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Nocturnal Melatonin and Cortisol Secretion in Newly Admitted Psychiatric Inpatients

Implications for Affective Disorders

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Summary. Melatonin secretion has been suggested as a marker of both circadian and noradrenergic dysfunction in affective disorders. Seventy-two newly admitted psychiatric inpatients [49 with major depressive disorder (MDD), 12 with schizophrenia, and 11 with intermittent depressive disorder (IDD)] underwent neuroendocrine screening at 0200, 0800, 1600 and 2300 hours prior to and the day following dexamethasone administration. All groups showed a drop in cortisol following dexamethasone. Dexamethasone nonsuppression was found in 20 of 49 patients with MDD, in none of the schizophrenics and in none of those with intermittent depressive disorder. Mean melatonin levels decreased significantly after the administration of dexamethasone across all four groups. Overall, the schizophrenic group had a significantly greater mean melatonin level than each of the other three groups, whereas the three depressive groups did not differ significantly from one another. Only at 2300 hours did both the schizophrenic group and the MDD patients with normal dexamethasone suppression show significantly greater melatonin levels than the MDD patients with dexamethasone nonsuppression or the IDD group. The observed trend for a low circadian melatonin profile in IDD patients with superimposed personality disorders is puzzling.

Key words: Melatonin – Cortisol – Depression

Introduction

There is now mounting evidence that the pathophysiology of melancholia and the mechanism of action of antidepressive treatments involve both alterations in circadian rhythms (Wehr and Wirz-Justice 1982; Kripke et al. 1986) as well as changes in central noradrenergic sensitivity (Charney et al. 1981; Siever and Davis 1985). Melatonin secretion from the pineal gland during darkness is activated by the noradrenergic system (Axelrod 1974). Melatonin is also known to regulate circadian and other rhythms (Armstrong et al. 1986). Circulating melatonin is unique in that it seems to have a modulatory rather than a primary role, by influencing time/phase relationships in the actions of hormones, neurotransmitters, and enzymes (Brown and Niles 1982). It is thus not surprising that melatonin secretion has been suggested as a marker of both circadian and noradrenergic dysfunction in affective disorders.

To date, low night-time circulating serum levels of melatonin have been found in several studies of depressed patients (Wirz-Justice and Arendt 1979; Mendlewicz et al. 1979; Claustrat et al. 1984; Beck-Friis et al. 1985a, b; Brown et al. 1985, 1987; Souêtre et al. 1988). Preliminary data also suggest that melatonin production in depressed patients is increased when treated with antidepressants which acutely augment adrenergic stimulation of the pineal gland (Thompson et al. 1985; Sack and Lewy 1986; Murphy et al. 1986; Nair et al. 1988).

A functional relationship between the pineal gland and the hypothalamic-pituitary-adrenal (HPA) axis has also been suggested in affective disorders. Low nocturnal melatonin secretion, hypercortisolemia and nonsuppression on the dexamethasone (DEX) suppression test (DST) have been shown to correlate in some (Claustrat et al. 1984; Beck-Friis et al. 1985a), but not in all (Brown et al. 1985; Branchey et al. 1982; Nair et al. 1985; Sharma et al. 1989) studies. We have recently proposed that the availability of melatonin along the retinal-hypothalamic-pineal (RHP) axis may have important implications in the genesis of depressive states, and that the neuroendocrine dysregulation along the HPA axis is only a sec-

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ondary event (Steiner et al. 1987). The present study tries to determine further the potential diagnostic relevance of nocturnal pineal activity and to assess the possible interaction between the HPA and RHP axes in newly admitted psychiatric inpatients.

Subjects and Methods

Subjects. Newly admitted patients to the Clinical Studies Program, McMaster Adult Inpatient Psychiatric Unit, St. Joseph's Hospital were approached with a view to recruitment into the study. Subjects of either sex were eligible unless they had severe medical problems, or met other DST exclusion criteria (Carroll 1982). A physical and neurological examination, urinalysis, blood chemistry profile (SMA-12) and thyroid function tests were obtained. Any subject with a history of drug or alcohol abuse, or of major medical illness such as hypertension, diabetes or other endocrine disorder, with abnormal clinical or laboratory findings, or who had to be maintained on any medication that might interfere with the neuroendocrine measures, including long-acting psychotropics, was excluded. Seventy-two patients ranging in age from 17 to 81 years, willing and able to give informed consent formed the inception cohort.

Patients were interviewed by one of the psychiatrists and by the research nurse using the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer 1978), and classified according to Research Diagnostic Criteria (RDC) (Spitzer et al. 1978). For patients who met RDC for intermittent or minor depressive disorder (IDD), the interview was supplemented by DSM III[26] diagnoses for personality disorders (PD). Twenty-nine were men and 43 were women. Twelve qualified for the diagnosis of schizophrenia (SCH), 49 were in an acute major depressive disorder (MDD) episode and 11 had an intermittent or minor depressive disorder superimposed on a personality disorder (IDD/PD). The mean ($\pm$ SD) ages for the SCH, MDD, and IDD/PD groups were 35.3 ± 16.1, 45.7 ± 14.5, and 39.4 ± 13.1 years respectively.

The Hamilton rating scale for depression (HRSD; 17-item) (Hamilton 1960) was completed on each subject in order to assess the level of depression at the time of the study. The mean ($\pm$ SD) HRSD scores of the three patient groups were 19.3 ± 14.9, 22.9 ± 10.3, and 17.4 ± 7.5 respectively. Pre-menopausal women were studied during the follicular phase of their menstrual cycle. All patients were kept medication-free for at least 8 days prior to and throughout the study.

Neuroendocrine Protocol. Patients were kept under controlled dark/light conditions, i.e. in the darkness, blindfolded, and lying in bed, between 2130 and 0600 hours. Samples for melatonin and cortisol were collected using individual venipuncture at 0200, 0800, 1600 and 2300 hours. Night samples were drawn under the illumination of a dim red flashlight aimed at the antecubital area. Patients were ambulatory during the days and were served standard hospital meals. At the end of the 1st day of sampling at 2305 hours, 1 mg DEX in tablet form was administered orally. Repeat sampling for melatonin and cortisol followed on the 2nd day again at 0200, 0800, 1600 and 2300 hours. The HRSD was administered during the 2nd day of the study, and body height (cm) and weight (kg) and season of year were also recorded.

The standardized overnight DST was administered in accordance with previously published guidelines (Carroll et al. 1981). The test was considered abnormal [nonsuppression; DST (+)] if any postdexamethasone serum cortisol level (day 2, 0800, 1600 or 2300 hours) exceeded 138 nmol/l (SI units). All samples were allowed to clot under refrigeration and then centrifuged; serum aliquots were pipetted and frozen at $-20°C$ until analysis.

Assays. Serum cortisol was measured in duplicate by a modified competitive protein binding method (Keane et al. 1975). This method combines a simple deproteinization step with the improved specificity for corticol of horse transcortin. Continuous internal as well as external quality controls comparing our method with radioimmunoassay kits are satisfactory for both high and low cortisol levels. Melatonin was assayed as described by Brown et al. (1983) using a highly specific anti-melatonin serum. The sensitivity of the assay (85% displacement) varied between 4 and 6.6 pg/ml serum. Water blanks were lower than the detection limit. The recovery of authentic melatonin added to serum samples was 87%. At melatonin concentrations of 20.8 and 100.7 pg/ml of serum, the intra-assay coefficients of variance were between 6% and 8%. Compared with a gas chromatography negative chemical ionization mass spectrometry assay, the correlation was $r = 0.983$.

Statistical Analysis. The study has a between and within analysis of variance (ANOVA) design, also known as split-plot or repeated measures (Kirk 1982; Neter et al. 1985). More specifically, the overall design is a one between two within ANOVA. The between factor is group status and has four levels, corresponding to Major Depressive Disorder/Dexamethasone Suppression Test nonsuppressor (MDD/DST+), Major Depressive Disorder/Dexamethasone Suppression Test suppressor (MDD/DST−), the IDD/PD, and the SCH groups. The within-subjects factors are time and day with the first factor having four levels corresponding to the four sampling periods and the second factor having two levels corresponding to the 2 days measurements were made.

Specific substantive and methodological requirements necessitate the performing of additional analyses which do not utilize the entire overall design. For instance, nocturnal melatonin levels are of particular interest, necessitating restricting the analysis to the 0200 hours sampling period. Similarly, melatonin levels for the 2 days must be considered independently in view of the DEX administration prior to the 2nd day; that is, if the data yield a difference across days, the levels for each day must be examined separately.

In view of non-normality and heterogeneity of variance observed in the data, a number of transformations were examined (Kirk 1982; Beck-Friis et al. 1984). It was determined that a logarithmic transformation best normalized the distribution and homogenized the variance. Log transformation was also used for serum cortisol in all statistical analysis. Although the substantive analyses were performed on the transformed variables, for the sake of clarity means and standard deviations are presented in the original untransformed units.

Results

Twenty of the 49 patients who qualified for the RDC of an episode of MDD were DST positive. The remaining 29 MDD patients, the 12 schizophrenics, and the 11 with IDD/PD (9 of them qualified for borderline PD) were all DST negative.

An analysis of age differences across all four groups yielded a nonsignificant effect, as did an analysis of the MDD group versus the other two groups. A separate analysis comparing the age of the MDD group with each of the other groups (Students' *t*-test) yielded a nonsignificant probability value when compared with the IDD/PD group, and a nonsignificant trend for the MDD group to be older than SCH group. There was no difference in HRSD scores across *all four* groups (MDD/DST+: 23.0 ± 11.9; MDD/DST−: 22.9 ± 8.7; IDD/PD: 17.4 ± 7.5; SCH: 19.3 ± 14.9). The relevant analysis across the three groups excluding the DST variable also yielded a highly nonsignificant effect. The cortisol and melatonin results for the four groups throughout the 2 days of the study are presented in Table 1. The relevant DST/cortisol data are summarized in Table 2. Mean cortisol values were calculated for each day over the four measure-

Table 1. Cortisol and melatonin results for the four groups of patients over 2 days of the study

			MDD/DST+	MDD/DST−	IDD/PD	SCH
Cortisol (nmol/l, mean ± SD)	Day 1	0200	160.0 ± 131.3	125.6 ± 105.2	57.7 ± 50.2	94.1 ± 86.4
		0800	459.5 ± 140.8	411.0 ± 138.0	418.1 ± 139.9	352.5 ± 74.7
		1600	276.3 ± 83.0	214.6 ± 132.4	203.5 ± 81.3	224.1 ± 74.1
		2300	104.0 ± 65.6	81.2 ± 52.5	44.5 ± 16.9	70.0 ± 45.7
	Day 2	0200	59.0 ± 42.7	40.6 ± 15.5	39.0 ± 20.7	31.6 ± 5.7
		0800	253.5 ± 171.2	38.9 ± 18.5	32.7 ± 9.0	30.0 ± 0.0
		1600	231.8 ± 120.1	40.7 ± 22.1	34.0 ± 9.6	30.0 ± 0.0
		2300	94.2 ± 90.5	41.0 ± 21.1	35.4 ± 12.1	30.8 ± 2.8
Melatonin (pg/ml, mean ± SD)	Day 1	0200	50.7 ± 53.4	51.7 ± 40.0	34.3 ± 28.8	58.5 ± 35.7
		0800	18.5 ± 19.5	19.6 ± 16.1	25.3 ± 22.3	32.3 ± 19.7
		1600	14.4 ± 9.4	20.7 ± 17.0	19.3 ± 15.8	24.1 ± 15.6
		2300	25.8 ± 27.6	41.8 ± 40.3	17.2 ± 9.4	45.8 ± 23.0
	Day 2	0200	36.2 ± 25.1	38.8 ± 23.0	24.1 ± 14.9	55.8 ± 33.6
		0800	21.1 ± 19.9	18.6 ± 11.1	13.5 ± 9.1	25.7 ± 17.1
		1600	14.1 ± 8.0	19.8 ± 15.4	16.3 ± 13.9	23.1 ± 19.3
		2300	33.4 ± 47.8	34.0 ± 32.8	19.9 ± 9.0	45.3 ± 30.9

Owing to missing data, the effective n for the MDD/DST+ group ranges from 16 to 20, for the MDD/DST− group it ranges from 28 to 29, and for the IDD/PD group it ranges form 10 to 11. The SCH group had no missing data

Table 2. Pre- and post-dexamethasone serum cortisol (nmol/l; mean ± SD)

Group	Pre	Post
MDD/DST+	251.7 ± 78.3*	159.6 ± 94.6**
MDD/DST−	208.1 ± 75.4	40.6 ± 11.7
IDD/PD	183.7 ± 54.3	33.7 ± 9.3
SCH	185.2 ± 49.5	30.6 ± 2.1

Mean values calculated for each day over the four sampling times. The MDD/DST+ group had the highest baseline (* $P<0.05$) and post-DEX (** $P<0.001$) levels; the remaining three groups did not differ from one another

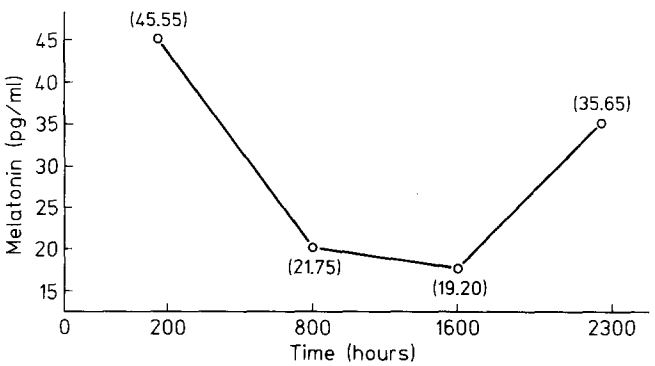

Fig. 1. Graphic illustration of serum melatonin profile for entire sample ($n=72$). Nocturnal mealtonin (0200 and 2300 hours) was significantly elevated when compared with daytime (0800 and 1600 hours) levels in all subjects ($P<0.001$)

ment periods. The groups were found to differ significantly with respect to baseline levels [$F(3,66)=3.20$, $P<0.05$], as well as postdexamethasone levels [$F(3,62)=27.37$, $P<0.001$]. Duncan's multiple range test (Duncan 1955; Kramer 1956) revealed that the MDD/DST + group had the highest baseline and postdexamethasone levels ($P<0.05$) and the remaining three groups did not differ from one another.

An analysis of the full experimental design on logarithmically transformed melatonin levels revealed the following: main effects for groups ($F(3,61)=3.49$, $P<0.05$, day, $F(1,61)=5.15$, $P<0.05$, and time, $F(3,183)=31.91$, $P<0.001$, and no significant interactions. The day effect revealed that melatonin levels decreased from before the administration of DEX (32.6 ± 17.5) to after (28.4 ± 15.9). In view of this finding, it would be inappropriate to combine the melatonin profiles from both days. However, the lack of significant interactions indicates that the decrease in melatonin is consistent across the four groups and is not disproportionately related to any one group.

An orthogonal decomposition of the time repeated measures effect (Kirk 1982) revealed that a quadratic trend provides the best fit to the data ($t=7.59$, $P<0.001$). In view of the fact that the levels of this measure represent the 0200, 0800, 1600 and 2300 hours sampling periods, the quadratic trend provides evidence for elevated nocturnal levels of melatonin. This effect is graphically illustrated in Fig. 1.

The groups' main effect from the total design ANOVA had to be examined in greater detail. Multiple comparisons conducted to investigate this effect further revealed that the SCH group yielded a significantly greater mean melatonin level (38.8 ± 17.4) than each of the other three groups ($P<0.05$); however, the means of the MDD/DST+, MDD/DST−, and IDD/PD groups did not significantly differ from one another (29.0 ± 14.5; 30.3 ± 15.0; 22.5 ± 12.3, respectively).

Table 3. Nocturnal serum melatonin (pg/ml; mean ± SD) collapsed across the 2 days

Group	0200 hours*	2300 hours**
MDD/DST+	45.5 ± 32.1	30.0 ± 26.7
MDD/DST−	45.2 ± 27.9	37.9 ± 28.6***
IDD/PD	29.2 ± 17.2	18.5 ± 7.5
SCH	57.2 ± 29.1	45.6 ± 25.0****

* Groups effect $P < 0.08$
** Groups effect $P < 0.002$
*** MDD/DST− vs MDD/DST+ and MDD/DST− vs IDD/PD ($P < 0.05$)
**** SCH vs MDD/DST+ and SCH vs IDD/PD ($P < 0.001$)

Correlation coefficients were computed between both logarithmically transformed total melatonin secretion scores and nocturnal melatonin secretion scores (0200 hour samples) and the following variables: age, sex, height, weight, and height/weight ratio. Results revealed that only the relation between age and total melatonin secretion yielded a significant correlation ($r = -0.31$, $P < 0.01$). Including age as a covariate in the full design ANOVA did not, however, influence the substantive results of the analysis. As is indicated in Fig. 1, the 0200 hours sampling period yielded the highest mean melatonin levels. This sampling period was therefore used in examining differences in nocturnal melatonin secretion.

The relation of total and nocturnal melatonin levels to depressive symptomatology (HRSD) and to season of the year were also examined in the full design ANOVA. However, no significant relations were found.

The ANOVA on nocturnal (0200 hours) melatonin levels [one between (groups), one within (day) repeated measures ANOVA] yielded a significant day effect [$F(1, 68) = 4.06$, $P < 0.05$], consistent with the full design analysis, but yielded a groups effect which only approached conventional levels of statistical significance [$F(3, 68) = 2.39$, $P < 0.08$). Even though the 0200 hours sampling is generally found to yield the peak melatonin secretion level the 2300 hours sampling was also examined. The ANOVA performed on these data yielded a highly significant groups effect [$F(3, 67) = 5.43$, $P < 0.002$] but a nonsignificant day effect (see Table 3). Further analysis of the 2300 hours data reveals that the SCH group has a significantly greater mean melatonin level than the MDD/DST+ group and the IDD/PD group ($P < 0.001$); moreover, the MDD/DST− group has a significantly greater mean than the MDD/DST+ group and the IDD/PD group ($P < 0.05$). Thus, despite the fact that the MDD/DST+ group cannot be statistically differentiated from the IDD/PD group and the MDD/DST− group cannot be differentiated from the SCH group, the MDD/DST+ group does yield a lower level of melatonin than does the MDD/DST− group and the SCH group.

Discussion

This study was primarily undertaken to determine the potential diagnostic relevance of overnight serum melatonin secretion in newly admitted psychiatric inpatients and to assess the possible relationship between dysregulated HPA and RHP axes in depressive states.

We found that acute inpatients diagnosed as MDD and who are identified as nonsuppressors on the DST exhibit significantly lower levels of nocturnal melatonin than both patients diagnosed as MDD but who are identified as suppressors on the DST and patients with the diagnosis of schizophrenia. However, this finding is statistically significant only at the 2300 hours nocturnal sampling period.

There are two possible explanations for finding these differences reliably at 2300 hours and not at 0200 hours:

1. The influence of the DEX administration. Whereas a significant day effect was found for the full design as well as at 0200 hours, the 2300 hours sampling yielded a highly nonsignificant effect.

2. Sampling methods and individual variation. Whereas the present study sampled melatonin at only two time periods during the night, other studies have collected a greater number of samples (Beck-Friis et al. 1984; Lynch et al. 1987). Beck-Friis et al. (1984), for example, sampled every 2 h during the night and then analyzed the maximum melatonin levelfor each patient. Lynch et al. (1987) have also shown that there is "very considerable variation among individuals in peak melatonin levels, time courses, and total amounts of melatonin secreted". Thus, although previous studies have found the peak melatonin level to occur at 0200 hours for the *group,* peak levels for *individual* patients may well occur at a variety of different times. Lynch et al. (1987) also pointed out that a period of acclimatization is required in order to reduce this variability in individual levels. Consistent with this, the 2300 hours sampling period which yielded the substantive findings in the present study also happens to represent the time period with the greatest duration of acclimatization and although this study was not designed to control for circadian rhythmicity, the possibility that some of the patients were phase-advanced has to be considered.

The observed trend in our personality disorders patients for a low circadian melatonin profile is puzzling. This group consistently yielded the lowest mean melatonin level and was indistinguishable from the MDD/DST+ group at the 2300 hours sampling period. It is possible that these preliminary noted differences in a small group of the IDD/PD patients occur not because of a process intrinsic to the depressive illness, but rather because of secondary behavioral accompaniments of this state. Change in a small group of patients with secondary depression has also been reported in neuroendocrine studies along the hypothalamic-pituitary-gonadal axis (Ettigi et al. 1979). The study of a possible link between these two sets of findings would appear to be necessary in a large group of patients with personality disorders.

Despite the fact that all groups exhibited a similar degree of depressive symptomatology (as evidenced by the HRSD scores), the melatonin profile of the schizophrenia group appeared to be significantly different from that of the depression groups, and patients experiencing de-

pressive symptoms in addition to a personality disorder appeared to be more similar to depressives than to non-depressives. The lack of a control group of normal volunteers and the lack of axis II diagnosis for possible personality disorders in the MDD and schizophrenia groups preclude us from making a statement about the finding. On the other hand, the nocturnal melatonin levels in our schizophrenia group are very similar to results reported in healthy men (melatonin assays for these two studies performed by the same laboratory, see Arato et al. 1985). The inter-individual variations in our patient population are extreme but are also very similar to those reported by others for both normal volunteers and patients (Claustrat et al. 1984; Arato et al. 1985; Sack et al. 1986). We have no explanation for these extreme individual variations. Our data fail to support the notion that such differences can be explained by differences in sex, weight/height ratio, or seasonality. Studies on the effect of age on melatonin production in humans are still very inconsistent. A decline of melatonin production with age has been shown by some (Sack et al. 1986; Iguchi et al. 1982; Touitou et al. 1984; Nair et al. 1986), whereas others found that age had no effect (Beck-Friis et al. 1984; Wirz-Justice and Richter 1979; Arendt et al. 1982; Illnerova et al. 1985). In some of the reports a decline in melatonin production was only evident in the very old. Our findings demonstrating an influence of age as a covariate are consistent with previous research in the larger samples (Beck-Friis et al. 1984; Iguchi et al. 1982; Touitou et al. 1984). In our study 14 of the 72 patients were over 55 but only 2 were over 75 years of age.

The relationship between obesity and melatonin production is unclear (Sack et al. 1986; Arendt et al. 1982; Claustrat et al. 1986). Our data show a lack of a significant relation between melatonin and body height, which is inconsistent with recent research (Beck-Friis et al. 1984). Differences in melatonin sampling may account for some of these discrepancies. We have excluded from this study patients with extreme obesity or anorexia because some data have suggested an association between these states and abnormalities along the HPA and RHP axes (Brown et al. 1989; Kennedy et al. 1989).

Seasonal changes in human melatonin production have been suggested by some investigators (Wirz-Justice and Arendt 1979; Touitou et al. 1984), and in a recent preliminary report depressed patients revealed high summer and low winter melatonin values, whereas the control group had low summer and high winter values (Dietzel 1987). With the more recent establishment of a reliable assay for the urinary melatonin metabolite 6-sulphatoxy-melatonin (6-S-MEL) (Arendt et al. 1985; Kennaway and Royles 1986) it appears that this measurement more accurately reflects the amount of melatonin production when compared with infrequent blood sampling. Similarly, outpatients who were studied throughout the year did not show, as a group, any significant seasonal differences in total amounts of melatonin (Beck-Friis et al. 1984). Our study, though, was not designed to, and did not measure possible phase shifts in the different diagnostic groups across the seasons.

The decrease in melatonin levels following the DEX administration suggests that the HPA and RHP axes are not entirely independent. Beck-Frijs et al. (1985a) also reported that DEX affected melatonin secretion with a significant decrease of melatonin at 0800 hours after DEX administration. However, the opposite effect, a highly significant increase in melatonin excretion during the night following DEX has recently been reported in children and adolescents (Lang et al. 1986). Moreover, the fact that MDD patients who are DEX nonsuppressors exhibited a significantly lower level of nocturnal melatonin than did MDD patients who are DEX suppressors suggests that the two axes do in fact interact in depression. Although the design precluded determining the causal precedence of the two systems, the findings nonetheless demonstrate that individuals experiencing a major depressive disturbance who have neuroendocrine dysregulation along the HPA axis have a lower availability of melatonin along the RHP axis than individuals experiencing a major depressive disturbance but no abnormality along the HPA axis.

Studies in other situations do not support a generalizable link between the HPA and the RHP axes at the hypothalamic level. Pronounced changes in melatonin but not cortisol rhythms during the menstrual cycle indicate that fluctuations in melatonin are not necessarily associated with changes along the HPA axis. Furthermore, these menstrual cycle related changes in melatonin are not due to stress which would also affect cortisol levels (Hariharasubramanian et al. 1985). A dissociation of corticosterone and melatonin levels has also been observed in rats in response to an acute stress paradigm (Seggie 1985). Reports on the direct effects of melatonin on the HPA axis are conflicting, some suggesting inhibition (Preslock 1984), others stimulation (Niles et al. 1977). It is still unclear whether low melatonin levels are a specific marker for depression. It is speculated that it is not the absolute amount but rather the availability and timing of melatonin along the RHP axis which has important implications in the genesis of depressive disorders (Steiner et al. 1987; Reiter 1987). Studies measuring overnight urinary 6-S-MEL levels in different patient populations should make the task of identifying diagnostically meaningful sensitive and specific phase shifts in melatonin production easier.

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