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Diurnal excretion of urinary cortisol, cortisone, and cortisol metabolites in chronic fatigue syndrome

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Abstract

Objective: The aim of this study was to obtain comprehensive information on basal hypothalamic–pituitary–adrenal (HPA) axis activity in chronic fatigue syndrome (CFS) patients who were not affected by medication or comorbid psychiatric disorder likely to influence the HPA axis. **Method:** Steroid analysis of urine collections from 0600 to 2100 h at 3-h intervals in CFS patients and in controls. **Results:** Urinary free cortisol and cortisone concentrations showed a significant normal diurnal rhythm, but levels were lower across the cycle in CFS. In contrast, while urinary cortisol metabolites also showed a normal diurnal rhythm, levels were not significantly different between the CFS and controls at any time. Derived metabolite ratios were similar in both groups. **Conclusion:** This study provides further evidence for reduced basal HPA axis function in patients with CFS, based on lower free cortisol and cortisone levels, but this is not corroborated by cortisol metabolite data. The difference between these measures cannot be explained by an altered timing of the diurnal rhythm.

Keywords: Chronic fatigue syndrome (CFS); Diurnal rhythm; Metabolism; Urinary cortisol; Urinary cortisone

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 [1]. The aetiology of CFS remains unclear, although there is evidence that biological, psychological, and social factors all play a part [2]. Many of the symptoms of CFS can also be associated with glucocorticoid deficiency states, and low serum cortisol was reported in early studies of patients with CFS and other fatigue states [3,4]. These results–from the evening and morning, respectively–could reflect a general hypocortisolaemia in CFS. However, other studies have shown no differences in serum cortisol levels [5,6]. Thus, there remains some inconsistency in research to date using serum cortisol to measure basal hypothalamo–pituitary–adrenal (HPA) axis function in CFS.

Assessment of HPA axis function by urine analysis offers advantages. Samples are obtained by a noninvasive, stress-free procedure and are easier to collect than blood [7,8]. Urinary free cortisol is considered to reflect the integrated, unbound plasma cortisol levels and was originally used in examining the

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hypercortisolism of Cushing's disease [7,8]. Urinary free cortisol levels have generally shown good agreement with plasma cortisol levels in hypercortisolaemic states [7], and elevated levels in depression are reduced following treatment, mirroring clinical improvements [9]. However, observations in CFS have again reached variable conclusions. Four studies have found a low basal output of urinary free cortisol over 24 h [3,10–12] and two found no change [13,14]. It is possible that this variability might be explained by changes in steroid metabolism, rather than changes in circulating cortisol levels per se because free cortisol in urine represents only 2–3% of the urinary cortisol metabolites [15].

To overcome the problem outlined above, we first examined the 24-h urinary excretion of total cortisol metabolites (TCM) in patients with CFS and found them to be unchanged in comparison with that of healthy controls (Jerjes et al., unpublished data). This method, which is based on gas chromatography, and quantifies >95% of cortisol production per day, provides a sensitive means of detecting changes in rates of cortisol secretion, as has been demonstrated in asthmatics treated with inhaled glucocorticoids [16]. It also permits examination of changes in cortisol metabolism such as cortisol–cortisone interconversion. Cortisol converts reversibly into cortisone in blood, under the control of the 11-β-hydroxysteroid dehydrogenase (11-β-HSD Types 1 and 2) enzyme. Alteration in this equilibrium has been reported in various diseases [17,18].

The apparent difference of cortisol production in CFS based on serum point estimation and integrated values in urine might be explained by changed timing of the diurnal rhythm. This is supported by observations that CFS-like symptoms can also be seen in some conditions in which the circadian clock is phase shifted, such as seasonal affective disorder and major depression [19–21]. Few studies have attempted to measure the diurnal or circadian rhythm of cortisol in CFS. MacHale et al. [22] demonstrated a significantly lower diurnal change of serum cortisol in CFS based on evening and morning sampling over two consecutive days. Additionally, there was a significant positive relationship between the degree of diurnal variation in cortisol and measures of functional capacity. In two studies based on 4-h blood sampling, Hamilos et al. [14] reported a flattened diurnal rhythm of plasma cortisol in patients with CFS, whereas Racciatti et al. [5] did not find a significant change in cortisol rhythm in CFS. We therefore aimed to recruit a new group of well-characterised CFS patients free from medication or comorbid psychiatric disorders that might confound assessment of the HPA axis and measure the levels of urinary free cortisol, cortisone, and their metabolites across a diurnal cycle to provide further information regarding the status of the HPA axis in CFS. We hypothesised that we would find a reduction in free cortisol output throughout the day, and that this would also be accompanied by a change in measures of the diurnal rhythm of cortisol and its metabolites.

Materials and methods

Participants

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. Participants were interviewed by experienced psychiatrists who used the semi-structured interview for CFS of Sharpe et al. [23] and DSM-IV to determine the presence of any psychiatric diagnoses. Participants were eligible for inclusion if they fulfilled the 1994 Center for Disease Control (CDC) criteria for CFS [1] 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. 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 of the original CDC diagnostic criteria in 1994 permitted the 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. None of them had taken part in any of our previously published studies.

Twenty healthy volunteers (10 males and 10 females) were recruited among the staff and student body at KCH and were well matched for age, sex, and BMI with the CFS patients. They were all in good health, without any serious medical illness or history of psychiatric disorder. Participants were all studied during winter, between October 2002 and March 2003. All participants had normal dietary habits, taking breakfast, lunch, and dinner at about the same time. All participants habitually went to bed between 2300 and 0100 h and got up between 0600 and 0800 h. All participants were asked to limit their intake of caffeine and alcohol during the collection period. While these agents may have effects on the HPA axis, it was considered that short-term avoidance of habitual intake would result in more disturbance of the axis. All participants were instructed to carry out sample collections at weekends to avoid possible increase of cortisol levels that might result from stress on working days. No female participants were on oral contraceptive or were pregnant. All participants gave written, informed consent and ethical approval for the study was obtained from our local committee.

Questionnaires

All participants completed the Hospital Anxiety and Depression scale (HADS) [24] for symptoms of anxiety and depression and the Pittsburgh Sleep Quality Index (PSQI; [25]) for sleep disturbance. Patients completed further questionnaires to characterise their illness: the Chalder