As a result, relatively minor physical or psychological stressors may be transduced into an inflammatory response by triggering the release of inflammasomes and subsequently proinflammatory cytokines [73, 74]. This process would be expected to evoke a pathological illness with symptoms such as those found in CFS patients [31, 75–77]. Further work is needed to quantify the inflammatory response in CFS patients. Cytokine-mediated inflammation may also explain the prevalent pain and hypersensitivity that affects CFS patients [78].

A vascular aetiology of CFS has also been proposed. This is a current research interest of our group and is exemplified by the relationship and overlap between CFS and postural orthostatic tachycardia syndrome (POTS) [79, 80] which typically presents with fatigue, dizziness, and an inability to
exercise. HPA axis dysregulation, particularly hypocortisolaemia, can cause hypotension and may possibly mediate the fatigue experienced by CFS patients by inducing orthostatic hypotension and hence reducing cerebral perfusion [81].

7. Relationship between HPA Axis Dysfunction and Symptoms

The demonstrated association between the magnitude of HPA axis dysfunction and symptom severity highlights the relationship between the endocrinology and the disorder [8, 82, 83]. This is further emphasised by the demonstration that HPA axis dysregulation is a poor prognostic factor for CFS patients undergoing psychological treatment [22, 84]. The HPA axis dysregulation may have a causal role in CFS; it may be consequent on the disorder or it may be an epiphenomenon. Experimentally induced, or pathological, hypocortisolaemia (such as that seen in Addison's disease) is associated with symptoms typical of CFS, including fatigue, weakness, and abdominal pain, but it is also associated with a range of other features which are not typical of CFS [19, 85]. Further work to delineate the relationship between HPA axis dysfunction and fatigue in Addison's disease and other hypocortisolaemic states would be of benefit [86, 87].

8. Opportunities for Novel Therapeutic Strategies in Treatment of HPA Axis Dysfunction in CFS

Cognitive behavioural therapy (CBT) and graded exercise plans have demonstrated efficacy but with significant interindividual variation [4, 23, 78, 89]. These therapies modify illness perception and allow patients to make adjustment to optimise energy expenditure. CBT has been shown to increase cortisol levels by reversing some of the effects induced by low activity levels, depression and stress in early life [8, 82, 90, 91]. In addition, many pharmacologic treatments have been investigated for CFS including psychostimulants, corticosteroids, anti-inflammatories, and antidepressants [92–94]. There is currently no evidence to suggest that any of these medications have an advantage to patients though antidepressants are widely prescribed [95].

Low-dose hydrocortisone [96–98] and DHEA [42] have both been used as treatment agents in pilot studies in CFS, and have benefitted some patients. There is an argument for further trials of steroid treatment in patients selected on the basis of adrenal insufficiency, but the potential impact of long-term treatment including Cushing's syndrome, osteoporosis, extreme mood changes, and seizures cautions against this approach [99]. The HPA axis though remains a potential target for novel treatment strategies in CFS and this has been examined in studies utilizing animal models to examine traditional medicines with a putative HPA axis effect; for example, Shilajit, a traditional Indian medicine, reduced immobility and increased climbing behavior whilst increasing adrenal weight and corticosterone levels in the forced swim test in rats [72] and Myelophyl, based on compounds used for fatigue in Chinese medicine, increased glucocorticoid receptor expression in the hypothalamus and hippocampus, and altered expression of cytokines such as interleukin (IL-10) and tumour necrosis factor-alpha (TNF-α) using the chronic cold stress and restraint model in mice [100].

One of the most interesting proposals is the switch to a new steady state from chronic hypocortisolaemia to a healthy, reactive state using the model-based predictive control (MPC) solution originally proposed by Gupta and colleagues [35]. This requires a pharmacologically induced short-term hypocortisolaemia in order to increase ACTH release to a threshold level following which a new equilibrium state is attained even in the absence of the pharmacological agent [19].

9. Conclusion and Further Research

HPA axis dysregulation appears to be associated with CFS. A credible body of evidence suggests a mechanism by which genetic and environmental factors (and their interaction) may serve to create an endocrine milieu which may impact on immune and vascular processes and thus putatively precipitate and maintain the symptoms experienced by those with a diagnosis of CFS. Nonetheless the abnormalities are subtle, and there is marked variation in basal and challenge tests in CFS patients and a real risk that these so-called abnormalities are simply confounds or epiphenomena.

The findings that successful psychological treatments normalise the HPA axis dysregulation together with the reports that HPA axis dysregulation is a poor prognostic factor do give optimism that treatments targeting the HPA axis may have efficacy alone or in the augmentation of more established psychological, behavioural, or pharmacological treatments.

The recent launch of the UK ME/CFS Research Collaborative [101] demonstrates the commitment of the government and associated funding bodies to pursue research into the understanding and treatment of this potentially debilitating disorder. This next decade may see an enhanced understanding of individual facets of CFS including its genetic and epigenetic signature, immune and vascular processes, the fine detail of HPA axis regulation, and the symptoms and psychological underpinning of the disorder. These should be examined using a network approach to map the intricate relationships and should allow consideration of whether CFS, as it is currently defined, is a unitary construct or if it represents multiple illnesses with different causes, albeit with similar symptom patterns. In addition, prospective studies may demonstrate vulnerability and trait factors and
help to explain why some patients develop these symptoms. Hopefully, we can dispel any lingering Cartesian dualism and translate the psychological and biological understanding into holistic therapeutic programmes and novel treatment strategies. Progress is continuously being made; however, for patients who have had their lives destroyed, the development of a cure cannot come fast enough.

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References


