

Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome

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Abstract

The objective of this study was to evaluate and compare the basal circadian and pulsatile architecture of the HPA axis in groups of patients with FMS, CFS, or both syndromes with individually matched control groups. Forty patients with either FMS ($n = 13$), FMS and CFS ($n = 12$), or CFS ($n = 15$) were matched by age (18–65), sex, and menstrual status to healthy controls. Subjects were excluded if they met criteria for major Axis I psychiatric disorders by structured clinical interview (SCID). Subjects were admitted to the General Clinical Research Center where meals and activities were standardized. Blood was collected from an intravenous line every 10 min over 24 h for analysis of ACTH and cortisol. Samples were evaluable for ACTH in 36 subject pairs and for cortisol in 37 subject pairs. There was a significant delay in the rate of decline from acrophase to nadir for cortisol levels in patients with FMS ($P < .01$). Elevation of cortisol in the late evening quiescent period was evident in half of the FMS patients compared with their control group, while cortisol levels were numerically, but not significantly, lower in the overnight period in patients with CFS compared with their control group. Pulsatility analyses did not reveal statistically significant differences between patient and control groups. We conclude that the pattern of differences for basal circadian architecture of HPA axis hormones differs between patients with FMS and CFS compared to their matched control groups. The abnormalities in FMS patients are consistent with loss of HPA axis resiliency.

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1. Introduction

An enduring historical literature has described patients who report disabling physical symptoms such as musculoskeletal pain, fatigue, sleep disturbance, difficulties in concentration, and mood disturbances particularly depression and anxiety. Upon examination, these patients show no laboratory or radiographic abnormalities useful in clinical diagnostic assessment. Notable in their clinical presentation is the frequent report of symptom onset or exacerbation during periods of physical or emotional stress. Among these clinical conditions, fibromyalgia syndrome (FMS) and chronic fa-

tigue syndrome (CFS) have generated the most intense investigation. While the hallmark feature of FMS is pain, and of CFS, disabling fatigue, close examination reveals considerable symptom similarity between the two (Buchwald, 1996; Goldenberg et al., 1990). This propensity for symptom overlap has led many to speculate that FMS and CFS may represent clinical variants of the same process. However, some differences exist including an older mean age of patients with FMS compared with CFS (Buchwald, 1996).

We have previously proposed that the stress-responsive nature of both FMS and CFS provides an important clue to their proper understanding (Crofford and Demitrack, 1996). An individual's response to stress, either physical or emotional, includes activation of the hypothalamic–pituitary–adrenal (HPA) axis, which is

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accomplished via secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the paraventricular nucleus of the hypothalamus (Chrousos and Gold, 1992). Interaction of these neurohormones with specific receptors on corticotroph cells of the anterior pituitary trigger release of adrenocorticotropin (ACTH) which then stimulates secretion of cortisol from the adrenal cortex. In addition to its stress-dependent activation, the HPA axis exhibits a pronounced spontaneous near 24 h, or circadian, rhythm. In humans, this circadian rhythm is entrained to the light–dark and sleep–wake cycles (Czeisler, 1995). The trough of HPA axis activity occurs in the evening and peak activity normally occurs just before waking. Stress-induced secretion is superimposed on the basal circadian rhythm. There is evidence that the stress responsiveness and negative feedback regulation of the HPA axis varies across the day; hence specific alterations in the timing, intensity, and duration of any stress stimulus may result in widely varying patterns of HPA axis activity (Dallman et al., 1992). It is thought that under normal conditions the HPA axis may be a closed-loop system. Therefore, activation of cortisol secretion by stress results in a homeostatic correction ensuring that 24 h integrated cortisol levels are maintained in the normal range (Dallman et al., 1992).

Although alterations of HPA axis activity have been reported in both FMS and CFS, detailed examination of the studies addressing HPA axis function in these conditions has yielded inconsistent results. Furthermore, when taken in aggregate, previous data suggest differences in the characteristics of altered HPA function with hyperactivity of the axis in FMS and hypofunction in CFS (Crofford and Neeck, 2000). It is important to note that most studies of patients with FMS have not specifically excluded patients with CFS or provided information on the number of subjects with CFS included in the study. Particularly if the specific HPA axis alterations differ between patients that are pain-dominant or fatigue-dominant, these methodological issues may provide explanation for inconsistent findings.

Most, but not all, studies of FMS patients have reported increased daytime plasma or salivary cortisol levels (Adler et al., 1999; Catley et al., 2000; Crofford et al., 1994; Griep et al., 1998; McCain and Tilbe, 1989). Two studies reported low urine free cortisol levels (Crofford et al., 1994; Griep et al., 1998), while another reported normal urinary cortisol levels (Adler et al., 1999). Provocative tests have demonstrated normal or increased ACTH and blunted cortisol responses after injection of exogenous CRH, distinct from the findings in depressed patients (Crofford et al., 1994; Griep et al., 1993, 1998; Reidel et al., 1998). After insulin-induced hypoglycemia, one group reported a similar pattern to that of CRH-stimulation testing (Griep et al., 1993), but another group reported a normal pituitary–adrenal

response to hypoglycemia (Adler et al., 1999). Adler et al. (1999) reported a reduced ACTH/cortisol ratio in FM patients, but these same authors and Griep et al. (1998) reported a normal cortisol response to exogenous infusion of ACTH 1–24. There is currently no consensus as to the overall state of HPA axis activity in FMS.

In CFS, plasma and urine cortisol levels were reported as low (Demitrack et al., 1991). The ACTH response to CRH is blunted and cortisol response is normal or blunted (Demitrack et al., 1991; Scott and Dinan, 1998). Furthermore, the peak cortisol response to exogenous ACTH is blunted and adrenal gland size is diminished (Demitrack et al., 1991; Scott and Dinan, 1998; Scott et al., 1999). The majority of studies are consistent with hypoactivity of the HPA axis, though whether this occurs as a result of a central or peripheral abnormality is not known.

We and others have proposed that disruption in the integrity of the HPA axis may be a proximate cause of many of the somatic, cognitive, and emotional symptoms that characterize patients with either FMS or CFS (Chrousos and Gold, 1992; Crofford and Demitrack, 1996; Clauw and Chrousos, 1997; Sternberg, 1993). We hypothesized that analysis of the basal pulsatile and circadian architecture of ACTH and cortisol would clarify abnormalities of the HPA axis in patients with FMS, CFS, or both disorders. In order to characterize the detailed basal function of the HPA axis, we studied patients with either or both conditions, free of concurrent major psychiatric illness, who were individually matched for age, sex, and menstrual status to healthy, sedentary control subjects. Comparisons were made between the three mutually exclusive patient groups and their matched control groups. Comparisons between patient groups could not be made because of demographic differences. Because pituitary–adrenal hormones are secreted in a pulsatile manner with both circadian and ultradian circadian rhythmicity, we employed a technique of intensive, frequent, discrete blood sampling across the 24-h hormonal cycle to characterize fully basal ACTH and cortisol secretion.

2. Methods

2.1. Subjects

All patients were recruited from rheumatology, infectious disease or primary care outpatient clinics at the University of Michigan Medical Center. One of three clinicians experienced in the diagnosis of FMS and CFS (LJC, NCE, and MAD) evaluated each patient. History and physical exam data were reviewed and consensus regarding patient diagnoses was reached among all clinicians. Diagnoses of FMS and/or CFS were made using 1990 American College of Rheumatology criteria and

1988 Center for Disease Control and Prevention, respectively (Fukada et al., 1994; Wolfe et al., 1990). Control subjects were recruited from community advertisements and University publications or bulletin boards. Control subjects were sedentary as defined by no regular exercise other than those involved in activities of daily living for a minimum of 2 months prior to study. Informed consent was obtained from both subject groups using documents approved by the University of Michigan institutional review board.

Subjects were between the ages of 18 and 65 years, non-smokers with a normal or near normal body habitus (BMI < 31), and no significant or unstable medical conditions other than FM and/or CFS. No subject engaged in shift work or traveled across more than 3 time zones within 3 months prior to study. Controls were also excluded if first degree relatives had a history of major depressive disorder (Holsboer et al., 1995). Subjects meeting study entrance criteria were referred for evaluation of psychiatric disorders by a structured clinical interview (SCID-II/III or SCID IV after this instrument became available). Any patient or control subject meeting criteria for major Axis I psychiatric disorders prior to study was excluded from further evaluation. In order to fully characterize the multidimensional behavioral accompaniments of these clinical conditions, additional symptom and functional assessments were performed using validated questionnaires. All subjects completed the profile of Mood states (POMS), the Pittsburgh Sleep Quality Index (PSQI), and the Arthritis Impact Measurement Scale (AIMS)-2, excluding the mood and level of tension scales.

Pregnancy tests, urine analysis, urine drug screen, TSH, CBC with platelets, and differential and basic metabolic profile (including electrolytes, renal and hepatic function tests) were performed or reviewed for all patient and control subjects. Significant abnormalities on these screening tests resulted in exclusion from further consideration for study.

Fifty-five patients were identified as potential study subjects. Fifteen of these were excluded due to SCID results indicating active Axis I psychiatric disorders ($n = 5$), inability to discontinue medication ($n = 4$), personal issues ($n = 3$), positive pregnancy test ($n = 2$), and positive urine drug screen ($n = 1$). Of the 60 control subjects screened for inclusion, 20 were excluded for reasons including personal issues ($n = 12$), abnormal lab results ($n = 3$), SCID results indicating active Axis I psychiatric disorder ($n = 2$), irregular menstrual cycling ($n = 1$), positive drug screen ($n = 1$), or inability to discontinue medication ($n = 1$).

Subjects were individually matched for sex and age ± 4 years except for one pair in which there was an 8-year age difference. Female subjects were matched by menstrual status (premenopausal, postmenopausal without estrogen replacement therapy (ERT), post-

menopausal with ERT) except that one 40 year old postmenopausal patient on ERT was paired with a 36 year old premenstrual control. All premenopausal subjects were studied during the follicular phase of the menstrual cycle (days 1–10).

Medications, including herbal remedies, were discontinued at least 10 days prior to study except stable doses of estrogen replacement therapy (ERT) or thyroid hormone. Fluoxetine was discontinued at least 2 months prior to study. No subject had received glucocorticoids in any form for 3 months prior to study and subjects receiving chronic glucocorticoids in any form were excluded. One subject was receiving a stable dose of anti-hypertensive medication (enalapril).

2.2. Sample collection

Twenty-four hour urine samples were collected on three consecutive days within 2 weeks of study and stored at 4°C. Subjects were admitted to the General Clinical Research Center (GCRC) on the evening prior to 24-h sampling in order to acclimate to the environment. Standard meals were provided at regular times (07:30, 12:00, and 17:30). During the procedure, subjects were required to rest quietly in a bed or chair and television or radio use was prohibited. A log recording subject activities was kept during study.

A large bore intravenous catheter was inserted into the antecubital or other large arm vein 1 h prior to the first blood draw. This was attached to a needleless double stopcock assembly with an intravenous line for withdrawal of samples. Intravenous fluids (0.45 saline) were infused between sample withdrawals to keep the catheter open and heparin (1000 U/liter) was added to fluids if blood return during sampling diminished. Blood withdrawals occurred every 10 min for 24 h beginning at 09:00. During overnight sampling, blood was drawn with the aid of a flashlight and nurses recorded whether the subjects were awake or asleep.

Samples (2.8 ml) were placed directly into a pre-chilled polypropylene tube with 250 μ l of 20 mg/ml of EDTA solution to prevent clotting and inhibit proteolytic activity. The sample was then capped, gently inverted, and placed on ice. All samples were spun at 2700 rpms for 10 min within 2 h of collection. Previous studies in our laboratories have validated the stability of ACTH and cortisol when samples remained on ice for up to 4 h. The plasma was aliquoted into labeled storage tubes and frozen at -80°C until assayed.

2.3. Hormone assay

ACTH assays were performed first, followed by cortisol. Samples were thawed and kept on ice throughout the assays. Plasma ACTH concentrations were measured in duplicate using a dual-immunoradiometric

assay that is highly specific for intact ACTH (Nichols Institute Diagnostics, San Juan Capistrano, CA). Plasma cortisol levels were quantified by radioimmunoassay (Coat-a-Count, Diagnostic Products Corporation, Los Angeles, CA). Steps were taken to minimize the effect of error in both assays. All samples were run as case-control pairs on the same day using kits from the same lot. During assay the patient and control tubes were arranged side by side. The addition of trace with a repeater was done in a snaking patterning, weaving back and forth between the two groups to avoid repeater-error affecting one group more than another. In addition, counting drift was minimized by rotating between patient and control tubes while loading the gamma counter.

Sensitivity for ACTH assays is calculated at 1 pg/ml while sensitivity for cortisol assays is at 0.2 µg/dl. Inter-assay variability, 6.60% for ACTH and 3.53% for cortisol, was ascertained from internal control plasma samples used in every assay. Intra-assay variability for ACTH and cortisol assays was 7.19 and 6.45%, respectively.

2.4. Pulsatility and statistical analysis

The ACTH and cortisol were analyzed for 72 subjects (36 patients and 36 age-matched controls). There was one additional pair for cortisol (a total of 74 subjects). The data for three pairs were excluded due to an excess of missing data or significant and prolonged hormone elevations due to unusual circumstances during the study period (vomiting or excessive needle relocations). Missing values were linearly interpolated unless the value at the time point following the missing value was high, in which case the value preceding the missing value was substituted in order to avoid a pseudo pulse. In three subjects some data were replaced by interpolated values due to localized circumstances (e.g., hormone peak at the time of needle relocation as noted in study logs). Except in five cases where the series were truncated due to missing terminal data, all 144 points were used in the analysis, and in these cases the parameter estimates, e.g., number of pulses, were rescaled to 24 h. To reduce the influence of outliers in the pulsatility analysis, the upper and lower 20% of values were removed in order to calculate the mean (also called a 20% trimmed mean).

The 144 time points of observation were broken into six pre-determined 4-h intervals for analysis: 22:00–1:50, 2:00–5:50, 6:00–9:50, 10:00–13:50, 14:00–17:50, and 18:00–21:50. These times were chosen to assure that the first time period would overlap the expected end of the quiescent period since patients with major depressive disorder often display an early rise of cortisol (Sachar et al., 1973). The area under the curve (AUC) was computed using the trapezoidal rule for each period. ACTH and cortisol means, standard errors, minimums,

and maximums were calculated on both the original and log (base e) scales. A repeated measures analysis of variance (ANOVA) on the logged data was used to test the difference in mean hormone level over time between patients and controls both as a whole and within diagnostic subgroups.

The cortisol quiescent period onset and offset were determined using the method described by Van Cauter et al. (1996). A paired *t* test was used to detect differences between cases and controls.

Evidence for hormonal pulse activity was approached with a recently validated algorithm, Smoothing Baseline Plus Pulses (SBPP), which allows for a changing baseline (Guo et al., 1999; Young et al., 2001). This algorithm identifies every time point at which there is significant secretion. The fitted parameters from the analyses consist of average baseline, number of secretory episodes, average amplitude, and hormone half-life. Half-life, total secretion, average amplitude, and average baseline were log (base e) transformed and the number of secretory episodes was square root transformed prior to analyses with a paired *t* test.

All behavioral measures were compared across groups using ANOVA with post hoc Bonferroni comparisons as indicated. Individual comparisons between patient groups and their individually matched controls were performed using paired *t* tests.

3. Results

3.1. Subject characteristics

Clinical characteristics of the study groups are reported in Table 1. CFS patients were younger and had a shorter duration of illness than patients with FMS.

Current and past psychiatric diagnoses in the mood and anxiety disorders realm are reported in Table 2. Current diagnoses in the anxiety disorders classification included only specific or social phobias and one patient with sub-threshold panic disorder which were not exclusionary. These anxiety disorders occurred in both patients and control subjects in all three groups. There is little data by which one could determine if these disorders could affect HPA axis evaluation. Past psychiatric diagnoses were notable for a higher rate of lifetime mood and anxiety disorders in patients. The observed prevalence is also higher than that expected from the known lifetime prevalence of these illnesses in the general population. There was no past history of substance abuse in any patient.

The nosologic category of the somatoform disorders, specifically somatoform pain disorder and undifferentiated somatoform disorder, are phenomenologically indistinguishable from the definitions for CFS and FMS. Therefore, classification into these diagnoses was not

Table 1
Clinical characteristics of study subjects^a

		Age (years)	Illness duration (months)	% Female	Number of tender points	Menstrual status		
						% Pre	% Post w/ERT	% Post w/o ERT
FM	Patient (n = 13)	49.8 ± 5.4	211.5 ± 175.6	100	14.5 ± 2.0	38.5	46.2	15.4
	Control (n = 12)	51.0 ± 5.03	N/A	100	0.917 ± 1.8	41.7	41.7	16.7
FM and CFS	Patient (n = 12)	37.4 ± 13.7	58.3 ± 34.4	100	14.67 ± 2.0	66.7	25.0	8.3
	Control (n = 12)	37.75 ± 10.8	N/A	100	0.833 ± 1.4	75.0	16.7	8.3
CFS	Patient (n = 15)	35.0 ± 8.7	35.9 ± 24.8	73.3	6.4 ± 3.9	90.9	0.0	9.1
	Control (n = 15)	35.1 ± 9.2	N/A	73.3	0.4 ± 1.1	90.9	0.0	9.1

^a Note that 1 FM patient was not matched, 1 FM pair and 1 CFS pair were not evaluable with regard to their hormone data, and 1 FM pair was evaluated for cortisol but not ACTH.

Table 2
SCID characteristics of study population

		Current diagnoses ^a		Past diagnoses	
		Anxiety (%)		Mood (%)	Anxiety (%)
FM	Patient (n = 13)	2 (15.4)		3 (23.1)	4 (30.8)
	Control (n = 12)	1 (8.3)		0	1 (8.3)
FM and CFS	Patient (n = 12)	1 (8.3)		2 (16.7)	1 (8.3)
	Control (n = 12)	1 (8.3)		0	1 (8.3)
CFS	Patient (n = 15)	3 (20.0)		3 (20.0)	3 (20.0)
	Control (n = 15)	1 (6.7)		0	2 (13.3)

^a Current anxiety disorders were simple or social phobias or sub-threshold panic or generalized anxiety disorders. All current anxiety diagnoses were also present in the past and some patients had panic disorder in the past.

considered useful for estimation of the prevalence of current psychiatric disease burden. Nevertheless, 80% (32 of 40) patients met SCID criteria for these somatoform disorders. Two patients met criteria for somatization disorder (Briquet's syndrome), both in the FMS group. Analysis of FMS data with or without these patients (and their matched controls) did not alter the results.

For all the behavioral instruments, scores on total and most sub-scale measures were, as expected, significantly different from the values obtained in the healthy control group. For the POMS, all values were significantly different between patient and control groups ($P < .01$). Additionally, ANOVA with Bonferroni post hoc tests revealed a significant difference between the FM and CFS patient groups (27.23 ± 7.63 vs. 56.13 ± 7.32 , $P < .05$). The PSQI was applied to determine the degree of impaired sleep (Buysse et al., 1991). All subject groups were significantly ($P < .001$) different than their controls, but not significantly different from each other (FMS, 10.1 ± 1.03 ; FMS/CFS, 8.50 ± 1.06 ; CFS, 9.4 ± 1.34 ; all controls combined, 3.23 ± 0.42). The physical component (using normalized scale scores) of

the AIMS-2 demonstrated significant ($P < .005$) functional impairment for all subject groups compared with controls. Again, there were no significant differences among subject groups (FM, 1.77 ± 0.41 ; FM/CFS, 2.18 ± 0.42 ; CFS, 2.60 ± 0.29 ; all controls combined, 0.11 ± 0.05).

3.2. Mean cortisol and ACTH

For all patient and control groups there was a significant interaction between hormone level and time period for both ACTH and cortisol with the usual circadian variation, i.e., levels increasing in the early morning and decreasing thereafter (Figs. 1 and 2). Examination of group by time interaction identified a significant decrease in the rate of decline from acrophase to nadir for cortisol levels in patients compared with their controls, particularly striking for the FMS patient group ($P < .01$) (Fig. 2A). In the early morning periods, there were several hours (05:00–07:00) where patients with CFS had numerically lower (but non-significant) cortisol levels compared with their controls (Fig. 2C). Patients with both FMS and CFS had evening and early morning

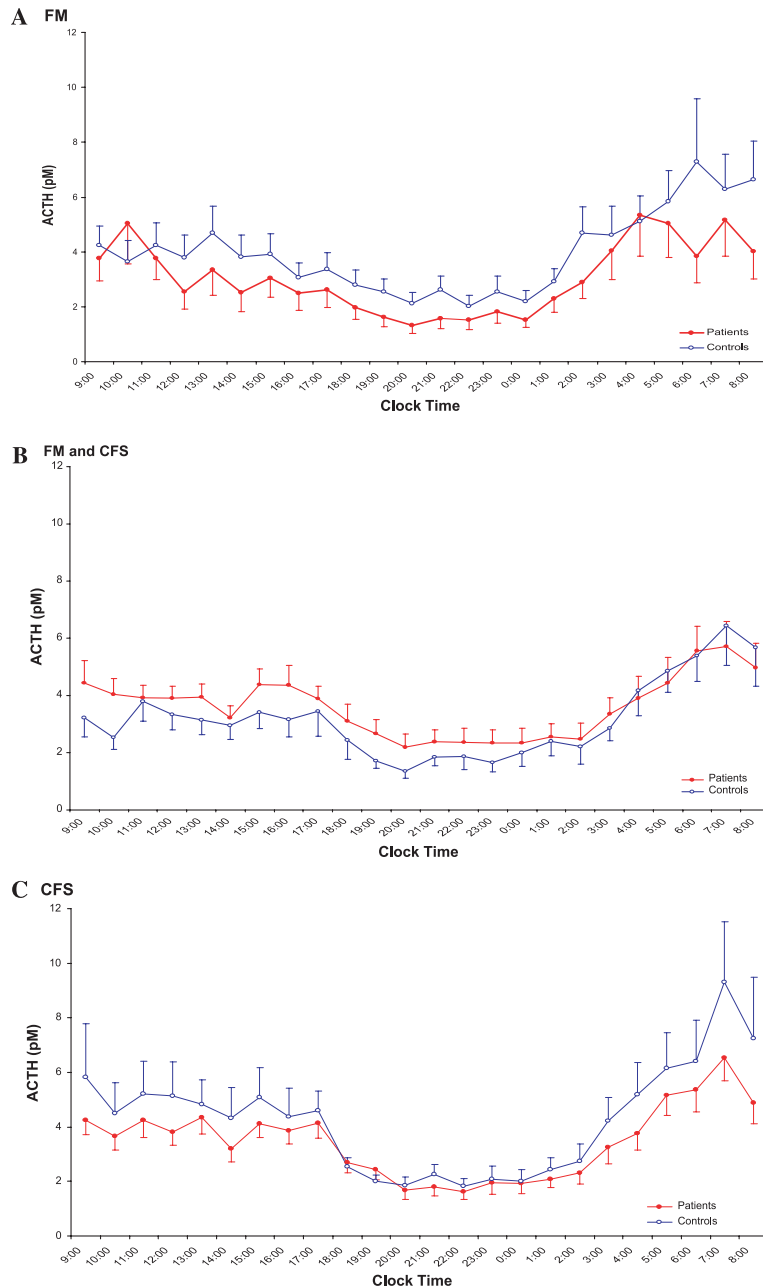


Fig. 1. Mean basal ACTH levels in patients with FM (A), FM, and CFS (B), and CFS (C). Symbols (filled, patients and open, controls) represent the average levels over 1 h (6 samples per subject). It should be noted that averaging eliminates the discrete pulses seen in individual subjects. There were no significant differences between patients and controls.

values intermediate to patients with either diagnosis alone (Fig. 2B).

There were no significant differences between patient and control groups for mean ACTH or cortisol over the entire 24-h period or in any given time period. However, 24-h mean cortisol levels greater than 10 $\mu\text{g}/\text{dl}$ have been considered elevated, though there is clearly a continuum among normal subjects affected by age and gender. Of the 11 women with FMS studied, 5 (45%) had levels above 10 $\mu\text{g}/\text{dl}$ compared with 2/11 (18%) of the matched control group. There was no difference between

women with CFS (2/10, 20%) or those with both FMS and CFS (1/12, 8%) and their respective control group (1/10, 10% and 1/12, 8%, respectively).

Effects of hormonal status were also detected. Pre-menopausal women of all groups had the lowest cortisol levels, while postmenopausal women on HRT had the highest levels. Male patients and their healthy controls had higher cortisol levels overall, with 2/4 in each group reaching levels higher than 10 $\mu\text{g}/\text{dl}$. These gender differences are consistent with data reported by Van Cauter et al. (1996).

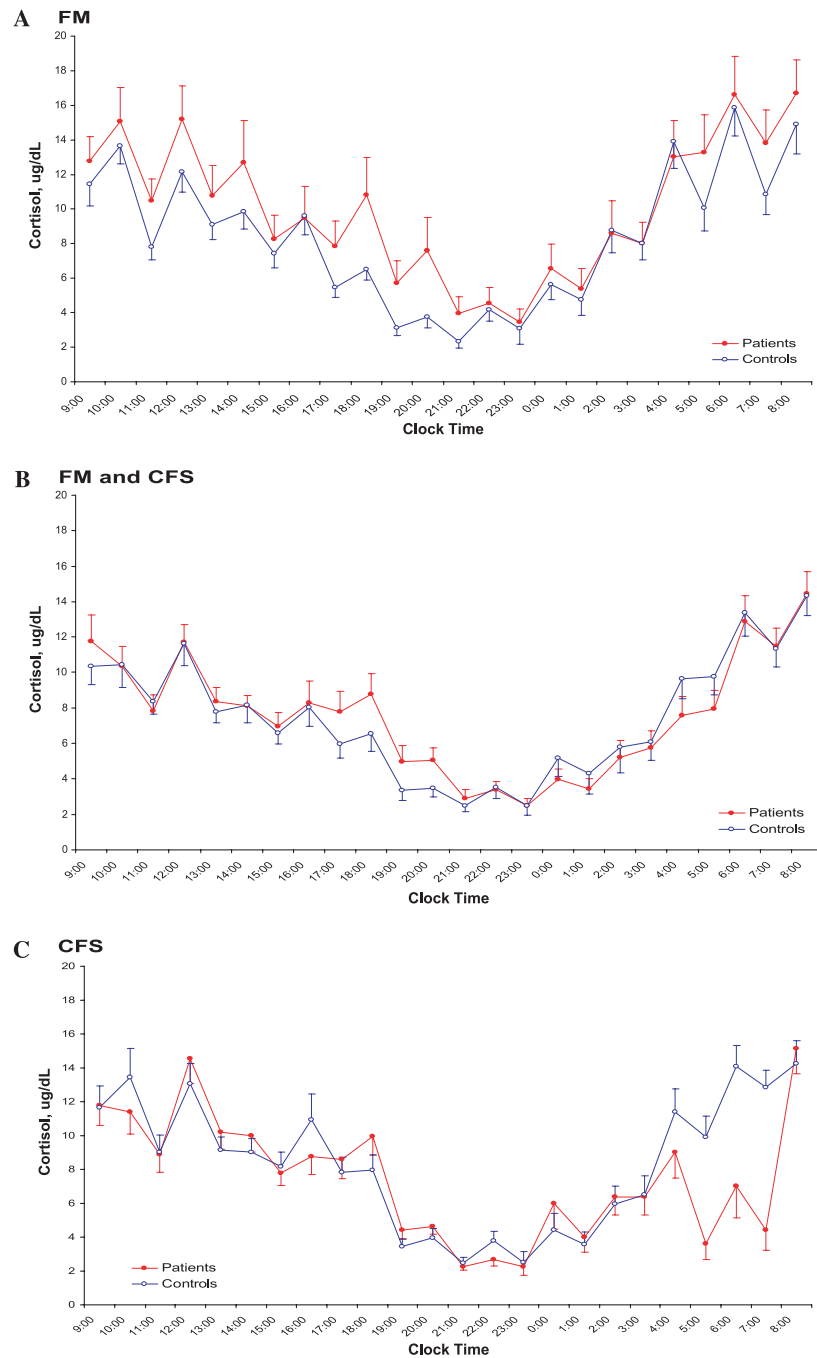


Fig. 2. Mean basal cortisol levels in patients with FM (A), FM and CFS (B), and CFS (C). Symbols (filled, patients and open, controls) represent the average levels over 1 h (6 samples per subject). It should be noted that averaging eliminates the discrete pulses seen in individual subjects. In (A and B), the delayed decline of cortisol from acrophase to nadir in patients compared with controls can be appreciated (18:00 to 21:00 clock time), though the finding is less well appreciated in patients with both FM and CFS. In (C), depressed cortisol levels in the early morning (05:00 to 07:00 clock time) can be appreciated.

Mean (3 collections) urinary free cortisol levels were available in a subset of patients. There were no significant differences between FMS patients ($n = 6$; 92.5 ± 19.4 nmol/24 h, mean \pm SE) and controls (100.3 ± 25.7 nmol/24 h), FMS/CFS patients ($n = 9$; 89.7 ± 15.7 nmol/24 h) and controls (106.3 ± 15.7 nmol/24 h) or CFS patients ($n = 9$; 148.7 ± 25.5 nmol/24 h) and controls (116.9 ± 16.0 nmol/24 h).

3.3. ACTH:cortisol ratios

We determined the mean ACTH to cortisol ratios for each subject using values for ACTH at time = x and values for cortisol at time = $x + 10$ min. Ratios changed over time with increased ratios during the nadir of the circadian rhythm in most subjects. There were no significant differences between patient and control groups

for mean ACTH:cortisol ratios. The ratios did not correlate with history of major depressive disorder or anxiety disorders. Ratios also did not correlate significantly with hormonal status or age.

3.4. Acrophase, nadir, and quiescent periods

In the analysis of the log (base e) maximum amplitude (difference between acrophase and nadir) for ACTH, there were no significant differences (Table 3). However, in the analysis of the time at which the maximum occurred, there was a difference between cases and controls ($P < .05$) with patients' maximum amplitude occurring at a later time than controls. This difference is, however, hard to interpret since we did not control for habitual bedtimes. This difference did not depend on specific diagnosis. For cortisol, there were no significant differences in maximum amplitude or the time at which the maximum occurred.

We adopted the definition of Van Cauter et al. (1996) to identify the cortisol quiescent period onset as six consecutive samples below $5 \mu\text{g}/\text{dl}$ and offset as six consecutive samples above $5 \mu\text{g}/\text{dl}$. Table 4 shows the mean onset and offset of the quiescent period for cortisol. Of the 11 patients with FM, 5 never met criteria for a quiescent period. Of the remaining patients, 1 other had a markedly shortened quiescent period and 5 had

prolonged quiescent periods, accounting for the early onset and late offset compared with the FM controls as seen in Table 5. Patients with both FM and CFS also had a delayed quiescent period offset ($P < .05$).

3.5. Pulsatility analysis

The summary measures for ACTH and cortisol using the SBPP algorithm are given in Tables 5 and 6, respectively. There were no significant differences for any summary measures of ACTH or cortisol, including the number or amplitude of secretory episodes, hormone half-life, or average baseline. There was a trend toward a higher average cortisol baseline in patients with FM compared with their matched controls ($P = .056$).

4. Discussion

This study was designed to examine the hypothesis that patients with FMS, CFS, or both disorders exhibit baseline alterations of pituitary–adrenal function. There have been no previous studies in which patients with FMS, CFS, and FMS/CFS were examined separately using the same experimental design and conditions. We cannot directly compare patients groups, only the

Table 3
Circadian characteristics of ACTH and cortisol secretion

		ACTH		Cortisol	
		Acrophase ^a	Amplitude	Acrophase	Amplitude
FM ^b	Patients ($n = 10/11$)	07:40 ± 66.2 (min)	4.26 ± 0.83	08:13 ± 48.7 (min)	12.65 ± 1.38
	Controls ($n = 10/11$)	06:48 ± 35.9	4.66 ± 0.89	07:35 ± 47.5	10.94 ± 0.73
FM/CFS	Patients ($n = 12$)	09:48 ± 76.3	3.97 ± 0.49	08:31 ± 32.8	10.23 ± 1.10
	Controls ($n = 12$)	07:15 ± 45.1	4.81 ± 0.72	07:48 ± 25.2	10.40 ± 0.87
CFS	Patients ($n = 14$)	07:10 ± 20.4	4.48 ± 0.38	07:45 ± 28.6	12.03 ± 0.83
	Controls ($n = 14$)	06:37 ± 23.1	6.99 ± 2.00	07:56 ± 37.0	12.71 ± 1.01

^a Acrophase delayed in patients vs. controls $P < .05$ in all groups.

^b Ten patients with FM evaluable for ACTH, 11 for cortisol.

Table 4
Quiescent period for cortisol

		Onset (Mean clock time ± SEM in minutes)	Offset (mean clock time ± SEM in minutes)
FM	Patients ($n = 6$) ^a	17:00 ± 64	02:30 ± 50 ^b
	Controls ($n = 6/11$)	18:40 ± 20/19:00 ± 20	01:20 ± 45/00:50 ± 32
FM/CFS	Patients ($n = 12$)	19:50 ± 30	03:20 ± 25 ^b
	Controls ($n = 12$)	18:10 ± 50	02:30 ± 25
CFS	Patients ($n = 14$)	19:40 ± 23	02:20 ± 34
	Controls ($n = 14$)	19:10 ± 12	02:30 ± 30

^a Five of 11 patients with FM never met criteria for entering a cortisol quiescent period (Van Cauter et al., 1996). Data for controls given for both individually matched controls and for the entire group.

^b Significantly delayed compared with individually matched controls $P < .05$.

Table 5
SBPP summary data for ACTH (mean \pm SE)

		Secretory episodes	Avg. amplitude (pM)	Avg. baseline (pM)	Half-life (min)	Total AUC	AUC pulses
FM	Patients (n = 10)	22.0 \pm 5.5	3.1 \pm 0.9	1.8 \pm 0.4	21.7 \pm 3.7	4412 \pm 789	1885 \pm 471
	Controls (n = 10)	28.0 \pm 3.3	2.1 \pm 0.3	2.4 \pm 0.4	22.3 \pm 3.3	5705 \pm 911	2215 \pm 409
FM/CFS	Patients (n = 12)	26.6 \pm 3.7	1.8 \pm 0.3	2.2 \pm 0.3	30.6 \pm 7.7	5191 \pm 512	1954 \pm 218
	Controls (n = 12)	25.1 \pm 3.1	2.0 \pm 0.3	1.8 \pm 0.3	31.2 \pm 5.2	4928 \pm 690	2306 \pm 326
CFS	Patients (n = 14)	35.2 \pm 3.0	1.4 \pm 0.2	1.8 \pm 0.2	27.7 \pm 2.3	5347 \pm 584	2833 \pm 428
	Controls (n = 14)	29.3 \pm 2.6	1.9 \pm 0.4	2.4 \pm 0.5	27.1 \pm 3.6	6126 \pm 1198	2701 \pm 531

Table 6
SBPP summary data for cortisol (mean \pm SE)

		Secretory Episodes	Avg. Amplitude (μ g/dl)	Avg. Baseline (μ g/dl)	Half-life (min)	Total AUC	AUC pulses
FM	Patients (n = 11)	39.6 \pm 3.2	3.2 \pm 0.5	4.1 \pm 0.8*	35.4 \pm 3.2	14,549 \pm 1786	8564 \pm 1412
	Controls (n = 11)	40.1 \pm 4.0	3.1 \pm 0.4	2.8 \pm 0.4	40.6 \pm 6.1	12,166 \pm 763	8402 \pm 1010
FM/CFS	Patients (n = 12)	43.9 \pm 6.3	2.4 \pm 0.3	3.0 \pm 0.3	37.9 \pm 3.5	10,964 \pm 679	6661 \pm 790
	Controls (n = 12)	47.6 \pm 4.1	2.3 \pm 0.2	2.4 \pm 0.4	40.6 \pm 5.1	10,715 \pm 682	7212 \pm 677
CFS	Patients (n = 14)	45.5 \pm 4.1	3.3 \pm 0.4	3.1 \pm 0.5	32.3 \pm 4.6	11,930 \pm 684	7575 \pm 876
	Controls (n = 14)	46.3 \pm 3.9	2.6 \pm 0.1	2.7 \pm 0.4	37.8 \pm 3.6	11,882 \pm 663	8086 \pm 636

* $P = 0.56$ compared with matched controls.

manner in which they differ from controls, due to group differences in age, gender, and hormonal status.

An identifiable circadian rhythm was preserved in all groups of patients and controls. However, there were differences between patients and control subjects with respect to the circadian changes of ACTH and cortisol levels. There was a delay in the decline of cortisol in all patients groups compared with their controls (significant group \times time interaction). These alterations of cortisol secretion were most evident in patients with FMS, resulting in elevated evening cortisol levels in accordance with previously published data (Crofford et al., 1994; McCain and Tilbe, 1989). In fact, half of the FMS patients never met criteria for a quiescent period. Rather than being due to an increase in number or amplitude of pulses, elevated cortisol levels were accounted for by the non-pulsatile baseline component.

Although this study was not designed to directly compare patients with FMS and CFS, the pattern of circadian change in each patient group compared with their controls was different in some respects. The elevated quiescent period cortisol levels in patients with

FMS were not evident in CFS patients and blunted in those patients with both FMS and CFS. On the other hand, depressed early morning cortisol levels in CFS patients were not evident in the FMS patients and were intermediate in patients with both FMS and CFS. These data suggest that while HPA axis physiology may be altered in both FMS and CFS, the specific changes may be different. These data indicate that precise definition of the patient population is required to compare studies. Failure to control for, or stratify by, the presence of debilitating fatigue (as required in the definition of CFS), may be responsible for some of the differences in reported HPA axis function in the literature for FMS.

One interpretation of basal hypercortisolemia with lack of circadian variation is decreased resiliency of the HPA axis. That is, there is a decreasing ability of the HPA axis to return to baseline after a challenge (Sapolsky et al., 1986). During our study, meals represent a physiologic stimulus to activation of the HPA axis as previously reported (Follenius et al., 1982). Increased quiescent period cortisol levels in our FMS patients could represent prolonged secretion, or loss of resiliency

after physiologic stimulation of the axis related to meals or other activities. Daytime pain could also stimulate HPA axis activity leading to elevated cortisol levels. Supporting the association between musculoskeletal pain and elevated cortisol levels, a study from Korszun et al. (2002) demonstrated elevated daytime cortisol levels in patients with temporomandibular disorder whose pattern was similar to patients with FMS. It is also plausible that the elevated cortisol in the quiescent period reflects diminished function of the mineralocorticoid receptor thought responsible for controlling HPA axis activity, particularly during the circadian nadir (Arvat et al., 2001). It has recently been reported that changes in mineralocorticoid receptor function contribute to altered negative feedback in the elderly (Otte et al., 2003).

Of the 7 patients with a previous history of MDD in whom hormone data were evaluable, 3 (43%) had elevated mean cortisol levels (>10 mg/dl). In previous studies of actively depressed patients, only a subset of patients (22–23%) manifest elevated baseline cortisol levels (Halbreich et al., 1985; Young et al., 2001). The study from Young et al. (2001) was performed using the same methodology as the study reported here. In that study, there were no significant differences in basal cortisol levels comparing depressed patients with matched control subjects as a group. In that study, only 6 of 23 patients showed elevated mean serum cortisol levels (>9.7 mg/dl). The patients with increased cortisol levels also had elevated ACTH levels suggesting, as in our study, that elevated cortisol is a consequence of elevated ACTH.

The pulsatility analysis revealed no significant differences in either the number or amplitude of ACTH and cortisol pulses between patient and control groups. There was a suggestion that the fewer ACTH pulses in FM patients compared with controls reflect the influence of a subgroup of patients. We had expected, but did not observe, alterations in the pulse frequency or amplitude in the patients with CFS. In depressed patients, older pulse detection algorithms found increased ACTH pulses (Deuschle et al., 1997; Mortola et al., 1987). Only one study reports increased numbers of cortisol pulses in depressed patients (Deuschle et al., 1997). While others found no differences between depressed patients and controls (Linkowski et al., 1985; Mortola et al., 1987; Young et al., 2001).

Our findings differ from the study of Klerman et al. (2001), who found no differences in the circadian variation of cortisol in patients with FMS. There are several possible explanation for these differences. First, the presence or absence of CFS was not reported in that study. Second, the aim of that study was to evaluate circadian phase using a protocol that eliminated environmental cues, so was performed under a 40-h constant condition. It is plausible that the altered levels of cortisol

in our study are accounted for by responses to environment stimuli such as meals, sleep or activity-dependent symptoms that were eliminated by Klerman et al. (2001).

In summary, we confirmed elevated evening plasma cortisol levels in patients with FMS compared with matched normal control subjects, a finding that is blunted in patients with concomitant CFS. Similarly, low early morning plasma cortisol levels in patients with CFS are normalized in patients also meeting criteria for FMS. A neuroendocrine subgroup of patients with FMS was identified on the basis of an absent or markedly shortened quiescent period. The etiology of elevated evening cortisol levels in these FMS patients is uncertain. However, we hypothesize that FMS may approximate HPA axis physiology in normal aging where the primary disorder is thought to be a loss of resiliency of the HPA axis after activation (Seeman and Robbins, 1994). Activation of the HPA axis in this and other studies of FMS patients could be physiologic (e.g., meals) or pathologic (musculoskeletal pain). Loss of resiliency is consistent with the hypothesis of wear and tear related to lifelong exposure to stress, perhaps due to hippocampal defects in feedback inhibition that may be mediated by diminished mineralocorticoid receptor function (Otte et al., 2003; Van Cauter et al., 1996). Patients with FMS may exhibit similar physiology, but advanced relative to their chronological age due to increased exposure to daily stress. Loss of resiliency could account for some of the cognitive and sleep disorders observed in patients with FMS (Born et al., 1989; Holsboer et al., 1988; Lupien et al., 1994; McEwen and Sapolsky, 1995). The hypothesis that the HPA axis is hypoactive in patients with CFS is suggested by low early morning plasma cortisol levels. However, we did not find evidence of decreased pulse frequency or amplitude suggesting hypoactivity of the central components of the axis.

These data, taken together with previous findings, further strengthen the concept that there are biologic similarities and differences between patients with FMS, whose predominant complaint is pain, and those with CFS and debilitating fatigue (Crofford and Neeck, 2000). Both are associated with perturbations of HPA axis physiology, yet there are subtle qualitative differences in the specific findings. Our data may have clinical implications for the treatment of patients with FMS and CFS, with certain treatments being possibly more effective in patients with different symptoms and neuroendocrine profiles.

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