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Enhanced feedback sensitivity to prednisolone in chronic fatigue syndrome

Walid K. Jerjes[a,*], Norman F. Taylor[a], Peter J. Wood[b], Anthony J. Cleare[c,d]

[a]*Department of Clinical Biochemistry, Guy's, King's and St Thomas' School of Medicine, Bessemer Road, London SE5 9RS, UK*
[b]*Regional Endocrine Unit, Southampton General Hospital, Southampton SO16 6YD, UK*
[c]*King's College London, Institute of Psychiatry, Section of Neurobiology of Mood Disorders, Division of Psychiatry and Psychological Medicine, De Crespigny Park, London SE5 8AF, UK*
[d]*National Affective Disorders Unit, Bethlem Royal and Maudsley Hospitals, Monk's Orchard Road, Beckenham, Kent BR3 3BS, UK*

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Summary
Objective: Enhancement of negative feedback control of the HPA axis in patients with chronic fatigue syndrome (CFS) has been reported using the low dose dexamethasone suppression test. We have developed the use of prednisolone (5 mg) as a more physiologically appropriate alternative to dexamethasone in the investigation of mild degrees of glucocorticoid resistance or supersensitivity. The objective of the study was to use this test to look for alterations in negative feedback control of the HPA axis in CFS patients.
Methods: Fifteen patients with CFS were recruited after fulfilling strict criteria including the absence of comorbid psychiatric diagnosis. They collected urine between 0900 and 1800 h and saliva at 0900 h pre-prednisolone. At midnight, they took prednisolone (5 mg) orally and then collected urine and saliva at the same intervals the following day.
Results: Salivary cortisol was lower in CFS subjects pre-prednisolone than controls. Urinary cortisol metabolites were lower in CFS subjects pre-prednisolone, but did not reach significance. Both measures were significantly lower in CFS subjects post-dose. Mean percentage suppression of both salivary cortisol and urinary cortisol metabolites was significantly higher in CFS compared to controls.
Conclusion: There is enhanced sensitivity of the HPA axis to negative feedback in CFS as demonstrated using the prednisolone suppression test. This provides further evidence of alterations in the control of the HPA axis in patients with established CFS.

*Corresponding author. Tel.: +44 20 7346 4131; fax: +44 207 737 7434.
E-mail address: w_jerjes@yahoo.co.uk (W.K. Jerjes).

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1. Introduction

Chronic fatigue syndrome (CFS) is characterised by persistent debilitating fatigue and exhaustion, together with a number of other characteristic symptoms, unexplained by identifiable organic disease (Fukuda et al., 1994). Since many of the symptoms of CFS can also be associated with glucocorticoid deficiency states, evaluation of HPA axis activity in CFS has been undertaken in numerous studies. As a result of this, it has been hypothesised that some features of CFS are a result of moderate hypocortisolism. The majority of the well designed studies in this area have demonstrated low levels of cortisol in blood, urine or saliva (reviewed by Cleare, 2003). More recently, we have also found low levels of urinary and salivary free cortisol in a well characterised group of 15 CFS patients free from medication or comorbid psychiatric disorders (Jerjes et al., 2005, 2006a). However, the research in this area is not entirely consistent, and some other studies have shown no differences in serum cortisol levels (Racciatti et al., 1998; Altemus et al., 2001), and we have found no difference in 24 h urinary cortisol metabolite excretion between CFS and control subjects (Jerjes et al., 2006c).

A second hypothesis is that CFS symptoms result from alterations in central neuroendocrine pathways underlying the control of the HPA axis. Specifically, it has been suggested that there is deficient suprahypothalamic drive, reflected in reduced hypothalamic output of corticotropin-releasing hormone (CRH, Demitrack et al., 1991). Being the principal modulator of the stress response, CRH not only modulates endocrine and autonomic responses but also influences nociception and behaviour (Clauw and Chrousos, 1997). Several symptoms such as lethargy, pain and fatigue have been associated with a deficiency of hypothalamic CRH secretion (Gold and Chrousos, 1999).

Third, enhancement of negative feedback control of the HPA axis has also been proposed as a cause of a hypofunctional HPA axis in CFS (DeKloet et al., 1998). Preliminary reports suggested a heightened negative feedback in CFS subjects using dexamethasone (Poland et al., 1996) or hydrocortisone infusion (Lavelle and Dinan, 1996), while Gaab et al. (2002) examined salivary cortisol levels before and after low dose dexamethasone (0.5 mg), finding greater suppression in CFS, although levels of salivary cortisol in CFS were not different from controls pre-medication. However, dexamethasone may not be physiologically appropriate, since it has much higher relative affinity for the glucocorticoid receptor over the mineralocorticoid receptor (DeKloet et al., 1998), does not bind to corticosteroid binding globulin (Pugeat et al., 1981), and has a much longer half life compared with cortisol (Cassidy et al., 2000).

We have recently reported the use of prednisolone (5 mg) for investigation of mild degrees of glucocorticoid resistance or hypersensitivity, based on cortisol assay in a convenient pre and post dose saliva sample at 0900 h or on a urine sample collected 0900–1800 h (Jerjes et al., 2006b). Suppression was found to be approximately 50% for both saliva and urine in healthy subjects, but correlation between these measures was not established. Thus, the objective of the study was to explore alterations in negative feedback control of the HPA axis in CFS patients, using the prednisolone suppression test and assessing both saliva and urine approaches. We hypothesised that there would be enhanced negative feedback sensitivity in patients with CFS in comparison to healthy subjects.

2. Materials and methods

2.1. Subjects

Fifteen patients with CFS (7 males and 8 females) were recruited via the CFS clinic at King's College Hospital (KCH), which sees secondary and tertiary care referrals from the south of the United Kingdom. Subjects were interviewed by experienced psychiatrists who used the semi-structured interview for CFS of Sharpe et al. (1997) and DSM-IV to determine the presence of any psychiatric diagnoses. Subjects were eligible for inclusion if they fulfilled the 1994 Centers for Disease Control (CDC) criteria for CFS (Fukuda et al., 1994) without any exclusionary psychiatric disorder as per these criteria. Further inclusion criteria stipulated an age range of 25–60 years and the absence of any history of neurological, endocrine or cardiovascular disorder. In order to obtain as pure a measure of the HPA axis as possible, we tested only patients who had never taken any psychotropic medication or had been abstinent from such medication for at least 2 months. Furthermore, although the modification in 1994 of the original CDC diagnostic criteria permitted inclusion of patients with comorbid major depression or anxiety disorders, patients with a current major depressive episode or anxiety disorder as defined by DSM-IV criteria were excluded from this study because of their potential impact on the HPA axis. Patients were recruited consecutively over about 6 months. We have reported previously on these CFS patients in terms of the diurnal rhythm of salivary, urinary cortisol and cortisol metabolites, and found that they had lower salivary and urinary cortisol across the day without any differences in cortisol metabolites (Jerjes et al., 2005, 2006a).

Twenty healthy volunteers (10 males and 10 females) as described in Jerjes et al. (2006b) were recruited from among the staff and student body at KCH and were matched for age and BMI with CFS patients. They were all assessed to be in good health without any serious medical illness or history of psychiatric disorder. Subjects were all studied during wintertime hours, between October 2002 and March 2003. All subjects had normal dietary habits, taking breakfast, lunch and dinner at about the same time. All subjects were asked to limit their intake of caffeine and alcohol during the collection period. All subjects were instructed to carry out sample collections at weekends to avoid possible increase of cortisol levels, which might result from stress on working days. No female subjects were on the oral contraceptive or pregnant. All subjects habitually went to bed between 2300 and 0100 h and got up between 0700 and 0800 h. All subjects gave written, informed consent and ethical approval for the study was obtained from our local committee.

Patients and healthy controls collected urine between 0900 and 1800 h and provided saliva at 0900 h only (Day 1). At midnight, all subjects took prednisolone (5 mg) and collected urine and provided saliva at the same times the