



Circadian Profiles of Cortisol, Prolactin, and Thyrotropin in Seasonal Affective Disorder

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To determine whether circadian profiles of various plasma hormones are abnormal in patients with winter seasonal affective disorder (SAD), we obtained 24-hour profiles of plasma cortisol, prolactin, and thyrotropin in subsets of a sample of 22 depressed patients with SAD on and off light therapy and in subsets of a sample of 24 normal controls. Cortisol levels did not differ between patients and controls, and levels in patients were not affected by light therapy. Prolactin levels were lower in patients than in controls throughout the day ($p < 0.03$) but were unaffected by light therapy. Independent of patient vs. control status, prolactin levels were higher in women than in men throughout the day ($p < 0.003$). Thyrotropin levels were no different in patients and controls, but levels in patients were lower following light therapy ($p < 0.05$).

Key Words: Seasonal affective disorder, cortisol, prolactin, thyrotropin, circadian rhythms

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Introduction

Seasonal affective disorder (SAD) is characterized by recurrent fall/winter depressions with spring/summer remissions and has been categorized as a pattern of recurrent major depressive episodes in the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed, revised (*DSM-III-R*) (American Psychiatric Association 1987; Rosenthal et al 1984). Characteristics of the winter depressive phase include hypersomnia, carbohydrate craving, increased ap-

petite, and low energy. These clinical symptoms are treated effectively with bright light therapy (Oren and Rosenthal 1992; Terman et al 1989). Although several biological abnormalities have been reported to occur in SAD, the significance of these findings has yet to be determined (Rosenthal and Wehr 1992).

The study of hormones in depressive disorders has been considered a useful strategy for understanding the neurobiology of human brain functioning over the four decades since elevated plasma cortisol was first described in depression (for an early review, see Rubin and Mandell 1966). Subsequent neuroendocrine studies in patients with mood disorders have been directed at discovering state and trait markers of these conditions and understanding the pathophysiological mechanisms that underlie affective symptoms and vulnerability. Insofar as the release of hormones is stimulated, inhibited, or modulated by neu-

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rotransmitters and neuropeptides, neuroendocrine profiles can provide information about these regulatory brain systems that have been postulated to be abnormal in affective disorders (Sachar 1985; Stokes 1988). Patterns of hormone secretion can also provide information about the circadian system, which may be abnormal in certain psychiatric conditions (Wehr and Goodwin 1981).

Two of the leading theories explaining the pathophysiology of SAD are built on the premise that abnormal circadian rhythms cause the disorder and that successful normalization of those rhythms contributes to the resolution of the disorder. The "phase-shift" hypothesis of SAD (Lewy and Sack 1986) was developed from the capacity of bright light in the morning to advance circadian rhythms and simultaneously produce an antidepressant effect. According to this theory, patients with SAD generally have delayed circadian rhythms, and morning bright light therapy successfully treats the depressive symptoms by correcting the phase-delay in circadian rhythms. The "amplitude" theory of SAD posits that the increased amplitude of circadian body rhythms (e.g., temperature, melatonin, heart rate) that can be generated by properly timed bright light accounts for the efficacy of bright light therapy in the disorder (Czeisler et al 1987; Kronauer 1987; Kronauer and Frangioni 1987).

Hypothalamic-pituitary-adrenal axis (HPA) function has been widely reported to be overactive in patients with endogenous depression (Stokes and Sikes 1988). Because the HPA system is involved in arousal and response to stress, the reports by patients with SAD of being sluggish and of feeling increased dysphoria after stress may indicate abnormalities in this axis. One of the first objective indications of such an abnormality was the demonstration that the adrenocorticotrophic hormone (ACTH) response to corticotropin (CRH) is blunted in patients with SAD and that light therapy tends to normalize this response (Joseph-Vanderpool et al 1991).

Studies of prolactin in depression have found mixed results; some found elevated prolactin in depressed patients and others no differences between patients and controls (Baumgartner et al 1988). Studies of basal prolactin in SAD have also yielded inconsistent results. Two studies have shown that prolactin was reduced in patients with SAD compared to normal subjects (Depue et al 1990; Stojek et al 1991). Another found that basal prolactin did not differ between patients with SAD and normals, but that effective light therapy reduced the prolactin level in patients with SAD (Németh 1992). An earlier study from our group indicated that prolactin levels were raised in patients with SAD (Jacobsen et al 1987), but the unusually low prolactin levels seen in the controls in that study limit the meaning of that finding. Because sleep, which facilitates the secretion of prolactin, has been shown to be

disturbed in SAD (Anderson et al 1994), investigation of circadian profiles of prolactin is warranted.

Nocturnal thyroid-stimulating hormone (TSH) has been found to be blunted in depressed patients (Bauer and Whybrow 1988). Although thyrotropin-releasing hormone (TRH) challenge tests of the hypothalamic-pituitary-thyroid axis are normal in patients with SAD (Oren and Rosenthal 1992; Rosenthal et al 1984), these patients show multiple disturbances in energy regulation, including an abnormal resting metabolic rate (Gaist et al 1990), a slower recovery to normal resting temperature after an exercise challenge test (Arbisi et al 1989), and higher peripheral temperature (Schwartz et al 1993). Because the hypothalamic-pituitary-thyroid axis is involved in thermoregulation, TSH profiles are of specific interest in this population.

Therefore, in this study we evaluated the 24-hour profiles of cortisol, prolactin, and TSH in patients with SAD and age- and gender-matched normal controls and the effect of light therapy on these profiles in patients with SAD.

Methods and Materials

Subjects

All patients were required to meet lifetime criteria for SAD (Rosenthal et al 1984); score a total of at least 14 on the 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1967) during the untreated condition of the study; and be free of psychotropic medication for at least 1 month prior to admission. (A longer "washout" period was not required because no patient had received fluoxetine prior to participation in the study.) Eleven patients met criteria for unipolar depression, 10 had bipolar II depression, and 1 had bipolar I depression (Spitzer et al 1978). The patients and normal controls were recruited through a newspaper advertisement. All were screened and evaluated by means of the Structured Clinical Interview for DSM-III-R (American Psychiatric Association 1987) diagnoses (SCID-R) (Spitzer et al 1988). When possible, controls were matched for age and gender. Controls with personal or first-degree-relative histories of psychiatric illness or any significant medical illness were excluded. All subjects were also screened with routine physical and laboratory examinations prior to entry. All subjects gave informed consent for participation.

The cortisol and prolactin data presented here combine the data previously reported by Skwerer and colleagues (1988) with data obtained subsequently. Seven patients and 10 controls were added to the previous cortisol data set, and 8 patients and 10 controls were added to the previous prolactin data set. We combined these data

Table 1. Mean and Standard Deviation for Demographic Features of Subjects (Number in Each Category, Age, HDRS, and Atypical Depression Score (ATY) (Rosenthal and Heffernan 1986)

	Gender	Patients		Off-Light		On-Light		Controls	
		<i>n</i>	Age (years)	HDRS	ATY	HDRS	ATY	<i>n</i>	Age (years)
Cortisol	M	8	40 ± 9	22 ± 7	11 ± 3	7 ± 3	3 ± 3	8	40 ± 9
	F	13	40 ± 10	17 ± 7	11 ± 4	8 ± 5	4 ± 4	12	41 ± 12
Prolactin	M	9	41 ± 9	23 ± 7	12 ± 5	7 ± 3	3 ± 3	9	41 ± 9
	F	13	40 ± 10	17 ± 7	11 ± 4	8 ± 5	4 ± 4	15	41 ± 11
TSH	M	5	43 ± 11	23 ± 8	12 ± 5	6 ± 2	3 ± 2	6	43 ± 11
	F	4	41 ± 16	12 ± 3	7 ± 3	10 ± 4	4 ± 5	6	41 ± 10

because small sample sizes can yield type II errors and all of these specimens were collected and analyzed in the identical manner described below. The combined results are consistent with those earlier findings. A previous TSH study had been performed on seven patients and five normal controls. Because we used different plasma collection methods and assays in the two TSH studies, however, we did not combine those data.

Blood samples were drawn from the same set of 22 patients and 24 controls. Cortisol data were available on 21 patients and 20 normal controls. Prolactin data were available for 22 patients and 24 normal controls. TSH was analyzed for 9 patients and 12 normal controls. Patient and control groups had similar age and gender distributions (see Table 1).

Design

Patients were studied under two conditions: untreated "off-light" and treated "on-light." Controls were studied only in the off-light condition. In the off-light condition, subjects stayed in ordinary room light (about 300 lux) for 2.5 hours between 6:00 AM and 9:00 AM and for 2.5 hours between 6:00 PM and 9:00 PM for at least 9 days prior to the study. The on-light condition consisted of 5 hours daily of 2500 lux full-spectrum fluorescent light (Rosenthal et al 1985), administered for 2.5 hours between 6:00 AM and 9:00 AM and 2.5 hours between 6:00 PM and 9:00 PM, for at least 9 days prior to the study. The sequence of the two conditions was counterbalanced. All subjects remained on an inpatient research unit at the National Institutes of Health (NIH) for the hormonal sampling, but were at home during the remainder of the study.

On the days of venipuncture, an intravenous catheter was inserted into each subject's forearm at 8:00 AM and blood was obtained hourly from 9:00 AM through 8:00 PM, then half-hourly through 3:00 AM the following day, then hourly again through 8:00 AM. Samples were collected during the winters of 1985 through 1988. Sleep was permitted only between 11:00 PM and 7:00 AM in a dark

room on the nights of sampling. Prior to the procedure on each condition, patients' levels of depression were assessed with the HDRS and with an atypical depression scale (ATY) frequently used in studies of SAD (Rosenthal and Heffernan 1986).

Despite the ideal design of studying all women at the same points in their menstrual cycles, the brevity of winter and other logistic constraints prevented us from achieving this goal. Three of the female patients and five of the controls were postmenopausal. Eight of the 10 menstruating female patients were studied during the same phase of their menstrual cycle in both treatment conditions (four in the first half of their cycle and four in the second half). Five of the menstruating normal controls were studied in the first half of their cycle and five in the second half.

Assay Methods

Blood samples were centrifuged immediately after they were drawn and the plasma was frozen at -20° C. Assays were performed by Hazleton Laboratories (Vienna, VA). The sensitivities and the intra- and interassay coefficients of variation of cortisol, prolactin, and TSH were 0.2–0.5 μ g/dl, 3.4% and 11.9%; 1.8 ng/ml, 6.4% and 16.9%; 0.03 mU/L, 2.6% and 3.1%, respectively. Plasma samples for both patients in the on- and off-light conditions and for normal controls were assayed in the same batches, with the delay from sample collection to assay the same in patients and controls.

Statistics

Depression ratings were compared with paired *t* tests. Hormonal data were examined with analyses of variance (ANOVAs) corrected for repeated measures (Greenhouse and Geisser 1959). In the first ANOVA for cortisol and TSH, we compared the off-light and on-light conditions in SAD patients using two repeated factors (time and condition). In the second ANOVA for cortisol and TSH, we compared patients in the off-light condition with normal

controls with one repeated factor (time) and one grouping factor (patients vs. normals). To account for the normal tendency for serum prolactin to be higher in women than in men (Thorner et al 1992), gender was considered as a second grouping factor and ANOVAs were performed otherwise as described above. We performed a further ANOVA comparing prolactin profiles between unipolar and bipolar depressed patients. In addition to the analysis of the overall profiles, we examined several particular dependent variables in order to be able to address aspects of the phase-shift and amplitude theories of SAD: peak and time of peak plasma hormone levels, and curve amplitudes (peak-trough difference) for each individual were compared between patients off and on light therapy and normal controls with two-tailed *t* tests. We performed Pearson correlations between HDRS scores and patients' area under the curve (AUC) for the 24-hour profile for each hormone, and between the change in HDRS in patients and change in AUC between light conditions for each hormone.

Results

Effects of Light on Mood

For the entire sample of 22 patients, mood was significantly better in the light-treated condition (see Table 1). Mean HDRS \pm SD was 19 ± 8 in the off-light condition and 8 ± 4 in the on-light condition ($t = 5.4$, $df = 21$, $p < 0.0001$). Mean ATY \pm SD was 11 ± 4 in the off-light condition and 4 ± 3 in the on-light condition ($t = 6.3$, $df = 21$, $p < 0.0001$).

Cortisol

The ANOVAs and the individual profile factors showed no significant difference in the cortisol profile for patients between the two conditions for patients nor between patients and controls (see Figure 1 and Table 2). There was neither a correlation between the AUC of patients in the off-light condition and their HDRS score nor between the change of AUC and the change in HDRS in patients in the off-light vs. on-light conditions.

Prolactin

Plasma prolactin levels for patients off-light were significantly lower than those of the controls for the entire 24-hour period ($F = 5.7$, $df = 1,41$, $p < 0.03$) (see Figure 2). Analysis of variance showed no difference between the off-light and on-light conditions in patients. There were no other differences in the prolactin profile between patients and controls nor between patients before and after light treatment (see Table 3). There was neither a correlation

between the AUC of patients in the off-light condition and their HDRS score nor between the change of AUC and the change in HDRS in patients in the off-light vs. on-light conditions.

Independent of light condition and patient vs. control grouping, prolactin levels were higher in women than in men in both ANOVAs (patients off- vs. on-light: $F = 15$, $df = 1,39$, $p = 0.0004$; patients off-light vs. controls: $F = 10$, $df = 1,41$, $p < 0.003$). (see Figure 3). There was no interaction between gender and light condition or between gender and group in the ANOVAs (gender \times light condition: $F = 1.3$, $df = 1,39$, $p > 0.2$; gender \times patient/control group: $F = 0.59$, $df = 1,41$, $p > 0.4$). Post-hoc *t* tests of peak plasma levels and amplitude in patients on- and off-light and in controls showed significantly higher levels in women than in men (peak in patients off-light: $t = 3.2$, $df = 20$, $p = 0.004$; peak in patients on-light: $t = 3.4$, $df = 20$, $p = 0.003$; peak in controls: $t = 2.3$, $df = 22$, $p = 0.03$; amplitude in patients off-light: $t = 3.1$, $df = 20$, $p = 0.006$; amplitude in patients on-light: $t = 3.3$, $df = 20$, $p = 0.004$; amplitude in controls: $t = 2.3$, $df = 22$, $p = 0.03$) (see Table 3).

Analysis of variance showed no difference between the prolactin levels in unipolar vs. bipolar patients.

Thyroid-Stimulating Hormone

TSH levels were significantly lower in patients during the on-light condition than the off-light condition ($F = 5.4$, $df = 1,8$, $p < 0.05$) (see Figure 4). There were no other differences in the TSH profile between patients and controls nor between patients before and after light treatment (see Table 4). There was neither a correlation between the AUC of patients in the off-light condition and their HDRS score nor between the change of AUC and the change in HDRS in patients in the off-light vs. on-light conditions.

Discussion

We shall first comment on our findings with regard to each of the plasma hormones studied and then attempt to synthesize our findings with respect to broader theories of SAD.

Cortisol

We found no difference between patients (on either condition) and normal controls with respect to plasma cortisol levels or timing. In contrast, cortisol levels in major depression have generally been found to be elevated (Charlton et al 1987; Jarrett et al 1983; Linkowski et al 1985; Pfohl et al 1985). This abnormality has been

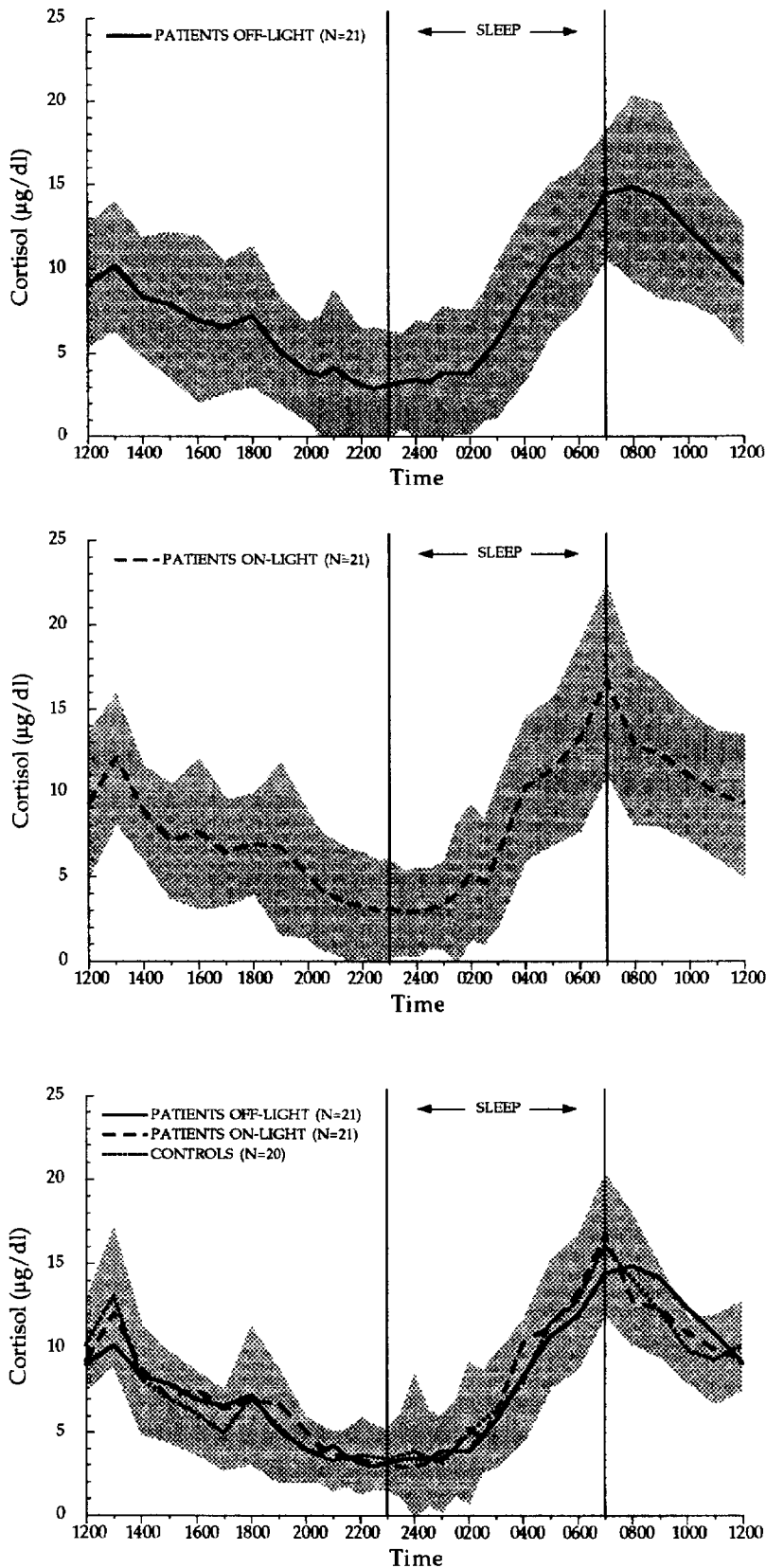


Figure 1. The upper panel depicts the mean and standard deviation of the circadian profile of plasma cortisol in patients with SAD in the off-light condition. The middle panel reflects the patient profile in the on-light condition. The lower panel depicts the mean and standard deviation of the circadian profile of plasma cortisol in normal controls in the off-light condition, with the mean levels for patients in the two light conditions superimposed. There is no difference among the different profiles.

Table 2. Mean and Standard Deviation for Plasma Cortisol Profile in the 21 Patients and 20 Controls Studied

	Patients Off-Light	Patients On-Light	Controls
Peak level ($\mu\text{g}/\text{dl}$)	17.8 ± 4.8	18.3 ± 4.8	18.1 ± 3.3
Time of peak level	$08:00 \pm 01:00$	$07:00 \pm 04:00$	$08:00 \pm 02:00$
Amplitude ($\mu\text{g}/\text{dl}$)	16.8 ± 4.1	16.9 ± 4.7	16.4 ± 3.2

There were no significant differences identified between the groups.

attributed by some to a hyperactive HPA axis (Sachar et al 1970) and by others to sleep disturbances in depressed patients (Halbreich et al 1985; Jarrett et al 1983). The atypical vegetative symptoms seen in SAD have led to the hypothesis that HPA axis functioning may actually be abnormally low in SAD (Demitrack et al 1991; Joseph-Vanderpool et al 1991). This possible abnormality might be detected by measuring free cortisol (the biologically active fraction of the total plasma cortisol that we measured) or by studies that measure total cortisol secretion. CRH infusions in patients with SAD producing blunted ACTH responses that were somewhat normalized by effective light therapy and abnormal cortisol and ACTH responses to infusions of meta-chlorophenylpiperazine (m-cpp) support the hypothesis of abnormal HPA function in SAD (Joseph-Vanderpool et al 1991).

Prolactin

The results of prolactin studies in depression are mixed, with some studies showing no difference between levels in depressed patients and normal controls (Baumgartner et al 1988; Jarrett et al 1987; Linkowski et al 1980) and others showing elevated levels of prolactin in depression (Halbreich et al 1979; Mai et al 1985; Mendlewicz et al 1980). Linkowski and colleagues (1989) reported that during the acute phase of depressive illness in men the nocturnal secretory phase of prolactin started earlier in patients than in healthy controls. We did not observe any phase difference between patients and controls in this study, perhaps because our sampling rate was not as high as that of Linkowski and colleagues.

We found evidence of lower prolactin levels in patients in both conditions, compared with controls. The large variances in prolactin levels seen prevent the use of prolactin as a diagnostic trait marker for SAD. Nevertheless, our finding is compatible with, and extends the data of two groups (Depue et al 1990; Stojek et al 1991) that found lower prolactin levels in patients with SAD compared with normal controls in afternoon plasma samples. Depue and colleagues found low prolactin levels across seasons and light conditions and suggested that low prolactin levels are a trait marker of SAD. This is

consistent with our finding that effective light therapy did not restore plasma prolactin to normal levels. Because a large proportion of SAD patients meet criteria for bipolar II disorder (Oren and Rosenthal 1992), our data are also compatible with those of Mendlewicz and colleagues (1980) who found low mean plasma prolactin levels in depressed bipolar patients due to reduced nocturnal secretion of the hormone. Our data conflict with a recent report of high afternoon prolactin levels in men with SAD compared with control men (Arbisi et al 1994). Our data are also inconsistent with the higher basal prolactin concentrations that we found in patients with SAD in a prior study and the lack of difference between patients and controls found by another group (Jacobsen et al 1987; Németh 1992). Although we acknowledge the discrepancy between our present and past findings, the result presented here appears stronger than our previous study because it is derived from circadian profiles rather than from single time point measurements as in the earlier studies. Because dopamine is a prolactin-inhibiting factor (Ben-Jonathan 1985), our results also support the hypothesis of abnormal dopamine functioning in SAD first suggested by Depue and colleagues (1989).

Low prolactin levels in patients with SAD in winter may be a manifestation of their seasonal dysregulation as well. Recent data in humans show that prolactin secretion patterns are responsive to changes in photoperiod (Wehr et al 1993). Animal models support this concept. For example, fall-winter decreases in prolactin levels are commonly a mediator of the response to changing daylength in seasonally breeding mammals (Curlews 1992) and increases in endogenous prolactin levels may be critical for the development of seasonal coat color changes in other mammals (Duncan and Goldman 1984a, b).

It is well known that prolactin secretion is stimulated by sleep and inhibited by sleep deprivation (Sassin et al 1973). Although patients with SAD sleep more in winter than in summer, their delta sleep is reduced in winter compared with controls (Anderson et al 1994). If delta sleep deprivation in particular were to inhibit prolactin release, the diminished delta sleep in patients might explain our finding. Sleep differences between the groups, however, are unlikely to explain in full the prolactin differences, as we observed low prolactin levels in patients with SAD during the day as well as during the night.

Independent of patient vs. control status, these data support the notion that serum prolactin is higher in women than in men of similar age (Frohman 1987). This difference is thought to be secondary to the effects of estrogens on prolactin-producing genes (Thorner et al 1992). Because estrogen raises prolactin levels in women, it is possible that the lowered prolactin levels seen in women

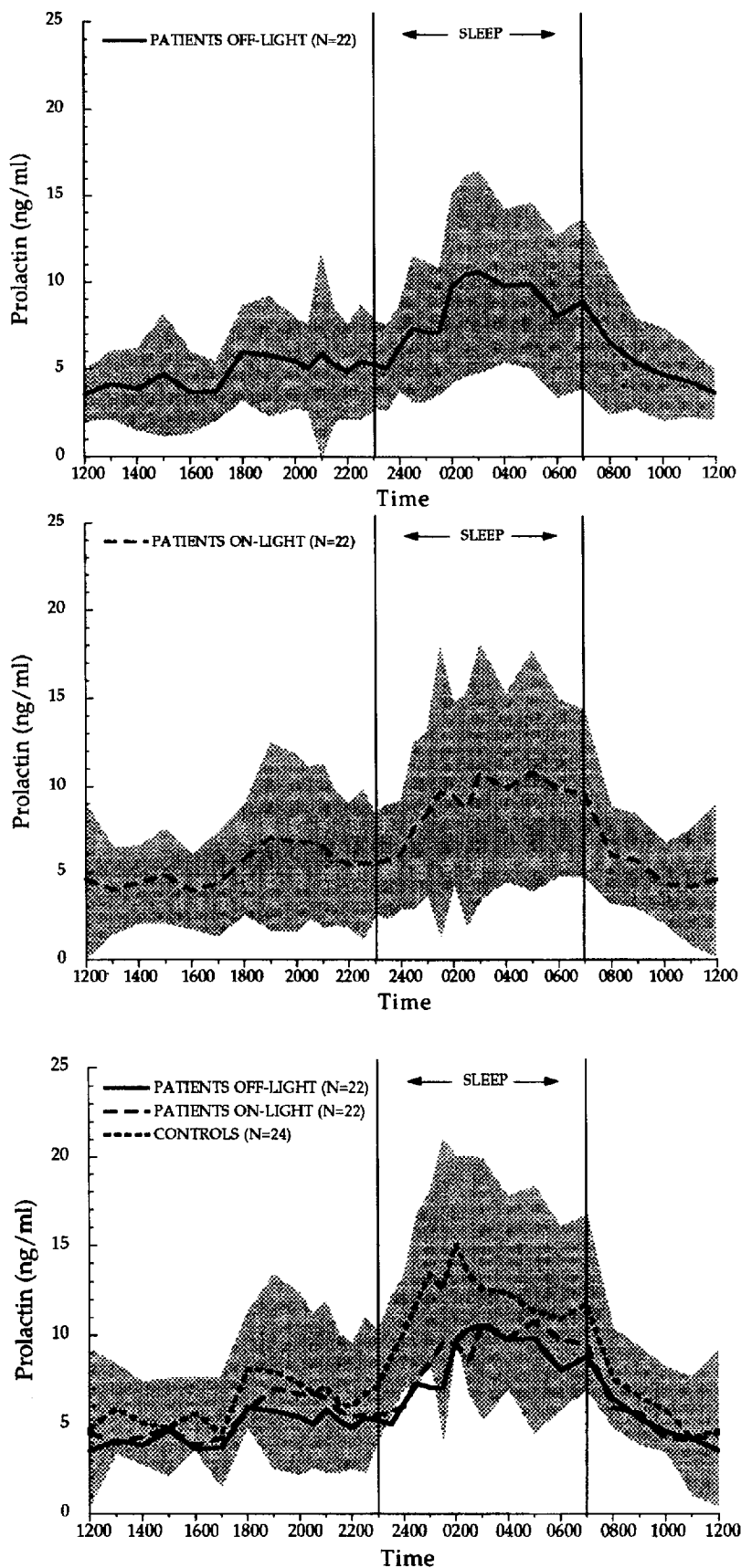


Figure 2. The upper panel depicts the mean and standard deviation of the circadian profile of plasma prolactin in patients with SAD in the off-light condition. The middle panel reflects the patient profile in the on-light condition. The lower panel depicts the mean and standard deviation of the circadian profile of plasma prolactin in normal controls in the off-light condition, with the mean levels for patients in the two light conditions superimposed. Levels in patients are significantly less than in controls ($p < 0.03$).

Table 3. Mean and Standard Deviation for Plasma Prolactin Profile in the 22 Patients and 24 Controls Studied

	Pts Off-Light	Pts On-Light	Controls
Women	(n = 13)	(n = 13)	(n = 15)
Peak level (ng/ml)	19.1 ± 5.9	19.0 ± 7.0	24.1 ± 11.0
Time of peak level	02:00 ± 04:30	03:00 ± 03:00	01:30 ± 04:00
Amplitude (ng/ml)	16.8 ± 5.7	16.4 ± 6.6	21.2 ± 10.3
Men	(n = 9)	(n = 9)	(n = 9)
Peak level (ng/ml)	11.2 ± 5.3	10.6 ± 2.4	15.2 ± 4.2
Time of peak level	01:00 ± 05:00	03:30 ± 02:30	01:30 ± 05:30
Amplitude (ng/ml)	9.3 ± 5.5	8.9 ± 2.5	12.8 ± 4.4
Women and men	(n = 22)	(n = 22)	(n = 24)
Peak level (ng/ml)	15.8 ± 6.8	15.6 ± 7.0	20.8 ± 9.5
Time of peak level	01:30 ± 04:30	03:30 ± 02:30	01:30 ± 04:30
Amplitude (ng/ml)	13.7 ± 6.6	13.3 ± 6.4	18.1 ± 9.1

Beyond the gender differences, there were no significant differences identified between the groups.

with SAD may reflect low estrogen levels. We know of no data addressing this point.

Thyroid-Stimulating Hormone

Our previous study of TSH in SAD (Skwerer et al 1988) showed that TSH was reduced in patients with SAD in untreated and treated conditions. Attempts to replicate this small sample study, however, have shown no difference in thyroid indices in patients with SAD (Bauer et al 1993). Although in this study we found no difference between patients and normals, we did find that light treatment reduced TSH levels in patients. Although sleep differences between the two light treatment conditions might be associated with the difference seen in patients (Parker et al 1976; Sack et al 1988), the fact that the elevation was seen across the 24-hour period makes sleep an unlikely contributor to the difference. Our power to find a difference between patients on and off lights and to find other TSH profile differences was limited by our small sample size, given the variance observed, thereby making the likelihood of a type II error probable. Nevertheless, our sample size in this 24-hour study was greater than in that reported previously. The reported low TSH values in patients with SAD (Skwerer et al 1988) were consistent with thermoregulatory abnormalities in nonseasonal depression (Skwerer et al 1988; Sou tre et al 1986, 1988) and were compatible with those reported by other groups in nonseasonal depression (Kjellman et al 1984; Sack et al 1988; Sou tre et al 1986; Weeke and Weeke 1980). In studies of normal individuals, TSH and core body temperature, respectively, have been found to be comparatively elevated during the winter and reduced during the summer (Lacoste and Wirz-Justice 1989; Levendosky et al 1991).

The higher TSH levels in patients in the untreated vs. the treated state in this study may explain the higher

peripheral temperatures seen in untreated patients with SAD in winter (Schwartz et al 1993) as well as the slower recovery to resting core body temperature after an exercise challenge test (Arbisi et al 1989). High TSH levels might also explain the elevated resting metabolic rates seen in untreated patients with SAD in winter (Gaist et al 1990), although we have not been able to replicate this latter finding (Peeke, P, personal communication, 1993). The reduction in TSH brought on by light therapy in SAD may account for observed reductions in nocturnal core body temperature (Rosenthal et al 1990) and resting metabolic rate (Gaist et al 1990) following such treatment. Further study of TSH in concert with resting metabolic rate and temperature would allow for testing this hypothesis.

Relevance to Mechanistic Theories of SAD

The results from the three plasma hormones studied here in patients with SAD do not present a coherent picture of the causes or pathophysiology of the disorder. The circadian profiles of these hormones can, however, be used to address four proposed mechanisms for the pathophysiology of SAD: the phase delay theory (Lewy et al 1987); the amplitude theory (Czeisler et al 1987); the dopamine theory (Depue et al 1989); and the serotonin theory (Jacobsen et al 1989).

We recognize that masking effects of sleep and artificial lighting (Wehr et al 1993) as well as our studying female subjects at various points in the menstrual cycle (Leibenluft et al 1994) might have obscured the underlying profiles of cortisol (Weitzman et al 1983), prolactin (Sassin et al 1973), and TSH (Parker et al 1976). By constraining the sleep interval in this study to 11:00 PM through 7:00 AM we might have confounded measurement of the underlying natural profile of our subjects. Other forms of analysis of circadian rhythms (Nelson et al 1979;

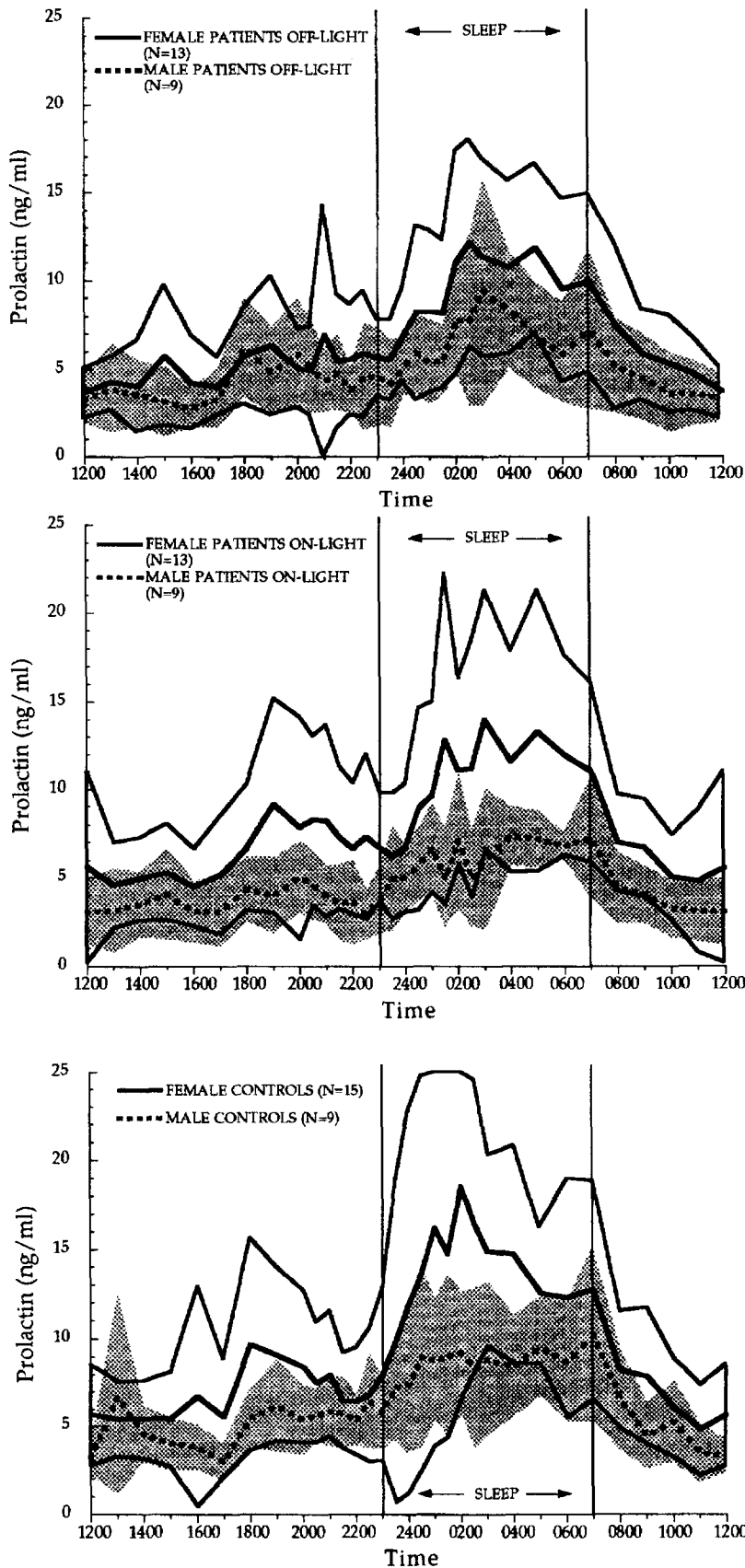


Figure 3. The upper panel depicts the mean and standard deviation of the circadian profile of plasma prolactin in male and female patients with SAD in the off-light condition. The middle panel reflects the patient profile in the on-light condition. The lower panel depicts the mean and standard deviation of the circadian profile of plasma prolactin in normal controls in the off-light condition. In each panel female means are depicted by a dark line, with two dark lines serving as bounds for the standard deviations. For the sake of symmetry with the other panels, the upper bounds of the standard deviation that were higher than depictable on the graph were arbitrarily cut off at 25 ng/ml. Male means are depicted by a broken line, with the shaded area serving as bounds for the standard deviations. Levels in men are significantly higher than those in men, independent of light condition and patient vs. control group.

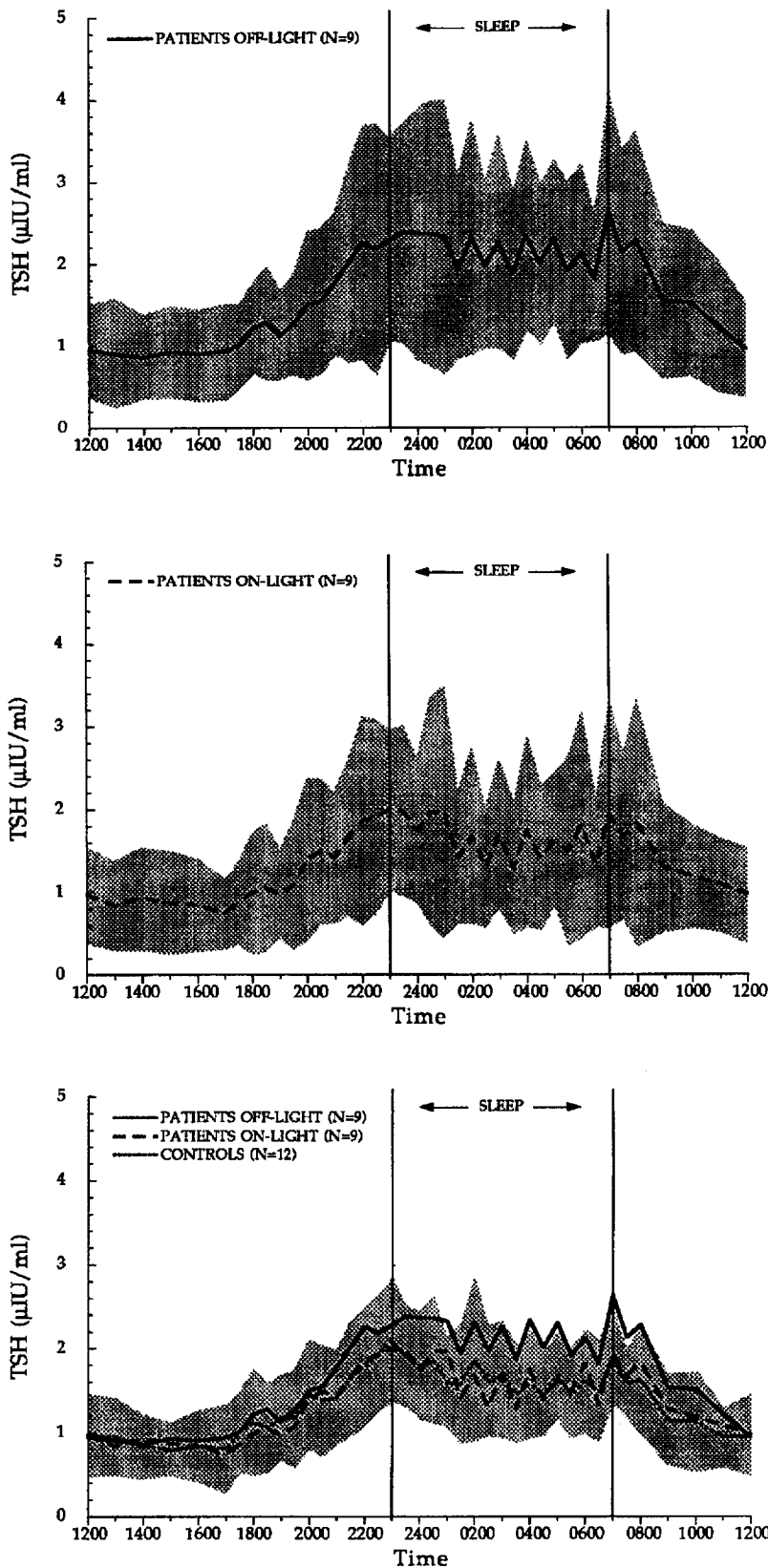


Figure 4. The upper panel depicts the mean and standard deviation of the circadian profile of plasma TSH in patients with SAD in the off-light condition. The middle panel reflects the patient profile in the on-light condition. The lower panel depicts the mean and standard deviation of the circadian profile of plasma TSH in normal controls in the off-light condition, with the mean levels for patients in the two light conditions superimposed. Levels in patients off-light are significantly higher than in patients on-light ($p < 0.05$).

Table 4. Mean and Standard Deviation for Plasma TSH Profile in the 9 Patients and 12 Controls Studied

	Patients Off-Light	Patients On-Light	Controls
Peak level (μ IU/ml)	3.0 \pm 1.5	2.4 \pm 1.4	2.5 \pm 0.8
Time of peak level	04:00 \pm 03:00	00:30 \pm 02:30	01:00 \pm 03:00
Amplitude (μ IU/ml)	2.3 \pm 1.0	1.7 \pm 1.0	1.8 \pm 0.6

There were no significant differences identified between the groups.

Wehr et al 1993) might also have yielded different assessments of phase. Complete 24-hour profiles of melatonin in SAD and profiles of all three of these hormones under strict "constant routine" conditions (Minors and Waterhouse 1984) would be especially useful as a way to evaluate these possibilities. Indeed, reports suggest that the TSH and temperature acrophase of subjects with SAD measured under a constant routine is significantly phase-delayed relative to controls (Dahl et al 1990, 1993).

The phase delay hypothesis argues that SAD is typically associated with a delay in timing of circadian rhythms that is corrected (phase-advanced) by properly timed early-morning light therapy. Melatonin secretion in the evening has been used as a phase marker to assess timing of circadian rhythms in SAD. Technical difficulties with our melatonin assay prevented us from assessing melatonin levels as part of this study. We did not, however, find any evidence of altered circadian timing of cortisol, prolactin, or TSH in patients with SAD vs. controls or between light therapy conditions in patients.

The amplitude hypothesis argues that the symptoms of SAD may be caused by reduced amplitude of the circadian rhythms of a variety of physiological variables and that light therapy treats the disorder by increasing the amplitude. We found no evidence that the circadian amplitude in hormonal rhythms is different in patients with SAD vs. controls, or that effective light therapy as administered in this study affects the amplitude of hormonal rhythms. In a previous study, we were unable to find diminished amplitude of circadian temperature in patients with SAD, although the amplitude was significantly increased after effective light therapy (Rosenthal et al 1990). We know of no other data that support the amplitude hypothesis. Moreover, a recent study has confirmed normal amplitudes of circadian temperature in depressed patients with SAD and could not demonstrate any change in temperature amplitude associated with the therapeutic effects of light (Wirz-Justice et al 1994).

The dopamine hypothesis argues that dopamine function is abnormal in various aspects of the central nervous system in patients with SAD. Supporting data involve

systems of eye blink rate regulation (Depue et al 1990), heat loss response to thermal challenges (Arbisi et al 1989), and prolactin regulation (Depue et al 1990). A complementary theory links retinal dopamine function to SAD (Oren 1991). Because of the close linkage of dopamine to the secretion of prolactin (Ben-Jonathan 1985), findings by Depue et al and those of our present study are consistent with the idea of dopamine dysregulation in SAD. Some studies of ophthalmic function and levodopa treatment for SAD are less supportive of a dopaminergic abnormality in the syndrome (Barbato et al 1993; Oren et al 1994), but studies of electrooculograms in SAD suggest ophthalmic abnormalities, perhaps consistent with retinal dopaminergic dysfunction (Lam et al 1991; Ozaki et al 1993). Since the linkage between dopamine and prolactin is better characterized than that between prolactin and other neurotransmitters, this study supports a particular, if ill-defined, role of dopamine.

The serotonin hypothesis argues that serotonin function is abnormal in various aspects of the central nervous system in patients with SAD. Our present finding of reduced prolactin in patients with SAD, along with results from one study indicating that patients with SAD have exaggerated prolactin responses to infusions of the serotonergic agonist m-cpp, and another indicating that light suppressed prolactin responses to m-cpp, are consistent with the hypothesis that SAD might involve a central nervous system serotonin deficiency (Rosenthal et al, unpublished data). Nevertheless, our results differ from those of a study demonstrating high baseline prolactin levels in (presumably predominantly) nonseasonal depressives and blunted prolactin responses in that group to infusions with the serotonergic agonist fenfluramine (Siever et al 1984). This latter study was used to argue that nonseasonal depressives also had a serotonin deficiency. These studies, of course, are based on nonphysiological challenges. It may be that under physiological conditions the effect of serotonin on prolactin secretion is primarily associated with the suckling-induced rise in prolactin (Ben-Jonathan 1985). In view of contradictory data in seasonal and nonseasonal depressives on prolactin levels, both at rest and following serotonergic challenges, further data are necessary to clarify whether serum prolactin levels and prolactin responses to infusions of serotonergic agonists are meaningful measures of baseline central nervous system serotonin status (Golden et al 1992).

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