



Levels of DHEA and DHEAS and responses to CRH stimulation and hydrocortisone treatment in chronic fatigue syndrome

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Summary Background: An association between chronic fatigue syndrome (CFS) and abnormalities of the hypothalamo-pituitary–adrenal axis has been described, and other adrenal steroid abnormalities have been suggested. Dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S), apart from being a precursor of sex steroids, have other functions associated with memory, depression and sleep. It has been suggested that CFS may be associated with a state of relative DHEA(-S) deficiency. Therefore we investigated basal levels of DHEA(-S), the cortisol/DHEA molar ratio and the responsiveness of DHEA to stimulation by corticotrophin-releasing hormone (CRH). Recent studies have also suggested that low dose hydrocortisone may be effective at reducing fatigue in CFS. We therefore also assessed these parameters prior to and following treatment with low dose oral hydrocortisone.

Methods: Basal levels of serum DHEA, DHEAS and cortisol were measured in 16 patients with CFS without depression and in 16 controls matched for age, gender, weight, body mass index and menstrual history. CRH tests (1 µg/kg IV) were carried out on all subjects and DHEA measured at 0, +30 and +90 min. In the patient group, CRH tests were repeated on two further occasions following treatment with hydrocortisone (5 or 10 mg, PO) or placebo for 1 month each in a double-blind cross over study protocol.

Results: Basal levels of DHEA were higher in the patient, compared to the control, group (14.1 ± 2.2 vs. 9.0 ± 0.90 ng/ml, $P = 0.04$), while levels of DHEAS in patients (288.7 ± 35.4 µg/dl) were not different from controls (293.7 ± 53.8 , $P = \text{NS}$). Higher DHEA levels were correlated with higher disability scores. Basal cortisol levels were higher in patients, and consequently the cortisol/DHEA molar ratio did not differ between patients and controls. Levels of DHEA (8.9 ± 0.97 ng/ml, $P = 0.015$) and DHEAS (233.4 ± 41.6 µg/dl, $P = 0.03$) were lower in patients following treatment with hydrocortisone. There was a rise in DHEA responsiveness to CRH

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in the patients after treatment but this did not attain significance (AUC_c : 2.5 ± 1.7 ng/ml h pre-treatment vs. 6.4 ± 1.2 ng/ml h post-hydrocortisone, $P = 0.053$). However, those patients who responded fully to hydrocortisone in terms of reduced fatigue scores did show a significantly increased DHEA responsiveness to CRH (AUC_c : -1.4 ± 2.5 ng/ml h at baseline, 5.0 ± 1.2 ng/ml h after active treatment, $P = 0.029$).

Conclusions: DHEA levels are raised in CFS and correlate with the degree of self-reported disability. Hydrocortisone therapy leads to a reduction in these levels towards normal, and an increased DHEA response to CRH, most marked in those who show a clinical response to this therapy.

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1. Introduction

Operational criteria for the diagnosis of chronic fatigue syndrome (CFS) (Fukuda et al., 1994) include the presence of debilitating fatigue of greater than 6 months duration which causes substantial disability and is not alleviated by rest. Associated features include lymphadenopathy, memory impairment, sore throat, joint or muscle pain, headache and post-exertional malaise. Co-existing psychiatric diagnoses including depression, somatisation and anxiety disorders are not uncommon and can occur in up to 75% of patients with CFS (Wessely et al., 1998). This can often complicate analysis of endocrine dysfunction due to hypothalamic-pituitary-adrenal axis dysfunction associated with psychiatric morbidity (Holsboer, 1995).

Whilst the aetiology of CFS remains somewhat enigmatic, an increasing body of evidence suggests that there are specific abnormalities in the HPA axis that differ from those seen in depression (Parker et al., 2001). The cardinal feature of "pure" CFS—i.e. that occurring in the absence of depression—would appear to be relative hypocortisolaemia which does not appear to be explained by inactivity alone (Cleare et al., 2001a; Parker et al., 2001). This is apparent in measurements of endogenous 24 h urinary cortisol excretion (Demitrack et al., 1991; Scott and Dinan, 1998; Cleare et al., 2001a), reduced early morning serum cortisol levels (Hamilos et al., 1998; Moorkens et al., 2000) and reduced salivary cortisol estimations (Strickland et al., 1998). In terms of adrenal responsiveness, various studies have shown reduced cortisol response to both synacthen (Scott et al., 1998a) and corticotrophin-releasing hormone (CRH) (Scott et al., 1998b; Cleare et al., 2001b) challenge.

Initial studies employing hydrocortisone as a therapeutic measure were largely disappointing

(McKenzie et al., 1998) although we were able to show a significant improvement in fatigue and disability scores following one month's treatment with physiological replacement doses of hydrocortisone (Cleare et al., 1999).

Other adrenal steroids have now become the focus of some attention. Dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S) are derived from the zona reticularis of the adrenal (as opposed to glucocorticoids which are produced in the zona fasciculata) and DHEA-S circulates at levels of about one order of magnitude greater than those of cortisol. Reduction in circulating DHEA and DHEA-S has been associated with a number of age related conditions including coronary artery disease (Feldman et al., 1998, 2001) memory impairment (van Niekerk et al., 2001) and type 2 diabetes (Barrett-Connor and Ferrara, 1996). In a large cross sectional study, DHEA and DHEA-S were found to be inversely correlated with depression scores (Barrett-Connor et al., 1999) and treatment of depressive disorder with DHEA has been at least partially successful (Wolkowitz et al., 1999). In CFS some initial studies would suggest that a reduction in circulating DHEA(-S) levels is also apparent (Kuratsune et al., 1998; Scott et al., 1999; van Rensburg et al., 2001). Also, there are studies suggesting that there is an impaired adrenal responsiveness of DHEA to synthetic ACTH stimulation (De Becker et al., 1999) and (in a small uncontrolled trial of CFS patients selected to have low DHEA levels) that DHEA treatment may improve a number of the symptoms of CFS (Himmel and Seligman, 1999).

However, endogenous cortisol production and adrenal responsiveness in depression and CFS are altered in opposing directions, which raises the question why zona reticularis derived hormones should behave in an identical fashion in the two conditions? Consequently, we aimed to establish

basal levels of DHEA and DHEA-S in patients with pure CFS who had been extensively screened for psychiatric co-morbidity, to assess pituitary-adrenal DHEA responsiveness using the CRH test, and to investigate whether normalisation of basal cortisol levels with physiological replacement doses of hydrocortisone would affect DHEA(-S) levels or responsiveness to stimulation.

2. Methods

2.1. Subjects

Sixteen patients with CFS were recruited into the study from the referrals to CFS clinics at King's College Hospital, London. Patients were extensively screened in order to exclude a detectable organic cause for their fatigue by both physical and biochemical examination including urinalysis, thyroid function tests, morning cortisol, full blood count, liver function tests, urea and electrolytes. All patients were interviewed using a semi-structured interview for CFS and psychological disorder (Sharpe et al., 1997) by a psychiatrist (A.J.C.). Included subjects had to fulfil both international consensus criteria for CFS (Sharpe et al., 1991; Fukuda et al., 1994) and be free from co-morbid psychiatric disorder as defined in the Diagnostic and Statistical Manual of Mental Disorder (4th revision, DSM-IV). Patients with an illness duration of more than 100 months were excluded. All were drug free for a minimum of 2 months prior to endocrine testing, with the exception of 3 patients using oral contraception or hormone replacement. Female patients and matched controls were tested during day 1–7 of their menstrual cycle.

A group of 16 control subjects was recruited from volunteers and staff members and carefully matched for sex, age, weight, oral contraceptive use, body mass index (BMI), and menstrual history. None of the controls had a history of significant medical problems, CFS or DSM-IV psychiatric disorder.

The hospital ethics committee approved all procedures. All patients and controls gave written informed consent.

2.2. Procedures

After basal measurement of DHEA and DHEA-S, all patients and controls underwent a dynamic challenge test using CRH according to a standardised protocol. Patients fasted from midnight of the preceding day and attended the investigation unit at 09:00 h on the test day. An intravenous cannula

was inserted into a forearm vein, and kept patent throughout by the use of heparinised saline (1 ml bolus of 10 units heparin after each sample was drawn). After cannulation, subjects remained relaxed and semi-recumbent throughout the procedure. Following a resting period of 15 min, a minus 30 min sample was obtained followed by the 0 min sample. One microgram per kilogram body weight of human hCRH (Shire Pharmaceuticals, Andover, UK) was administered by bolus IV injection and further samples drawn at 30 and 90 min for estimation of DHEA. Serum was allowed to clot before separation, and then frozen at -20°C .

The patients were also taking part in a randomised controlled trial of hydrocortisone as a therapy for CFS, as reported elsewhere (Cleare et al., 1999). This paper reports results only from the 16 subjects who were recruited from King's College Hospital, London into that trial. Basal DHEA(-S) measurements and CRH tests were repeated in the patients after each 28 day block of treatment with either hydrocortisone or placebo, administered in a double-blind, crossover fashion. The dose of hydrocortisone was chosen to be 5 mg in the first half of the sample and 10 mg in the second half; doses were chosen to equate to a hypothesised reduction in urinary free cortisol output of 30–40%, as previously shown (Cleare et al., 1999). In this sub-sample, 11 patients received 5 mg and 5 patients 10 mg. Subjects also underwent a *D*-fenfluramine challenge test and an insulin stress test as part of the protocol (Cleare et al., 2001b), but the order was such that basal DHEA (-S) levels and the CRH test were always measured before these other tests. As previously reported, approximately one-third of patients derived significant benefit on active treatment (Cleare et al., 1999).

All subjects completed a number of self-assessment scales. Fatigue was measured using the fatigue scale of Chalder et al. (Chalder et al., 1993); disability using the Medical Outcomes Study short form 36 (SF-36) (Stewart et al., 1988) and the Work and Social Adjustment Scale (WAS) (Mundt et al., 2002); psychological symptoms using the General Health Questionnaire (GHQ) (Goldberg, 1972); and somatic symptoms using the symptom checklist of 40 items (SCL) (Wittenborn and Buhler, 1979).

2.3. Hormone assays

DHEA and DHEAS were measured by IRMA using kits purchased from Diagnostics Systems Laboratories (DSL, Webster, TX, USA). The DHEA assay

has a sensitivity of 0.02 ng/ml with intra-assay coefficients of variation (c.v.s) of 5.6%, 10.6% and 7.3% at 1.24, 2.63 and 7.3 ng/ml, respectively. Between assay c.v.s were 10.2%, 7.8% and 7.0% at 0.98, 2.55, 10.34 ng/ml, respectively. The sensitivity of the DHEAS assay was 1.7 µg/dl with intra-assay c.v.s of 9.4% and 6.3% at 20.3 and 593.3 µg/dl, respectively. Between assay c.v.s were 9.6% and 9.9% at the same analyte levels. Cortisol was measured using a solid-phase radioimmunoassay (RIA) from DPC, California, USA. Intra-assay c.v.s were 4.8% at 85 nmol/l, 4.7% at 273 nmol/l and 3.0% at 551 nmol/l. Inter-assay c.v.s were 5.2% at 91 nmol/l, 4.0% at 579 nmol/l and 6.4% at 993 nmol/l. Sensitivity was 5.5 nmol/l.

2.4. Analysis

Area under the curve values for the DHEA responses were calculated using the trapezoidal method on baseline corrected data. Analysis of data showed the DHEA and DHEA-S results to be normally distributed; therefore, statistical testing for between group comparisons was undertaken using independent *t*-tests or ANOVA with gender added as a covariate where relevant. Paired *t*-tests were used for within group comparisons to assess the effect of intervention. Correlations were calculated using Pearson's product-moment coefficients. Data are given as mean ± standard error (m ± sem).

3. Results

Subjects and controls were closely matched for age, sex, weight or BMI. Demographic and clinical data on patients and controls are given in Table 1.

DHEA levels and the DHEA response to CRH testing assessed by area under the curve corrected for baseline (AUC_c) did not differ significantly by gender. DHEAS was significantly lower in females (228.9 ± 29.5 µg/dl) than males (395.1 ± 59.0 µg/dl, *t* = 2.81, *P* = 0.009).

3.1. Comparison of CFS patients and controls

Levels of DHEA were higher in patients compared to controls (14.1 ± 2.2 vs. 9.0 ± 0.90 ng/ml, *t* = −2.16, *P* = 0.04), but basal levels of DHEAS did not differ between groups (288.7 ± 35.4 µg/dl in patients vs. 293.7 ± 53.8 µg/dl in controls, *t* = 0.08, *P* = 0.94). There was no gender by condition interaction effect on DHEAS levels with ANOVA. The DHEA response to CRH testing is illustrated in Fig. 1 and Table 2. Although patients showed less responsiveness than controls (AUC_c: 2.5 ± 1.7 vs. 5.8 ± 1.7 ng/ml h), this did not attain significance (*t* = 1.37, *P* = 0.18). Baseline levels of cortisol were higher in CFS subjects (515.3 ± 54.7 nmol/l) than controls (336.9 ± 38.4 nmol/l, *t* = −2.67, *P* = 0.012). Subsequently, there was no difference in the molar DHEA/cortisol ratio between groups (15.0 ± 2.7 in patients, 12.0 ± 1.6 in controls, *t* = −0.97, *P* = 0.34).

Correlational analysis was undertaken separately for the patient group to avoid spurious findings due to inter-group differences. There was a significant correlation between more disability and higher basal DHEA levels, both on the total SWAS score (*r* = 0.58, *P* = 0.019) and the SF-36 physical function score (*r* = −0.59, *P* = 0.016; the sign is reversed for the SF-36 as lower scores

Table 1 Details of subjects

	Patients (<i>n</i> = 16)	Controls (<i>n</i> = 16)
Age (y)	31.6 (2.3)	30.8 (1.7)
Gender	6M:10F	6M:10F
Weight (kg)	67.8 (3.8)	69.5 (3.6)
Body mass index (kg/m ²)	23.5 (1.1)	24.0 (0.9)
Illness duration (months)	30 (19)	—
Fatigue score	26.2 (0.9) ^a	10.8 (0.9)
GHQ-12	17.1 (1.9) ^a	10.9 (1.4)
Beck depression inventory	10.5 (1.4) ^a	4.1 (1.1)
Work and Social Adjustment Scale (0–40, higher more disabled)	22.8 (1.6) ^a	0.8 (0.5)
SF-36 physical function subscale (0–100, lower more disabled)	49.4 (5.1) ^b	96.3 (1.8)

Mean values (standard errors in parentheses).

^aHigher than controls (*P* < 0.05).

^bLower than controls (*P* < 0.05).

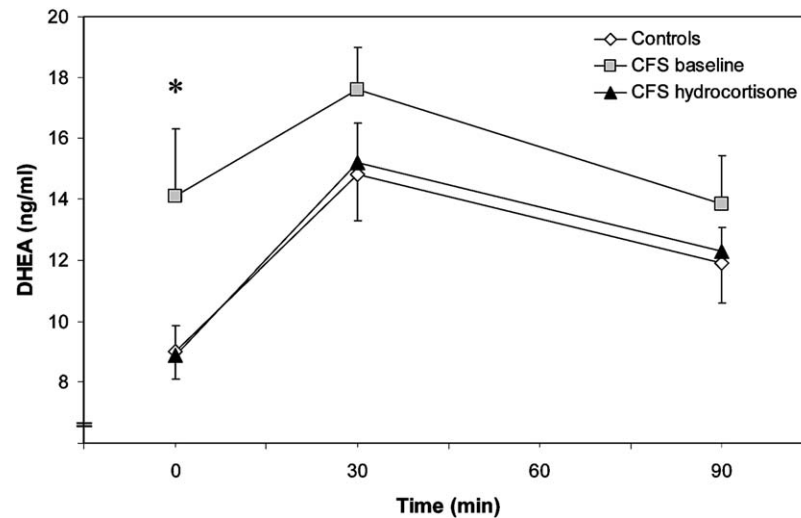


Fig. 1. DHEA levels measured before (0 min) and after (30, 60, and 90 min) administration of 1 $\mu\text{g/kg}$ human-CRH in: (a) medication-free CFS patients (shaded squares); (b) CFS patients after 28 days of hydrocortisone (closed triangles); and (c) healthy controls (open diamonds). Asterisk (*) represents higher DHEA levels at 0 min in patients compared to controls (independent *t*-test) and to post-hydrocortisone state (paired *t*-test)—see text.

mean more disability). The correlation between fatigue and DHEA levels showed a trend towards significance ($r = 0.48$, $P = 0.06$). Correlations were also seen using the AUC_c values: as well as correlations between lower AUC_c values and higher disability (total WSAS: $r = -0.61$, $P = 0.013$; SF-36 physical function $r = 0.50$, $P = 0.050$), there was a link between more reported physical symptoms on the SCL and lower AUC_c values ($r = -0.74$, $P = 0.001$). Once again, there

was a trend in the direction of fatigue being linked to lower AUC_c responses ($r = -0.43$, $P = 0.09$). There were no correlations between clinical variables and either DHEAS or the molar cortisol/DHEA ratio. In summary, correlational analysis showed that the clinical status of patients in terms of disability and symptoms was linked to a pattern of high basal DHEA and low AUC_c DHEA responses to CRH.

Table 2 DHEA/DHEAS values at rest and after CRH challenge (measured as baseline corrected area under the curve— AUC_c) in controls and in patients before and after 28 days of hydrocortisone treatment. Values for patients are subdivided according to clinical response to hydrocortisone treatment

	Basal DHEA (ng/ml)		Basal DHEAS ($\mu\text{g/dl}$)		DHEA response to CRH (AUC_c) (ng/ml h)	
	Untreated	Following hydrocortisone	Untreated	Following hydrocortisone	Untreated	Following hydrocortisone
Controls $n = 16$	9.0 ± 0.90	—	293.7 ± 53.8	—	5.8 ± 1.7	—
Patients (all) $n = 16$	14.1 ± 2.2^a	8.9 ± 0.97^b	288.7 ± 35.4	233.4 ± 41.6^c	2.5 ± 1.7	6.4 ± 1.2^d
Patients (responders) $n = 5$	15.2 ± 3.1	10.0 ± 1.4	280.6 ± 53.2	241.6 ± 63.5^c	-1.4 ± 2.5	5.0 ± 1.2^e
Patients (non-responders) $n = 11$	12.9 ± 3.1	8.4 ± 1.3	298.4 ± 51.7	229.3 ± 56.1^c	3.7 ± 2.3	7.1 ± 1.7

^a $P = 0.04$ vs. controls.

^b $P = 0.015$ vs. basal (pre-treatment) DHEA.

^c $P < 0.05$ vs. basal (pre-treatment) DHEAS.

^d $P = 0.053$ vs. basal (pre-treatment) AUC_c DHEA.

^e $P = 0.029$ vs. basal (pre-treatment) AUC_c DHEA.

3.2. Effects of hydrocortisone

Basal levels of DHEA (8.9 ± 0.97 ng/ml, $t = 2.78$, $P = 0.015$) and DHEAS (233.4 ± 41.6 µg/dl, $t = 2.29$, $P = 0.03$) were significantly lower after treatment of the patients with hydrocortisone, and there was a non-significant trend towards a rise in the DHEA response to CRH to 6.4 ± 1.2 ng/ml h ($t = -2.11$, $P = 0.053$). There was no differential effect of the two doses of hydrocortisone.

We further divided the patients into responders ($n = 5$) and non-responders ($n = 11$) based on a reduction in fatigue scores to a level at or below that of the population mean (Cleare et al., 1999). Responders showed a significant rise in DHEA response to CRH during active treatment compared to baseline (AUC_c: -1.4 ± 2.5 ng/ml h baseline vs. 5.0 ± 1.2 ng/ml h following hydrocortisone), a pattern not seen in non-responders. There was a trend for responders to treatment to have a lower pre-treatment cortisol/DHEA ratio (9.6 ± 1.4) compared to that of non-responders (17.5 ± 3.7 , $P = 0.067$). The cortisol/DHEA ratio after treatment with hydrocortisone was 17.9 ± 4.4 , not significantly different from the pre-treatment value; there was no differential change in cortisol/DHEA ratio seen in responders or non-responders.

4. Discussion

The major findings in this study include the higher basal DHEA levels in unmedicated patients with CFS compared with an age/sex/BMI matched control population, which were linked to self-reported disability. This difference was not apparent following subsequent hydrocortisone therapy. Following hydrocortisone therapy, those patients who responded fully in terms of normalisation of fatigue score demonstrated a significant increase in responsiveness of DHEA to CRH testing. There were no demonstrable differences in basal DHEAS, although patients demonstrated a significant reduction following hydrocortisone. The cortisol/DHEA ratio did not differ between patients and controls.

The observations about basal DHEA levels are at odds with several other published studies in CFS. For example, Scott et al. (Scott et al., 1999) studied a group of CFS patients free of co-morbid psychiatric illness and found a significant reduction in DHEA levels compared with both depressed patients and healthy controls, although this finding was not replicated in a subsequent study by this group (Scott et al., 2000). Additionally, Scott and colleagues failed to show any difference in basal

cortisol levels between normal controls and depressed patients in the original paper. Similarly, other studies have reported low (Kuratsune et al., 1998; van Rensburg et al., 2001) or normal (Ottenweller et al., 2001) morning DHEAS levels in CFS. More in keeping with our findings, one previous study reported a non-significant trend for higher levels of 09:00 h DHEA in patients with CFS (De Becker et al., 1999). Similarly, Goldberg and Lichten (Goldberg and Lichten, 1995) reported a case series of 140 females with CFS, and found that 20% had DHEAS levels above the reference range. However, this was a preliminary report for full publication at a later date; it did not include healthy controls, and gives few details on clinical characteristics and assessment procedures. Overall, disagreements between studies may reflect several factors, including differing clinical characteristics of different samples of CFS sufferers, differential rigor in diagnostic procedures, the inclusion in some studies of subjects on medication or with significant psychiatric co-morbidity (both of which may be associated with DHEA abnormalities) and time of sampling, amongst other factors reviewed extensively elsewhere (Cleare, 2003).

The response of DHEA to stimulation is of interest, since this may reflect disturbances of the adrenal gland metabolic pathways or reserve. Alternatively, it may represent another expression of basal levels of DHEA; for example, further increases above baseline may be inhibited in the presence of high basal DHEA tone. Although there was no significant difference in the DHEA response to CRH between patients and controls, the direction was similar to results obtained by De Becker and colleagues, who found a reduced DHEA response using a direct adrenal challenge with 250 µg of synthetic ACTH (De Becker et al., 1999). However, a study using a smaller dose (1 µg) of synthetic ACTH failed to find absolute differences in DHEA response, though it did note that there was an alteration of the DHEA/cortisol ratio response over time in CFS, a pattern not seen in healthy controls (Scott et al., 2000).

Treatment with hydrocortisone produced an expected fall in DHEA levels; indeed, in these subjects the DHEA level returned to that of healthy controls. Also, as shown in Fig. 1, the response over time then mirrored that of healthy controls too. This increase in DHEA response to challenge was most pronounced in those who were responders to hydrocortisone treatment, and who also had the lowest pre-treatment DHEA responses. This can be interpreted in a number of ways.

First, it could be related to a presumed relative hypocortisolism in CFS, so that DHEA levels are raised, and the DHEA response to challenge accordingly less pronounced. Once the relative hypocortisolism is reversed, with hydrocortisone therapy, then the normal pattern of DHEA responses returns. Alternatively, there could be abnormalities in DHEA pathways themselves. For example, a deficiency in the 21-hydroxylase enzyme has been suggested by some as a potential cause for raised DHEA synthesis (Goldberg and Lichten, 1995). However, the marked inconsistency in the literature so far would appear to argue against a specific alteration in CFS in general. Third, it could be argued that the changes are all in fact secondary to the clinical improvement, and that the subsequent changes in sleep, activity or stress levels may secondarily lead to alterations in DHEA (and other neuroendocrine) measures. Against this, most subjects remained unwell, though the fact that the largest changes with hydrocortisone therapy were confined to the responders provides some support. Alternatively, we have previously argued that the responders to hydrocortisone therapy may be those with abnormal glucocorticoid receptor sensitivity, and that they correspondingly show larger physiological responses to hydrocortisone in addition to larger anti-fatigue effects (Cleare et al., 2001c). Thus, the larger increases in leptin after hydrocortisone in treatment responders, as seen in this previous study, may mirror the larger alterations in DHEA levels and responses to challenge seen in the present study.

DHEA has been suggested as a potential treatment for CFS. Himmel and Seligman (Himmel and Seligman, 1999) have treated 23 females with DHEA on the basis of low basal DHEAS with some improvement in pain and fatigue scores and activities of daily living. However, no controlled studies, or studies on unselected CFS patients, have yet been published. Our findings would not support such an approach in CFS. On the other hand, there have been a number of recent studies that have investigated the role of DHEA supplementation in patients with adrenal insufficiency. In this condition, DHEA(-S) levels appear to be reduced in parallel to the reduction in cortisol, and replacement therapy with DHEA appears to give additional benefits over and above that seen with cortisol replacement (Arlt et al., 1999; Hunt et al., 2000). In particular, fatigue ratings drop and well-being increases. Theoretically, given the possible impairment in adrenal function in CFS, this might be relevant in any pharmacological strategy for an effective replacement regime. Once again, however, our findings of increased levels of DHEA in

CFS argue against this, as does the finding that the improvement of fatigue is linked to reductions in DHEA and DHEAS levels.

One of the problems with using dynamic pharmacological studies to measure DHEA responses to stimulation is that they represent a supraphysiological challenge to the adrenals, and may not reflect the situation in a patient's normal environment. Future work might extend the ongoing work looking at more naturalistic and physiologically relevant stressors in CFS, such as exercise (Ottenweller et al., 2001) or social stress (Gaab et al., 2002), to look at DHEA responses both alone and in relation to cortisol responses. It is also of interest to note the recent literature regarding the importance of the cortisol/DHEA ratio in major depression, where an emerging literature suggests that it is a high cortisol/DHEA ratio that may be the most important indicator of excessive physiological effects of cortisol on the brain (Goodyer et al., 2001; Young et al., 2002). In other words, either low DHEA or high cortisol could contribute to the excess cortisol effect on the brain. In CFS, on the other hand, either low cortisol concentrations, as found in some studies, or high DHEA concentrations, as found in this study, could contribute to a deficient cortisol effect on the brain. We failed to find alterations of the cortisol/DHEA ratio in this study; however, we only took one cortisol sample, which is likely to be insufficient for a true assessment of basal cortisol levels (Cleare, 2003). Sequential measures of cortisol and DHEA, and the use of non-invasive techniques such as saliva collection, are likely to give more accurate data on the cortisol/DHEA ratio in CFS. Such measurements should be undertaken in future studies.

In conclusion, our finding of raised basal DHEA levels in CFS raises doubts about previous suggestions of a decrease in DHEA(-S) levels. Similarly, that finding questions the rationale for DHEA replacement for CFS, as does the finding that patients who improve with hydrocortisone therapy show a reduction in DHEA and DHEAS. Finally, we provide some support for previous work suggesting an impairment in the adrenal DHEA response to pharmacological challenge, and found that a low dose hydrocortisone replacement therapy can reverse that abnormality, most strikingly in those deriving therapeutic benefit. If DHEA(-S) is important in the pathophysiology of CFS, we feel that observing responses to pharmacological or physiological challenges may be a more useful line of enquiry than just measuring basal levels.

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