ORIGINAL ARTICLES

Cortisol Regulation in Posttraumatic Stress Disorder and Major Depression: A Chronobiological Analysis

Rachel Yehuda, Martin H. Teicher, Robert L. Trestman, Robert A. Levengood, and Larry J. Siever

The aim of the present study was to evaluate the pattern of basal cortisol release in PTSD and major depression using a chronobiological analysis. Plasma for cortisol determination was obtained from 15 combat veterans with PTSD, 14 subjects with major depression, and 15 normal men every 30 min during a 24-hour period of bed rest. Raw cortisol data were modeled using standard and multioscillator cosinor models to determine the best fitting functions for circadian, hemicircadian, and ultradian components of cortisol release. PTSD subjects had substantially lower cortisol levels, and displayed a pattern of cortisol release that was better modeled by circadian rhythm. PTSD subjects also showed a greater circadian signal-to-noise ratio than the other groups. In contrast, depressed patients displayed a less rhythmic, more chaotic pattern of cortisol release. The pattern of cortisol secretion and regulation observed in the PTSD group under baseline conditions may reflect an exaggerated sensitization, whereas the chronobiological alterations in depression may reflect dysregulation, of the hypothalamic–pituitary–adrenal (HPA) axis.

Key Words: Posttraumatic stress disorder, major depressive disorder, cortisol, hypothalamic–pituitary–adrenal axis, circadian rhythm, sensitization, biological clocks

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Introduction

In contrast to the hypercortisolism associated with major depressive disorder (Gold et al 1988; Stokes and Sikes 1987), individuals with posttraumatic stress disorder (PTSD) show a lower mean basal 24-hour urinary cortisol excretion compared to normals (Yehuda et al 1990) and other psychiatric patients (Mason et al 1986; Yehuda et al 1993a). Furthermore, a larger number of lymphocyte glucocorticoid receptors (Yehuda et al 1993a and b; Yehuda 1991) and an enhanced suppression of cortisol following oral dexamethasone administration (Yehuda et al 1993c, provisionally accepted) have been observed in PTSD, whereas patients with major depression have a smaller number of glucocorticoid receptors on lymphocytes (Yehuda 1993a; Lowy et al 1989; Whalley et al 1986; Gormley et al 1985), and display a blunted cortisol response to dexamethasone (APA Task Force 1987; Carroll et al 1981) compared to normals.

From the Post-Traumatic Stress Disorder Program and Mood and Personality Disorder Program of the Psychiatry Department at Mount Sinai School of Medicine and Bronx Veterans Affairs, New York, New York (RY, RLT, RAL, LJS); and Developmental Biopsychiatry and Clinical Chronobiology Program, McLean Hospital, and Department of Psychiatry, Harvard Medical School, Boston, Massachusetts (MHT).

Address reprint requests to Rachel Yehuda, PhD, Bronx Veterans Affairs—116/A, 130 West Kingsbridge Road, Bronx, NY 10468.

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Together, these data suggest that in addition to the classic pattern of augmented hypothalamic–pituitary–adrenal (HPA) axis responses to stress, there may be a contrasting paradigm of cortisol abnormalities following stress, characterized by diminished cortisol levels as a result of a stronger or more sensitive negative feedback inhibition.

The aim of the present study was to further characterize the pattern of basal cortisol regulation in PTSD compared to that of major depression. Because cortisol release is strongly influenced by circadian and ultradian rhythms (Weitzman et al 1983), a chronobiological analysis was conducted to elucidate the intrinsic regulatory dynamics controlling cortisol levels under baseline conditions. Because of previous data demonstrating a stronger negative feedback inhibition in PTSD, we hypothesized that the chronobiological parameters generated by the analyses would demonstrate a pattern of cortisol regulation that would reflect a more sensitized neuroendocrine system. A sensitized system can be defined as one that is primed to respond more vigorously to the same or similar challenge (Post 1992). We hypothesized that a sensitized cortisol system in PTSD would be associated with a strengthening of the fundamental regulatory dynamic, reflected by a stronger circadian pattern, a greater signal-to-noise ratio (i.e., reflecting less random fluctuations), and a resultant decrease in basal cortisol levels secondary to the enhanced regulation. In contrast, biological systems in major depression have been described as being dysregulated (Siever and Davis 1985). In a dysregulated system, there is down-regulation of control mechanisms leading to a diminished response of the system to endogenous signals (e.g., an attenuated negative feedback inhibition) (Siever and Davis 1985). We therefore expected the cortisol rhythms of depressed patients to show a weakening of the fundamental regulatory dynamic, reflected by a more noisy or chaotic secretory pattern (i.e., an attenuated circadian pattern with a poor fit of the actual cortisol levels to models of circadian rhythm), a lower signal-to-noise ratio, and possibly increased cortisol release secondary to the loss of negative feedback regulation.

Methods

Subjects

PTSD subjects were 15 combat Vietnam veteran outpatients (mean ± SD 44.0 ± 2.6 years) who were diagnosed by the consensus of three experienced clinicians based on scores from two structured diagnostic interviews, the Structured Clinical Interview for the DSM-III-R (Spitzer et al 1987) and the Clinician-Administered PTSD Scale (Blake et al 1990), and psychiatric and trauma history of the patient. Axis I diagnoses other than PTSD were made using Research Diagnostic Criteria with the Schedule for Affective Disorders and Schizophrenia (Spitzer et al 1978). Subjects with primary mood or anxiety disorder other than PTSD, psychotic disorder, or substance dependence within 6 months were excluded from this group. Depressed subjects were 14 male outpatients (49.5 ± 14.2 years) who did not meet criteria for PTSD or any other primary axis I disorder (mean Hamilton Depression Rating Scale score 29.46 ± 7.3). Fifteen normal male controls (47.5 ± 12.5 years) with no personal or family history of major psychiatric disorder were also recruited. All subjects were medically healthy by history, physical examination, and laboratory screens (including SMA-18, complete blood count with differential, glucose, blood urea nitrogen, creatinine, thyroid function tests, liver function tests, stool guaiac, chest x-ray, and electrocardiography). Subjects were medication free for at least 2 weeks and were maintained on a low-monoamine diet for at least 3 days prior to the start of the protocol.

Procedure

Subjects were admitted to the clinical research center on the evening preceding the test day and maintained on a standardized diet, with no food allowed from midnight until 6:00 PM the following day. At 8:00 AM on the morning of the study, an i.v. was inserted, and after a 2-hour adaptation period, blood samples were obtained every 30 min for a 24-hour period. Subjects were kept supine for the duration of the study. The sleep/wake status of each subject was recorded every 30 min. Blood samples were assayed for cortisol using radioimmunoassay (interassay coefficient of variation 4.0%).

Data Analysis

Raw cortisol data were modeled using standard and multioscillator cosinor models (Teicher and Barber 1990). The single oscillator model determined the best fitting 24-hour cosine function, and provided information on the amplitude, timing, and goodness-of-fit of this rhythm. The multioscillator model included additional cosine functions to evaluate ultradian (i.e., shorter nondiurnal) fluctuations in cortisol release, and included a 12-hour (hemicircadian) component that may represent the nonsinusoidal nature of the circadian rhythm, as well as the degree of rhythmicity of cortisol, and has been shown to enhance modeling of temperature (Czeisler et al 1989; Jewett et al 1991) and locomotor activity (Satlin et al 1991; Teicher et al 1993) rhythms. Initial analysis revealed that ingestion of the

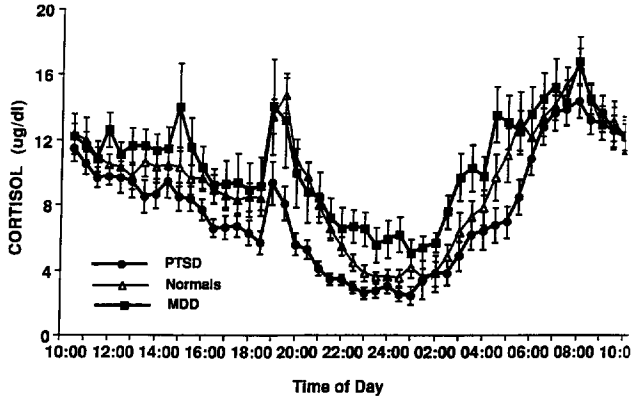

Figure 1. Plasma cortisol concentrations over the 24-hour diurnal cycle in posttraumatic stress disorder (PTSD), normal, and depressed subjects. Data represent the mean ± SD for 15 PTSD, 15 normal, and 14 depressed subjects.

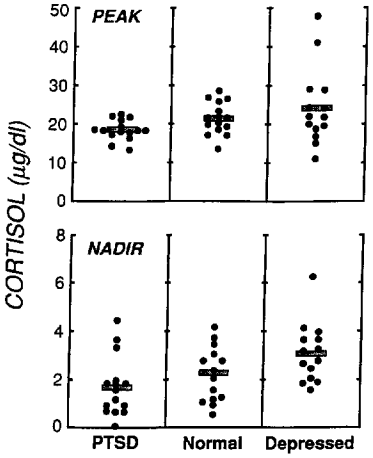

Figure 2. Plasma cortisol concentrations at the circadian peak and nadir of hormone release in posttraumatic stress disorder (PTSD), normal, and depressed subjects. Data represent the individual cortisol values for each subject at the highest (peak) and lowest (nadir) point of cortisol secretion during the 24-hour period. The shaded line indicates group means.

meal at 6:00 PM led to postprandial increases in cortisol in the three groups. To rule out that the chronobiological parameters generated by the analysis reflected an artifact of group differences in postprandial cortisol, the raw cortisol data were reanalyzed without the 6:30 PM and 7:00 PM time points. There were no significant differences in the chronobiological parameters whether these points were included or omitted from the analysis. The data presented below reflect analyses performed without the 6:30 PM and 7:00 PM postmeal cortisol time points.

Significant differences in raw cortisol values and chronobiological parameters between the three groups were determined using repeated measures analysis of variance (ANOVA) (group × time) and one-way ANOVAs, respectively, followed by tests of significance at each time point. Group differences in four sleep parameters were also evaluated by one-way ANOVA. Group differences between PTSD vs. normal, PTSD vs. depressed, and normal vs. depressed subjects were ascertained using *t* tests. All results occurring with a probability of less than .05 were considered significant.

Results

Figure 1 depicts the raw cortisol values for the three groups over the 24-hour period. Two-way repeated measures ANOVAs revealed main effects of group [$F(2,41) = 5.523$, $p < 0.01$] and time [$F(248,1968) = 36.91$, $p < .0001$], as well as a significant group × time interaction [$F(96,1968) = 1.328$, $p < .02$]. PTSD subjects had lower cortisol levels than normals in the late evening and early morning hours (i.e., between 16:00 and 22:30, and again at 00:30 and 04:30–05:00). Compared to the depressed group, PTSD subjects additionally had lower cortisol levels between 20:30 and 00:30, and between 02:30 and 05:00. Depressed subjects, in comparison to normals, had elevated cortisol levels predominantly between 22:00 and 24:00, 01:00 and 03:00, and at 04:00. When Bonferroni post hoc tests were used to correct for the number of comparisons made ($n = 49$), PTSD subjects were significantly different from normals (i.e., at $p < .002$) between 19:00 and 21:00, and significantly different from depressed subjects from 22:00 to 23:00 and at 04:00. Minimum and maximum cortisol levels corresponding to the nadir and peak of hormone release during the 24-hour period are depicted in Figure 2. ANOVA revealed a significant group difference for both nadir [$F(2,41) = 4.98$, $p = .01$] and peak [$F(2,41) = 3.10$, $p = .05$] cortisol levels, with depressed patients showing significantly higher nadir and peak hormone level compared to the other groups. Subjects in the PTSD and normal groups did not differ in peak or nadir cortisol levels. ANOVA also revealed a significant group difference in the amount of time that cortisol levels were below 5 µg/dL [$F(2,31) = 9.68$, $p = .0004$], with PTSD patients showing significantly more time spent in the nadir of cortisol secretion than subjects in the two other groups. Figure 1 also shows a significant rise in cortisol levels for all three groups at 18:30 compared with 18:00 [$F(1,41) = 33.17$, $p = .0001$], which likely reflected the ingestion of a light meal at 18:00. The lack of significant group × time interaction for this effect [$F(1,42) = .32$, not significant] indicated that the postmeal rise in cortisol was comparable for all three groups.

Table 1. Summary of Chronobiological Parameters

Parameters	PTSD (n = 15)	Normal (n = 15)	Depressed (n = 14)	$F(2,41)$	p value	PTSD vs. Normal	PTSD vs. Depressed	Normal vs. Depressed
Cosinor model								
Mesor	7.45 ± 1.69	9.06 ± 1.92	10.27 ± 3.04	5.64	0.007	0.02	0.004	ns
Circadian amplitude	4.89 ± 1.19	4.25 ± 1.05	4.61 ± 1.57	0.94	ns	ns	ns	ns
Circadian acrophase	09:32 ± 01:15	09:43 ± 01:29	09:49 ± 01:57	0.08	ns	ns	ns	ns
Circadian quotient (amplitude/mesor)	67.56 ± 16.92	47.74 ± 10.76	46.01 ± 14.41	10.74	0.0002	0.0005	0.001	ns
Goodness of fit (r)	0.788 ± 0.081	0.666 ± 0.117	0.670 ± 0.116	6.36	0.004	0.003	0.004	ns
Circadian error (% residual variance)	37.35 ± 12.55	54.38 ± 14.23	53.90 ± 13.89	7.58	0.002	0.002	0.002	ns
Multicosine model								
Mesor	7.49 ± 1.71	9.29 ± 2.00	10.37 ± 3.10	5.72	0.006	0.01	0.004	ns
Circadian amplitude	4.71 ± 1.23	4.25 ± 1.11	4.70 ± 1.67	0.57	ns	ns	ns	
Circadian acrophase	09:36 ± 01:17	09:54 ± 01:30	09:58 ± 03:01	0.14	ns	ns	ns	ns
Circadian quotient (amplitude/mesor)	64.89 ± 17.42	46.37 ± 9.60	45.93 ± 14.06	8.77	0.0007	0.001	0.003	ns
Hemicircadian amplitude	2.18 ± 0.96	3.09 ± 1.09	2.20 ± 1.56	2.68	0.08	0.02	ns	0.08
Hemicircadian acrophase	06:36 ± 01:37	06:22 ± 01:55	06:27 ± 02:05	0.06	ns	ns	ns	ns
Hemicircadian quotient	29.99 ± 12.72	33.69 ± 10.35	20.31 ± 11.59	5.1	0.01	ns	0.04	0.003
Ultradian amplitude	1.68 ± 0.86	2.03 ± 0.81	2.28 ± 0.95	1.56	ns	ns	0.10	ns
Ultradian frequency	5.35 ± 3.10	5.44 ± 2.32	4.37 ± 1.86	0.82	ns	ns	ns	ns
Ultradian quotient	23.09 ± 9.99	21.68 ± 5.67	21.96 ± 6.70	0.13	ns	ns	ns	ns
Goodness of fit (r)	0.902 ± 0.049	0.892 ± 0.032	0.831 ± 0.066	8.09	0.001	ns	0.003	0.004
Residual error (% variance)	18.41 ± 8.79	20.32 ± 5.71	30.39 ± 10.94	7.87	0.001	ns	0.003	0.004

PTSD = posttraumatic stress disorder; ns = not significant.

Results of the chronobiological analyses are summarized in Table 1. Cosinor analyses revealed significant group differences in a number of parameters including the mesor (mathematically corrected mean level of cortisol), amplitude of the circadian waveform, the circadian quotient (i.e., signal-to-noise ratio as reflected by the circadian amplitude corrected for differences in the mesor), and measures reflecting the quality of the fit of the data to the circadian model (i.e., goodness-of-fit correlation coefficient, and estimate of unexplained variance, or circadian error). The mesor was 22% lower in PTSD subjects than controls, and 38% lower compared to depressed subjects. The mesor in the depressed group was 13% higher than in normals. There were no significant group differences in the acrophase (time of circadian peak). In contrast, other parameters reflecting the quality of circadian rhythm revealed significant group differences between the PTSD and the other two groups. For example, the circadian quotient was 41% greater in the PTSD group compared to normals, and 47% greater than that of the depressed group. The circadian cosine model provided a substantially better fit to the data for PTSD than for either normal controls or depressed patients, as indicated by the significantly higher goodness-of-fit coefficients and the significantly smaller percentages of circadian error for PTSD compared to other groups. None of the parameters generated by the cosinor model differentiated the normal from the depressed group.

When data were fitted by the multioscillator model, group differences in circadian components were similar to those obtained using the single cosine model, in that PTSD patients continued to display a substantially lower mesor and greater circadian quotient compared to the two other groups. Multioscillator cosinor analysis provided a substantially better goodness-of-fit of the data to the model in all three groups as compared to the single oscillator model, and also allowed the detection of significant group differences on hemicircadian and ultradian parameters, providing even further discrimination between groups in regard to patterns of basal cortisol regulation (Table 1). For example, the hemicircadian amplitude was found to be 29% lower in PTSD patients compared to normals, and 29% lower in depressed patients compared to normals. Thus, depressed patients were comparable to PTSD patients in failing to demonstrate a normal hemicircadian amplitude. On the other hand, there was a nonsignificant trend for depressed patients to have a higher ultradian

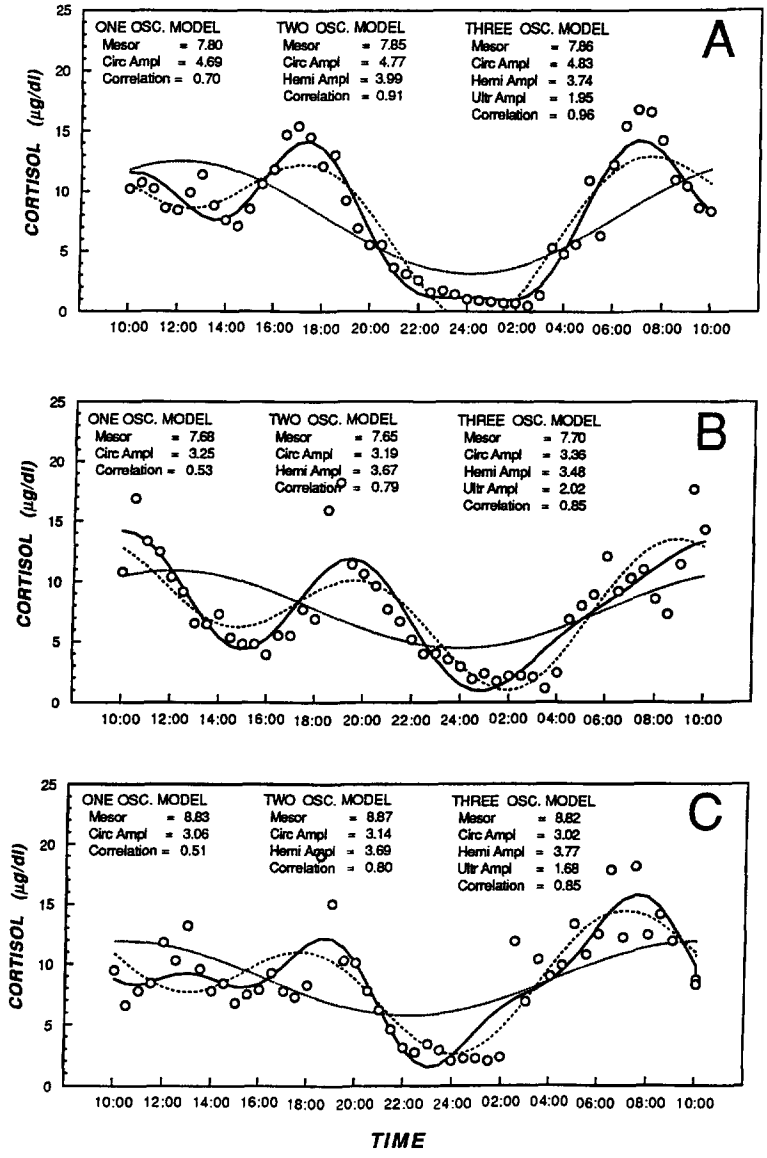

Figure 3. Time-series data of three individual normal controls representing single- and multioscillator cosinor modeling of raw cortisol values over the 24-hour period. The dotted line represents the fit provided by the one-oscillator model, the hatched line represents the fit provided by the two-oscillator model, and the solid line represents the curve provided by the three-oscillator model.

amplitude than PTSD patients, whereas neither depressed nor PTSD patients were substantially different on this measure compared to normals. Depressed patients also showed a substantially lower circadian, hemicircadian, and ultradian quotient compared to patients with PTSD, reflecting a significantly more chaotic or noisy pattern of cortisol release in the former group. Finally, the multioscillator cosine analysis allowed the detection of significant differences between the depressed and normal groups in goodness-of-fit and residual error parameters. It was observed that the overall fit of the data was significantly worse in the depressed patients than in the controls and PTSD subjects, likely reflecting a weakening in the amplitude or temporal pattern of the intrinsic rhythm, or diminished regulation allowing for more random fluctuations.

Figure 3 depicts representative time series of cortisol values from three normal men, and illustrates the nature of the estimated fit of these data by the different cosinor models. In all three examples, the multioscillator cosinor model provided a better fit (correlation) of the raw cortisol data compared with the cosinor analysis. Other features of the normal pattern of cortisol secretion, such as the presence of a hemicircadian pattern of cortisol release in addition to the normal diurnal (i.e., circadian) pattern, can also be readily observed. Figure 4 depicts similar time-series data for three representative PTSD patients. These examples show that the raw cortisol data are well modeled

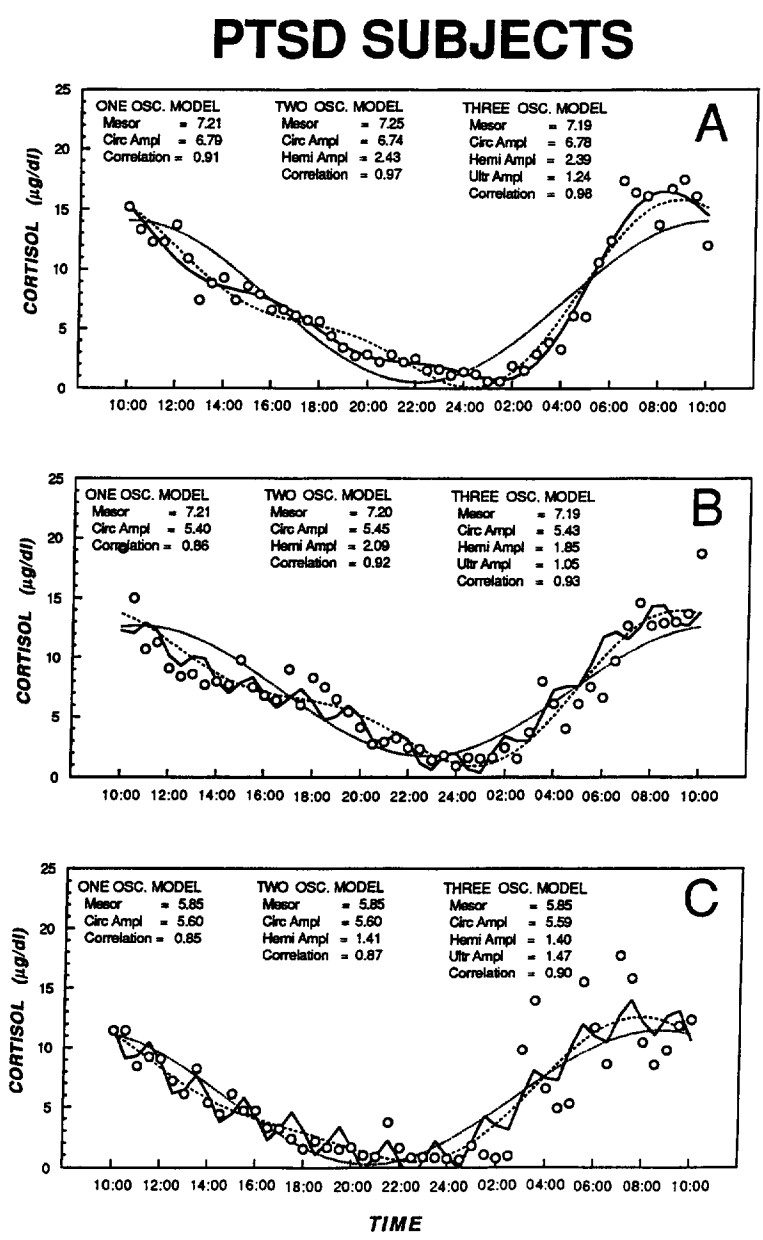

Figure 4. Time-series data of three individual posttraumatic stress disorder (PTSD) subjects representing single- and multioscillator cosinor modeling of raw cortisol values over the 24-hour period. The dotted line represents the fit provided by the one-oscillator model, the hatched line represents the fit provided by the two-oscillator model, and the solid line represents the curve provided by the three-oscillator model.

by the single cosine parameters. Furthermore, there appears to be a virtual absence of other (i.e., hemicircadian and ultradian) rhythms. Figure 5 demonstrates a further contrast between depressed patients compared to those in the other two groups, primarily in the fact that the raw data of the depressed patients are generally poorly modeled by both cosine and multicosine oscillator models, and by virtue of the greater variability in this group in peak and nadir of cortisol.

Table 2 summarizes information about sleep patterns during the 24-hour study in the three groups. There were no significant group differences in the duration of sleep, in the time of sleep onset or waking, or in the number of awakenings during the 24-hour period. There were no significant correlations between sleep and chronobiological parameters.

Discussion

The findings demonstrate lower cortisol levels, particularly in the evening and early morning, and a stronger circadian rhythm of cortisol, in PTSD compared to normal or depressed subjects. The range as reflected by the peak and nadir values was comparable to that of normals. Thus, low cortisol in PTSD appears to result from a prolonged nadir and shorter durations of peak cortisol release.

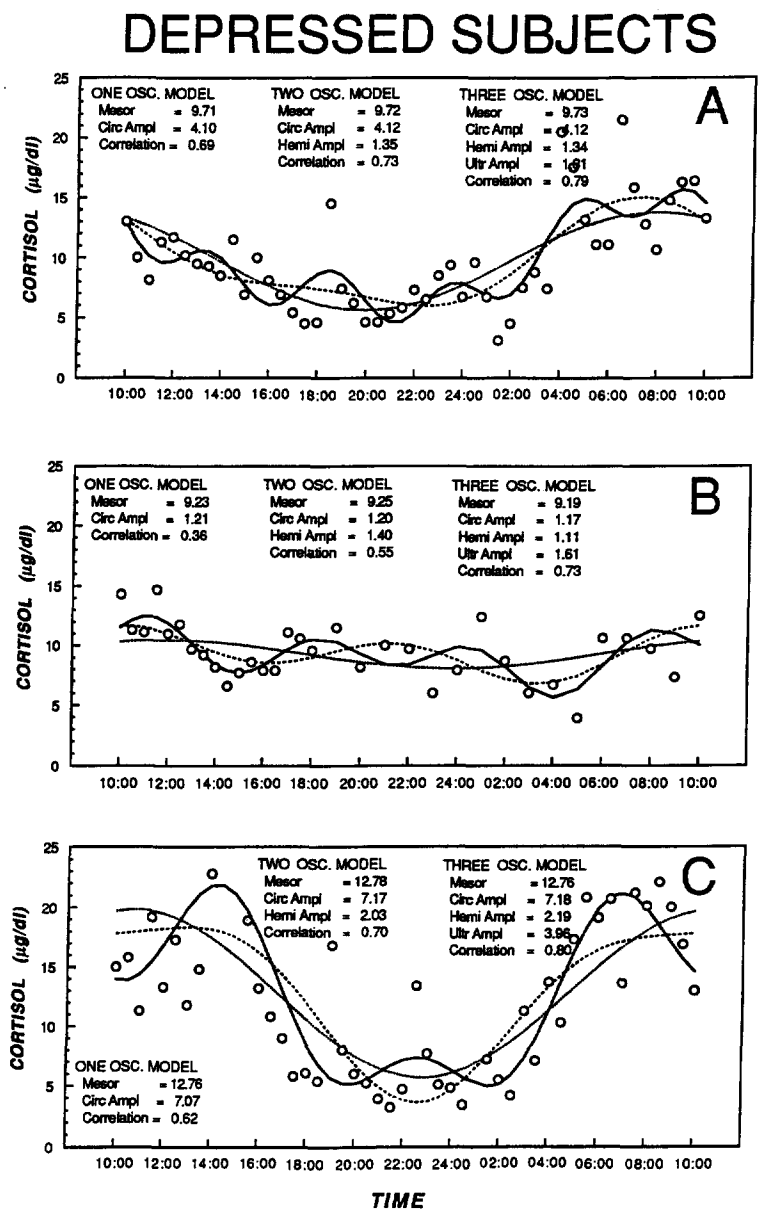

Figure 5. Time-series data of three individual depressed subjects representing single- and multioscillator cosinor modeling of raw cortisol values over the 24-hour period. The dotted line represents the fit provided by the one-oscillator model, the hatched line represents the fit provided by the two-oscillator model, and the solid line represents the curve provided by the three-oscillator model.

In contrast, depressed patients showed significantly higher levels of cortisol compared to normals at certain time points during the 24-hour period, particularly in the early morning hours. The mesor was not significantly higher, owing to the larger range of cortisol secretion in the depressed group. The greater variation in cortisol is consistent with hypercortisolism occurring in only a subgroup of depressed patients (Sachar et al 1973; Halbreich

Table 2. Summary of Sleep Parameters

Parameters	PTSD (n = 15)	Normal (n = 15)	Depressed (n = 11)	F
Hours of sleep	5.04 ± 1.45	5.32 ± 1.45	5.55 ± 1.46	1.06, ns
Time of sleep onset	00:58 ± 1.34	00:43 ± 1.24	23:49 ± 0.58	2.35, ns
Waking time	6:55 ± 0.4	6:49 ± 0.53	7:08 ± 0.47	0.62, ns
Number of awakenings	1.5 ± 1.5	1.0 ± 1.2	2.0 ± 1.4	1.65, ns

PTSD = posttraumatic stress disorder; ns = not significant.

et al 1985; Linkowski et al 1985; Pfohl et al 1985; Mortola et al 1987; Dahl et al 1991).

Standard cosine analysis determined that cortisol fluctuations during the 24-hour period followed a stronger circadian pattern in the PTSD group compared to the normal or depressed groups, but this analysis did not differentiate normal and depressed patients on any circadian parameter. The multicosinor analysis, which provided a better model evidenced by the substantially enhanced goodness-of-fit of the data in all three groups, did allow the detection of significant group differences on a number of noncircadian (i.e., hemicircadian and ultradian) parameters, providing further discrimination of basal cortisol regulation between groups. The multioscillator analysis also demonstrated a more chaotic cortisol secretion in depressed patients, evidenced by the significantly lower goodness-of-fit coefficient and higher estimate of residual error.

A stronger circadian rhythm of cortisol in PTSD is consistent with previous findings of enhanced negative feedback of cortisol. PTSD patients appear to have a stronger negative feedback of cortisol, as evidenced by an increased number (Yehuda et al 1991, 1993a) and sensitivity (Yehuda et al 1995) of type II glucocorticoid receptors. Because glucocorticoid receptors are regulated by changes in circadian rhythmicity (Reul et al 1987), the present findings of a stronger circadian rhythm may underlie previously observed HPA-axis alterations in PTSD.

The greater signal-to-noise ratio observed in PTSD is compatible with the idea that the HPA axis may be maximally responsive to stress-related cues in this disorder. An enhanced signal-to-noise ratio describes a system with a maximally low background and, accordingly, a potentially greater capacity to respond to the environment. Many symptoms of PTSD, such as hypervigilance, increased startle, and augmented psychological distress and physiological arousal to reminders of the trauma, reflect exaggerated responsiveness. Furthermore, laboratory studies have found marked sympathetic nervous system activation to mental representations of traumatic events in PTSD (Pitman et al 1987; Shalev and Rogel-Fuchs 1993).

In contrast, depressed patients showed a more dysregulated pattern of cortisol release, as indicated by the relatively poor fit of the data to either the cosinor or multicosinor models compared to PTSD and normal subjects. Unlike PTSD, depressed patients show an insensitivity to external stimuli and environmental stressors. For example, depressed dexamethasone nonsuppressors fail to dishabituate to tones and to discriminate between novel and familiar stimuli (Reus et al 1985), and therefore show an attenuated ability to perceive or respond to environmental change (Mirken and Coppen 1980; Reus 1984).

That depressed subjects showed a significantly more dysregulated or chaotic pattern of cortisol secretion, but not necessarily a greater production of cortisol over a 24-hour period, suggests that increased cortisol release may not be a necessary feature of HPA-axis dysregulation in depression. Although hypercortisolism is considered a central and defining characteristic of HPA-axis dysregulation in depression (Gold et al 1988; Stokes and Sikes 1987), and most findings of HPA-axis functioning in this disorder are compatible with hypercortisolism, increased plasma or urinary levels of cortisol have only been observed in about half of depressed patients studied (Gold et al 1988; Stokes and Sikes 1987). Furthermore, evidence for reduced negative feedback of cortisol as reflected by abnormal dexamethasone suppression tests has also only been observed in half of depressed individuals (Gold et al 1988; Stokes and Sikes 1987; APA Task Force 1987; Carroll et al 1981), and not necessarily the same individuals that display hypercortisolism (Meller et al 1988; Stokes and Sikes 1987). Thus, the present data provide a more unifying model of cortisol dysregulation than the concept of hypercortisolism, which can be mathematically defined as more chaotic. If chaos or dysregulation are the underlying abnormalities in depression, this partially explains why it has been so difficult to capture the homogenous nature of cortisol regulation in depression. Multicosine analysis may provide a relatively simple mathematical tool to ascertain in earlier studies whether cortisol patterns in depression were more complex or chaotic than normal.

Several methodological limitations in this study mitigate against uncritical acceptance of these results. First, sampling over a single diurnal cycle may provide only limited information about chronobiological parameters. Second, the laboratory setting itself likely provides some disruption of normal sleep patterns in subjects. Although in the present study no significant group differences were observed in variables such as hours of sleep, number of awakenings, and time of sleep onset and awakening, the measures obtained do not substitute for more rigorous study of activity and sleep architecture. Because sleep disturbances are known to be present in both PTSD (Ross et al 1989; Lavie et al 1987) and major depression (Fehm et al 1987), it is possible that some of the differences observed may be related to different sleep profiles in the PTSD and depressed subjects. Further studies examining polysomnographic recordings and plasma cortisol levels in tandem are therefore warranted.

This study is noteworthy for extending observations of the distinct nature of HPA-axis findings in PTSD and major depression, and for suggesting that there may be two discrete conceptual models that may best describe the nature of HPA-axis alterations in these disorders (i.e.,

"sensitization" and "dysregulation"). Important clinical implications may result from the findings that PTSD and depressed patients show contrasting paradigms of cortisol regulation. For example, PTSD and major depressive disorder have a substantial degree of symptom overlap (i.e., of symptoms such as insomnia, impaired concentration, social withdrawal, emotional numbing, and guilt), and a high rate of diagnostic comorbidity. The present data show that regardless of these similarities, the two syndromes may be differentiated on the basis of different patterns of baseline cortisol release. In so doing, the data may offer some explanation for the lack of effectiveness of, or in some cases, atypical responses to, standard antidepressants in patients with PTSD (Southwick et al 1994). The data suggest that future work examining biological rhythms of other systems in PTSD are also warranted.

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