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# Hypothalamic-Pituitary-Adrenal Axis Function in Chronic Fatigue Syndrome

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**Key Words**
Challenge test · Cortisol · Corticotropin-releasing factor · Fatigue · Neuroendocrinology · Stress

**Abstract**
There is evidence for a hypofunction of the hypothalamic-pituitary-adrenal (HPA) axis in a proportion of the patients with chronic fatigue syndrome (CFS), despite the negative studies and methodological difficulties. In this review, we focus on challenge studies and on the role of the HPA axis in the pathogenesis of CFS. Mild hypocortisolism, blunted adrenocorticotropin response to stressors and enhanced negative feedback sensitivity to glucocorticoids are the main findings. Several underlying mechanisms have been proposed. Currently, it is a matter of debate whether these disturbances have a primary role in the pathogenesis of CFS. However, even if the HPA axis dysfunctions are secondary to other factors, they are probably a relevant factor in symptom propagation in CFS.


## Introduction

Chronic fatigue syndrome (CFS) is characterized by unexplained, profound disabling and long-lasting fatigue that is of new or definite onset, that is not the result of ongoing exertion and that is not substantially alleviated by rest. The fatigue must be accompanied by at least 4 or more of the following case-defining symptoms during at least 6 months of consecutive illness: sore throat, tender cervical or axillary lymph nodes, muscle pain, multijoint pain, postexertional malaise, unrefreshing sleep, headaches and impaired memory or concentration [1]. The suggestion that CFS may be related to a dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis derives from clinical similarities between CFS and states of glucocorticoid deficiencies [2], as well as from early observations of reduced adrenocortical activity in chronically fatigued patients [3]. Furthermore, there is evidence for an involvement of physical and psychological stress in vulnerability, onset and/or perpetuation of CFS [4–11]. In the past, stress has generally been associated with HPA axis hyperactivity, resulting in hypercortisolism. However, chronic stress can also lead to HPA axis hypoactivity, as is the case in several stress-related disorders [12–14]. In

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this review, we will mainly focus on HPA axis-related challenge studies and on possible pathophysiological mechanisms in CFS.

## HPA Axis Disturbances in CFS

*Basal Hormonal Changes*

Studies on basal plasma cortisol (single or serial measures), free salivary cortisol and urinary free cortisol have been reviewed extensively by Parker et al. [15] and by Cleare [2]. In summary, in about half of the investigations there was evidence for lowered cortisol levels in CFS. There is only 1 report of elevated salivary cortisol levels in CFS [16]. In all the other studies, no differences were found between CFS patients and control individuals. More recently, the study by Jerjes et al. [17] provided further evidence for reduced basal HPA axis function in CFS. The group of 15 CFS patients without psychiatric comorbidity showed lower urinary free cortisol and corticosterone concentrations than the group of 20 healthy control individuals, whereas diurnal rhythm was normal in CFS patients. Furthermore, Roberts et al. [18] reported a lower salivary cortisol response to awakening in 56 CFS patients compared with 35 control individuals. In contrast, Di Giorgio et al. [19] found no abnormalities in the levels of plasma cortisol in a sample of 15 CFS patients, although they reported reduced levels of adrenocorticotropic hormone (ACTH) over a full circadian cycle and during the physiological morning peak. Finally, regarding basal hormone concentrations in CSF, Demitrack et al. [20] measured cerebrospinal fluid levels of corticotropin-releasing factor (CRF) and ACTH in 19 CFS patients and 26 control individuals, but no differences were apparent. The authors considered this finding to be 'inappropriately normal' in CFS, given the reduction in glucocorticoid secretion in the periphery (and thus reduced negative feedback) [20, 21].

*Challenge Tests*

Hypothalamic and Pituitary Function

Table 1 presents an overview of HPA axis-related challenge tests that have been undertaken in CFS. The insulin tolerance test (ITT) is a standardized method for assessing the entire HPA axis [22]. To the best of our knowledge, only 1 study demonstrated reduced ACTH responses in the ITT in CFS [23]. In 2 relatively large studies [24, 25] and 1 small study [26], there were no significant differences in ACTH responses in the ITT between CFS patients and healthy control individuals. These data do not provide strong evidence for a disturbed HPA axis regulation in CFS, although the ITT may be too blunt to be useful in detecting more subtle changes [2]. Demitrack et al. [20] and Scott et al. [27] reported significantly lower ACTH responses after CRF in CFS patients in comparison with healthy individuals, whereas two other research groups did not find any differences in the CRF challenge [24, 28]. In addition, Altemus et al. [29] argued that the ACTH response to arginine vasopressin (AVP) acts as an indirect index of hypothalamic CRF levels. They found a trend towards a reduced ACTH response to AVP in CFS, which they attributed to a lower ambient level of hypothalamic CRF. Alternatively, Scott et al. [30] hypothesized that a deficit in endogenous AVP could contribute to the attenuated ACTH response in the CRF test. Using desmopressin (DDAVP), an AVP analog, they found that coadministration of DDAVP with CRF normalized the blunted ACTH response to CRF. Consequently, they suggested that CFS may be associated with AVP deficiency and upregulated AVP receptors on the pituitary. Furthermore, blunted ACTH responses to other stressors have been reported in CFS: naloxone [31], exercise and social stress [23]. Finally, in the study by Gaab et al. [32], patients with CFS showed an enhanced and prolonged suppression of salivary free cortisol after the administration of a low-dose of dexamethasone (0.5 mg), pointing to enhanced sensitivity to the negative feedback of glucocorticoids at the pituitary level. In accordance with these findings, we observed lower salivary free cortisol responses in the combined low-dose dexamethasone/CRF test in CFS patients than in control individuals [Van Den Eede, et al., unpubl. data].

Adrenal Function

In the above-mentioned investigations, an inconsistency can be observed in the relationship between ACTH and cortisol responses in challenge tests. More specifically, a reduced ACTH response in CFS patients has been associated with: (1) lower cortisol responses [27] (but without any correlation between the two variables); (2) no difference in cortisol responses [20, 23, 31]; (3) higher salivary cortisol [23] (table 1). In order to clarify this issue and to examine adrenal function in CFS, several ACTH challenge studies have been performed. In 2 studies with 1 μg of ACTH or more, there were no differences in cortisol responses between CFS patients and healthy individuals [33, 34], suggesting that adrenal insufficiency is unlikely to play a significant role in CFS. In contrast, Scott et al. [35] and Demitrack et al. [20] reported reduced cortisol responses in the ACTH test. The findings of chal-

**Table 1.** Overview of HPA axis-related challenge tests in CFS

| Author | Subjects | CFS duration years | MDD | Challenge | Time of testing | ACTH[1] | Cortisol[1] |
|---|---|---|---|---|---|---|---|
| Demitrack et al. [20] | 19 CFS<br>18 CON | 7.2<br>(n = 30) | 3[2] | oCRF (1 μg/kg) | 8 p.m. | lower (net) | no difference (plasma) |
| | 12 CFS<br>10 CON | 7.2<br>(n = 30) | ? | ACTH (0.003, 0.01 μg/kg) | 6 p.m. | – | higher (net, plasma) |
| | | | | ACTH (0.1, 1 μg/kg) | 6 p.m. | – | lower (net, plasma) |
| Scott et al. [27] | 14 CFS<br>14 CON | 4.8 | none | oCRF (100 μg) | 1 p.m. | lower (net) | lower (net, plasma) |
| Scott et al. [31] | 13 CFS<br>13 CON | 4.8 | none | naloxone (125 μg/kg) | 1 p.m. | lower peak ACTH and AUC (net?) | no difference (plasma) |
| Scott et al. [30] | 13 CFS<br>13 CON | 5.0 | none | oCRF (100 μg) | 1 p.m. | lower (net) | lower (net, plasma) |
| | | | | DDAVP (10 μg) | 1 p.m. | no difference | no difference (plasma) |
| | | | | DDAVP (10 μg) + oCRF (100 μg) | 1 p.m. | no difference | no difference (plasma) |
| Altemus et al. [29] | 19 CFS<br>19 CON | 3.7 | none | AVP (1 mIU/kg/min, 1 h) | 9.30 a.m. | interaction disorder and ACTH; trend towards reduced peak value | interaction disorder and cortisol (plasma) |
| Inder et al. [28] | 12 CFS<br>11 CON | ? | none | oCRF (1μg/kg) | 10 a.m. | no difference | no difference (plasma) |
| | | | | naloxone (125 μg/kg) | 10 a.m. | no difference | no difference (plasma) |
| Cleare et al. [24] | 37 CFS<br>28 CON | ? | none | hCRF (1 μg/kg) | 9 a.m. | no difference | cortisol lower (net, plasma; with ACTH as covariate) |
| | | | | ITT (0.15 U/kg) | 9 a.m. | no difference | no difference (plasma) |
| Bearn et al. [26] | 9 CFS<br>10 CON | 5.4 | none | ITT (0.15 or 0.1 U/kg) | 10 a.m. | no difference | no difference (plasma) |
| Moorkens et al. [25] | 73 CFS<br>21 CON | 1.5 | none | ITT (0.15 U/kg) | variable | no difference | no difference (plasma) |
| Gaab et al. [23, 32] | 21 CFS<br>20 CON | 5.6 | 1 | ITT (0.15 U/kg) | 9 a.m. | lower (net and total) | higher cortisol (net, salivary; group by time effect) |
| | | | | TSST | 9–10 a.m. | lower (total) | no difference (plasma or salivary) |
| | | | | Cycle test | 14 p.m. | lower (total) | no difference (plasma or salivary) |
| | | | | DST (0.5 mg) | | – | hypersuppression (salivary) |
| | | | | awakening | awakening | – | no difference (salivary) |
| Van Den Eede et al. [unpubl.] | 34 CFS<br>25 CON | 2.7 | none | DEX (0.5 mg) + hCRF (100 μg) | 15 p.m. (CRF) | – | lower cortisol (total, salivary)[3] |
| Scott et al. [35] | 20 CFS<br>20 CON | ? | 3 | ACTH (1 μg) | 2 p.m. | – | lower peak cortisol (net, plasma) |
| Hudson et al. [34] | 20 CFS<br>20 CON | ? | none | ACTH (1 μg) | 12 a.m. | – | no difference (plasma) |
| Gaab et al. [32] | 18 CFS<br>18 CON | 5.6 | 1 | ACTH (1.25 μg) | 2 p.m. | – | no difference (plasma or salivary) |
| | | | | ACTH (225 μg) | 3 p.m.? | – | no difference (plasma or salivary) |

CON = Control individual; DST = dexamethasone suppression test; hCRF or oCRF = human or ovine corticotropin-releasing factor; ITT = insulin tolerance test; MDD = major depressive disorder (current); TSST = Trier Social Stress Test.

[1] Results in CFS patients compared to control individuals; 'net' refers to the absolute increase of the hormone (corrected for basal value). [2] Score on Hamilton Depression Scale >16. [3] Net salivary cortisol responses lower in patients, but not statistically significant.

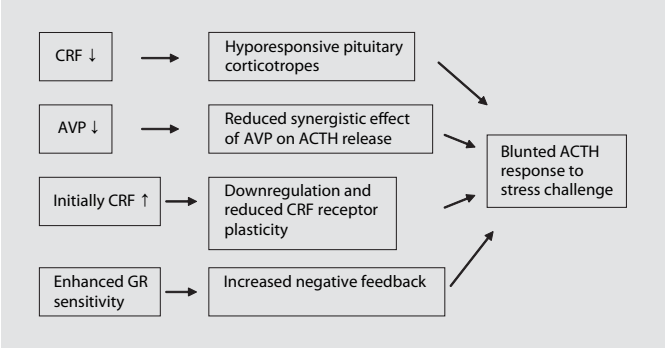


**Fig. 1.** Proposed mechanisms for blunted ACTH response in challenge tests. GR = Glucocorticoid receptor.

lenge studies taken into account, both research groups interpreted these results as a diminished adrenocortical reserve in CFS, secondary to a reduced stimulation from pituitary ACTH. Interestingly, Scott et al. [36] demonstrated that an abnormal ACTH test (8 out of 32 CFS patients) was associated with reduced adrenal gland size on CT scan. Furthermore, Demitrack et al. [20] found that low doses of ACTH (0.003 μg/kg or 0.01 μg/kg) were associated with higher cortisol responses, suggesting hypersensitivity of the adrenal gland in CFS. Taken together, the adrenal gland may be hypersensitive to low doses of ACTH due to hypocortisolism and there may be a diminished adrenocortical reserve in CFS, secondary to a reduced stimulation from pituitary ACTH.

*Confounding Factors*

Methodological difficulties in HPA axis-related research in CFS have extensively been discussed by Cleare [2, 37]. Therefore, we will only briefly mention some issues that are in the interpretation of the challenge tests. Although the presence of major depression has been mentioned in most of the challenge studies as a possible confounder (HPA axis hyperactivity [38]) (table 1), there are other comorbid conditions that may have an influence on HPA axis function in CFS and that have not been reported systematically in most of the articles. For instance, CFS has been associated with a higher prevalence of early-life stress (ELS; sexual, physical and emotional maltreatment during childhood) [6, 10]. ELS is characterized by a central hyperactivity of the CRF system [39], which is in contrast with the proposed CRF hypoactivity in CFS. As a consequence, it may be that CFS patients with a history of ELS constitute a subgroup with a different neuroendocrine function. In support of this, CFS patients without a history of ELS showed significantly lower cortisol responses than CFS patients with ELS and control individuals in the combined low-dose DEX/CRF test [Van Den Eede et al., unpubl. data]. Discrepancies have also been found in fibromyalgia, a condition that is related to CFS [40]. Several studies in patients with fibromyalgia resulted in exaggerated ACTH responses in challenge tests, inversely to the findings in CFS [41–44]. While HPA axis physiology may be altered in both fibromyalgia and CFS, the specific changes may be different. Furthermore, the length of illness may be a confounding factor. In the study by Demitrack et al. [20], patients with particularly long length of illness were included, compared with the study by Moorkens et al. [25] (table 1). As to this, Gaab et al. [45] found a significant negative correlation between the ACTH response in the ITT and both the length of illness and the severity of fatigue symptomatology. There may also be an influence of the day time of testing. The 2 CRF challenge studies resulting in reduced ACTH responses in CFS were performed in the afternoon or in the evening [20, 27], whereas the 2 negative studies were conducted in the morning [24, 28] (table 1). Finally, other factors such as menstrual status and oral contraceptives may have an influence on HPA axis function [46].

## Pathogenesis

*Mechanisms*

Globally, about half of the above-mentioned basal hormone and challenge studies indicated a hypofunction of the HPA axis, whereas no significant differences in HPA axis function between CFS patients and control individuals were apparent in the other studies. The following mechanisms underlying hypocortisolism have been proposed [12, 14]:

- Reduced biosynthesis of releasing factors (CRF, AVP, ACTH) or cortisol.
- Hypersecretion of a secretagogue with subsequent downregulation of the target receptors.
- Increased negative feedback sensitivity to glucocorticoids.
- Decreased availability of free cortisol.
- Reduced effects of cortisol on the target tissue (relative cortisol resistance).

Several of these mechanisms may underlie the blunted ACTH responses to stressors and may be involved in the pathogenesis of CFS (fig. 1). There may be a defect at or above the level of the hypothalamus, resulting in a deficiency in the release of CRF and/or other secretagogues that serve to activate the pituitary. In turn, this chronic

hypodrive may lead to hyporesponsive pituitary corticotropes [20, 21]. On the basis of their findings in the DDAVP challenge, Scott et al. [30] suggested that a deficit in endogenous AVP may contribute to the attenuated ACTH response in the CRF test, rather than a deficit in central CRF (see also 'Challenge Tests'). Alternatively, the same authors hypothesized that desensitization of the CRF receptors on the anterior pituitary corticotropes may underlie the blunted ACTH response after CRF. According to this theory, an elevation of CRF in the initial stress period produces a downregulation of the CRF receptor that fails to normalize following a reduction in CRF levels. This failure could be due to an abnormality in CRF receptor plasticity [27]. However, a receptor downregulation is difficult to reconcile with the above-mentioned CRF hypodrive and to the best of our knowledge, an abnormality in CRF receptor plasticity has not been reported in CFS. Furthermore, there is evidence for enhanced sensitivity to the negative feedback of glucocorticoids in CFS as the main mechanism underlying hypocortisolism in CFS [32]. Further support for enhanced sensitivity for glucocorticoids in CFS comes from in vitro studies, showing that lower concentrations of DEX were needed to inhibit interleukin production and proliferation of peripheral blood mononuclear cells from subjects with CFS [47–50]. The permanently enhanced negative feedback may lead to an increased central inhibitory tone, resulting in reduced hypothalamic CRF expression [32]. Increased negative feedback at the pituitary level may partly account for the blunted ACTH responses in the challenge tests, although the fact that basal cortisol levels were not shown to confound the ACTH responses in the study by Scott et al. [27] argues against this explanation.

It has to be remarked that disturbances at different levels of the HPA axis in stress-related pathology do not always match with each other in a sense of a global hypo- or hyperfunction of the stress system, as proposed by Chrousos and Gold [51]. In posttraumatic stress disorder (PTSD) for instance, a central CRF hyperactivity has been reported, together with (paradoxically) reduced cortisol output and enhanced glucocorticoid negative feedback [52, 53]. Thus, hypocortisolism does not necessary imply a global HPA axis hypofunction, and further research on the central CRF system in CFS is required. In analogy with PTSD, ELS has been associated with central HPA axis hyperactivity in animal and human studies [39]. However, studies on the disturbances of the glucocorticoid feedback mechanism in ELS in human have been less conclusive. Rinne et al. [54] demonstrated that ELS was associated with an enhanced ACTH and cortisol response in the combined high-dose DEX/CRF test in women with borderline personality disorder and ELS compared to a control group without ELS, pointing to an enhanced central CRF drive and/or a reduced glucocorticoid negative feedback in ELS. In contrast, there have also been reports of an enhanced glucocorticoid negative feedback in patients who experienced ELS [55, 56]. However, in both studies, patients with ELS showed a high comorbidity of current PTSD (94 and 68%, respectively), a syndrome that has been associated with enhanced glucocorticoid negative feedback [53]. Further research on the neuroendocrine correlates of ELS and on its role in CFS is required.

*Role of the HPA Axis in the Pathogenesis of CFS*

From a pathophysiological point of view, it is tempting to consider a primary role for the observed HPA axis hypofunction in the pathogenesis of CFS. There are indications that physical or psychological stress is a predisposing and/or precipitating factor in CFS [4–11]. The CRF system is a major component of the stress system, and the HPA axis constitutes its peripheral effector [51]. Chronic stress has been associated with HPA axis hypofunction [12–14]. Moreover, CRF is itself a behaviorally active neuropeptide, next to its key role in the regulation of metabolic, neuron-endocrine and autonomic adaptations to stress [57]. Central administration of CRF to animals has been demonstrated to induce signs of physiological and behavioral activation [58, 59]. There is also evidence that CRF is involved in the regulation of spontaneous waking as an excitatory peptide [60] and that CRF has analgesic properties [61]. Consequently, the reduction in the availability of central nervous system CRF may contribute to the lethargy and to the pain symptoms in CFS, in addition to its role in the reduced HPA axis output [20].

Neuroendocrine factors such as CRF and growth hormone-releasing hormone have a profound influence on sleep regulation [62]. In major depression for instance, evidence points to a causal relationship between CRF hyperactivity and polysomnographic disturbances [62]. More precisely, intracerebrovascular injection of CRF decreases slow-wave sleep in animals, and there is evidence that CRF promotes REM sleep. A decrease in non-REM sleep (decrease of stage 2 sleep and slow-wave sleep) and REM disinhibition (shortened REM latency, prolonged first REM period and elevated REM density) are polysomnographic characteristics of major depression [62]. In CFS however, studies have not identified characteristic polysomnographic disturbances [4]. In a recent general population-based study by Reeves et al. [63], there were

no significant differences in rates of primary sleep disorders between CFS patients and nonfatigued control individuals, and there were no differences in sleep architecture either (with the exception of a higher mean frequency of obstructive apnea per hour of night-time sleep in the CFS group, which was not clinically meaningful).

Furthermore, there is a possible link between the HPA axis and immune disturbances in CFS. More precisely, inflammatory mediators such as interleukin-1 recruit the hypothalamic CRF containing neurons in a negative feedback loop in which glucocorticoids exert immunosuppressive effects to prevent the immune response from overshooting. If hypothalamic neurons fail to response adequately to cytokine stimulation, the resultant failure of adequate glucocorticoid-mediated restraint of the immune system results in a hyper-immune state [13, 64]. According to Dantzer [65], proinflammatory cytokines produced by cells of the innate immune system act on the central nervous system via afferent and humoral pathways to trigger a brain cytokine system that organizes the sickness response in its subjective, behavioral and metabolic components. Finally, other neurobiological pathways may also be involved primarily or secondarily in the HPA axis dysfunction. Serotonergic, noradrenergic and dopaminergic input acts to stimulate the HPA axis. Studies measuring cortisol and prolactin responses to serotonin agonists have provided evidence for a disturbed relationship between the serotonergic system and the HPA axis in CFS [15].

Currently however, it is a matter of debate whether the HPA axis disturbances have a primary role in the pathogenesis of CFS. In his critical review, Cleare [37] states that there is no specific change to the HPA axis in CFS and that the observed disturbances are of multifactorial etiology, with some influencing factors (such as profound inactivity or sleep disturbances) occurring as consequence of the illness. According to this author, the HPA axis is probably not an important factor in the early stages of the fatigue genesis. Instead, HPA axis changes may develop somehow later in the natural history of the disorder. Supporting this notion, the level of HPA axis dysfunction in CFS has been found to be correlated to the length of illness [45]. Furthermore, two prospective investigations demonstrated that becoming fatigued during the first 6 months after an acute precipitant was not linked to hypoactivity of the HPA axis [66, 67]. However, in contrast with these studies, Glass et al. [68] found that amongst regularly exercising individuals, some develop fatigue, musculoskeletal pain and mood changes after a brief period of exercise cessation, while other remained asymptomatic; the symptomatic subjects were characterized by lower HPA axis, autonomic and immune function. The authors speculated that a subset of healthy individuals who have a hypoactive function of the biological stress response systems (unknowingly) exercise regularly to augment the function of these systems and to suppress symptoms. These individuals may be at risk for developing 'chronic multisymptom illnesses' when a stressor leads to lifestyle changes that disrupt regular exercise. It has been proposed that after a period of chronic stress and associated 'allostatic load' [70] the stress system may switch from hyper- to hyporesponsiveness via changes in autoregulatory feedback mechanisms, resulting in a typical fatigue/pain/low mood symptom cluster [12, 69]. This dynamic view on the HPA axis in stress-related disorders is supported by the investigations from Houshyar et al. [71] in rats, demonstrating that enhanced HPA axis responses and decreased sensitivity to negative feedback of glucocorticoids may alter into reduced HPA axis responses and increased negative feedback sensitivity after chronic stress. Large longitudinal studies in humans are necessary to examine how HPA axis disturbances evolve in time and to determine if they precede the development of stress-related disorders, although such studies are difficult to perform because only a small percentage of individuals who are exposed to any stressor will develop symptoms [68]. In addition, genetic studies in humans are required to examine if polymorphisms in HPA axis-related target genes are associated with CFS, in analogy with research in affective disorders [38, 72–75]. According the study by Goertzel et al. [76], three major candidate genes in CFS are tryptophan hydroxylase, catechol-O-methyltransferase and glucocorticoid receptor. This study has been criticized because of the small number of gene variants that have been investigated and because of the limited number of CFS patients that were included [77]. Recently however, Rajeevan et al. [78] observed an association of multiple single nucleotide polymorphisms in the glucocorticoid receptor gene (NR3C1, gene ID: 2908) with chronic fatigue (patients: n = 95; controls: n = 42).

When considering the role of the HPA axis in the pathogenesis of CFS, it is important to mention that hypocortisolism is not a specific finding in CFS; it has been observed in several stress-related and bodily disorders [14]. Halbreich [79] has proposed the following possibilities for the interpretation of nonspecific neuron-endocrine abnormalities:

- Endocrine abnormalities may be more specific to clusters of symptoms.
- Endocrine abnormalities represent a generalized nonspecific imbalance (due to stress) and actual symp-

toms depend on other variables (location of defect, genetics, low threshold in particular system, …).
- Endocrine abnormalities represent a disturbance in a specific central nervous system region (e.g. limbic system); any pathology that involves that region will be associated with the endocrine abnormalities.
- The current diagnostic system is engraved in stone; endocrine abnormalities are of no diagnostic value.

As to the link between hypocortisolism and symptomatology, treatment trials have provided modest evidence that some patients experience an alleviation of symptoms when hypocortisolism is reversed (see the section below). Given the link in conditions such as Addison's disease between low cortisol and symptoms similar to those seen in CFS [80], it might be argued that, even if HPA axis disturbances are secondary to other factors, low levels of cortisol in CFS could be a factor relevant in symptom propagation and perpetuation [37].

### Hydrocortisone Replacement Therapy

There have been three randomized controlled trials testing the hypothesis that hydrocortisone might be effective in the treatments of CFS. In the first study, 70 patients were randomized to receive either active (13 mg/m$^2$ of body surface area at 8 a.m. and 3 mg/m$^2$ at 2 p.m.) or placebo treatment for 3 months [81]. There was a moderate but significant benefit of hydrocortisone on a global health scale, but not on other more specific measures of fatigue or disability. A second study used much lower doses of hydrocortisone (5–10 mg daily) [82]. Thirty-two subjects entered a placebo-controlled crossover trial, with 28 days on each treatment. There was a clinically significant fall in self-reported fatigue scores in 34% of the patients on active treatment, compared to 13% on placebo. However, Blockmans et al. [83] found no differences between treatment with a combination therapy (hydrocortisone 5 mg/day and 9-α-fludrocortisone 50 μg/day) and placebo in a 6-month randomized double-blind crossover study in 100 CFS patients. Taken together, hydrocortisone replacement therapy cannot be recommended for clinical use because of the limited benefit, because of the loss of efficacy upon discontinuation [82] and because of the adrenal suppression when using higher doses [81]. However, the symptomatic improvement in 2 of the 3 trials is concordant with an evolvement of the HPA axis in symptom propagation in CFS.

### Conclusion

In conclusion, the HPA axis remains an intriguing field of research in CFS. Globally, there is evidence for a reduced cortisol output and HPA axis hypofunction in a proportion of patients with CFS, despite the negative studies and methodological difficulties. Mild hypocortisolism, blunted ACTH responses in challenge tests and enhanced negative glucocorticoid feedback are the main findings. Several underlying mechanisms have been proposed, but further research on the central CRF system in CFS is needed. Additional studies in humans are also required to examine how HPA axis disturbances evolve in time and to determine their role in the predisposition for stress-related disorders. It is likely though that the HPA axis is a relevant factor in symptom propagation in CFS, even if the disturbances are secondary to other factors.

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