<https://www.ncbi.nlm.nih.gov/pubmed/26063326>

Top 10 genetic markers associated with CFS based on weighted genetic variation (WGV) estimated by the Bayesian model

| **SNP ID** | **Proxy SNP** | | **Gene symbola** | | **SNP annotationa** | **WGV** | **SE of WGVb** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| rs1396862 | rs1218523 | | CRHR1 (IMP5) | | Intron (missense codon) | 2.31 | 0.0334 | |
| Sr. no. | Gene symbol | NCBI rsID | | Chr. | Position | Homo-zygous-1 | Homo-zygous-2 | Hetero-zygous | | Weighted genetic variation |
| 129 | *CRHR1* | rs1396862 | | 17 | 41258778 | 0.03 | 0.57 | 0.40 | | 2.31 |

<https://www.ncbi.nlm.nih.gov/pubmed/18986552>

Average absolute value of severity associations for the SNPs within eight candidate genes.

| **Gene Name** | **Gene Location** | **Average Correlation (SD)** | **Count of SNPs in candidate gene** | **Most Correlated SNP** | | |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | Name | Correlation | p-value |
| CRHR1 | 17q21 | 0.03 (0.02) | 6 | rs242940 | 0.069 | 0.531 |

<https://www.ncbi.nlm.nih.gov/gene/1394>

This gene encodes a G-protein coupled receptor that binds neuropeptides of the corticotropin releasing hormone family that are major regulators of the hypothalamic-pituitary-adrenal pathway. The encoded protein is essential for the activation of signal transduction pathways that regulate diverse physiological processes including stress, reproduction, immune response and obesity. Alternative splicing results in multiple transcript variants. Naturally-occurring readthrough transcription between this gene and upstream GeneID:147081 results in transcripts that encode isoforms that share similarity with the products of this gene.

<http://www.uniprot.org/uniprot/P34998>

G-protein coupled receptor for CRH (corticotropin-releasing factor) and UCN (urocortin). Has high affinity for CRH and UCN. Ligand binding causes a conformation change that triggers signaling via guanine nucleotide-binding proteins (G proteins) and down-stream effectors, such as adenylate cyclase. Promotes the activation of adenylate cyclase, leading to increased intracellular cAMP levels. Inhibits the activity of the calcium channel CACNA1H. Required for normal embryonic development of the adrenal gland and for normal hormonal responses to stress. Plays a role in the response to anxiogenic stimuli.4 Publications

#### GO - Molecular functioni

* [corticotrophin-releasing factor receptor activity](https://www.ebi.ac.uk/QuickGO/term/GO:0015056) Source: UniProtKB

[View the complete GO annotation on QuickGO ...](http://www.ebi.ac.uk/QuickGO/annotations?geneProductId=P34998)

#### GO - Biological processi

* [activation of adenylate cyclase activity](https://www.ebi.ac.uk/QuickGO/term/GO:0007190) Source: ProtInc
* [adenylate cyclase-activating G-protein coupled receptor signaling pathway](https://www.ebi.ac.uk/QuickGO/term/GO:0007189) Source: UniProtKB
* [cell surface receptor signaling pathway](https://www.ebi.ac.uk/QuickGO/term/GO:0007166) Source: InterPro
* [cellular response to corticotropin-releasing hormone stimulus](https://www.ebi.ac.uk/QuickGO/term/GO:0071376) Source: UniProtKB
* [corticotropin secretion](https://www.ebi.ac.uk/QuickGO/term/GO:0051458) Source: UniProtKB
* [female pregnancy](https://www.ebi.ac.uk/QuickGO/term/GO:0007565) Source: ProtInc
* [G-protein coupled receptor signaling pathway](https://www.ebi.ac.uk/QuickGO/term/GO:0007186) Source: Reactome
* [immune response](https://www.ebi.ac.uk/QuickGO/term/GO:0006955) Source: ProtInc
* [negative regulation of voltage-gated calcium channel activity](https://www.ebi.ac.uk/QuickGO/term/GO:1901386) Source: UniProtKB
* [parturition](https://www.ebi.ac.uk/QuickGO/term/GO:0007567) Source: ProtInc
* [regulation of adenylate cyclase activity involved in G-protein coupled receptor signaling pathway](https://www.ebi.ac.uk/QuickGO/term/GO:0010578) Source: UniProtKB
* [regulation of corticosterone secretion](https://www.ebi.ac.uk/QuickGO/term/GO:2000852) Source: UniProtKB

[DB09067](https://www.drugbank.ca/drugs/DB09067) Corticorelin ovine triflutate

<https://www.ncbi.nlm.nih.gov/pubmed/27766535>

# Hypothalamic-Pituitary-Adrenal Hypofunction in Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) as a Consequence of Activated Immune-Inflammatory and Oxidative and Nitrosative Pathways.

[Morris G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Morris%20G%5BAuthor%5D&cauthor=true&cauthor_uid=27766535)1, [Anderson G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Anderson%20G%5BAuthor%5D&cauthor=true&cauthor_uid=27766535)2, [Maes M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Maes%20M%5BAuthor%5D&cauthor=true&cauthor_uid=27766535)3,4,5,6.

### [Author information](https://www.ncbi.nlm.nih.gov/pubmed/27766535)

### Abstract

There is evidence that immune-inflammatory and oxidative and nitrosative stress (O&NS) pathways play a role in the pathophysiology of myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS). There is also evidence that these neuroimmune diseases are accompanied by hypothalamic-pituitary-adrenal (HPA) axis hypoactivity as indicated by lowered baseline glucocorticoid levels. This paper aims to review the bidirectional communications between immune-inflammatory and O&NS pathways and HPA axis hypoactivity in ME/CFS, considering two possibilities: (a) Activation of immune-inflammatory pathways is secondary to HPA axis hypofunction via attenuated negative feedback mechanisms, or (b) chronic activated immune-inflammatory and O&NS pathways play a causative role in HPA axis hypoactivity. Electronic databases, i.e., PUBMED, Scopus, and Google Scholar, were used as sources for this narrative review by using keywords CFS, ME, cortisol, ACTH, CRH, HPA axis, glucocorticoid receptor, cytokines, immune, immunity, inflammation, and O&NS. Findings show that activation of immune-inflammatory and O&NS pathways in ME/CFS are probably not secondary to HPA axis hypoactivity and that activation of these pathways may underpin HPA axis hypofunction in ME/CFS. Mechanistic explanations comprise increased levels of tumor necrosis factor-α, T regulatory responses with elevated levels of interleukin-10 and transforming growth factor-β, elevated levels of nitric oxide, and viral/bacterial-mediated mechanisms. HPA axis hypoactivity in ME/CFS is most likely a consequence and not a cause of a wide variety of activated immune-inflammatory and O&NS pathways in that illness.

<https://www.ncbi.nlm.nih.gov/pubmed/21946893>

The weight of current evidence supports the presence of the following factors related to hypothalamic-pituitary-adrenal (HPA) axis dysfunction in patients with chronic fatigue syndrome (CFS): mild hypocortisolism; attenuated diurnal variation of cortisol; enhanced negative feedback to the HPA axis; and blunted HPA axis responsiveness. Furthermore, HPA axis changes seem clinically relevant, as they are associated with worse symptoms and/or disability and with poorer outcomes to standard treatments for CFS. Regarding etiology, women with CFS are more likely to have reduced cortisol levels. Studies published in the past 8 years provide further support for a multifactorial model in which several factors interact to moderate HPA axis changes. In particular, low activity levels, depression and early-life stress appear to reduce cortisol levels, whereas the use of psychotropic medication can increase cortisol. Addressing these factors-for example, with cognitive behavioral therapy-can increase cortisol levels and is probably the first-line approach for correcting HPA axis dysfunction at present, as steroid replacement is not recommended. Given what is now a fairly consistent pattern of findings for the type of HPA axis changes found in CFS, we recommend that future work focuses on improving our understanding of the cause and relevance of these observed changes.

<https://www.ncbi.nlm.nih.gov/pubmed/21549189>

Hypocortisolism is a frequent finding in individuals with chronic fatigue syndrome (CFS) with other research findings implying potential dysregulation of glucocorticoid signaling. Glucocorticoid signaling is under the influence of several pathways, several of which are of interest in the study of CFS. Oxidative stress and decreased antioxidant capacity are known to disrupt the hypothalamic-pituitary-adrenal (HPA) axis (Epel et al., 2004) and the presence of histone deacetylases (HDAC) could also impact glucocorticoid signaling. The intent of this pilot study was to investigate the relationship among oxidative stress elements, select HDAC's (2/3) and glucocorticoid receptor signaling in an elderly sample with CFS. Findings suggest increased histone deacetylase activity, lower total antioxidant power, in the context of decreased plasma cortisol and increased plasma dehydroepiandrosterone concomitant with decreased expression of the encoding gene for the glucocorticoid receptor. These findings support the presence of HPA axis dysregulation in elderly individuals with CFS.

<https://www.ncbi.nlm.nih.gov/pubmed/17596739>

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.

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 Key Words Challenge test Cortisol Corticotropin-releasing factor Fatigue Neuroendocrinology Stress Abstract There is evidence for a hypofunction of the hypothalamicpituitary-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. Copyright © 2007 S. Karger AG, Basel Received: August 29, 2006 Accepted after revision: March 17, 2007 Published online: June 27, 2007 Filip Van Den Eede, PhD Department of Psychiatry, University Hospital Antwerp (UZA) Wilrijkstraat 10 BE–2650 Edegem (Belgium) Tel. +32 3 821 49 11, Fax +32 3 825 16 41, E-Mail filip.van.den.eede@uza.be © 2007 S. Karger AG, Basel 0302–282X/07/0552–0112$23.50/0 Accessible online at: www.karger.com/nps HPA Axis Function in Chronic Fatigue Syndrome Neuropsychobiology 2007;55:112–120 113 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]

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 HPA Axis Function in Chronic Fatigue Syndrome Neuropsychobiology 2007;55:112–120 117 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 biolog ical 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- Van Den Eede /Moorkens / Van Houdenhove /Cosyns /Claes 118 Neuropsychobiology 2007;55:112–120 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] .