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Research report

Contrasting neuroendocrine responses in depression and chronic fatigue syndrome

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Abstract

Hypothalamic-pituitary-adrenal (HPA) axis and central 5-HT function were compared in chronic fatigue syndrome (CFS), depression and healthy states. 10 patients with CFS and 15 patients with major depression were matched for age, weight, sex and menstrual cycle with 25 healthy controls. Baseline-circulating cortisol levels were highest in the depressed, lowest in the CFS and intermediate between the two in the control group ($P = 0.01$). Prolactin responses to the selective 5-HT-releasing agent *d*-fenfluramine were lowest in the depressed, highest in the CFS and intermediate between both in the healthy group ($P = 0.01$). Matched pair analysis confirmed higher prolactin responses in CFS patients than controls ($P = 0.05$) and lower responses in depressed patients than controls ($P = 0.003$). There were strong inverse correlations between prolactin and cortisol responses and baseline cortisol values. These data confirm that depression is associated with hypercotisolaemia and reduced central 5-HT neurotransmission and suggest that CFS may be associated with hypocortisolaemia and increased 5-HT function. The opposing responses in CFS and depression may be related to reversed patterns of behavioural dysfunction seen in these conditions. These findings attest to biological distinctions between these disorders.

Keywords: Chronic fatigue syndrome; Depression; 5-HT; Hypothalamic-pituitary-adrenal axis; Cortisol; *d*-Fenfluramine

1. Introduction

The association between stressful life events and depressive illness is a well-established one (Paykel et al., 1989). There is increasing evidence to suggest that the neurobiological mechanisms underlying the stress response, particularly activation of the hypothalamic-pituitary-adrenal (HPA) axis, may be relevant to the pathophysiology of depression (Dinan, 1994). Possible effects of HPA axis activity on central serotonin (5-HT) function are of interest in establishing relationships between the stress response and the neurochemical abnormalities thought to underlie depression.

Both 5-HT and HPA axis function are abnormal in depressive illness. The serotonin depletion hypothesis of depression is supported by diverse studies while hypercortisolism is the most reproducible endocrine abnormality in this disorder (Deakin et al.,

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1990; O'Keane et al., 1992; Dinan, 1994). Recently, dynamic 5-HT neuroendocrine challenge studies in depression have demonstrated a relationship between reduced 5-HT neurotransmission and hypercortisolaemia (Deakin et al., 1990; O'Keane et al., 1992). Preclinical studies have demonstrated that glucocorticoids exert an inhibitory effect on central 5-HT neurotransmitter function (De Kloet et al., 1986). Thus, novel hypotheses have emerged suggesting that chronic HPA axis activation, secondary to ongoing psychosocial stressors (Deakin et al., 1990) or abnormal stress responses (Dinan, 1994), gives rise to reduced brain monoamine function in depression.

In contrast to the HPA axis overdrive in depression, there is preliminary evidence to suggest that the chronic fatigue syndrome (CFS) may be associated with subtle reductions in HPA axis function, such as reduced 24-h urinary-free cortisol (Demitrack et al., 1991). Also, 5-HT neurotransmission, as assessed by prolactin responses to the 5-HT_{1A} agonist buspirone, is increased in CFS relative to healthy and depressed control samples (Bakheit et al., 1992). Thus, CFS may be associated with reduced HPA axis activity and increased 5-HT function and depression with the reverse, i.e., HPA axis overdrive and decreased 5-HT neurotransmission.

We tested this hypothesis using a neuroendocrine challenge paradigm. 5-HT pathways from the dorsal raphe nuclei to the paraventricular nucleus of the hypothalamus are thought to bring about the secretion of the hypothalamic-pituitary releasing peptides involved in the release of prolactin and ACTH from the anterior pituitary (Checkley, 1980). Measuring serial prolactin or cortisol responses to 5-HT agonist drugs is, thus, used as an index of hypothalamic 5-HT neurotransmitter function. *d*-Fenfluramine is the most selective 5-HT-releasing agent used in monoamine neuroendocrine studies to date and reliably elevates prolactin and cortisol responses in healthy subjects compared with placebo (O'Keane et al., 1991; Feeney et al., 1993; Goodall et al., 1993; Gorard et al., 1993). Prolactin and cortisol responses to *d*-fenfluramine are blunted in unmedicated depressives in association with increased circulating cortisol concentrations (O'Keane and Dinan, 1991). We measured baseline circulating cortisol levels and prolactin and cortisol responses to *d*-fenfluramine in a group of CFS sufferers and depressed patients to test the hypothesis that responses in CFS would be the reverse of those in depression. Matched healthy control samples provided comparison groups.

2. Subjects and methods

2.1. Subjects

50 subjects entered the study: 10 patients (6 male and 4 female) with CFS together with 10 closely matched healthy control subjects; and 15 patients (6 male, 9 female) with major depressive disorder (MDD) with 15 healthy control subjects. Patients were drawn from those referred to psychiatry outpatient clinics at the Maudsley or Kings College Hospitals. Depressed subjects fulfilled criteria for MDD as defined by the Diagnostic and Statistical Manual of Mental Disorders (Third Edition, Revised; DSM-III-R). Depression was rated using the Hamilton rating scale for depression (HAM-D; Hamilton, 1960) and only those with a score of ≥ 17 were eligible for inclusion.

CFS patients fulfilled the Centre for Disease Control (CDC) criteria for CFS (Holmes et al., 1988); essentially, patients meeting the CDC criteria must have persisting or relapsing, debilitating fatigue for at least 6 months in the absence of any medical diagnosis which would explain the syndrome. CFS subjects also satisfied alternative recent consensus criteria for CFS (Sharpe et al., 1991). More recently, the original CFC criteria have been modified to allow patients with co-morbid depression to receive a diagnosis of CFS (Schluederberg et al., 1992; Fekuda et al., 1994). However, to get a valid comparison in this study, we excluded these patients. Staff and student volunteers from the two hospitals were used as control subjects; none had a history of psychiatric disorder. All subjects were medication-free for at least 3 months. Subjects were carefully matched with controls for age within 10 years, weight within 10 kg, gender and, for female subjects, the stage of their menstrual cycle. All subjects gave written, informed consent and the procedures were approved by the hospital ethics committees.

2.2. Neuroendocrine procedure

Subjects presented at 09:00 having fasted from midnight. A cannula was inserted into a forearm vein

Table 1
CFS patients compared with controls

Patient	Age	Weight (kg)	Control	Age	Weight (kg)	Diff[baseline CORT] [1] (nmol/l)	Diff[ΔCORT] [1] (nmol/l)	Diff[ΔPROL] [1] (IU/l)
1	56	63	1	53	69	−130	110	40
2	30	82	2	34	85	−20	20	−20
3	43	65	3	37	55	−310	80	250
4	28	57	4	28	60	−140	80	80
5	31	74	5	29	77	90	170	150
6	28	60	6	27	62	−210	140	140
7	32	77	7	31	70	30	120	250
8	38	81	8	34	72	70	−310	−70
9	47	85	9	38	88	80	−30	−20
10	32	74	10	33	70	70	−60	10

[1] Difference in value of patient relative to control (see text).

and after a 15-min period baseline blood samples were taken for cortisol and prolactin estimation. 30 mg *d*-fenfluramine was then administered orally. Further samples were taken for cortisol and prolactin at 1-h intervals for the next 5 h. A standard light snack was served after 1 h. Subjects remained relaxed and semi-recumbent throughout the procedure. Hormone concentrations were measured blind to subject status in the Department of Clinical Biochemistry, Kings College Hospital. Prolactin was measured using an immunoradiometric magnetic solid-phase assay (MAIA Clone, Serono, UK) described by Rattle et al. (1984) and cortisol by the solid-phase RIA of DPC Coat-a-count (CA, USA).

2.3. Analysis

The peak hormonal response to *d*-fenfluramine (Δ value) was determined by subtracting baseline from peak concentrations after drug administration. The decline in hormone concentrations that occurred at 0–1 h represented recovery from the stress re-

Table 2
Depressed patients compared with controls

Patient	Age	Weight (kg)	Control	Age	Weight (kg)	Diff[Baseline CORT] [1] (nmol/l)	Diff[ΔCORT] [1] (nmol/l)	Diff[ΔPROL] (IU/l)
1	57	68	1	53	69	90	10	−30
2	42	68	2	44	76	30	−20	100
3	20	52	3	22	58	620	−220	−80
4	33	65	4	31	70	140	−30	−10
5	47	85	5	40	89	−10	−440	−170
6	28	53	6	30	62	20	−30	30
7	28	53	7	34	52	410	−330	−180
8	46	39	8	45	48	−110	−90	−360
9	28	66	9	27	70	180	110	−90
10	32	71	10	34	70	190	−410	0
11	40	79	11	44	80	100	80	−50
12	28	60	12	22	59	110	−100	−230
13	37	55	13	37	52	−90	140	−160
14	20	86	14	29	77	−190	70	−140
15	43	76	15	38	86	260	−100	−150

[1] Difference in value of patient relative to control (see text).

sponse to cannulation and natural circadian falls and, thus, 1-h values were taken as a more accurate baseline.

We analysed hormonal variables in two ways. (1) We examined the data for both of the test groups and controls and performed an ANOVA across the three groups. We excluded the 5 females in the depressed group who were in the luteal phase of the menstrual cycle together with their controls from this comparison since all the CFS group females were follicular phase. This would otherwise have skewed the comparison given the large variability of *d*-fenfluramine responses seen through the menstrual cycle (O'Keane et al., 1991). We performed also Pearson product moment correlations on the total group. (2) We analysed each patient group in direct comparison to their control group since they were all matched individually for age, sex, weight and menstrual cycle. All of these variables may affect neuroendocrine data (Altomonte et al., 1987; McBride et al., 1990; O'Keane et al., 1991). In this analysis, each subject was compared with each control for each hormone measure (Table 1,Table 2 Table 2). The relative difference between the subject and control was calcualted to give a mean difference (mean diff[baseline values] and mean diff[Δ values]) and these mean differences were compared between the CFS and depressed groups using a Mann–Whitney *U* test. We also calculated 95% confidence intervals and correlations using Spearman's rank correlation coefficients, for these mean differences.

3. Results

3.1. Combined group comparisons

Mean ages in the depressed, CFS and control groups were 39.4, 35.4 and 34.8 years, respectively ($P = 0.6$). Basal prolactin values did not differ between the three groups ($P = 0.4$). Mean Δ prolactin (PROL) $\pm$SEM values were 21 ± 31 mU/l for the depressed, 141 ± 36 mU/l for the CFS and 90 ± 14 mU/l for the control groups ($F_{2,37} = 4.87$, $P = 0.01$). Fig. 1 shows the prolactin curves plotted for both groups against the combined control group while Table 3 gives the mean and SEM values at each time point.

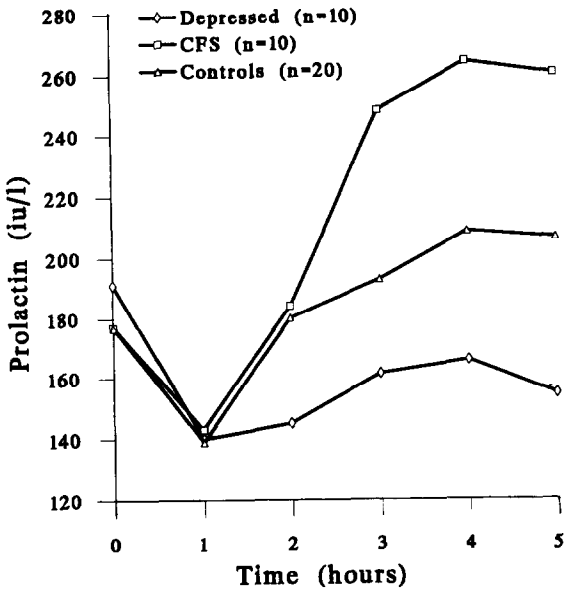

Fig. 1. Mean plasma prolactin concentrations after oral *d*-fenfluramine (30 mg) at 0 h in a depressed group, a group suffering from CFS and a healthy control group. SEM values are shown in Table 3.

Baseline cortisol (CORT) varied amongst the groups being highest in the depressed (428 ± 53.1 nmol/l), lowest in the CFS (226 ± 35.6 nmol/l) and intermediate between the two in the control (305 ± 21.4 nmol/l) group ($F_{2,37} = 5.12$, $P = 0.01$). Fig. 2 shows the cortisol curves plotted against the combined control groups, with mean and SEM values given in Table 4. Mean Δ CORT responses did not differ significantly across groups.

Table 3
Mean prolactin concentrations expressed as IU/l (SEM values in parentheses)

	0 h	1 h	2 h	3 h	4 h	5 h
CFS	345 (46)	226 (27)	305 (33)	285 (12)	280 (21)	250 (23)
Depression	550 (48)	425 (47)	430 (41)	445 (32)	420 (40)	390 (45)
Controls	366 (26)	304 (22)	327 (26)	374 (27)	349 (25)	291 (20)

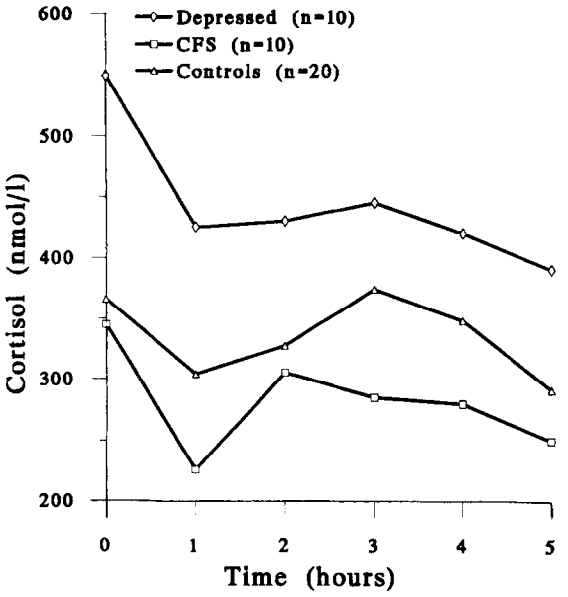

Fig. 2. Mean plasma cortisol concentrations after oral *d*-fenfluramine (30 mg) at 0 h in a depressed group, a group suffering from CFS and a healthy control group. SEM values are shown in Table 4.

There was an inverse relationship between baseline CORT and Δ CORT ($r = 0.49$, $n = 50$, $P = 0.0003$) and a positive relationship between Δ CORT and Δ PROL ($r = 0.32$, $n = 50$, $P = 0.02$).

3.2. Matched comparisons

CFS group

Mean age difference was 2.1 years and mean weight difference 1.0 kg (both NS). Mean diff[baseline PROL] was −10 IU/l (95% CI −47–59; NS). Mean diff[Δ PROL] was +81 IU/l and the 95% CI 1–161 IU/l. Paired *t* test indicated this was a significant difference ($t = 2.29$, df = 9, $P = 0.048$), with Δ PROL values higher in the CFS group than the controls (Table 1). Mean diff[baseline CORT] was −47 nmol/l (95% CI −148–54; NS) while mean diff[Δ CORT] was +32 nmol/l (95% CI −69–133; NS).

Depressed group

Mean age difference was 0.06 years and mean weight difference was 2.9 kg (both NS). Mean diff[baseline PROL] was +6 IU/l (95% CI −47–59). Mean diff[Δ PROL] was −104 IU/l and the 95% CI (−167 – −41). Paired *t* test indicated this was a significant difference ($t = 3.52$, df = 14, $P = 0.003$), Δ PROL values in the depressed group being lower than the control values (Table 2). Mean diff[baseline CORT] was +117 nmol/l (95% CI 3–231), with higher values in the depressed group ($t = 2.2$, df = 14, $P = 0.045$). Mean diff[Δ CORT] was −75 nmol/l (95% CI −165–14).

Comparison between CFS and depressed groups

Mean diff[baseline PROL] did not differ between the two groups ($z = 0.26$, $P > 0.5$). Mean diff[Δ PROL] was significantly higher in the CFS group than the depressed group ($z = 3.03$, $P = 0.002$) as was mean diff[Δ CORT] ($z = -2.11$, $P = 0.03$). Mean diff[baseline CORT] was higher in the depressed group ($z = -2.19$, $P = 0.03$)

Correlations

There were significant inverse correlations between diff[baseline CORT] and both diff[Δ CORT] ($r = -0.46$, $n = 25$, $P = 0.02$) and diff[Δ PROL] ($r = -0.39$, $n = 25$, $P = 0.05$). Thus, higher baseline cortisol values were associated with blunted hormonal responses. Diff[Δ CORT] and diff[Δ PROL] were positively correlated ($r = 0.53$, $n = 25$, $P = 0.01$).

Table 4
Mean cortisol concentrations expressed as nmol/l/l (SEM values in parentheses)

	0 h	1 h	2 h	3 h	4 h	5 h
CFS	177 (19)	143 (25)	184 (26)	248 (40)	264 (42)	260 (42)
Depression	191 (31)	140 (23)	145 (29)	161 (32)	166 (30)	154 (32)
Controls	177 (13)	139 (13)	180 (18)	193 (22)	208 (30)	206 (21)

4. Discussion

We have found that 5-HT-mediated responses to *d*-fenfluramine are raised relative to controls in a group of CFS sufferers and lowered relative to controls in a group of depressed patients. Conversely, cortisol levels were lowered in CFS patients and raised in depressed patients relative to controls. There were strong inverse correlations between the level of cortisol and the 5-HT-mediated responses. Importantly, the CFS and depressed groups differed on all three outcome measures (prolactin response, cortisol response and basal cortisol) after careful matching with controls.

Our findings support a large body of evidence indicating that depression is associated with hypercortisolism and reduced 5-HT function (Dinan, 1994; O'Keane and Dinan, 1991; O'Keane et al., 1992; Deakin et al., 1990). More specifically, they replicate previous findings of an association between hypercortisolaemia and blunted *d*-fenfluramine/prolactin responses (O'Keane et al., 1992). They also support preliminary findings of hypocortisolism and increased 5-HT neurotransmitter function in CFS (Demitrack et al., 1991; Bakheit et al., 1992). The demonstration of healthy control responses that fall mid-way between depression and CFS suggests that the neuromodulators measured in this study, HPA axis function and 5-HT neurotransmission, may be pathologically altered in opposite directions in these two conditions.

This CFS sample represents a subset of CFS patients in that they were not suffering from depression. The depressed subjects, on the other hand, had to score ≥ 17 on the HAM-D, which measures symptoms of 'endogenous' depression, such as anorexia, insomnia and agitation (Hamilton, 1960). Some of the symptoms found in CFS are the reverse of those found in this type of depression, i.e., hypersomnia and hyperphagia. Thus, hypercortisolism and reduced 5-HT function are associated with insomnia, anorexia and agitation whereas hypocortisolism and increased 5-HT function are associated associated with a reverse dysfunction in these behaviours. That HPA axis and/or 5-HT function may be causal in these reversed biological symptoms is suggested by preclinical evidence that CRH is an activating peptide giving rise to increased motor activity and general arousal and decreased feeding and sleep (Ur, 1991). 5-HT is also involved in the control of sleep, appetite and mood (Vogt, 1982). Whether the HPA axis dysfunction results in aberrant 5-HT neurotransmission or vice versa is not suggested by this study. Animal studies demonstrating inhibitory effects of glucocorticoids on central 5-HT synthesis suggest that HPA axis function may be the primary pathology (De Kloet et al., 1986). On the other hand, stress-induced CRH secretion is modulated by 5-HT (Delbende et al., 1992) and there is animal evidence that the 5-HT reuptake inhibitor antidepressants may work by reducing HPA axis function (Kitayama et al., 1988).

These findings suggest that depression and CFS are characterized by an exaggerated and a deficient stress response, respectively. Although our study cannot determine whether the opposing HPA axis and 5-HT function observed in CFS and MDD are of causal significance, they may be related to the reversed patterns of vegetative function observed in the two syndromes.

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