
Neuroendocrine Responses to d-Fenfluramine and Insulin-Induced Hypoglycemia in Chronic Fatigue Syndrome

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Chronic fatigue syndrome (CFS) is a disorder characterized by severe physical and mental fatigue and fatiguability of central rather than peripheral origin. We hypothesized that CFS is mediated by changes in hypothalamopituitary function and so measured the adrenocorticotrophic hormone (ACTH), cortisol, growth hormone, and prolactin responses to insulin-induced hypoglycemia, and the ACTH, cortisol, and prolactin responses to serotonergic stimulation with dexfenfluramine in nondepressed CFS patients and normal controls. We have shown attenuated prolactin responses to hypoglycemia in CFS. There was also a greater ACTH response and higher peak ACTH concentrations (36.44 ± 4.45 versus 25.60 ± 2.78 pg/ml), whereas cortisol responses did not differ, findings that are compatible with impaired adrenal cortical function. This study provided evidence for both pituitary and adrenal cortical impairment in CFS and further studies are merited to both confirm and determine more precisely their neurobiological basis so that rational treatments can be evolved.

Key Words: Chronic fatigue syndrome, cortisol, growth hormone, prolactin, d-fenfluramine, hypoglycemia

Introduction

Chronic fatigue syndrome (CFS) has attracted considerable controversy in recent years. Dispute exists concerning its definition, etiology, pathophysiology, and treatment. Progress has been made following the introduction of consensus criteria (Sharpe et al 1991; Schluederberg et al 1992), which

defines CFS as a condition associated with severe physical and mental fatigue and fatiguability, associated with functional impairment and other somatic symptoms, but without a conventional biomedical explanation.

Although early reports claimed that the abnormal fatigability was related to neuromuscular dysfunction, recent studies have shown that neuromuscular function is largely normal (Lloyd et al 1991; Rutherford and White 1991; Gibson et al 1993). Furthermore, the pattern of fatigue is of central, rather than peripheral, origin (Wessely and Powell 1989). In consequence, attention has shifted to the role of the central nervous system in CFS and neuroendocrine studies provide one means of exploring this. The hypothalamopituitary adrenal axis (HPA) has received particular attention be-

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cause HPA dysregulation is associated with depressive illness (Charlton and Ferrier 1989), the commonest form of psychiatric comorbidity found in CFS. Patients with CFS have reduced cortisol secretion rates and attenuated corticotrophin releasing hormone (CRH) responsiveness, findings that are most consistent with impaired HPA function (Demitrack et al 1991). HP activation is involved in the physiological response to stress/exercise, and fatigability may at least in part be mediated by impaired HP responsiveness.

One convenient standardized model of stress is the insulin tolerance test (ITT), which stimulates growth hormone (GH), prolactin (PRL), adrenocorticotrophic hormone (ACTH) and cortisol secretion in man (Fish et al 1986). We hypothesized that if patients with CFS mount defective stress responses they would exhibit impaired neuroendocrine responses to ITT compared with normal controls. We wished to determine if the CFS patients had abnormal responses independent of co-existing depression. Because depressed patients have attenuated neuroendocrine responses to ITT confounded by insulin resistance (Sachar et al 1971; Brunswick et al 1988) we confined the test to CFS patients who were not concurrently depressed.

Neuroendocrine strategies have also been applied to estimate central serotonin (5-HT) neurotransmission, as reflected by the size of the prolactin and cortisol responses to a range of serotonergic agonists. This strategy has recently been applied in CFS, not only because of the high comorbidity with depression in which serotonergic mediated neuroendocrine responses are attenuated (Bearn and Raven 1993), but also because of the role of 5-HT in the regulation of sleep, appetite, pain, and inflammation, all commonly disturbed in CFS (Leibowitz 1990; Jensen et al 1990). Bakheit et al (1992) have demonstrated enhanced prolactin responses to buspirone, a 5-HT agonist selective for 5-HT_{1A} receptors. In this study we have further explored serotonergic function using d-fenfluramine, which has a high degree of 5-HT specificity (Garatini et al 1987) and is clinically well-tolerated by patients. We sought to distinguish any specific changes in CFS by confining our study to nondepressed patients. We restricted the study to nondepressed patients with CFS in order not to confound or mask any specific changes attributable to CFS alone.

Methods

Subjects

Nine patients who had been referred to the psychiatric clinic at King's College Hospital specializing in chronic fatigue volunteered to participate in the study. All fulfilled recent consensus criteria for the diagnosis of chronic fatigue syndrome (Sharpe et al 1991). All had also been characterized as typical CFS as part of a recent multicenter diagnostic exercise, in which this center had participated (A. Wilson,

A. Lloyd, and I. Hickie, personal communications). The patients completed the General Health Questionnaire, a cut-off of 3-4 being used for probable psychological disorder (Goldberg 1972). They also completed a questionnaire specifically devised for the assessment of fatigue, which provides a dimensional measure of fatigue (Chalder et al 1993). A cut-off of 3 to 4 is used to indicate clinically significant fatigue. The maximum score is 11. Patients were all interviewed on two occasions separated by a minimum of 1 month by two psychiatrists (SW, JAB) to detect depressive disorder according to DSM III-R criteria (APA 1987). The Hamilton Rating Scale for depression (Hamilton 1967) was used to measure the severity of depression.

Patients were recruited if they were aged 18 to 60, had no history of epilepsy or cardiovascular disease, normal hematological and biochemical screening profiles and normal thyroid function, and had no abnormality on physical examination. None had taken any medication, including antidepressants for at least 12 weeks prior to the study and none of the women were using the oral contraceptive.

Seven patients underwent both an insulin tolerance test (ITT) and d-fenfluramine test, whereas two patients only had an ITT and two only had a d-fenfluramine test. Ten normal controls were recruited from the staff and student body of King's College and Maudsley Hospitals. They were all in good health, without a history of serious illness (particularly epilepsy and cardiovascular disease), medication free (including the oral contraceptive), normal on physical examination and had normal hematological and biochemical screening profiles. Eight controls underwent both an ITT and d-fenfluramine test and the remaining two only had a d-fenfluramine test.

In the premenopausal females, all tests were performed on day 3-5 of their menstrual cycle. All procedures took place on the Programmed Investigation Unit, King's College Hospital, ethical permission having been obtained from both the King's College Hospital and the Bethlem Royal and Maudsley Hospital ethical committees. All patients provided written informed consent before participating in the study.

Insulin Tolerance Test

After fasting from midnight, each subject arrived on the unit at 9 AM and had an indwelling intravenous cannula with a 3-way stopcock inserted into a forearm vein. After resting for 1 hr, crystalline synthetic insulin 0.15 u or 0.10 u per kg body weight was injected via the cannula. Blood samples for estimation of blood glucose were taken into fluoride tubes prior to the insulin injection and at 20, 30, 45, 60, 90, and 120 min. Another aliquot was taken into cooled heparinized tubes, centrifuged immediately and the plasma stored at -20°C for later estimation of ACTH concentration. The remainder was allowed to clot at 4°C, spun and serum stored

at -20°C prior to estimation of cortisol, prolactin, and growth hormone concentrations. All subjects were given an oral glucose drink to reverse symptoms of hypoglycemia if required. The criterion for hypoglycemic stress was a post-insulin glucose nadir ≤ 2 mmol/L. This was achieved in all subjects.

d-Fenfluramine Test

After fasting from midnight, each subject came to the unit at 9 AM and had an indwelling intravenous cannula with three-way stopcock inserted into a forearm vein. After resting for 1 hr, each subject swallowed 30 mg d-fenfluramine. Blood samples were taken prior to taking the d-fenfluramine and at 1, 2, 3, 4, and 5 hr. One aliquot was taken into cooled heparinized tubes, centrifuged immediately, and the plasma stored at -20°C for later estimation of ACTH concentration. The remainder was allowed to clot at 4°C , spun and serum stored at -20°C prior to estimation of cortisol, prolactin, and growth hormone concentrations. Everyone was given a light breakfast 1 hr after ingestion of fenfluramine, and rested quietly for the duration of the study.

Biochemical Analysis

Prolactin was measured by immunoradiometric assay (MAIAclone, Serono Diagnostic, Fleet, UK) calibrated against I.S. 84/500. Intraassay coefficient of variation (C.V.) was less than 5%, interassay CV less than 8%. Cortisol was measured by radioimmunoassay (Coat-A-Count, DPC, Glyn Rhonwy, UK). Intraassay CV was less than 8%, interassay CV less than 12% across the observed range. Growth hormone was assayed using reagents for immunometric assay from North East Thames Radioimmunoassay (London, UK). The assay was calibrated against I.S. 80/505; intraassay CV was less than 5% at values greater than 2 mU/L, and interassay CV was less than 10%. Immunometric assay of ACTH was carried out at the Department of Chemical Pathology, St. Thomas' Hospital, using the method of White et al (1987). Intraassay CV was less than 7% and interassay CV less than 10%.

Statistical Analysis

We compared the demographic data between the patient and control group using Student's *t*-test. We compared the hormone responses to insulin d-fenfluramine between the patient and control groups using the analysis of variance programme in the Statistical Package for Social Sciences (SPSS). Because growth hormone responses were not normally distributed we used the Wilcoxon's rank sum test to compare growth hormone responses (integrated as area under the curve) between the patient and control groups.

Results

Demographic Characteristics

The clinical characteristics of the patients are shown in Table 1. All fulfilled the criteria of Sharpe et al (1991) and all but one also complained of significant myalgia. LB was the only patient not to fulfill the Center for Disease Control (CDC) criteria (Holmes et al 1988). None of the patients were currently depressed, although one (GW) fulfilled the criteria for previous major depressive episode.

Insulin Tolerance Test

The ITT was conducted on nine patients (four women and five men) and eight controls (six women and two men). The mean age of the patient group was 36.6 ± 2.7 (SEM) years, which was significantly greater than the control group (25.9 ± 1.7 years) ($p < 0.01$). There was no significant difference between the body mass index of the patient group (25.3 ± 1.01) and the controls (23.6 ± 1.37).

An insulin-induced fall in blood glucose of greater than 50% was achieved in all cases. The blood glucose nadir at 30 min was 1.26 ± 0.12 mmol/L in the patient group and 1.19 ± 0.19 mmol/L in the controls (NS). The prolactin, growth hormone, cortisol and ACTH responses are shown in Figures 1, 2, 3, and 4 respectively. The prolactin response to hypoglycemia was significantly attenuated in the CFS patients ($F = 4.17$; $p = 0.04$). Although there was a trend toward an attenuated growth hormone response in the patients, this just failed to achieve statistical significance ($p > 0.05$). There was also a clear trend that peak GH concentrations were lower in the patients (53.69 ± 10.6 mmol/L $^{-1}$) than the controls (110.38 ± 28.70), although again this just failed to achieve statistical significance ($t = 1.94$; $df = 15$; $0.05 < p < 0.1$). Growth hormone data was also analyzed after excluding the four subjects (three controls, one patient) with baseline growth hormone concentrations of >5 mU/L in line with other studies, because high baseline concentrations of GH may inhibit GH release. Again, no statistical difference between the two groups was demonstrated ($p > 0.05$).

There was no difference in the cortisol ($F = 2.28$; $p = 0.14$) or ACTH ($F = 0.03$; $p = 0.86$) responses to hypoglycemia between the two groups. There was also no significant difference in peak ACTH, cortisol, and prolactin concentrations between the patients and controls.

d-Fenfluramine Test

The d-fenfluramine test was conducted on nine patients (four women and five men) and 10 controls (six women and four men). The mean age of the patient group (37.3 ± 3.5 years) was significantly greater than that of the controls (26.8 ± 1.5 years) ($p < 0.02$). The body mass index of the

Table 1. Clinical Characteristics of Patients with CFS

Patient	Sex	Age/ Yrs	Length of illness/yrs	Viral onset	Past anti- depressant treatment	Current psychiatric diagnosis	GHQ-12	Chalder fatigue score	Fenfluramine test	IST
MF	F	56	10	Yes	No	No	3	10	Yes	No
LB	F	44	4	No	No	No	3	10	Yes	Yes
PB	M	32	1	Yes	No	No	7	10	Yes	Yes
GW	M	39	2	Yes	Yes	Yes	9	8	Yes	Yes
MD	F	25	1	Yes	No	No	7	11	Yes	Yes
HR	M	27	8	No	No	No	11	11	Yes	Yes
SM	M	41	1	Yes	Yes	No	7	11	No	Yes
JM	M	49	15	Yes	Yes	No	3	11	Yes	Yes
CA	F	40	13	Yes	Yes	Yes	5	11	No	Yes
JM	F	32	4	Yes	No	No	2	10	Yes	Yes
MC	M	32	4	Yes	No	No	2	11	Yes	No

patient group (24.40 ± 1.12) did not differ significantly from that of the control group (23.00 ± 1.15). Everyone tolerated the d-fenfluramine well during the test, although some complained of general malaise the following day.

The cortisol, ACTH, and prolactin responses are shown in Figures 5, 6, and 7 respectively. Although there was no significant difference in the cortisol response ($F = 1.14$; $p = 0.29$), the ACTH response was significantly greater in the patient group ($F = 4.08$; $p = 0.04$). Peak cortisol concentrations achieved were not significantly different between the

patients ($372.2 \pm 17.30 \text{ mmol/L}^{-1}$) and controls ($401.0 \pm 15.82 \text{ mmol/L}^{-1}$) ($t = 1.23$; $df = 17$; $p > 0.2$). Significantly higher peak ACTH concentrations were achieved in the patients ($36.44 \pm 4.45 \text{ pgml}^{-1}$) than the controls ($25.6 \pm 2.78 \text{ pgml}^{-1}$) ($t = 2.11$; $df = 17$; $p = 0.05$), however.

There was no significant difference in the prolactin ($F = 2.28$; $p = 0.133$) response to d-fenfluramine between patients and controls, nor any significant difference in peak prolactin concentrations achieved. Across the two groups there was a significant suppression of both cortisol ($t = 7.21$;

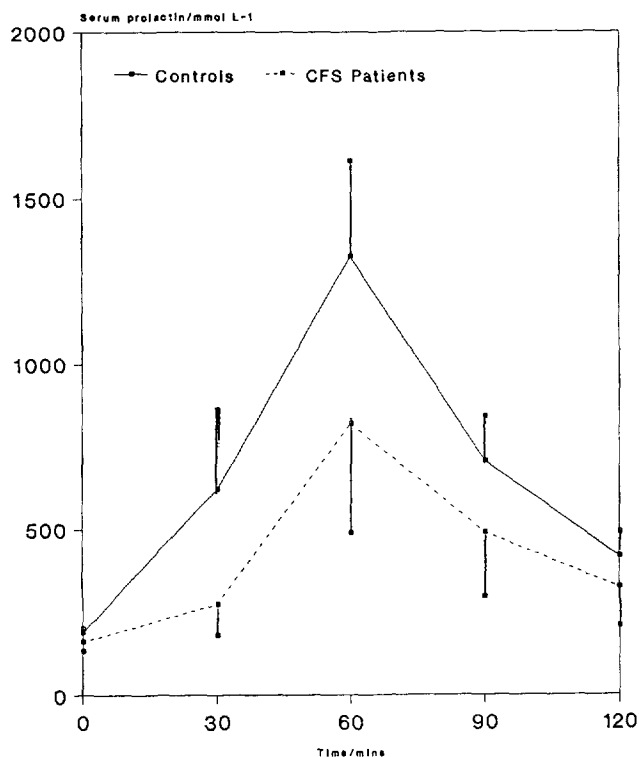


Figure 1. Mean serum prolactin concentrations \pm SEM during insulin tolerance test.

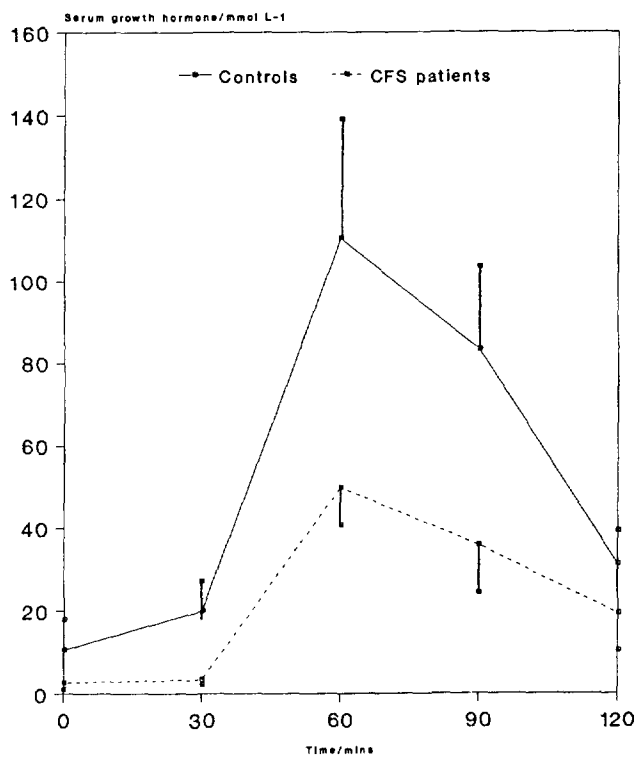


Figure 2. Mean serum growth hormone concentrations \pm SEM during insulin tolerance test.

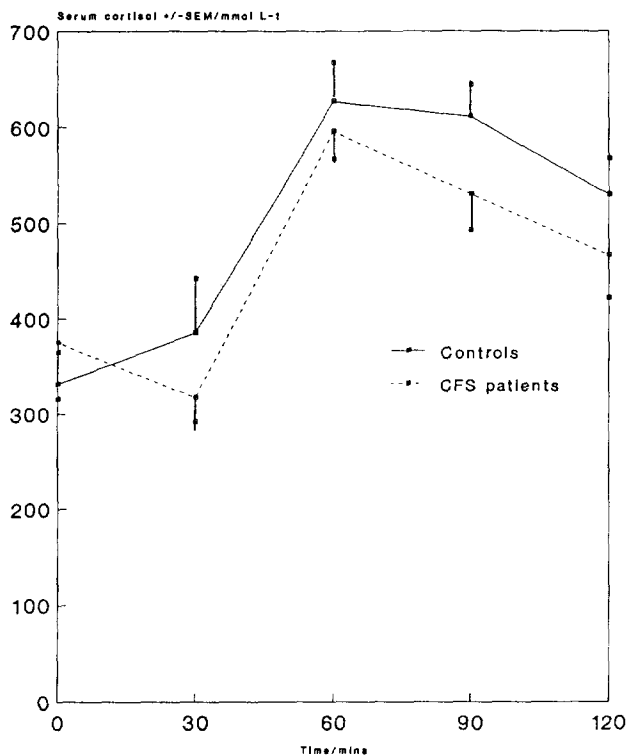


Figure 3. Mean serum cortisol concentrations \pm SEM during insulin tolerance test.

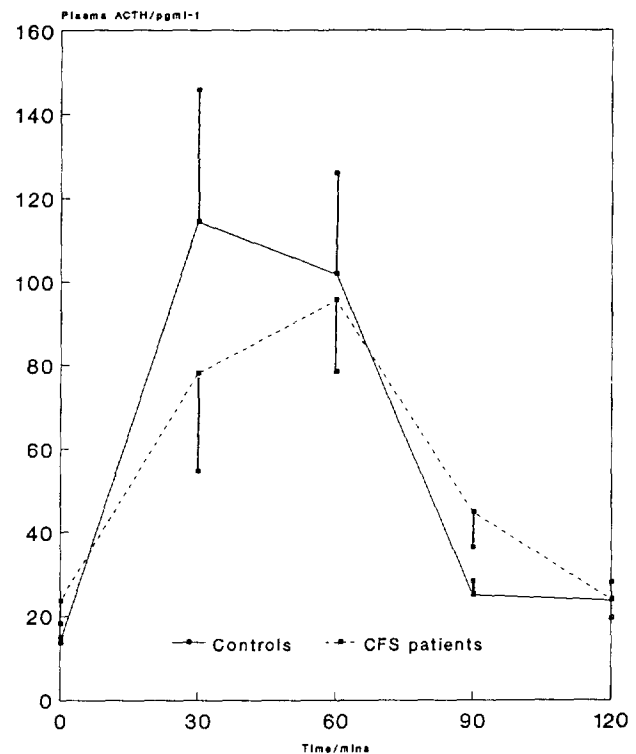


Figure 4. Mean plasma ACTH concentrations \pm SEM during insulin tolerance test.

df = 18; $p < 0.0001$) and prolactin ($t = 6.26$; d.f. = 18; $p < 0.001$) after 1 hr before enhanced secretion supervened.

Discussion

We have shown that patients with CFS have a selective impairment of hypothalamopituitary responsiveness to the stress of hypoglycemia, confined to the prolactin response, whereas GH, ACTH, and cortisol responses are not affected. We have shown a clear trend toward an attenuated GH response, however, and in a parallel study conducted by our group using an overlapping series of patients and controls, we have shown significantly reduced GH responses to hypoglycemia (T. Allain et al., unpublished data) so that our sample size may have been too small to detect a difference. Attenuated GH responses have also been demonstrated in depressed patients. The insulin-induced fall in blood glucose is significantly lower when patients are depressed compared with after recovery (Sacher et al 1971; Brunswick et al 1988), however. After correcting for insulin resistance, there is no longer any difference in growth hormone response between depressed patients and controls. In the present study, there is no difference in insulin sensitivity as determined by mean blood glucose nadir between the patient with CFS and controls and we were careful to exclude

concurrent depression as a confounding factor. Thus the impaired prolactin response cannot be accounted for by either depression or insulin resistance.

Prolactin secretion in response to hypoglycemia is mediated by 5-HT activation (Fish et al 1986) and it is possible that the attenuated prolactin response is related to subsensitivity of 5-HT hypothalamic neurons. The ACTH-cortisol response to ITT is also mediated through 5-HT activation (Cavagnini et al 1976), however, and our patients exhibit normal ACTH and cortisol responses. This finding fails to support a role for altered 5-HT neurotransmission in the attenuated prolactin response.

In this study the patients were significantly older than the control group. Age does not affect the growth hormone response to insulin-induced hypoglycemia (Brunswick et al 1988) or cortisol responsiveness (Nelson and Tindall 1978), however. Furthermore, the large intersubject variability in the prolactin response extends across a wide age range (Amsterdam et al 1987). Our control group was largely selected from employees or students at health centers and we acknowledge there may have been differences in lifestyle and physical activity that may bias our results. Obesity is an important influence (Fish et al 1986) but there was no difference in body mass indices between the patient and control groups. Gender matching was incomplete with a

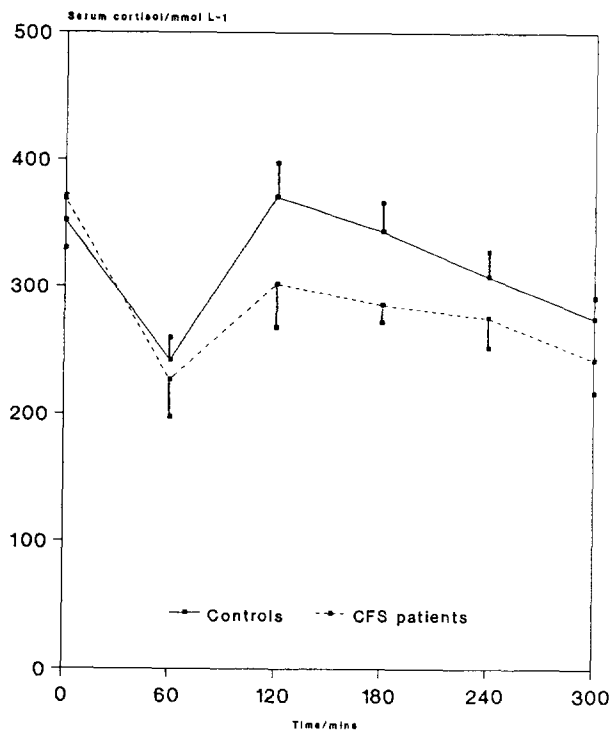


Figure 5. Mean serum cortisol concentrations \pm SEM after 30 mg dexfenfluramine.

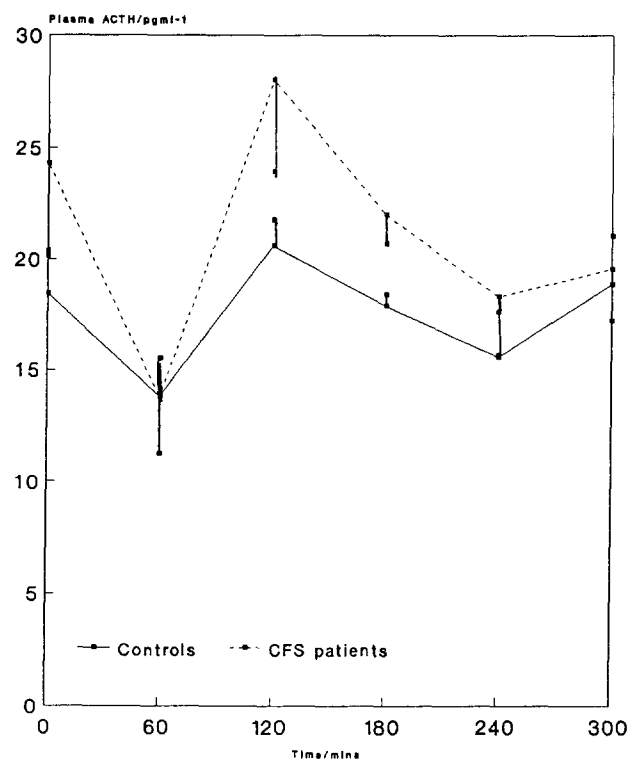


Figure 6. Mean plasma ACTH concentrations \pm SEM after 30 mg dexfenfluramine.

preponderance of women in the control group. In some studies women have lower growth hormone responses to ITT than men (Casper et al 1977; Osterman and Wide 1976). Other workers have failed to detect any difference between male and female neuroendocrine responsiveness to ITT and have combined data acquired from men and women in their analysis (Brunswick et al 1988).

We were unable to demonstrate any alteration in the prolactin response to d-fenfluramine in our patients. This contrasts with Bakheit's findings of an enhanced prolactin response to buspirone (Bakheit et al 1992) in CFS patients compared to both depressed patients and normal controls (who both exhibited similar responses). The difference was confined to the prolactin peak and did not extend to cumulative hormone secretion over the full 3-hr study period, however. In the present study there was no difference in peak prolactin levels between the patients and controls ($t = 1.04$; $p > 0.02$). Although Bakheit's finding may reflect increased postsynaptic 5-HT sensitivity, buspirone also has affinity for D2 dopamine receptors (Perowka 1985; Meltzer et al 1992), which may be confounding the serotonergic effects on prolactin secretion. d-Fenfluramine is highly 5-HT selective (Garatini et al 1987) and is thus advantageous as a 5-HT neuroendocrine probe, however. Prolactin responses to d-fenfluramine are attenuated in depressed patients (O'Keane and Dinan 1991) and this poten-

tially confounding factor was accounted for by the exclusion of depressed CFS patients from the present study. Our control group contained a slight excess of women and younger subjects than the patient group. Women tend to have enhanced prolactin responses, which also tends to decrease with age (McBride et al 1990), so the incomplete age and gender matching of patients and controls may have biased our findings.

In CFS patients, we have shown increased ACTH secretion in response to d-fenfluramine in the face of normal cortisol responses. This suggests that adrenal cortical function is impaired, although we have not confirmed this when activating the HPA during insulin induced hypoglycemia. In primary fibromyalgia syndrome (PFS), however, a condition very similar to CFS in that it is characterized by unexplained fatigue, myalgia, and sleep disturbance, cortisol responses to ITT are normal in the face of enhanced ACTH secretion, which is also consistent with impaired adrenal function (Griep et al 1993).

A recent rigorous study has shown that CFS patients exhibit HPA dysregulation, with lower urinary excretion rates of free cortisol and reduced evening plasma cortisol concentrations in conjunction with an elevated plasma ACTH (Demitrack et al 1991). ACTH responses to CRH are attenuated despite lower ambient cortisol levels, which are

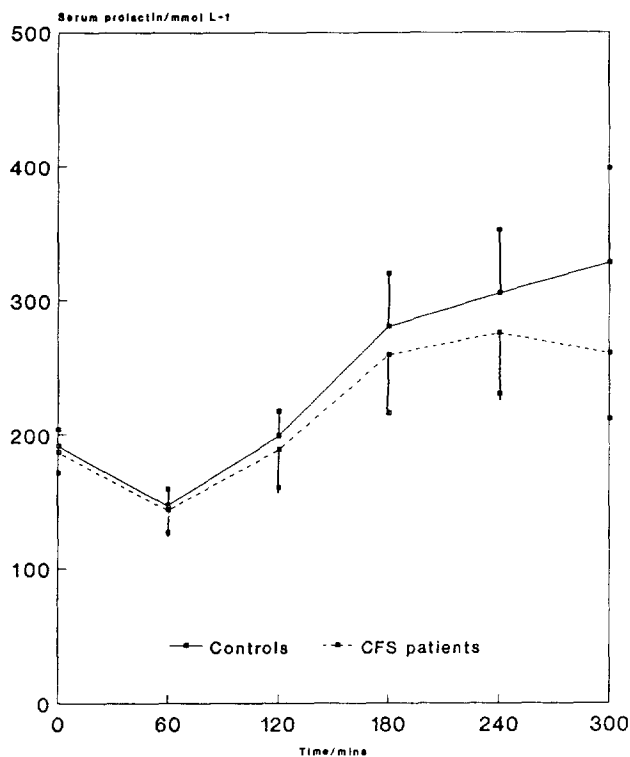


Figure 7. Mean serum prolactin concentrations \pm SEM after 30 mg dexfenfluramine.

therefore not inhibiting ACTH secretion. The impaired HPA activity cannot be due to primary adrenal insufficiency because cortisol responses to ACTH are preserved and pituitary insufficiency is unlikely because of elevated ACTH concentrations. Taken together these findings are most compatible with impaired hypothalamic function compromising CRH synthesis/secretion. Our findings suggest that further studies of adrenal cortical function are indicated, however.

In conclusion, we have demonstrated impaired prolactin responsiveness to metabolic stress in chronic fatigue syndrome, which cannot be explained by any concurrent depression. Neuroendocrine responses to d-fenfluramine provide evidence for impairment of adrenal cortical function. This study thus provides further evidence for hypothalamic dysfunction in chronic fatigue syndrome and further studies are merited to determine more precisely the basis of this dysfunction.

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References

- American Psychiatric Association (1987): *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. Washington, DC: American Psychiatric Press.
- Amsterdam JD, Schweizer E, Winokur A (1987): Multiple hormonal responses to insulin-induced hypoglycemia in depressed patients and normal volunteers. *Am J Psychiatry* 144:170-175.
- Bakheit AMO, Behan PO, Dinan TG, Gray CE, O'Keane V (1992): Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome. *Br Med J* 304:1010-1012.
- Bearn J, Raven P (1993): Neuroendocrine developments in psychiatric research. In Kerwin R, Dawbarn D, McCulloch J, Tamminga C, eds., *Cambridge Medical Reviews: Neurobiology and Psychiatry*, Vol 2, 71-96, Cambridge University Press.
- Brunswick D, Frazer A, Koslow S, et al (1988): Insulin-induced hypoglycemic response and release of growth hormone in depressed patients and healthy controls. *Psychol Med* 18:79-91.
- Casper R, Davis J, Pandey G (1977): Neuroendocrine and amine studies in affective illness. *Psychoneuroendocrinology* 2:105-113.
- Cavagnini F, Raggi U, Micossi P, Di Landro A, Invitti C (1976): Effect of an antiserotonergic drug, metergoline on the ACTH and cortisol response to insulin hypoglycemia and lysine-vasopressin in man. *J Clin Endocrinol Metab* 43:306-312.
- Chalder T, Berelowitz G, Pawlikowska T, et al (1993): Development of a Fatigue Scale. *J Psychosom Res* 37:147-153.
- Charlton B, Ferrier I (1989): Hypothalamo-pituitary adrenal axis abnormalities in depression: a review and a model. *Psychol Med* 19:331-6.
- Demitrack M, Dale J, Straus S, et al (1991): Evidence for impaired activation of the hypothalamic-pituitary adrenal axis in patients with chronic fatigue syndrome. *J Clin Endocrinol Metab* 73:1224-1234.
- Fish H, Chernow B, O'Brien J (1986): Endocrine and neurophysiologic responses of the pituitary to insulin-induced hypoglycemia: A review. *Metabolism* 35:763-80.
- Garatini S, Mennini T, Samanin R (1987): From fenfluramine racemate to d-fenfluramine: specificity and potency of the effects on the serotonergic system and food intake. *Ann NY Acad Sci* 499:156-66.
- Gibson H, Carroll N, Clague J, Edwards R (1993): Exercise performance and fatigability in patients with chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry* 56:993-998.
- Goldberg D (1972): Detecting psychiatric illness by questionnaire. *Maudsley Monograph*, 22. Oxford University Press, Oxford.
- Griep E, Boersma J, de Kloet E (1993): Altered reactivity of the hypothalamic-pituitary-adrenal axis in the primary fibromyalgia syndrome. *J Rheumatol* 20:469-74.

- Hamilton N (1967): Development of a rating scale for primary depressive illness. *Br J Soc Exp Psychol* 6:278-296.
- Holmes GP, Kaplan JE, Gantz NM et al (1988): Chronic fatigue syndrome: A working case definition. *Ann Intern Med* 108:387-389.
- Jensen K, Tuxen C, Pedersen-Bjergaard U, et al (1990): Pain, wheal and flare in human forearm skin induced by bradykinin and 5 hydroxytryptamine. *Peptides* 11:1133-8.
- Leibowitz B (1990): The role of serotonin in eating disorders. *Drugs* 39, (suppl)3:33-48.
- Lloyd A, Gandevia S, Hales J (1991): Muscle performance, voluntary activation, twitch properties and perceived effort in normal subjects and patients with the chronic fatigue syndrome. *Brain* 114:85-98.
- McBride P, Tierney H, De Meo M, et al (1990): Effect of age and gender on CNS serotonergic responsivity in normal adults. *Biol Psychiatry* 27:1143-1155.
- Meltzer H, Lee H, Nash J (1992): Effects of buspirone on prolactin secretion is not mediated by 5HT_{1a} receptor stimulation. *Arch Gen Psychiatry* 42:163.
- Nelson JC, Tindall DJ (1978): A comparison of the adrenal responses to hypoglycemia, metyrapone and ACTH. *Am J Med Sci* 275:165-172.
- O'Keane V, Dinan T (1991): Prolactin and cortisol responses to d-fenfluramine in major depression: evidence for diminished responsivity of central serotonergic function. *Am J Psychiatry* 148:1009-15.
- Osterman P, Wide L (1976): The insulin tolerance test after pre-treatment with dexamethasone. *Acta Endocrinol* 83:341-56.
- Perowtka S (1985): Selective interaction of novel anxiolytics with 5HT_{1a} receptors. *Biol Psychiatry* 20:971-9.
- Rutherford O, White P (1991): Human quadriceps strength and fatigability in patients with post-viral fatigue. *J Neurol Neurosurg Psychiatry* 54:961-4.
- Sachar E, Finkelstein J, Hellman L (1971): Growth hormone responses in depressive illness. 1. Response to insulin tolerance test. *Arch Gen Psychiatry* 25:263-9.
- Schluederberg A, Straus S, Peterson P, et al (1992): Chronic Fatigue Syndrome Research: Definition and Medical Outcome Assessment. *Ann Intern Med* 117:325-331.
- Sharpe M, Archard L, Banatvala J, et al (1991): Chronic Fatigue Syndrome: Guidelines for Research. *JR Soc Med* 84:118-121.
- Wessely S, Powell R (1989): Fatigue Syndromes: a comparison of chronic 'postviral' fatigue with neuromuscular and affective disorders. *J Neurol Neurosurg Psychiatry* 42:940-948.
- White A, Smith H, Hoadley M, Dobson SH, Ratcliffe JG (1987): Clinical evaluation of a two-site immunoradiometric assay for adrenocorticotrophin in unextracted human plasma using monoclonal antibodies. *Clin Endocrinol* 26:41-52.