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Does hypothalamic–pituitary–adrenal axis hypofunction in chronic fatigue syndrome reflect a 'crash' in the stress system?

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SUMMARY

The etiopathogenesis of chronic fatigue syndrome (CFS) remains poorly understood. Although neuroendocrine disturbances – and hypothalamic–pituitary–adrenal (HPA) axis *hypo*function in particular – have been found in a large proportion of CFS patients, it is not clear whether these disturbances are cause or consequence of the illness. After a review of the available evidence we hypothesize that that HPA axis hypofunction in CFS, conceptualized within a system-biological perspective, primarily reflects a fundamental and persistent dysregulation of the neurobiological stress system. As a result, a disturbed balance between glucocorticoid and inflammatory signaling pathways may give rise to a pathological cytokine-induced sickness response that may be the final common pathway underlying central CFS symptoms, i.e. effort/stress intolerance and pain hypersensitivity. This comprehensive hypothesis on HPA axis hypofunction in CFS may stimulate diagnostic refinement of the illness, inform treatment approaches and suggest directions for future research, particularly focusing on the neuroendocrine–immune interface and possible links between CFS, early and recent life stress, and depression.

Introduction

Chronic fatigue syndrome (CFS) consists of medically unexplained, incapacitating and persisting physical and mental fatigue, increased fatigability and widespread pain [1]. Although the condition remains an etiopathogenetic enigma [2–4], during the past decade more than a dozen of studies have provided evidence for HPA axis hypofunction in a substantial proportion of CFS patients. Particularly mild hypocortisolism (low to normal cortisol levels), blunted adrenocorticotropic hormone (ACTH) responses in challenge tests, and enhanced negative glucocorticoid feedback have been consistently demonstrated (see Ref. [5] for a review). More recent neuroendocrine CFS research, including population-based studies, came to largely similar conclusions [6–9].

Given the symptomatic links between CFS and other hypocortisolism-based conditions (such as Addison's disease) as well as the relative effectiveness of corticotherapy in CFS [5], it has been posited that HPA axis hypofunction may at least be involved in symptom propagation in CFS, even if the disturbances would be secondary to other factors [10,11].

Yet, a crucial question remains whether this neuroendocrine dysregulation plays a role in the etiopathogenetic processes leading to the illness, or could be better viewed as a consequence of the illness, related to inadequate cognitions, attitudes and coping behaviours. In the following paragraphs, after critically reviewing the evidence for both viewpoints, we will formulate a comprehensive hypothesis on HPA axis hypofunction in CFS, that primarily reflects a fundamental and persistent dysregulation of the neurobiological stress system. Within a system-biological perspective, we will particularly focus on disturbances at the neuroendocrine–immune interface.

Is HPA axis hypofunction a consequence of CFS?

There is some evidence to suggest that neuroendocrine dysregulation in CFS is secondary. Indeed, changes in the HPA axis seem to be more pronounced the longer CFS exists [12], and HPA axis changes could not be detected in post-EBV infection and post-surgery patients who were fatigued at six months follow-up [13,14]. However, the latter studies concerned broadly defined sub-acute or chronic fatigue, which may be different from more strictly defined CFS.

Furthermore, inadequate coping in CFS – involving sleep disturbances and lack of activity – has been suggested to result in HPA axis hypofunction [3,10,11], but evidence supporting this assumption is not convincing. Studies show that CFS patients are quite heterogeneous with regard to sleep, some presenting with severe

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nightly sleep loss (and even sleep–wake cycle reversal) but others showing normal or exaggerated sleep duration [15]. Of note, chronic insomnia has been related to *increased* plasma levels of ACTH and cortisol [16]. In line with this, many CFS patients show high heart rate and low heart rate variability during sleep, pointing to continuous nightly arousal [17].

Activity patterns also markedly differ. A small subgroup of patients is constantly bedridden, but many succeed in being relatively active by 'staying within their energy envelope' [18], even though they periodically engage in 'bursts' of over-activity followed by post-exertional malaise [19].

Finally, other secondary factors such as anxiety and/or depressive symptoms in reaction to disability or lack of support [4], and concomitant widespread pain [20,21] may influence the HPA axis as well, most likely however in the direction of *hyper*function.

Is HPA axis hypofunction a causal factor in CFS?

A vulnerability factor?

According to some authors, HPA axis hypofunction in CFS and other functional somatic syndromes may be based on a shared biological vulnerability with depression [22], e.g. via common genetically-determined impairment of stress response systems [23,24]. However, this view is inherently problematic since depression includes melancholic and atypical subtypes, characterized by HPA axis hyper- and hypofunction, respectively [25–27].

The role of early adversities – though increasingly considered a psychobiological risk factor for CFS [28–31] – is also equivocal, as illustrated by two studies showing contrasting results when comparing cortisol responses in CFS patients with and without childhood trauma history [32,33].

Similarly, in a prospective study investigating predictors of fibromyalgia (a syndrome that strongly overlaps with CFS) [34], mixed neurohormonal data were found in 'at risk' individuals, i.e. *low* cortisol levels in morning saliva, *high* levels in evening saliva and *high* post-dexamethasone cortisol [35].

Nonetheless, despite these confusing data, an experimental study demonstrated that among healthy individuals undergoing exercise deprivation, those who subsequently experienced profound fatigue, musculoskeletal pain and mood changes had lower initial cortisol levels, suggesting that preceding HPA axis hypofunction may indeed increase the risk of CFS(-like) symptoms [36].

An HPA axis 'switch'?

The view that, at the early stages of CFS, a 'switch' may take place from HPA axis hyper- to hypofunction is tempting because of its face validity. Indeed, the overwhelming majority of patients describe the onset of their symptoms as 'a loss of resilience' – a 'crash' in their own words – which sharply contrasts with their premorbid state [37]. The latter seems to be characterized – as recent studies confirm – by a high level of activity, achievement, over-commitment, perfectionistic traits and perseverance [38,39] often in the face of accumulating adversity and emotional burden [31,40] and even during or in the aftermath of an exhausting viral infection [41].

Such a 'switch' would also be plausible because of its resemblance to the hypocortisolism following intense traumatic stress in PTSD (although in this disorder hypocortisolism usually co-exists with persisting hypothalamic overdrive). However, recent data suggest that low cortisol in PTSD may already exist before the occurrence of the trauma [42].

Furthermore, an HPA axis 'switch' may provide an explanation for the high prevalence of preceding depression in CFS and fibromyalgia [43], at least when assuming that a former affective illness would be characterized by HPA axis *hyper*function.

Hypocortisolism may develop through reduced synthesis or depletion of HPA axis hormones, receptor down-regulation, and/or increased negative feedback sensitivity of the HPA axis [44]. Moreover, whereas during chronic or traumatic stress a 'switch' to hypocortisolism may prevent possible deleterious effects of excessive glucocorticoid exposure, CFS and related disorders may be interpreted as a maladaptive *over*-adjustment [44], forcing the HPA axis to a persistent alternate steady state [45].

Interestingly, at last, the 'switch' view is supported by some animal and human data. After withdrawing rodents from morphine dependence (considered to be a chronic stressor) the animals initially showed decreased negative glucocorticoid feedback, followed (after eight days) by a 'switch' to *increased* feedback sensitivity as well as reduced CRH and/or AVP function in response to stress [46]. Similarly, from a meta-analysis of human stress studies it was concluded that a negative association exists between time since onset of the stressor and HPA axis activity, supporting the model of initial activation of the stress system followed by diminished activity over time [47].

Hypothesis: HPA axis hypofunction in CFS is linked to a fundamental and persistent dysregulation of the neurobiological stress system

CFS in a system-biological perspective

Although the evidence for all of the above views is insufficient, an HPA axis 'switch' in vulnerable individuals following prolonged physical and/or psychosocial stress seems to be a plausible etiopathogenetic hypothesis in CFS, from a clinical as well as research point of view. On the other hand, it should be acknowledged that a sharp 'cause-or-consequence' dichotomy cannot fully account for the complex neuroendocrine determination of the illness. A *nonlinear* or *recursive* way of conceptualizing HPA axis hypofunction within in a system-biological perspective would be more appropriate [48–51].

This view would be congruent with the notion that the HPA axis is not only a nonlinear system in its own [45] but also 'embedded' in the inherently recursive network of the neurobiological stress system, comprising a whole range of mutually interacting neurochemical mediators and modulators [52–54].

Moreover, this system-biological perspective would imply that the neuroendocrine dysregulation leading to CFS may take different shapes and occur at different degrees at different time points. Consequently, HPA axis hypofunction observed in an individual patient may be the result of a complex interplay between multiple factors: vulnerability and resilience of the stress system, based on gene–environment interactions and including early trauma; premorbid stress-induced dysregulation and counterregulation at various levels of the HPA axis; initiating or interfering physical triggers such as infections, physical injury or sleep disturbances; and, not in the least, effects of cognitive, affective, and behavioural consequences of the illness and associated current life stress [4,32,44].

CFS as an abnormal sickness response

Applying the above perspective to recent insights into the neuroendocrine–immune interface [55–58], the typical symptom cluster of CFS may be best understood as resulting from a disturbed balance, evolving over time [59–61], between glucocorticoid and inflammatory signaling pathways. In these circumstances, indeed, a hypofunctional HPA axis may eventually loose its immune-

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restraining capacity, which – particularly after a stress system challenge such as physical or mental effort – may lead to excessive proinflammatory cytokine release (e.g. via the transcription factor NF-kappa-B) [56]. Cytokines subsequently affect the brain and provoke a pathological sickness response consisting of flu-like malaise, light fever, lethargy, hyperalgesia, sensory hypersensitivity, low mood, sleepiness, concentration problems and social withdrawal, forcing the organism to change priorities and succumb to behavior that promotes recovery ('sickness behavior') [62,63].

The exact mechanisms underlying this neuroendocrine–immune disequilibrium remain unknown, although different possibilities arise: insufficient glucocorticoid receptor stimulation by low cortisol – even in spite of increased glucocorticoid sensitivity [55,64]; impaired glucocorticoid receptor functioning by early trauma [31] or stress-related immune activation [56,57]; and glucocorticoid-induced changes in pro- and anti-inflammatory cytokine balance [61,65]. All these disturbances may, through recursive interactions, precipitate a feed-forward inflammatory cascade explaining the persistent course of the illness.

It should however be noted that evidence for short-term abnormalities in cytokine activity have not been established in CFS and seemingly conflicting data exist [66–68]. On the other hand, proinflammatory cytokines may promote long-term neurochemical sensitization in the brain [69] leading to disturbances in sensory interoception [70] and, via conditioning effects [62], to cognitive-perceptual biases affecting expectation and memory [71] – including the occurrence of an immunological 'extended altered self state' [72] – which may offer an alternative explanation for the persistence of the illness.

Diagnostic and therapeutic implications

Understanding CFS primarily as a dysregulation of the stress system may give impetus to current efforts to refine diagnostic criteria of the illness, by putting more emphasis on key-aspects of the patients' illness experience, namely a dramatic loss of tolerance for all kinds of physical and mental load, including impaired recovery [73]. Moreover, this comprehensive, neurobiologically-based view on the etiopathogenesis of the illness could counterbalance tendencies to split up CFS into a 'neurological' and 'psychiatric' subtype, which does not seem to be in keeping with clinical reality [74].

Another implication concerns the use of cognitive-behavioural therapy (CBT) which has been proved to be an evidence-based treatment in CFS [2]. When interpreting neuroendocrine disturbances as merely secondary to the illness, CBT-therapists may in the first place be expected to correct distorted perceptions, beliefs, attributions and behaviours related to symptoms, and encourage patients to give up their 'CFS' label in order to facilitate recovery [75]. Although recently modest neurohormonal changes [76] and effects on brain volume [77] have been demonstrated after CBT, many uncertainties regarding treatment goals, modes of action, indications and long-term effectiveness of this therapeutic approach remain, particularly when applied to CFS patients in a naturalistic clinical setting [4].

In contrast, when considering HPA axis hypofunction in CFS as being part of a dysregulation of the stress system – in line with McEwen's 'allostatic (over)load' concept [78] – CBT-therapists (or therapists from another theoretical orientation) may have a different focus. They may assist patients in restoring 'allostasis', meaning a normalization of neuroendocrine–immune functioning in response to physical or mental challenge. To that aim they may help patients, in a personalized way, to accept their condition and functional limitations [79], subsequently search for a better physical and mental balance by adjusting load to tolerance, and maintain this 'new equilibrium' in the long run, taking a lifelong risk of relapse into account [80]. Whether pharmacological interventions may have additional therapeutic value, i.e. enhance this 'natural' process of neurobiological recovery by more directly correcting HPA axis hypofunction, remains to be investigated [81].

Follow-up studies comparing both viewpoints on aims and strategies of CBT, particularly with regard to mediating therapeutic processes, underlying mechanisms of change, and long-term outcome (including risk of relapse) are badly needed [4].

Research agenda

The above-described etiopathogenetic hypothesis on CFS may have important heuristic value, particularly since it may stimulate research on a dysregulated 'crosstalk' between the neuroendocrine and the immune system.

At the neuroendocrine side, further exploring long-term effects of – early and recent – life stress on HPA axis functioning seems to have high research priority. For example, large groups of CFS patients with and without well-defined childhood trauma, and with and without associated mood disorder or post-traumatic stress symptoms should be compared, by basal circadian cortisol measures as well as neuroendocrine challenge tests [31,82]. Importantly, multiple measurements should be carried out at different phases of the illness and spread over several days (i.e. by 'experience sample methods') [83], since neuroendocrine dysregulations may not only vary over time, but also be subtle and correlate with fluctuating symptom severity and current stressors [84]. In this context, the contribution of genetic polymorphisms [85–87], the modulating role of neurohormonal substances such as oxytocin [88], and psychological factors such as attachment style [89] should also be investigated.

At the immunological side, given the ambiguous results of previous immune research, cytokine profiling in CFS patients should be further pursued. Preferentially, these measurements should be carried out following exertion (e.g. after a maximal exercise test) when the patient experiences 'post-exertional malaise'. Recent evidence linking childhood abuse with adult inflammation should be replicated via longitudinal studies [90]. Brain mechanisms of cytokine-induced behavioural changes should be more thoroughly examined [91].

Furthermore, neuroendocrine-immune research should compare CFS with anxiety disorders, mood disorders or somatoform disorders, since evidence is accruing that all these conditions may be characterized by low-grade inflammation [92,93]. Possible immunological links between CFS and melancholic versus atypical depression should be studied, for example by comparing these illnesses with regard to the occurrence of post-exertional malaise.

Finally, more detailed research is needed to confirm the assumption that individuals at risk for CFS go on 'pushing' themselves in spite of overwhelming physical and/or emotional burden, even after experiencing a depressive episode or an incapacitating infection [37,39,41]. Are these patients right when they describe their eventual ailment in terms of an *'allostatic crash'*?

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