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# Circadian profiles of melatonin in melancholic depressed patients and healthy subjects in relation to cortisol secretion and sleep

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**Abstract**

Circadian secretion of melatonin was measured in melancholic depressed patients ($n = 9$) and age- and sex-matched healthy control patients ($n = 9$). The mean age of the depressed patients was 29 years, i.e. younger than in most earlier studies, and a drug-free interval of 3 weeks preceded the investigations. Melatonin secretion was similar in depressed patients and healthy subjects with no significant differences at any of the time points, thus not confirming earlier studies in which depressed patients were found to have lower melatonin levels than control patients. The discrepancy between our result and earlier studies may be explained by different patient characteristics such as age, duration of illness, previous treatment, and alcohol intake. It is conceivable that a diminution of nocturnal melatonin secretion in depressed patients might only occur during the long-term course of the depressive illness and/or its pharmacological treatment. © 1997 Elsevier Science Ireland Ltd.

*Keywords:* Affective disorder; Polysomnography; Circadian rhythms; Melatonin

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## 1. Introduction

Serum melatonin shows a circadian rhythm with high concentrations during the night and low levels during the day (Vaughan, 1984; Arendt et al., 1987). This endocrine rhythm is under neural control of the suprachiasmatic nuclei and is influenced by light (Moore and Klein, 1974; Lewy et al., 1980; Brown, 1994). The nocturnal production of melatonin by the pineal gland is predominantly controlled by noradrenergic fibers that project to β-adrenergic receptors on the pinealocytes and stimulate the synthesis of melatonin from its precursor serotonin via the pineal's time-keeping enzyme serotonin-*N*-acetyltransferase. Beta-blockers have been shown to suppress melatonin secretion (Demitrack et al., 1990). Melatonin secretion is of special interest in depression research for several reasons.

Down-regulation of β-adrenergic receptors seems to be a common feature of most antidepressants after their chronic administration (Sulser, 1981). A disturbance of central β-adrenergic activity might therefore be one underlying biological mechanism that is linked to neuroendocrine abnormalities in depressive patients. Since melatonin secretion is controlled by β-adrenergic receptors, a disturbance of melatonin secretion could be present during the acute phase of the illness and changes might occur with antidepressant treatment (Demisch, 1993).

Many earlier studies reported a reduction of melatonin secretion in depressed patients compared with healthy controls (Wetterberg et al., 1979, 1982; Mendlewicz et al., 1980; Wetterberg and Aperia, 1983; Beck-Friis et al., 1984; Claustrat et al., 1984; Brown et al., 1985; Frazer et al., 1985; Souêtre et al., 1989). Lewy et al. (1979) and Lewy (1983) reported greater melatonin levels in bipolar patients when they were manic than when they were depressed and suggested that the amplitude of melatonin production reflects state-dependent changes in noradrenergic function. In some studies, lower melatonin secretion occurred in those depressed patients with a hyperactivity of the hypothalamo-pituitary-adrenal (HPA) axis (Wetterberg and Aperia, 1983; Claustrat et al., 1984; Beck-Friis et al., 1985), and a relationship between cortisol hypersecretion and low melatonin was postulated. Later studies by Thompson et al. (1988) and Rubin et al. (1992) did not confirm significant differences of melatonin secretion between depressed patients and healthy subjects. In both studies there was even a trend towards higher melatonin levels in the depressed patients. Both groups emphasized that methodological differences might have produced these inconsistent findings. The major criticism of the earlier studies reporting low melatonin in depressed patients is the lack of individually matched control subjects. At present, a definite conclusion about whether melatonin secretion is disturbed in major depressive disorder cannot be drawn.

A variety of studies demonstrated sedative and sleep-promoting effects of melatonin, which consequently was used for the treatment of insomnia, especially in elderly patients (Haimov et al., 1995). Since about 90% of depressed patients suffer from disturbed sleep (Benca et al., 1992), it is of interest whether a low melatonin secretion correlates with the level of insomnia in depression.

The aim of this study was to measure circadian melatonin secretion in a relatively young group of untreated melancholic depressed patients in comparison with age- and sex-matched healthy control subjects. Furthermore, the relationship of melatonin and cortisol secretion to polysomnographic sleep parameters was investigated.

## 2. Methods

### 2.1. Subjects

Nine depressed in-patients (mean age: 29 years, S.D. = 7) and nine age- and sex-matched healthy control subjects (mean age: 28 years, S.D. = 7) were recruited for this pilot study. Table 1 presents demographic data. All patients were hospitalized for a major depressive episode meeting all DSM-III-R criteria for the melancholic subtype (American Psychiatric Association, 1987) and scored in the 'endogenous' range $> 5$ of the Newcastle index (Carney and Sheffield, 1972; Roth et al., 1983). The mean score on the 21-item Hamilton Rating Scale for Depression was 32 (S.D. = 6) at the time of the study. Only those

Table 1
Demographic data of the investigated patients

| No. | Diagnosis | Age | Gender | HAMD | Washout period | Duration of depressive symptomatology |
|---|---|---|---|---|---|---|
| 1 | 296.3 | 22 | Male | 36 | [a] | 2 weeks |
| 2 | 296.1 | 23 | Male | 36 | [a] | 10 months |
| 3 | 296.3 | 25 | Male | 30 | 4 weeks | 2 months |
| 4 | 296.3 | 32 | Male | 30 | 4 weeks | 5 months |
| 5 | 296.3 | 37 | Male | 28 | 3 years | 3 weeks |
| 6 | 296.1 | 44 | Male | 28 | 4 months | 2 months |
| 7 | 296.1 | 25 | Female | 33 | [a] | 2 months |
| 8 | 296.1 | 25 | Female | 35 | [a] | 3 months |
| 9 | 296.1 | 31 | Female | 31 | [a] | 9 months |
| Mean | | 29 | | 32 | | 3.9 months |
| S.D. | | ±7 | | ±6 | | ±3.7 |

[a] Never treated with psychotropic medication.

patients who were unmedicated at the time of admission to the hospital were recruited. Five patients had never received any psychotropic medication, four had not taken psychotropic drugs for at least 3 weeks before the experiments. Patients with alcohol abuse were excluded. The investigation was performed shortly after admission and after informed consent was obtained.

All subjects and patients were of normal height, and weight was within 15% of their ideal body weight. Sleep abnormalities, shift work, alcohol abuse, and any personal or family history of psychiatric disorder were additional exclusion criteria for the healthy subjects. Intake of any drugs was prohibited for 4 weeks before the beginning of the study. All subjects and patients had a full hematology and blood chemistry screen, physical and neurological examination, electrocardiogram, and electroencephalography. The study was performed according to the WHO Declarations of Helsinki (1964), Tokyo (1975), and Venice (1983). It was approved by the Local Ethical Committee of the Medical Faculty of the University of Munich.

The individual experiments were carried out during different seasons of the year. To test whether there were relevant seasonal differences that might have influenced the results, we calculated the time intervals between the dates of any single experiment and June 21, the date with the greatest light intensity during the year. The mean time interval was 3.4 months (S.D. = 1.6) in the group of depressed patients versus 3.8 months (S.D. = 1.5) in the group of healthy subjects ($P$ = 0.36, NS).

### 2.2. Procedure

The study was performed in the sleep laboratory of the Psychiatric Hospital of the University of Munich. The procedure has been described earlier (Voderholzer et al., 1993a). Each subject stayed 4 days in this unit for polysomnographic and hormonal studies. Sleep was recorded for 3 consecutive nights using standard electroencephalographic, horizontal electrooculographic, and submental electromyographic lead placements.

The first two polysomnograms served for adaptation to the laboratory conditions and to obtain baseline sleep parameters; the third was assessed during the blood sampling night. The polygraphic recordings were visually analyzed according to standard criteria (Rechtschaffen and Kales, 1968). Sleep onset was defined as the first 30-s epoch of stage II sleep followed by at least two epochs of any sleep stage. Rapid-eye-movement (REM) latency was defined as the time (in min) from sleep

onset to the first 30-s epoch of stage REM. On day 3, subjects and patients received a standardized breakfast at 07.15 h. At 07.45 h an indwelling catheter (Kowarski-Dakmed thromboresistant blood withdrawal needle and tubing set, 5 foot) was placed in a forearm vein. Blood was continuously drawn over 24 h until the next morning with a constant speed of 15 ml/h by using a pump (Dakmed ambulatory withdrawal pump, Model ML 6-5H). With this portable system the subjects could ambulate in the research unit, which was illuminated by natural light most of the day with a range of light intensity between 300 and 1500 lux. At 12.00 h and 17.00 h, lunch and dinner were served, respectively. Subjects were not allowed to sleep before 22.30 h, and EEG telemetric recording was also continued during the day.

From 19.00 h in the evening, the room was illuminated by artificial light with an average intensity of 200 lux. Lights were off between 22.30 h and 23.00 h. During the night, the blood withdrawal catheter was placed through a soundproof lock in an adjacent room to avoid disturbances due to the blood sampling procedure.

Serum for melatonin determination was sampled hourly, centrifuged, and stored at − 20°C until analysis. Melatonin concentrations were determined in the serum (400-$\mu$l samples) by a direct radioimmunoassay as described by Fraser et al. (1983). Tritiated melatonin tracer (specific radioactivity 87 Ci/mmol) was purchased from Amersham (Frankfurt, Germany), and melatonin antiserum (sheep antimelatonin antiserum, G/S/701-8483) was obtained from Guildhay Antisera (Surrey, UK). The lower detection sensitivity of the method was 2.5 pg melatonin/ml plasma; intra-assay variability was 6.7% (10 pg/ml) and 4.0% (50 pg/ml); and day-to-day assay variability using spiked control samples was 1.4% (10 pg/ml) and 1.3% (50 pg/ml), respectively.

Cortisol was sampled at 15-min intervals and measured by radioimmunoassay.

### *2.3. Data analysis*

The sleep and endocrine data were evaluated by analysis of variance and Student's *t*-tests. Comparisons were performed for each time point as well as for the overall 24-h (08.30 h–08.30 h), diurnal (08.30 h–22.30 h), and nocturnal (22.30 h–06.30 h) secretion. A statistical power analysis according to Cohen (1988) was performed for the mean differences in 24-h and night-time levels. Since the individual melatonin data were log-normally distributed, statistical analyses of melatonin secretion were performed on log-transformed data. For the evaluation of the time course of melatonin secretion, cross-correlation functions were calculated to test for phase differences between patients and control subjects. Concerning the circadian rhythm of cortisol secretion, we determined the quiescent period of cortisol secretion according to the definition of Linkowski et al. (1987): the quiescent period begins when concentrations lower than 50% of the 24-h mean occur in more than two consecutive samples and ends when concentrations higher than 50% of the 24-h mean occur in more than two consecutive samples. The end of the quiescent period is considered to be a good phase position marker of the cortisol rhythm. The relationship between sleep and hormonal parameters was evaluated by calculating Spearman rank correlation coefficients. All reported significance levels were two-tailed. A level of $P < 0.05$ was considered to be significant.

## 3. Results

Melatonin secretion showed considerable variability among both the depressed patients and the healthy control subjects (Fig. 1, Table 2). Mean values of the total 24-h, diurnal (08.30 h–22.30 h), and nocturnal secretion (22.30 h–06.30 h) did not differ significantly between the depressed patients and the healthy controls. The mean 24-h profiles (Fig. 2) demonstrate that apart from slightly lower nocturnal mean values in the group of depressed patients, the circadian melatonin production was similar between the two groups. Statistical analyses on log-transformed data did not demonstrate significant differences of melatonin values between the groups at any of the time points or for the means of the total 24-h ($P = 0.472$), diurnal ($P = 0.772$), or nocturnal secretion values ($P = 0.878$). The only statistically obvious trend was

found for the amplitudes, which were higher in healthy subjects ($P = 0.063$). Statistical power analysis demonstrated a small effect size of 0.21 for the mean differences in the 24-h levels and moderate effect sizes of 0.56 and 0.76 for the nighttime levels and the amplitude, respectively. In the depressed patients no correlation was found between the Hamilton depression scores and the means of melatonin secretion ($r = -0.10$, NS).

Comparable mean values of the 24-h, diurnal, and nocturnal melatonin secretion without significant differences were also found in comparisons of the subgroups of male and female depressed patients with their male and female controls (data not shown).

### 3.1. Melatonin and polysomnographic parameters

Table 3 presents sleep data from the baseline and blood sampling nights. The depressed patients had a significantly shorter REM latency and significantly more REM sleep compared with the controls. Two of the depressed patients, both older than 35 years, showed a sleep-onset REM period. Sleep efficiency was lower and sleep onset latency was longer in the group of depressed patients, both differences being significant only in the baseline night ($P < 0.05$, respectively, $t$-test). Significant night effects were detected by analysis of variance for sleep efficiency, which was lower during the catheter night, while the percentage of stage awake was lower in the baseline night. There was also a tendency for a lower amount of REM sleep in the catheter night compared with the baseline night.

The individual analysis of polysomnographically recorded sleep and nocturnal melatonin secretion did not reveal a consistent temporal relationship between certain sleep stages and the beginning of the nocturnal melatonin increase. The mean sleep onset time was similar in the depressed patients and in the healthy subjects (Table 2). The acrophase of melatonin occurred slightly earlier in the group of depressed patients compared with the healthy subjects (Table 2). A precise determination of the maximum is limited, however, because of the hourly sampling intervals. Cross-correlation function revealed a maximum coefficient of $r = 0.95$ when curves were shifted for 2 h, and a minimum correlation of $r = 0.05$ when curves were shifted for 14 h. This indicates a phase advance of 2 h in the group of depressed patients.

No significant correlations between sleep and melatonin parameters were found in the group of depressed patients, i.e. there was no obvious relationship between the extent of the sleep disturbance and melatonin secretion. In the group of healthy subjects means of nocturnal melatonin

Table 2
Mean values (mean ± S.D.) of different parameters of melatonin secretion, sleep onset and offset and the end of the quiescent period of cortisol secretion in nine depressed patients and nine healthy controls

| | Depressive subjects | Control subjects | $t$-test, $P$ value |
|---|---|---|---|
| 24 h (pg/ml) | 33 ± 19 | 36 ± 11 | 0.472 |
| Diurnal (pg/ml) | 25 ± 17 | 22 ± 7 | 0.772 |
| Nocturnal (pg/ml) | 49 ± 26 | 63 ± 24 | 0.878 |
| Amplitude (pg/ml)) | 79 ± 56 | 117 ± 43 | 0.063 |
| Acrophase | $1^{53}$ h ± 134 min | $3^{23}$ h ± 135 min | 0.173 |
| Latency of melatonin-maximum relative to sleep onset | 189 ± 104 min | 251 ± 151 min | 0.243 |
| Length of quiescent period of cortisol secretion | 343 ± 78 min | 443 ± 97 min | 0.028 |
| End of quiescent period of cortisol secretion | $2^{56}$ h ± 22 min | $4^{23}$ h ± 26 min | 0.022 |
| Sleep onset | $23^{15}$ h ± 18 min | $23^{19}$ h ± 31 min | 0.683 |
| Sleep offset | $6^{17}$ h ± 22 min | $6^{37}$ h ± 10 min | 0.275 |

*Note.* Statistical evaluation of the melatonin secretion was done on log-transformed data.

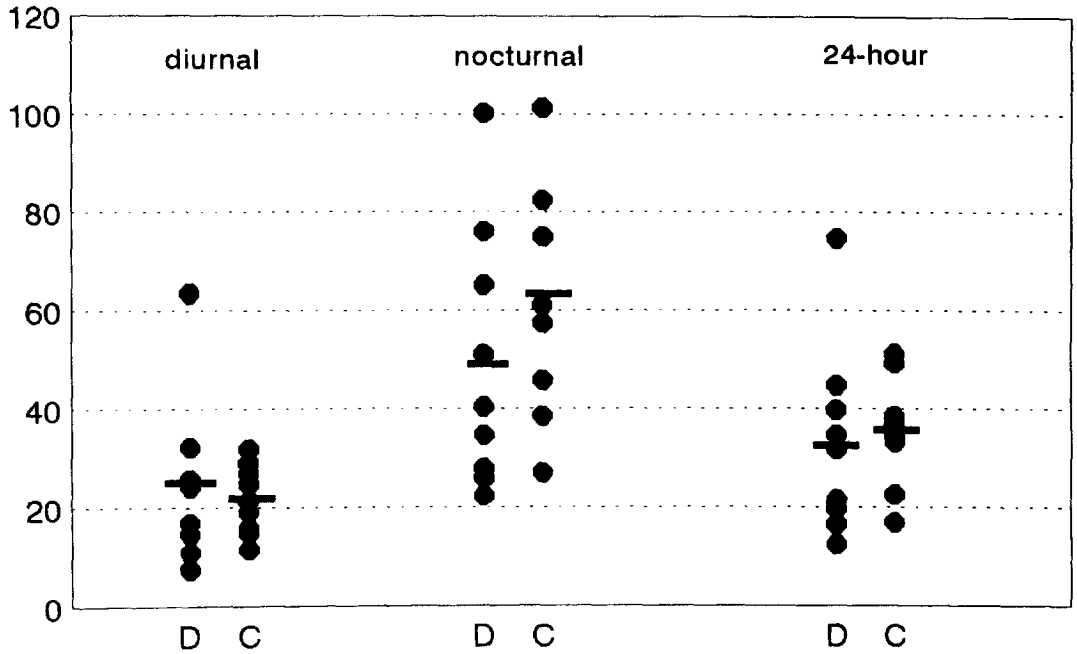


Fig. 1. Individual mean values of melatonin concentrations over 24 h (08.30–08.30 h, left panel), during the day (08.30–22.30 h, middle panel), and during the night (22.30–06.30 h, right panel) and means of it in nine unmedicated patients with melancholic depression (D) compared with nine age- and sex-matched healthy controls (C).

secretion correlated negatively with the amount of stage I sleep ($r = -0.90$, $P < 0.01$) and of REM sleep ($r = -0.73$, $P < 0.05$).

### 3.2. Melatonin and cortisol secretion

In the depressed patients the mean 24-h cortisol secretion was higher compared with that in the healthy subjects due mostly to a markedly elevated mean amount secreted between 22.30 h and 06.30 h ($P < 0.05$). The quiescent period of cortisol secretion was significantly shorter and ended significantly earlier in the depressed patients compared with the controls. The total 24-h, as well as the nocturnal secretion of cortisol and melatonin, correlated negatively with each other, but the coefficients of correlation were not statistically significant ($-0.43, -0.18$, respectively). The diurnal cortisol secretion, however, correlated significantly negatively with the mean melatonin levels during the day and during the night in the depressed patients ($r = -0.76$, $P < 0.05$; $r = -0.76$, $P < 0.05$, respectively).

In the group of healthy subjects, a different, even opposite result was found. The mean 24-h cortisol secretion showed a significant positive correlation with the mean melatonin secretion over 24 h ($r = 0.76$, $P < 0.05$). Regarding only the nocturnal mean values, this correlation was of a lower order ($r = 0.63$, $P < 0.07$, NS), whereas the diurnal levels of melatonin and cortisol secretion showed a significant positive correlation in the healthy subjects ($r = 0.83$, $P < 0.05$).

## 4. Discussion

We did not find significant differences of the 24-h melatonin secretion in this pilot study in nine relatively young and untreated melancholic depressed patients compared with age- and sex-matched healthy subjects. These findings are not in accord with those of a number of previous

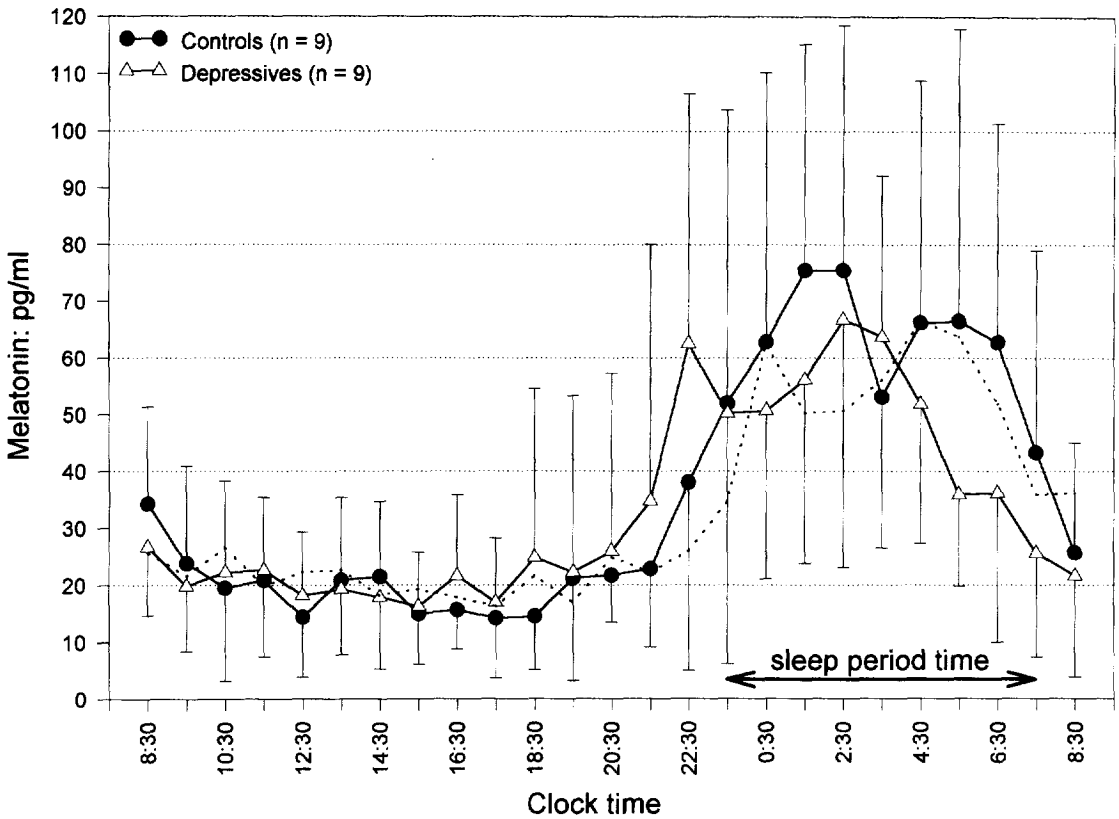


Fig. 2. Mean profiles of circadian melatonin secretion (±S.D.) in depressed patients ($n = 9$) and age- and sex-matched healthy controls ($n = 9$). Melatonin concentrations were measured in hourly intervals over 24 h. ——— indicates the approximate time when lights were off. Differences between the group of patients and control subjects were not significant at any of the time points. Cross-correlation function between the two curves revealed the highest positive correlation after a 2-h delay shift of the curve of the depressed patients (indicated as · · ·).

studies that found significantly lower levels of melatonin secretion in depressed patients than in healthy subjects (Wetterberg et al., 1979; Wetterberg and Aperia, 1983; Beck-Friis et al., 1984; Claustrat et al., 1984; Brown et al., 1985; Frazer et al., 1985; Souêtre et al., 1989). Our results are in agreement with studies by Jimerson et al. (1977), Thompson et al. (1988), and Rubin et al. (1992), who did not find significant differences between depressed and normal subjects. Rubin et al. (1992), who studied the largest group to date, found a trend towards a significantly elevated average nocturnal melatonin concentration that was accounted for by the premenopausal women in their sample. The male depressive patients did not differ significantly from their respective controls. Our results indicate that melatonin secretion, contrary to cortisol (Holsboer, 1995) or growth hormone secretion (Voderholzer et al., 1993b), is not altered in depression.

Compared with the melatonin levels determined by Thompson et al. (1988), our groups of depressed patients and control subjects had greater melatonin levels. This can be partly explained by the markedly lower mean ages in our study. In the study by Rubin et al. (1992), the mean curve of the depressed group increased to similar nocturnal mean values as in our study, whereas the controls had lower nocturnal mean values than in our study, which again might be

Table 3
Sleep parameters of nine depressed patients and nine healthy control subjects (mean ± S.D.)

| | Healthy controls | | Depressive patients | | ANOVA group effect df = 1 | | ANOVA night effect df = 1 | | ANOVA interaction df = 1 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline night | Blood sampling night | Baseline night | Blood sampling night | $F =$ | $P =$ | $F =$ | $P =$ | $F =$ | $P =$ |
| Time in bed | 484 ± 32 | 470 ± 37 | 485 ± 82 | 498 ± 45 | 2.38 | 0.142 | 0.58 | 0.458 | 0.02 | 0.895 |
| Sleep period time | 471 ± 30 | 450 ± 33 | 454 ± 79 | 479 ± 42 | 0.09 | 0.762 | 0.01 | 0.928 | 0.98 | 0.337 |
| Total sleep time | 443 ± 33 | 405 ± 45 | 414 ± 81 | 386 ± 59 | 1.04 | 0.324 | 6.40 | 0.022 | 0.13 | 0.718 |
| Sleep onset latency | 13 ± 6 | 19 ± 18 | 31 ± 22 | 21 ± 10 | 3.97 | 0.064 | 0.09 | 0.722 | 2.47 | 0.136 |
| Sleep efficiency | 92 ± 6 | 86 ± 8 | 82 ± 9 | 78 ± 16 | 3.78 | 0.070 | 5.32 | 0.035 | 0.17 | 0.681 |
| Awake (%) | 4 ± 4 | 9 ± 6 | 7 ± 5 | 16 ± 12 | 3.83 | 0.068 | 8.33 | 0.011 | 0.63 | 0.439 |
| Stage I (%) | 9 ± 6 | 7 ± 5 | 8 ± 4 | 8 ± 2 | 0.04 | 0.840 | 2.91 | 0.107 | 4.50 | 0.055 |
| Stage II (%) | 50 ± 6 | 48 ± 7 | 46 ± 46 | 42 ± 11 | 3.19 | 0.093 | 1.66 | 0.217 | 0.23 | 0.639 |
| Slow wave sleep (%) | 16 ± 10 | 17 ± 10 | 12 ± 8 | 12 ± 6 | 1.13 | 0.303 | 0.02 | 0.884 | 0.43 | 0.522 |
| REM sleep (%) | 18 ± 5 | 18 ± 6 | 26 ± 6 | 20 ± 4 | 5.19 | 0.037 | 4.34 | 0.054 | 3.81 | 0.069 |
| REM latency (min) | 81 ± 31 | 85 ± 32 | 48 ± 25 | 57 ± 44 | 5.19 | 0.037 | 0.54 | 0.474 | 0.12 | 0.739 |

partly explained by the different mean age. Also, since levels during daytime were higher in our study than in others, it cannot be ruled out that in addition to the lower mean age some lack of specificity of the assay might have contributed to this difference.

The discrepancy between our results and those of earlier studies may be explained by methodological differences. This has also been argued by Rubin et al. (1992). In some of the earlier melatonin studies, patients were not drug-free (Wetterberg et al., 1981; Beck-Friis et al., 1984) or the washout-period was only 1 week (Brown et al., 1985) or 10 days (Claustrat et al., 1984). Since receptor changes following antidepressant therapy may persist more than 1 week, it cannot be ruled out that low melatonin levels were attributable to the preceding drug treatment in these studies. In our study, five patients had never received psychotropic medication before and the others were studied after withdrawal from medication for more than 3 weeks.

Another possible explanation for the discrepancy could be the different ages of the investigated depressed patients. In most earlier studies, the mean age was much higher than in our study. One could speculate that a diminution of melatonin secretion develops during the course of the disease and therefore was not apparent in our comparatively young group of depressed patients. In some of the earlier studies, a control group was either absent or not matched for age (Mendlewicz et al., 1980; Wetterberg et al., 1981; Claustrat et al., 1984; Brown et al., 1985). The lower melatonin levels in depressed patients reported by these authors could be partly explained by the age-dependent decrease of melatonin secretion (Nair et al., 1984).

The recording of sleep parameters indicated the presence in our group of depressed patients of typical changes such as reduced REM latency and diminished sleep efficiency, both of which are common findings in depressed patients (Gillin et al., 1979; Benca et al., 1992).

The temporal association between the nocturnal melatonin increase and the sleep-wake cycle was similar with a slight trend towards an earlier maximum in the depressed patients. The statistical analyses of the hormone curves by cross-correlation function revealed the highest and lowest correlations by a 2-h and a 14-h shifting of the curves, respectively. This indicates a phase advance in the depressed patients. A definite conclusion, however, cannot be drawn because of too infrequent sampling intervals of 1 h and because of the small number or subjects. Further evidence for a phase-advanced circadian rhythm in our group of patients may be found in the fact that the end of the quiescent period of cortisol secretion, which is considered to be a good phase position marker, occurred about 1.5 h earlier in the depressed patients compared with the controls. This is consistent with earlier studies that reported a phase advance of neurochemical parameters (Wehr and Goodwin, 1983), hormone levels, and temperature in depressed patients (Linkowski et al., 1987; Sack et al., 1987).

Neither total sleep time nor sleep efficiency was correlated with nocturnal melatonin secretion in the depressed patients or the healthy subjects, i.e. there was no overall relationship between the extent of sleep disturbance and melatonin secretion. In the healthy subjects, however, higher nocturnal melatonin values correlated negatively with REM sleep and with stage I sleep. Since the amount of stage I may be an indicator of impaired sleep quality, this correlation may indicate a relationship between melatonin and sleep quality in healthy subjects. The negative correlation between melatonin and REM sleep is in agreement with earlier studies (Pavel et al., 1980; Birkeland, 1982).

Differences were found between depressed patients and healthy subjects regarding the relationship between melatonin and cortisol secretion. Nocturnal cortisol secretion was significantly elevated in the depressed patients and showed a negative but non-significant correlation with nocturnal melatonin secretion. Also, Rubin et al. (1992) did not find significant correlations between melatonin and cortisol measures in depressed patients. The female depressed patients in the study of Rubin et al., similar to our group of depressed patients, showed moderate negative correlations between their average nocturnal melatonin measures and all their cortisol measures.

In our group of healthy subjects, however, both hormones showed a significant positive correlation. The significance of this result is limited by the small number of subjects studied. Rubin et al. (1992), who studied a larger group of healthy subjects, did not find significant correlations between cortisol and melatonin in healthy subjects.

In conclusion, this study demonstrated that levels of melatonin secretion in young, untreated endogenous depressed patients are similar to those found in age- and sex-matched healthy subjects.

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