Differences in Nocturnal Melatonin Secretion Between Melancholic Depressed Patients and Control Subjects

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The authors took multiple serum samples for measurement of melatonin between 4:30 p.m. and 7:30 a.m. in seven male depressed patients with melancholia and five healthy male control subjects and found that melancholic patients had a significantly lower rise of melatonin. They also compared a second, separate group of 14 women and five men suffering from melancholic depression with seven healthy male control subjects and nine depressed women without melancholia. The melancholic patients had a significantly lower concentration of serum melatonin at 11:00 p.m. than either the control subjects or the nonmelancholic depressed patients. These findings support the possibility that the functioning of the pineal gland is altered in these patients.

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Serum melatonin (*N*-acetyl-5-methoxytryptamine) in humans and animals shows a circadian rhythm: highest concentrations are secreted during darkness (1, 2). In animals, the signal for this rhythm appears to originate in the suprachiasmatic nucleus (3) and is influenced by environmental lighting (4). Light impinging on the retina acts through a multisynaptic pathway to inhibit firing of neurons in the superior cervical ganglia, resulting in diminished release of norepinephrine from the sympathetic nerves that innervate the pineal gland (5). On release, norepinephrine activates β-adrenergic receptors on the pinealocyte to cause an increase in the synthesis of melatonin from its precursor, serotonin (6). A mechanism similar to that found in rats may occur in humans because propranolol blocks the nocturnal rise of melatonin in humans (7, 8) and the nocturnal rise is absent in patients with transection of the cervical spinal cord (9). Thus, in humans as well as in animals, melatonin secretion may serve as an index for both adrenergic functioning and circadian systems (10).

The development of techniques to measure melatonin accurately (11, 12) has fostered interest in the investigation of melatonin in patients with affective disorders because it has been speculated that affective disorder is associated with alterations in circadian rhythms (4, 13) or alterations in noradrenergic function (14, 15).

Although the first study of urinary melatonin levels in six depressed patients detected no abnormality compared with levels in six control subjects (16), subsequent studies of serum melatonin have suggested disturbances of melatonin secretion in affective disorders. Wetterberg et al. (17) reported lower melatonin and higher cortisol levels at midnight and 2:00 a.m. in a 48-year-old woman during a unipolar depressive episode compared with levels measured during a healthy period. Wirz-Justice and Arendt (18) noted lower melatonin levels in six patients with unipolar depression at 8:00 a.m. compared with the concentrations found in 12 healthy control subjects. Mendlewicz et al. (19) described an absence of the normal nocturnal increase of melatonin in three of four depressed patients compared with that measured in five normal subjects. Lewy et al. (20) reported higher plasma melatonin levels measured at 7:00 p.m., 2:30 a.m., 3:00 a.m., 7:00 a.m., 11:00 a.m., and 3:00 p.m. in four bipolar patients during the manic phase than in the depressed phase; values in the manic phase were higher than those measured in four normal control subjects. In a summary of a series of studies by his group, Wetterberg (21) described lower serum melatonin levels measured at 2:00 a.m. in 17 patients with major depression who were nonsuppressors of cortisol

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in response to dexamethasone compared with levels in 22 control subjects and 15 patients with major depression who had normal suppression of cortisol in response to dexamethasone.

Such results and our interest in the effects of antidepressants on noradrenergic function (22, 23) caused us to measure both daytime and nighttime concentrations of melatonin in patients with affective disorders and in healthy control subjects. The results show that patients with affective disorders, especially those with the clinical symptoms associated with melancholia, have a reduced nocturnal secretion of the pineal hormone.

METHOD

Two separate but related studies were performed, one in Philadelphia and one in New York City.

Philadelphia

In the first study two male outpatients with depression were studied at the Clinical Research Center of the Hospital of the University of Pennsylvania and five male inpatients with depression were studied at the Philadelphia Veterans Administration (VA) Medical Center. All patients met *DSM-III* criteria for major depressive disorder with melancholia. In addition, five healthy male control subjects with no significant medical or psychiatric history were studied. The seven patients were rated for severity of depression according to the Hamilton Rating Scale for Depression (24); they had to have a score of at least 18 on this 21-item scale to be included in the study. Demographic data on these subjects are shown in table 1.

Subjects were excluded if they had evidence of significant medical or neurological illness (as revealed by history, physical examination, or routine laboratory testing), alcohol or drug abuse, schizophrenia, or use of glucocorticoids within the previous 6 months. All patients were drug free for at least 7 days before testing. They had received no antidepressants within 2 weeks of testing or ECT within 3 months of testing. Informed consent was obtained from all subjects. Outpatients were admitted to the Clinical Research Center at the Hospital of the University of Pennsylvania on the afternoon of the study day. An indwelling catheter was inserted into an arm vein at 4:00 p.m., and blood was drawn at the following times for subsequent analysis of serum melatonin: 4:30, 6:00, 7:30, 9:00, and 10:30 p.m.; midnight; and 1:30, 3:00, 4:30, 6:00, and 7:30 a.m. Lights were turned off at 10:00 p.m. and turned on at 6:30 a.m. The room was completely darkened during the dark phase of sampling; blood was taken with the aid of a dim red light. Inpatients were studied at the VA Medical Center by using an identical procedure. Blood was stored at −4°C and centrifuged within 12 hours to obtain serum, which was frozen at −70°C until assayed within 2 months.

TABLE 1. Characteristics of Patients in Studies of Melatonin Secretion in Melancholic Depression

	Age (years)		Weight (kg)		Hamilton Scale Score	
Study Group	Mean	SE	Mean	SE	Mean	SE
Philadelphia sample						
Depressed male patients with melancholia (N=7)	42	4	76.7	3.4	31	3.4
Healthy male control subjects (N=5)	32	5	78.1	2.5	—	
New York sample						
Depressed male and female patients with melancholia (N=19)[a]	62.4	2.5	61.1	2.7	35.9	4.3
Depressed female patients without melancholia (N=9)[b]	57.3	4.5	64.0	4.7	23.1	1.7
Healthy male control subjects (N=7)	41.4	4.0	77.9	4.3	—	

[a]Depressed patients with melancholia were significantly older than control subjects ($t=4.5$, $df=10$, $p<.01$) and had significantly higher Hamilton scale scores than depressed patients without melancholia ($t=4.6$, $df=25$, $p<.001$).
[b]Depressed patients without melancholia were significantly older than control subjects ($t=2.7$, $df=13$, $p<.02$).

New York City

In the second study all of the patients were hospitalized on the inpatient clinical research unit of Payne Whitney Clinic (New York Hospital-Cornell Medical Center). Nineteen depressed patients with melancholia met all inclusion and exclusion criteria specified for the Philadelphia sample. Nine additional patients were studied who met *DSM-III* criteria for major depressive disorder without melancholia. Twenty-three patients were women (table 1); additional exclusion criteria for these women were pregnancy or use of oral contraceptives in the previous 6 months. Seven healthy male control subjects were also studied. Informed consent was obtained from all subjects.

In this study, blood was drawn by venipuncture at two time points, 9:00 a.m. and 11:00 p.m. Lights were turned off at 10:00 p.m. and on at 6:30 a.m. Blood was drawn during the dark phase in a darkened room with the aid of a dim flashlight. Both blood samples were centrifuged immediately, and the serum was obtained and stored frozen as described for the Philadelphia sample.

Diagnoses at both locations were made by research psychiatrists (R.B., J.H.K., J.A., S.C., and A.W.) on the basis of semistructured interviews. Interrater reliability for *DSM-III* diagnoses of major depression with and without melancholia and total Hamilton Rating Scale for Depression scores was established by five raters on the basis of seven videotaped interviews. Interrater agreement for the diagnosis of major depression with and without melancholia was 100%. The intraclass correlation coefficient for total Hamilton severity was .9 ($p<.001$) (25).

Dexamethasone Suppression Test

We gave the dexamethasone suppression test (DST) to 16 depressed patients with and seven depressed patients without melancholia in the New York City sample. The test consisted of oral administration of 1 mg of dexamethasone at 11:00 p.m. within 3 nights after sampling for melatonin was completed. On the day following administration of dexamethasone, blood was drawn at 8:00 a.m. and 4:00 p.m. for determination of cortisol in plasma. A patient whose cortisol value was 5 μg/dl or more at either time point after dexamethasone administration was considered a nonsuppressor (26).

Cortisol was determined by radioimmunoassay exactly as described previously (26).

Measurement of Melatonin

The concentration of melatonin in serum was measured by the radioimmunoassay procedure developed by Rollag and Niswender (11). Antiserum was obtained from Dr. Mark Rollag. This antiserum uses an ^{125}I-melatonin analog purchased from MELOY Laboratories, Inc. (Springfield, Va.). This assay is very sensitive: 2.5 pg of melatonin produces approximately an 8% reduction in total counts bound to the antiserum; 50% inhibition of binding is produced by about 30 pg of melatonin. Serial dilutions of human serum show parallelism with a standard curve, and the recovery of known amounts of melatonin to human serum is about 100%.

Both serum and standard concentrations of melatonin (0.5 ml) are extracted with chloroform; the extracted sample is taken to dryness and then reconstituted with a 0.1% gelatin buffer. The reconstituted sample is washed with petroleum ether and then 300 μl of the sample is used in the radioimmunoassay. Briefly, antibody and ^{125}I-melatonin analog are added to the samples, which incubate for 40–48 hours at 4°C. The antigen-antibody complex is precipitated by the addition of cold ethanol and collected by centrifugation at 1800 g for 30 minutes at 4°C. The ^{125}I bound is then measured by using a Beckman 4000 gamma counter. All samples and standards are assayed in triplicate.

Data Analysis

For melatonin results obtained in Philadelphia a two-way analysis of variance (ANOVA) was performed with the independent variables of diagnosis and time of sampling and the dependent variable of melatonin. Post hoc analyses used Duncan's multiple range test for comparison of multiple means.

For melatonin results obtained in New York City, two-sample t tests for parametric data, Mann-Whitney tests for nonparametric data, and Spearman's rank correlations for correlations of melatonin with age and melatonin with Hamilton scale scores were used. Pearson correlation coefficients for log-normalized distributions of melatonin and weight were calculated.

For the analysis of DST results, Fisher's exact test was used to determine differences in rates of nonsuppression versus suppression in melancholic and nonmelancholic groups, and the Mann-Whitney test was used to determine differences in melatonin between suppressors and nonsuppressors.

RESULTS

Philadelphia

The concentration of melatonin in serum in the subjects, who had 11 blood samples taken over a 15-hour period, is shown in figure 1. The concentration of melatonin in serum was less in all subjects when measured before the light was turned off. During the dark phase, the concentration of melatonin in serum rose in all study groups, as revealed by the significant effect of time of sampling ($F=23.9$, $df=10$, $p<.001$). However, it did not rise as much in the depressed patients with melancholia, as indicated by the significant interaction between diagnosis and time ($F=3.8$, $df=10$, $p<.001$). Post hoc analyses did not reveal any significant difference between the patients and control subjects at any individual time point. However, the mean±SE of the peak values of melatonin for each individual was less in the group of melancholic patients (53±10 pg/ml) than in the control group (89±9 pg/ml) ($p<.05$, $df=10$, t test).

There were slight but not significant differences in age between the patients and control subjects (table 1). However, there was no significant correlation with age and the peak value for each individual of melatonin measured in either the melancholic patients (Spearman $r=.3$) or the healthy control subjects (Spearman $r=0$). Total Hamilton scale score did not correlate with peak melatonin values (Spearman $r=.43$).

New York City

The results obtained in the study group in New York City for melatonin at 11:00 p.m. are shown in figure 2. Because mean±SE values obtained in male depressed patients with melancholia (40±10.8 pg/ml) were not significantly different from those measured in female depressed patients with melancholia (35±5.1 pg/ml) (Mann-Whitney test), results from male and female melancholic patients were combined. The mean value obtained for melancholic patients (36.4±4.6 pg/ml) was significantly lower than that measured in either control subjects (60.3±8.0 pg/ml, $p<.05$, Mann-Whitney test) or nonmelancholic depressed patients (58.6±9.6 pg/ml, $p<.05$, Mann-Whitney test). Because all control subjects were male, their values were compared independently with those found in the five male melancholic depressed patients; these two values were not significantly different. Similarly, because all

FIGURE 1. Concentration of Melatonin in Serum of Five Healthy Male Control Subjects and Seven Male Depressed Patients With Melancholia

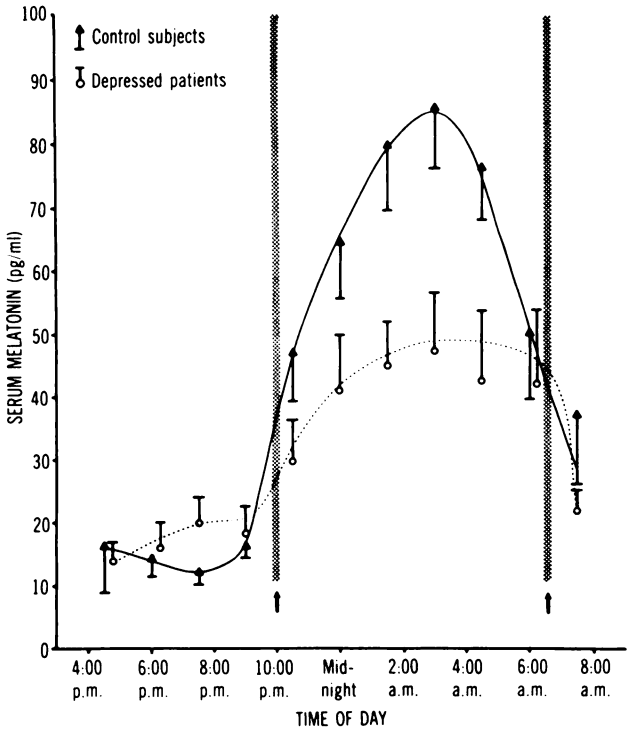
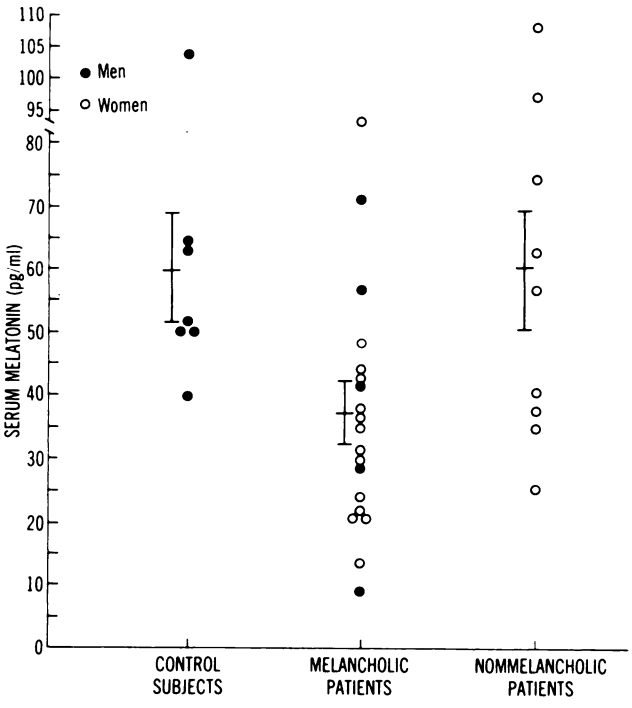


FIGURE 2. Concentration of Melatonin in Serum of Seven Healthy Control Subjects, 19 Depressed Patients With Melancholia, and Nine Depressed Patients Without Melancholia at 11:00 p.m.[a]



[a]Range shown is mean±SE.

nine nonmelancholic depressed patients were female, their mean melatonin value (58.6±9.6 pg/ml) was compared with the mean of the female melancholic depressed patients. A significant difference was found ($p<.05$, Mann-Whitney test) between these two groups.

No significant differences in the mean±SE 9:00 a.m. serum melatonin values were found among 18 of the melancholic depressed patients (14.0±2.0 pg/ml), eight of the nonmelancholic depressed patients (15.1±2.3 pg/ml), or the seven control subjects (14.0±2.9 pg/ml). (We missed getting the morning sample for one of the 19 melancholic depressed patients and one of the nine nonmelancholic depressed patients.)

There were no significant correlations between melatonin measured at 11:00 p.m. and age for melancholic patients, control subjects, nonmelancholic patients, or the entire sample (Spearman r ranged from −.1 to .6). The Pearson correlation coefficient for log-normalized distributions of melatonin levels at 11:00 p.m. and weights in all depressed patients was −.12 ($df=26$, $p>.5$). Although there was no significant correlation between melatonin at 11:00 p.m. and total Hamilton scale scores (Spearman $r=-.29$, $p>.1$) for all patients, total Hamilton scale scores were greater in melancholic than in nonmelancholic patients (table 1).

Dexamethasone Suppression Test

Of the 16 melancholic patients given the DST, 13 were nonsuppressors. In contrast, of six nonmelancholic patients given the DST, only one was a nonsuppressor. This difference in results of the DST between the melancholic patients and the nonmelancholic patients was significant ($p<.05$, Fisher's exact test). However, no significant reduction in values of melatonin measured at 11:00 p.m. was found in those who were nonsuppressors (41.3±6.2 pg/ml) compared with the values in suppressors (44.7±7.4 pg/ml) ($p>.7$, Mann-Whitney test).

DISCUSSION

The major finding from these studies was lower nocturnal concentrations of serum melatonin in patients with major depressive disorder, melancholic subtype, compared with that measured in either healthy control subjects or patients with major depression without melancholia.

This is seen most clearly in the study conducted in Philadelphia, in which serum samples were taken frequently through the night. The nocturnal rise of melatonin in the male melancholic patients was significantly lower than that measured in healthy male control subjects. This study did not include any nonmelancholic depressed patients. However, the one conducted in New York City did, and the value of melatonin measured at 11:00 p.m. in depressed female

patients with melancholia was significantly lower than that seen in depressed female patients without melancholia. Due to the small number of male melancholic patients studied in New York City, the value measured in these patients at 11:00 p.m. was not significantly different from that measured in the male control subjects. However, comparison of the values obtained in the male subjects studied in New York City shows excellent agreement with those obtained in the male subjects studied in Philadelphia (figure 1). Furthermore, the value obtained in the combined groups of male and female melancholic depressive patients was significantly lower than that measured in the male control subjects. Others (27–29) have shown minimal effects of gender on concentrations of melatonin in serum. Beck-Friis et al. (29) have shown, further, that not only are the minimal effects of gender unlikely to account for decreased nocturnal melatonin in depressive patients but the small effects of age and season are unlikely to account for the large effect of depression. Consequently, we think that all these results are consistent with the view that melancholic depressive patients have a reduced nocturnal rise of melatonin.

Although others have reported altered melatonin concentrations in major depression, this study, to our knowledge, is the first demonstration of an association between a diminished nocturnal rise of melatonin and the diagnosis of melancholia, a subtype of major depressive disorder.

Jimerson et al. (16) measured urinary melatonin levels in six patients with primary affective disorder before and after sleep deprivation. They were unable to demonstrate any abnormality using a relatively insensitive bioassay. Lewy et al. (20) reported that melatonin levels were higher in bipolar patients in their manic phase than in their depressed phase. Wetterberg et al. (17) found lower melatonin levels at midnight and 2:00 a.m. but not at 6:00 a.m. in a patient during one of many suicidal depressed episodes, in addition to an increase in cortisol secretion. Similar to our results, the absence of a nocturnal increase in melatonin was noted by Mendlewicz et al. (19) in three of four severely depressed women during depression and again 4 to 6 weeks later, after recovery. However, because they reported daytime melatonin levels on the order of 100 pg/ml, the validity of the assay used in the studies by Mendlewicz et al. must be questioned.

Wetterberg (21) reported an association between high serum cortisol, abnormal DST results, and low melatonin levels in acute depressive episodes. Even remitted, euthymic patients with normalization of cortisol levels continued to show low melatonin levels 6 weeks after recovery. Branchey et al. (30) also reported a similar association of cortisol hypersecretion and lowered melatonin with normalization of hypothalamic-pituitary-adrenal function but not melatonin after clinical recovery in three patients. In our study we noted an association between symptoms associated with melancholia and nonsuppression in the DST. In spite of this, we did not find any difference in the value of melatonin measured at 11:00 p.m. between DST suppressors and nonsuppressors. This result is at variance with that of Wetterberg (21). One reason for this might be that our values for melatonin were obtained at 11:00 p.m., which is clearly before the peak nocturnal value (figure 1). In the studies of Wetterberg (21), values for melatonin were taken at 2:00 a.m. and probably reflect peak values. Further studies are needed to clarify the nature, if any, of the association between abnormalities in hypothalamic-pituitary-adrenal activity and pineal function.

The reduced values of melatonin in the melancholic depressive patients were confined to the nocturnal values. Samples taken at 9:00 a.m. from the study group in New York City or serum taken between 4:30 and 9:00 p.m. from the groups in Philadelphia did not show even a trend for the melatonin concentration to be lower in the melancholic depressive patients than that in the control subjects. In contrast to these results, Wirz-Justice and Arendt (18) reported lower values of melatonin in six unipolar depressive patients compared with 12 normal control subjects in serum taken at 8:00 a.m.

Interestingly, Carroll (31) has reported DST nonsuppression to be particularly associated with melancholia, although the specificity of this finding remains controversial according to both previous and subsequent reports (26, 32, 33). Conflicting results on this issue may be partly related to the difficulty in operationalizing criteria for melancholia or an endogenous subtype (34) as well as differences in populations (e.g., age, severity of illness, inpatient or outpatient status), dose of dexamethasone, timing of DST during admission, etc. (26). In this regard it should be noted that virtually all melancholic patients in this study displayed significant degrees of psychomotor disturbance and self-reproach, in addition to lack of responsiveness to an initial drug-free period of treatment. Indeed, a high incidence of DST nonsuppression associated with melancholia but not a high degree of concordance between this abnormality and diminished nocturnal melatonin secretion was found.

Mechanisms underlying the decreased nocturnal rise in melatonin in melancholia are still unknown. There is evidence that depression may be associated with elevated sympatho-adrenal activity (35–38), and such activity, if prolonged, might cause subsensitivity of pineal β receptors. It would be useful to measure serum catecholamines and melatonin together in future studies. Alternatively, low nocturnal levels of melatonin might be an expression of a generalized defect in sensitivity of β-adrenergic receptors or of sympathetic transmission.

The diagnostic specificity of this finding of decreased nocturnal secretion of melatonin is unknown. One report (39) showed no decrease in nighttime melatonin in schizophrenia; another (40) showed decreased midnight secretion in schizophrenia, but this was primarily a function of differences between groups in body weight.

These preliminary findings of a decreased nocturnal rise of melatonin secretion in melancholia support the possibility that the functioning of either the pineal gland or its sympathetic input is altered in this population of patients. Further investigation will be necessary to confirm these findings and to clarify the relationship of melatonin to variables such as diagnosis, clinical state, and other proposed biological markers in affective disorders.

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