Brief report

Glucocorticoid receptor mediated negative feedback in chronic fatigue syndrome using the low dose (0.5 mg) dexamethasone suppression test

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Received 13 December 2007; received in revised form 2 May 2008; accepted 3 May 2008
Available online 24 June 2008

Abstract

Background: Chronic fatigue syndrome (CFS) is associated with hypocortisolism, but it is not yet clear the extent to which enhanced negative feedback may underlie this finding.

Methods: We undertook a low-dose dexamethasone (0.5 mg) suppression test in 18 CFS patients and 20 matched, healthy controls. We measured salivary cortisol levels at 0800 h, 1200 h, 1600 h and 2000 h before and after the administration of 0.5 mg of dexamethasone.

Results: Basal cortisol output was raised in this group of CFS patients compared to controls. Overall, the percentage suppression following dexamethasone administration was no different between CFS (mean ± sem: 80.4±4.4%) and controls (76.2±4.9 %). However, the sub-group of patients with CFS and comorbid depression (n=9) showed a significant hypersuppression of salivary cortisol in response to dexamethasone (89.0±1.9%; p<0.05 v controls).

Limitations: The sub-group analysis was on small numbers and should be considered preliminary. Dexamethasone probes only glucocorticoid medicated negative feedback but does not probe mineralocorticoid feedback, the other main physiological feedback mechanism.

Conclusion: We found partial support for the hypothesis of enhanced negative feedback in CFS but only in patients with comorbid depression and also in the context of a sample of patients with elevated basal cortisol levels, which is an atypical finding in the literature.

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Keywords: Chronic fatigue syndrome; HPA axis; Dexamethasone suppression test; Glucocorticoid receptor; Negative feedback; Neuroendocrinology
1. Introduction

Chronic fatigue syndrome (CFS) continues to challenge medical science: although widely felt to be a multifactorial illness with a biopsychosocial aetiology (Straus, 1996; Wessely et al., 1998), relatively little progress has been made in understanding putative biological components.

One line of research supports the presence of mild hypocortisolism in CFS (Cleare, 2003), in contrast to the hypercortisolism typically seen in depression (Dinan, 1994). Because of potential effects of depression on the HPA axis, most studies of CFS have excluded patients with comorbid depression. However, hypocortisolism has been found even in the presence of comorbid depression (Cleare et al., 2001a; Cleare, 2003).

Although a likely perpetuating factor in CFS (Cleare et al., 1999; McKenzie et al., 1998), the underlying cause of HPA axis disturbance in CFS is not understood. To date, it has not been possible to detect a specific abnormality at any particular level of the axis (Cleare, 2003). However, enhanced negative feedback in CFS has been consistently found. In particular, Gaab and colleagues found hyper-suppression of salivary cortisol to dexamethasone and concluded there is enhanced glucocorticoid receptor function in CFS, which could underlie previous findings of hypocortisolism (Gaab et al., 2002). Further support for this comes from in vitro studies (Visser et al., 1998, 2001a, 2001b), although there have also been conflicting findings (Kavelaars et al., 2000; Majeed et al., 1995).

On this background, we hypothesised that we would replicate the findings of hypersensitivity of CFS patients to low-dose dexamethasone suppression (Gaab et al., 2002), and aimed to disentangle the effect of comorbid depression.

2. Methods

2.1. Subjects

Twenty patients aged 18–65 were recruited from referrals to the CFS clinic at King’s College Hospital; because of protocol violations only 18 had useable data. Patients had thorough medical screening to exclude alternative causes for fatigue. All patients were interviewed using a semi-structured interview (Sharpe et al., 1997) for CFS, and fulfilled both major international consensus criteria (Fukuda et al., 1994; Sharpe et al., 1990). Psychiatric assessment used the Schedules for Clinical Assessment for Neuropsychiatry (SCAN) and DSM-IV. The presence of fibromyalgia (Wolfe et al., 1990) was an exclusionary criterion.

Twenty control subjects were recruited from staff, students and volunteers at our institutions. A present or past history of significant medical or psychiatric illness was excluded using a semi-structured interview and the SCAN.

All subjects were free from psychotropic medication, steroids, or medication known to affect the HPA axis for at least 2 months before testing. Females were tested during days 1–7 of their menstrual cycle. The institutional ethics committee approved all procedures. All patients and controls gave written, informed consent.

2.2. Questionnaires

The following questionnaires were used to assess illness characteristics: Chalder Fatigue Scale (Chalder et al., 1993); General Health Questionnaire-12 (Goldberg, 1972); Beck Depression Inventory (Beck et al., 1961); Pittsburgh Sleep Quality Index (Buysse et al., 1989); Medical Outcomes Survey Short Form 36 (Stewart et al., 1988); and the Work and Social Adjustment Scale (Mundt et al., 2002).

2.3. Dexamethasone suppression test protocol

Testing was undertaken at home on two consecutive weekdays other than a Monday for those working. Subjects woke according to their normal schedule, but took the first sample at 0800 h whilst still in bed, before eating or brushing their teeth. For 10 min before each sample, subjects remained sitting and did not drink, smoke or chew gum and listed ‘any difficult or tense conversations or other “hassles” that you have experienced in the last hour’. Saliva was collected at 0800 h, 1200 h, 1600 h, 2000 h on each day. At 11 pm on the first day, subjects took 0.5 mg dexamethasone. During collection, subjects were instructed not to contaminate the samples. Samples were kept in a refrigerator and sent back by post the following day. Upon receipt, samples were frozen at −20 °C until analysis. After defrosting and centrifugation (3000 rpm for 5 min), 50 μl of clear supernatant was used for duplicate analysis.

Assays were undertaken by the two laboratories involved in the study. To ensure good cross calibration, 660 samples of all concentrations between 0 and 60 nmol/l were measured at both laboratories. The resulting correlation coefficient was $r=0.97$; $p<0.0001$, suggesting a very high level of agreement.

2.4. Statistical analyses

Sigmastat v2.03 and Sigma plot v7.0 (Statistical-Solutions, Cork, Ireland) were used. Where data were
not normally distributed, or where there was a significant inequality of variance, non-parametric tests were used.

Our main outcome variable was the area under the time-cortisol concentration curves (AUC) after dexamethasone suppression calculated as a percentage reduction of the AUC on the day before dexamethasone administration (Pruessner et al., 2003).

Data are presented with means and sem, with median and IQR shown additionally where the data showed non-normal distribution.

3. Results

Details of patients and controls are shown in Table 1. Patients and controls were matched in age, BMI, and gender. Patients had higher mean BDI and GHQ scores than controls; half (n=9) had DSM-IV comorbid depression (CFS-DEP). Patients and controls did not differ in their pre-dexamethasone waking time.

Basal salivary cortisol output was significantly higher in CFS compared to controls. AUC values were: (1) All CFS patients — 115.3 (7.9) nmol/l h; (2) All controls — 42.8 (3.3) nmol/l h; (3) Non-depressed CFS (CFS-ONLY) — 121.1 (8.1) nmol/l h; and (4) CFS-DEP — 109.6 (13.8) nmol/l h [non-normal distribution: median and IQR 84.8 (82.4–142.8)]. On Mann–Whitney U-test, CFS patients saw whole (p<0.001), CFS-ONLY (p<0.001), and CFS-DEP (p<0.001) all had significantly raised basal cortisol output.

The percentage reduction in cortisol secretion produced by dexamethasone in controls was compared with that produced in CFS patients (Fig. 1). The reduction in cortisol in the patient group as a whole (mean=80.4%, sem=4.4; non-normal distribution — median=86.1%, IQR=81–92.5%) did not differ (p=0.254; Mann–Whitney U-test) from that of the controls (mean=76.2%, sem=4.9%; non-normal distribution — median=83.1%, IQR=77.5–87.5%). However, the CFS-DEP sub-group had a significantly (p=0.045; Mann–Whitney U-test) higher suppression of cortisol (mean=89.0%, sem=1.9%) than controls post-dexamethasone. The extent of cortisol suppression of the CFS-ONLY sub-group (mean=89.0%, sem=1.9%) did not significantly differ (p=0.88; Mann–Whitney U-test) from that of the controls. CFS-DEP patients (mean=89.0%, sem=1.9%) had significantly (p=0.045; independent t-test) higher suppression than CFS-ONLY patients (mean=71.8% sem=7.7%).

Table 1

<table>
<thead>
<tr>
<th>Patients</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>CFS</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>CFS-DEP</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>Age</td>
<td>39.1 (8.2)</td>
<td>39.5 (11.4)</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>10</td>
</tr>
<tr>
<td>Weight(kg)</td>
<td>74.6 (16.1)</td>
<td>70.2 (16.4)</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>24.1 (21.0–28.3)</td>
<td>25.0 (21.0–28.0)</td>
</tr>
<tr>
<td>BDI</td>
<td>16.0 (11.8–20.8)</td>
<td>0 (6–2.0)</td>
</tr>
<tr>
<td>GHQ</td>
<td>17.0 (12.8–22.8)</td>
<td>7.5 (6–10.0)</td>
</tr>
<tr>
<td>Length of illness (months)</td>
<td>78.4 (69.2)</td>
<td>–</td>
</tr>
<tr>
<td>Awaking time (hours after midnight)</td>
<td>7.3 (1.0)</td>
<td>7.0 (1.2)</td>
</tr>
<tr>
<td>Total fatigue</td>
<td>24.2 (6.7)</td>
<td>11.1 (0.6)</td>
</tr>
<tr>
<td>Physical function</td>
<td>48.6 (25.7)</td>
<td>96.0 (5.5)</td>
</tr>
<tr>
<td>Physical role</td>
<td>22.4 (36.5)</td>
<td>98.7 (5.6)</td>
</tr>
<tr>
<td>limitation</td>
<td>8.3 (3.1)</td>
<td>2.8 (1.2)</td>
</tr>
<tr>
<td>Pittsburgh Quality Sleep Index-Global Score</td>
<td>29.5 (9.3)</td>
<td>–</td>
</tr>
<tr>
<td>Work and Social Adjustment Scale</td>
<td>29.5 (9.3)</td>
<td>–</td>
</tr>
</tbody>
</table>

Mean values (SD) for parametric data and median (IQR) for non-parametric data. BDI = Beck Depression Inventory; GHQ = General Health Questionnaire; CFS-ONLY = Chronic Fatigue Syndrome; CFS-DEP = Chronic Fatigue Syndrome and Depression.

*Independent t-test; **Mann–Whitney; ***Chi square test.
Correlations were calculated using Spearman’s coefficients. We found no correlation between the main outcome measure (percentage suppression after dexamethasone) and most clinical variables undertaken separately in patients and controls. The values were: a) BMI (patients: \( r = 0.447, p = 0.062 \); controls: \( r = 0.049, p = 0.836 \)); b) BDI (patients: \( r = -0.157, p = 0.591 \); controls: \( r = -0.254, p = 0.275 \)); c) illness duration (patients only: \( r = -0.123, p = 0.621 \)); d) total fatigue (patients: \( r = -0.278, p = 0.275 \); controls: \( r = 0.0168, p = 0.942 \)); and e) SF-36 physical function (patients: \( r = 0.114, p = 0.696 \); controls: \( r = 0.223, p = 0.340 \)).

4. Discussion

Our main finding is that, whilst there was no alteration in dexamethasone suppression in the CFS group as a whole, the sub-group of CFS patients with comorbid depression did show hypersuppression.

Our findings provide some support for the earlier findings of hypersuppression to dexamethasone (Gaab et al., 2002), although in that paper it is not apparent that comorbid depression affected the results. Our interpretation of the hypersuppression is that glucocorticoid receptors are hypersensitive in CFS; thus, dexamethasone results in an enhanced negative feedback effect on the hypothalamus and pituitary gland. However, it remains unclear whether increased glucocorticoid receptor function is a primary change to the HPA axis in CFS, and hence responsible for hypocortisolism in some patients, or an adaptive response, for example to lowered circulating cortisol levels.

The clinical relevance of this finding is unclear, given no correlation between clinical variables and endocrine findings. However, this may reflect that symptom report in chronic fatigue syndrome is under many influences in addition to any underlying biological substrate (Wessely et al., 1998). Nevertheless, we found previously that a heightened leptin response to hydrocortisone (a putative marker of glucocorticoid receptor activity) predicted a therapeutic response to hydrocortisone treatment, and that increased glucocorticoid receptor sensitivity may therefore be linked to symptomatic status in CFS (Cleare et al., 2001b).

In this sample of CFS patients, we found that basal cortisol levels were significantly raised. This is an unusual finding in the literature: half of previous studies have found some degree of hypocortisolism, with the remainder usually finding no difference between CFS and controls (Cleare, 2003). There are a number of possible explanations for this. First, although comorbid depression could lead to an elevation in basal cortisol, we found no significant difference in between those with and without comorbid depression. However, the SCAN sets a stringent threshold for diagnosing depression, and many of our non-depressed patients had raised BDI scores. Thus, some CFS patients with minor or sub-threshold depressive symptoms may have influenced the results. On the other hand there was no correlation between depressive symptoms on the BDI and any endocrine measures. Interpreting these links is also difficult because of the overlap between symptoms of CFS and depression and because of differing response styles on self-report questionnaires like the BDI. Second, this sample may have differed from previous samples of CFS patients. We have previously argued that much of the variance in results between research groups and between different patient samples is because there are many factors in CFS that can influence the HPA axis (Cleare, 2003). These include comorbid psychiatric disorder, physical inactivity, chronic stress, use of medication and sleep disturbance (Cleare, 2004). Indeed, HPA axis disturbances may only become apparent after long durations of fatiguing illnesses (Candy et al., 2003; Rubin et al., 2005). It is therefore possible that, by chance, the pattern of these factors in this group of subjects was not such as to produce hypocortisolism. Third, the current experimental protocol differed in that subjects were due to take an experimental drug halfway through the experiment, potentially a source of worry. It may be that CFS patients were more concerned about this than controls and that their basal salivary cortisol levels were consequently increased. We did not assess this directly.

There are a number of limitations to discuss. First, although the sample size is similar to previous studies in the area, the sub-groups with and without depression are notably smaller. Thus, these and previous results support the need for a larger study of dexamethasone suppression in CFS. Second, we only used one dose of dexamethasone. Although we hypothesised that this would be a relatively low dose, we found a large percentage suppression even at 0.5 mg. Further studies could usefully employ several doses to provide individual dose–response curves (e.g. 0.1, 0.25, 0.5 and 1 mg). Third, we measured basal cortisol output on 1 day only, which may provide a less reliable baseline than using two or more days, as employed by Gaab et al. (2002). Also, there is a debate as to whether it is most appropriate to use a fixed time of day for morning samples in these studies or time relative to awakening, given the potential effect of awakening in stimulating cortisol release. It can be difficult to interpret a morning
sample at a fixed time as they are under the influence of both a circadian rhythm and a response to awakening (Wilhelm et al., 2007). In any case, there was no difference in waking time between groups suggesting that this does not account for the intergroup differences. Fourth, the use of salivary measures precluded the measurement of dexamethasone levels. Although unlikely, we cannot rule out pharmacokinetic differences between patients and controls. Finally, there are difficulties inherent in using dexamethasone. Whilst often interpreted as an assessment of physiological negative feedback, dexamethasone is a potent glucocorticoid receptor agonist with very little mineralocorticoid activity. In contrast, the physiological stress hormone cortisol does have significant activity at mineralocorticoid receptors.

In response to this final limitation, our group has recently pioneered the use of prednisolone given the pharmacodynamic and pharmacokinetic similarities to cortisol (Pariente et al., 2002). We recently reported an increased feedback response to prednisolone in CFS (Jerjes et al., 2007). We suggest that assessment of the mineralocorticoid receptor is important in understanding fully the status of negative feedback, and the HPA axis generally, in CFS.

In conclusion, we found partial support for the hypothesis of enhanced glucocorticoid receptor mediated negative feedback in CFS, but only in patients with comorbid depression, and in the context of a sample of patients with atypically elevated basal cortisol levels.

Role of funding source

Partial financial support for the staff and work in this study was received from: the Psychiatry Research Trust; the Linbury Trust; and the Joint Research Committee of King’s College Hospital. None of these bodies played a further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflicts of interest

The authors declare no conflict of interests relating to any of the contents of the submitted manuscript.

Acknowledgements

We are grateful for the work of Dorothy Blair, research nurse, in recruiting subjects for this study. Part of this work was carried out at the Chronic Fatigue Research Unit at King’s College Hospital and the South London and Maudsley NHS Trust directed by Professor Simon Wessely and Professor Trudie Chalder and we are grateful for their support and that of the staff in the unit.

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