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Effects of Low Oral Doses of Melatonin, Given 2–4 Hours Before Habitual Bedtime, On Sleep in Normal Young Humans

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Summary: Low oral doses of melatonin raise serum melatonin concentrations to those normally occurring nocturnally and facilitate polysomnographically assessed sleep onset when given at different time points throughout the day, without altering mood or performance on the morning following treatment. In the present study, 12 young healthy volunteers, free of sleep disturbances, received 0.3 or 1.0 mg of melatonin or placebo at 2100 hours, 2–4 hours prior to their habitual bedtime. Polysomnographic recording of overnight sleep began at 2200 hours and continued until 0700 hours the following morning, when subjects were awakened. Sleep onset latency and latency to stage 2 sleep were significantly decreased as a result of melatonin treatment. Neither dose of melatonin significantly altered sleep architecture. Administration of the lower dose of melatonin (0.3 mg) at 2100 hours elevated serum melatonin to levels within the normal nocturnal range (113 ± 13.5 pg/ml) at the time the sleep test was initiated. Neither melatonin dose caused "hangover effects", as assessed by self-reports or by mood and performance tests administered on the morning following treatment. These observations provide additional evidence that nocturnal melatonin secretion has a sleep-promoting function. They also indicate that an increase in serum melatonin concentrations, within the normal physiologic range, does not significantly alter sleep architecture in subjects with normal sleep who receive the treatment several hours prior to their habitual bedtime. **Key Words:** Melatonin—Pineal gland—Polysomnography—Sleep.

Despite general awareness of the unique characteristics of the pineal gland, particularly its rhythmic, photically entrainable secretion of melatonin at night (1–3), no function has been definitively associated in humans with either the pineal gland or its hormone, melatonin. Candidates for such a function include participation in the regulation of circadian rhythms (4,5), humoral communication of information about environmental lighting (and thus time of day) to the brain and other organs (6), regulation of reproductive physiology (7) and induction of sleep (8,9).

The concurrence of the release of melatonin from the pineal gland and the time during which most humans sleep (3) has led to a long-standing but unproved suspicion that the former process is causally related to the latter (10). Desynchronization of these two daily rhythms, behavioral rhythm of sleep time and rhythmic melatonin secretion, can occur as a result of: 1) complete blindness, when the melatonin rhythm free-runs, with a period usually longer than 24 hours; 2) pinealectomy or functional destruction of the pineal gland, resulting in a lack of melatonin production; or 3) temporal displacement of the daylight period, as in shift-work or transmeridian flight (the jet-lag syndrome). Such disruptions in the coordination of sleep and melatonin secretion were correlated with subjects' complaints of reduced sleep quantity and quality. The amelioration of such subjectively assessed sleep disturbances by timely administration of pharmacological doses of melatonin (11–13) was attributed to the involvement of melatonin in coordinating day–night behavioral rhythmicity. Timing of the evening augmentation in melatonin secretion or the onset of the urinary 6-sulfatoxymelatonin excretion has also been shown to correlate with the nocturnal increase in sleep propensity (14–16). These observations supported the idea of temporal association of the sleep process and nocturnal melatonin secretion, although they could not prove causal dependency between these two daily rhythms.

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Several investigators have examined the acute effects of pharmacological doses of melatonin on sleepiness and sleep. The results have been inconsistent. High doses tended to induce sleepiness and sleep during the daytime and late in the evening [1.25 mg/kg body weight intravenously (i.v.) (8); 50 mg i.v. (9); 50 mg orally (p.o.) (17); 80 mg p.o. (18); 75 mg p.o. (19)]. Lower pharmacological doses produced hypnotic effects in the afternoon [1.7 mg administered (20); 5 mg (21); 3 or 6 mg (22)] or increased evening fatigue [2 mg p.o., for 1 month (23)] in some cases, but failed in others [1 or 5 mg p.o. (24,25)] to change the onset or duration of sleep.

In humans and certain other mammals, the production of melatonin by the pineal gland or the excretion of melatonin or its metabolites typically declines with age (26–31), even though some elderly persons reportedly exhibit high melatonin levels (33,34). It is not clear whether the decline in melatonin production is a result of an age-related norepinephrine deficiency, which could decrease stimulatory input to the pineal gland, or perhaps of pineal gland calcification (26,35). Age-related decreases in melatonin, cortisol, prolactin and growth hormone production have been shown to parallel declines in sleep quantity and quality in healthy males (36). Haimov et al. (37) found that older people with insomnia displayed a lower excretion of 6-sulfatoxymelatonin (the main melatonin metabolite) than young people or older subjects not suffering from insomnia. These results suggest that a nocturnal melatonin deficiency may be a factor contributing to disrupted sleep patterns.

The purpose of the present study was to characterize the effects of augmented circulating melatonin levels, within the physiologic nocturnal range, on polysomnographic parameters of overnight sleep in young healthy volunteers with normal sleep quality.

METHODS

Twelve healthy male paid volunteers [28.5 ± 1.8 standard error of the mean (SEM) years of age] participated in the study after giving informed consent. The experimental protocol and the Subject's Consent Form were approved by the Massachusetts Institute of Technology (M.I.T.) Committee on the Use of Humans as Experimental Subjects. All volunteers reported that they did not have habitual sleep disturbances and were drug-free. On each test day volunteers completed self-report questionnaires regarding the onset of their evening sleepiness, their bedtime and the quality of their sleep on the previous night. The subjects were all nonsmokers, and they were asked to refrain from alcohol or caffeine consumption for 24 hours prior to each test session. Meals [provided by the M.I.T. Clinical Research Center (CRC)], reflecting a typical American diet (15% proteins, 35% fat and 50% carbohydrates), were served at 1700 hours (dinner) and 2030 hours (a small snack).

The study consisted of three double-blind, placebo-controlled test sessions. The treatment order for each session was determined using a 3 × 3 Latin square design to counterbalance order effects. Every volunteer participated in three test sessions, each of which was preceded by an adaptation night in the CRC, with at least 5 days elapsing between successive sessions. On the treatment nights, subjects received melatonin [0.3 or 1.0 mg (Nestle Co., Vevey, Switzerland) in gelatin capsules containing microcrystalline cellulose ('Avicel')] or placebo orally at 2100 hours and then retired in darkness 1 hour later, at 2200 hours. On the preceding adaptation night, subjects also retired at 2200 hours but did not receive any treatment. Sleep was recorded polysomnographically until 0700 hours the following morning, when subjects were awakened. The illumination levels were held at 150 lux until 2200 hours, then at <10 lux from 2200 hours to 0700 hours and 150 lux after 0700 hours.

At 1830 hours on the evening of each test session a catheter with a saline lock was established in each subject's forearm vein for withdrawing blood samples. These were collected at 1900 and 2150 hours and assayed for melatonin.

For polysomnographic recording, electroencephalographic (EEG) electrodes were placed according to the International 10/20 System (with recordings from C4-A1, C3-A2, C3-01 and C4-02), and electrooculographic and submental electromyographic electrodes were used for sleep staging. Signals from the electrodes and transducers were amplified by 18-channel preamplifier/multiplexor units; they were then digitized and recorded (DigiTrace Care Services Inc., Boston, MA). Thirty-second epochs of the polysomnographic record were staged according to the criteria of Rechtschaffen and Kales (38); the stages included wake; stage 1, 2, 3 or 4 sleep; and rapid eye movement (REM) sleep. Sleep onset latency was defined as the period elapsing between the time that lights were turned off and the appearance of three consecutive epochs of stage 1 sleep, or of one epoch of any other sleep stage. Latency to REM sleep was defined as the period elapsing between sleep onset and the appearance of one epoch of REM sleep. Wake after sleep onset (WASO) was defined as the total time scored as wakefulness between sleep onset and final wake-up. Sleep efficiency was defined as the ratio of total sleep time (TST) to time in bed. Complete sets of polysomnographic recordings were obtained from all 12 of the subjects, except for that of subject no. 6 after receiving the 1.0-mg dose of melatonin.

On the morning following treatment, at 0730 and 0930 hours, each subject completed a battery of computerized performance tasks and mood inventories that previous studies have shown to be adequate for evaluating the prevailing level of sleepiness. Four Choice Reaction Time, Simple Auditory Reaction Time, The Profile of Mood States (POMS) and the Stanford Sleepiness Scale (SSS) were measured. For details see Dollins et al. (39).

In nine subjects the endogenous melatonin secretion pattern was documented 7–10 days prior to the first testing session. Blood samples (3 ml each) were collected at hourly intervals for 24 hours, from 0900 hours to 0900 hours the following morning.

Melatonin concentrations were measured in duplicate serum samples (0.5-ml aliquots of samples collected from 0900 to 1900 hours; 0.2-ml aliquots of samples collected from 2000 to 0900 hours) using a radioimmunoassay (RIA) kit (Buehlmann Laboratories, Allschwil, Switzerland) that employs the Kennaway G280 antibody (40). The limit of detection was 0.5 pg/ml. The intraassay coefficients of variation for control samples were 7.2 (9 pg/ml) and 7.8% (22 pg/ml); the corresponding interassay coefficients of variation were 12.6 and 16.1%, respectively. The onset of melatonin production was defined as the time point at which serum melatonin concentration increased to two standard deviations (SDs) over the mean daytime level. Daily melatonin production was estimated by measuring the 24-hour areas under the serum time-concentration curves (area under the curve; AUC).

The after-treatment dependent measures were each assessed by using a repeated-measures analysis of variance (ANOVA). Orthogonal planned comparisons were used to evaluate differences among the melatonin/placebo treatment conditions when a significant ($p < 0.05$) treatment effect was found. The comparisons chosen were placebo versus each of two melatonin treatments, and 0.3 versus 1.0 mg of melatonin. Dependent variables included sleep questionnaire responses (mean time of evening sleepiness, mean bedtime) and sleep structure (TST, WASO, latency to sleep onset, latency to stage 2 sleep, latency to REM sleep, duration of sleep stages). The relationships among the dependent variables were tested for significance using Pearson's correlation. If pairs of variables were identified with a high degree of correlation then only one member of the pair was used. Group means were substituted for the missing data points from subject no. 6 (following the 1.0 mg dose). The relationship between the time of nocturnal onset in serum melatonin and the onset of evening sleepiness was tested for significance using Pearson's correlation. Only main effects that resulted in significant contrasts are reported.

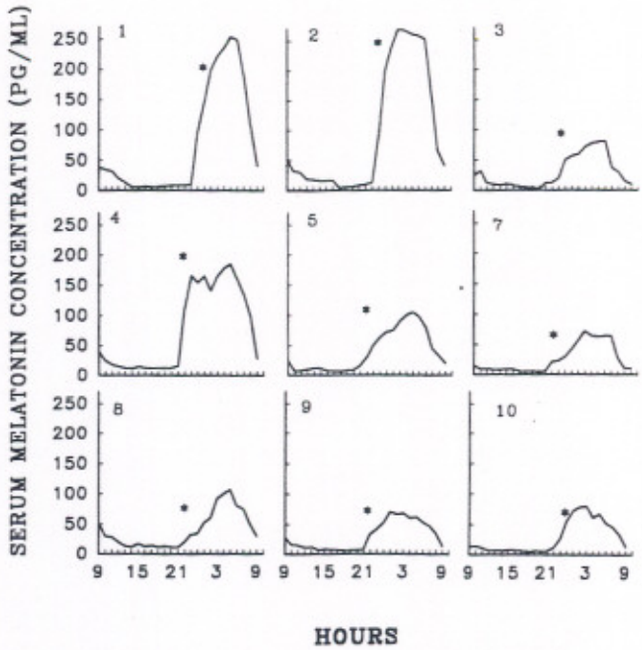

FIG. 1. Twenty-four-hour serum melatonin profiles measured from 0900 hours to 0900 hours (n = 9); the asterisk (*) indicates the time of the onset of habitual evening sleepiness.

RESULTS

Self-report questionnaires completed by the volunteers prior to each testing session regarding their sleep habits indicated that evening sleepiness tended to start at 2148 hours ± 12 minutes and habitual bedtime occurred at 0024 hours ± 11 minutes; mean sleep duration was 7.0 hours ± 14 minutes; mean estimated sleep onset latency at habitual sleep time was 16.0 ± 2.4 minutes.

The group of subjects that we studied exhibited peak endogenous serum melatonin levels ranging from 72 to 287 pg/ml (mean peak value of 145.3 ± 30.42). The mean AUC was 1,276.3 ± 238.67 pg/ml × hour; this exhibited marked interindividual variation, ranging from 627 to 2,361 pg/ml × hour.

Analysis of the relationship between the parameters of melatonin production and the habitual sleep behavior of the subjects revealed a clear correlation between the time of onset of nocturnal melatonin increase and the time of the onset of habitual evening sleepiness ($r = 0.81$; Fig. 1). Habitual bedtime, however, did not significantly correlate with the melatonin onset. Likewise, the time of melatonin increase and the duration of melatonin production did not correlate with individual peak melatonin levels nor with the AUC of melatonin.

Sleep under laboratory conditions is, of necessity, different from sleep at home due to the novelty of the environment and the need to place EEG electrodes. We

TABLE 1. *Sleep efficiency[a], latency to sleep onset and latency to stage 2 sleep after administration of placebo, 0.3 mg melatonin or 1.0 mg melatonin at 2100 hours*

	Sleep efficiency (%)			Sleep latency (minutes)			Latency to stage 2 sleep (minutes)		
Subject no.	Placebo	0.3 mg	1.0 mg	Placebo	0.3 mg	1.0 mg	Placebo	0.3 mg	1.0 mg
1	59.3	96.5	95.4	187.5[b]	12.5[b]	9.5[b]	214.0[b]	16.0[b]	14.0[b]
2	85.7	95.1	93.3	23.0	4.0	8.5	25.0	6.0	14.5
3	52.0	96.5	96.5	22.5	10.5	5.5	28.5	13.0	7.0
4	84.1	90.2	95.1	34.0	7.0	7.0	35.0	10.0	9.5
5	89.6	76.0	79.5	5.0	2.5	1.0	6.0	4.0	1.5
6	57.0	78.6		56.0	10.5		59.5	12.0	
7	95.4	92.5	96.6	5.5	6.5	4.0	9.5	10.0	6.0
8	91.1	93.8	91.8	31.0	22.5	28.5	34.0	30.0	31.0
9	74.4	97.2	97.6	11.0	9.5	12.5	15.0	12.0	15.0
10	89.5	89.3	92.7	6.5	4.0	11.5	9.5	9.5	15.5
11	92.7	86.9	93.0	19.5	18.0	13.0	27.5	22.0	19.5
12	87.0	94.5	90.6	27.5	10.5	21.0	32.0	12.0	25.0
Mean	79.8	90.6	92.9	21.9	9.6	11.2	25.6	13.0	14.4
SE	4.42	2.01	1.43	4.61	1.83	2.36	4.64	2.03	2.37

SE, standard error.
[a] Time in bed was 530 minutes.
[b] These data were excluded from the analysis (see text).

observed a wide variation in sleep onset latencies in our subjects on the nights they received placebo. Subject no. 1 appeared to be exceptionally sensitive to changes in his sleep environment: latency to sleep on the placebo night was 187.5 minutes, in contrast to a 35.7-minute mean value for the whole group of 12 subjects. Although his latency to sleep dramatically declined after melatonin treatment [to 12.5 (0.3-mg dose) or 9.5 minutes (1.0-mg dose)], he was considered to be an outlier ($p < 0.01$), and data obtained from him were not included in the group analysis. Thus the mean latency results reported represent analyses of data obtained on 11 subjects (Table 1).

Either dose of melatonin significantly ($p < 0.05$; ANOVA) decreased sleep onset latency and latency to stage 2 sleep, and increased sleep efficiency relative to placebo treatment, as assessed polysomnographically (Fig. 2; Table 1). The effects of the physiological (0.3 mg) and low pharmacological (1.0 mg) doses of melatonin did not differ significantly with respect to either parameter.

Within this group of volunteers no statistically significant alterations in sleep architecture were detected as a result of melatonin treatment. Latency to REM sleep did not significantly change, but had a tendency ($p = 0.17$) to decline after administration of the physiological (0.3-mg) dose of melatonin in comparison with placebo (Table 2). Neither dose of melatonin significantly affected the duration of sleep stages (Tables 2 and 3); the duration of slow-wave sleep tended to be lower after the administration of melatonin, but this decline was not significant. The number of awakenings did not differ on the nights that subjects were treated with melatonin or placebo; the time they stayed awake after sleep onset (WASO) had a tendency to decrease as a result of treatment with either melatonin dose (Table 2), although it was not significant.

Measurement of melatonin concentrations in the serum of the subjects confirmed that administration of the lower dose (0.3 mg) of the hormone at 2100 hours elevated serum melatonin to levels within the normal nocturnal range (112.6 ± 13.53 pg/ml) at the time the sleep test was initiated (Fig. 3). Administration of the 1.0-mg dose increased serum melatonin levels to supraphysiologic levels 50 minutes later (521.4 ± 71.25 pg/ml).

Analysis of subjective sleepiness and of reaction times in response to visual or auditory stimuli on the morning following treatment (at 0730 or 0930 hours) revealed no hangover effects from the melatonin treatment (Fig. 4), a finding similar to one that we reported earlier (41).

DISCUSSION

These data affirm that the induction of physiological concentrations of melatonin 2–4 hours prior to habitual bedtime has a sleep-promoting effect in healthy young males and significantly decreases latencies to sleep onset and to stage 2 sleep. These observations complement our earlier finding that similar small doses of melatonin, given at noon (42) or later in the afternoon [1800, 2000 or 2100 hours (41)], promote sleep initiation. Analysis of the overnight polysomnographic recordings revealed that low doses of melatonin do not significantly alter sleep architecture in young healthy males with normal sleep.

We attribute the observed hypnotic effects of melatonin to the acute action of this hormone on the sleep process initiated at the time of an anticipated evening

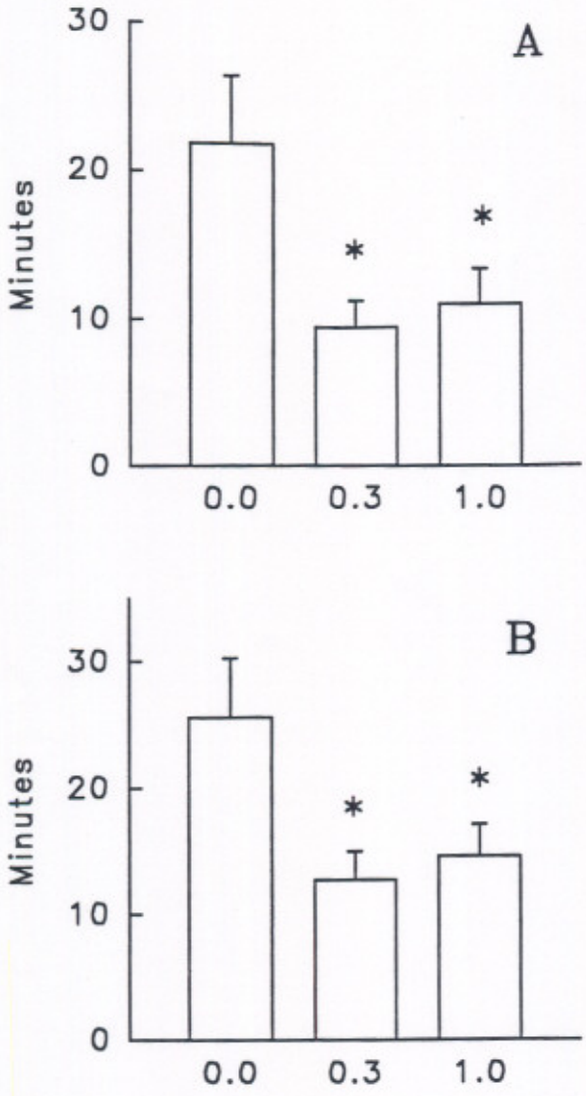

FIG. 2. Effects of melatonin (0.3 or 1.0 mg, p.o.) on average [standard error of the mean (SEM)] latency to: A) sleep onset and B) stage 2 sleep, relative to placebo (n = 11). Asterisk (*) indicates $p < 0.05$.

nadir in sleepiness (43). The alternative possibility is that melatonin, administered in the afternoon or early in the evening, prior to the onset of the nocturnal melatonin production, advances the oscillatory activity of the major circadian pacemaker, and, via this mechanism, advances the sleep–wake cycle. It has been shown that a single dose of the hormone, given in the afternoon or in the evening, may change the timing of the onset of the nocturnal increase in melatonin release (11,44), inducing a phase advance of up to 1 hour. The effect is highly dependent on the circadian time of melatonin administration. In our present and former experiments we administered melatonin at different time points (1200, 1800, 2000 or 2100 hours), 2–12 hours prior to subjects' habitual bedtimes or about 1–10 hours prior to the onset of the nocturnal increase in their melatonin production. We observed an increase in subjectively assessed sleepiness starting 15 minutes after administration and a decline in the objectively assessed latency to sleep onset when it was tested 1–2 hours later. According to the 'shift hypothesis', such an effect would require a comparable (up to 10 hours) shift in the activity of a major pacemaker that would result from the administration of a single dose of melatonin and would not depend on the time of treatment. This theoretical possibility is in contrast with experimental results obtained in other laboratories (11,44). Thus, we suggest that melatonin may directly promote the sleep process and that the daily increase in its production by the pineal gland is a part of a global multifactoral mechanism that provides the transition from wakefulness to sleep.

The reported effects of melatonin on sleep architecture in humans are quite variable. Anton-Tay (45), administering 1 g of melatonin daily, observed enhancement of stage 2 sleep, shortening of stage 4 sleep and an increase in the number of rapid eye movements. Cramer et al. (9) observed that 50 mg of the hormone administered i.v. at 2130 hours significantly decreased the latency to sleep onset, but had no significant effect on TST or on the relative duration of sleep stages. Waldhauser et al. (18) showed that ingestion of 80 mg of melatonin 1.5 hours prior to bedtime decreased sleep onset latency, stage 1 sleep and the number of awakenings, but increased stage 2 sleep and the mean REM interval. Hughes et al. (46) reported that after administering a range of pharmacological doses of melatonin (1–40 mg p.o.) to young males they observed an increase in stage 2 sleep and a decrease in stage 4 sleep, but no changes in REM sleep. In contrast, James et al. (24,25) failed to find consistent changes in sleep architecture in healthy subjects and insomniacs after the administration of 1- or 5-mg oral doses of melatonin.

Although we did not find statistically significant effects on sleep architecture in young healthy volunteers with the low melatonin doses that we used (0.3 or 1.0 mg), the changes in sleep patterns seen in some of the subjects tended to be similar to those reported by other investigators; there was a decrease in slow-wave sleep and a reduction in the duration of wakefulness during the night. Inconsistencies in the results obtained in different laboratories may be attributable to different doses (most of which increased serum melatonin to levels hundreds or thousands times greater than normal nocturnal levels) of the hormone used or variations in experimental protocols. Individual sensitivity to melatonin may vary as a function of age or gender and may also contribute to differences in the results.

Melatonin administration has also been described as

TABLE 2. *Duration of REM sleep (% of TST), latency to REM sleep and WASO after administration of placebo, 0.3 mg melatonin or 1.0 mg melatonin at 2100 hours*

	REM (% of TST)			REM latency (minutes)			WASO (minutes)		
Subject no.	Placebo	0.3 mg	1.0 mg	Placebo	0.3 mg	1.0 mg	Placebo	0.3 mg	1.0 mg
1	14	27.4	23.5	163.5	96	173	22.5	6	27
2	19.7	17.5	20.8	80.5	89.5	75	49	17.5	6
3	7.4	23.6	17.6	132.5	57	151	238.5	4	15
4	30.6	22.5	35.7	62.5	71.5	75.5	13.5	17	100
5	15.1	21.2	16.4	54.5	60.5	64.5	15.5	134.5	23
6	21.7	13.3		194.5	106		176.5	98.5	
7	22.5	11.7	16.4	73.5	64	123	16.5	31	12.5
8	16.6	18.2	18	82	95	89	4.5	5	15
9	27.1	28.3	24.8	126.5	127	98.5	126.5	8	9.5
10	22.5	20.7	13.1	113	95.5	131	48.5	47.5	23.5
11	18.6	25.7	14.8	82	82	111	18	48.5	19.5
12	25.4	22.9	16.7	102.5	89.5	123	34	18.5	34
Mean	20.1	21.1	19.8	105.6	86.1	110.4	63.6	36.3	25.9
SE	1.75	1.49	1.83	12.22	5.89	9.78	21.8	11.87	7.12

REM, rapid eye movement; TST, total sleep time; WASO, wake after sleep onset; SE, standard error.

affecting various animal species. Marczynski et al. (47) found that implantation of crystalline melatonin (15–30 μg) into subcortical structures in cats caused initiation of sleep soon thereafter, with an increase in the amplitude and a slowing of the electrical activity in the structures tested. Later, Goldstein and Pavel (48) observed the induction of slow-wave sleep in cats following intraventricular injection of 1–100 ng of melatonin; there was a 3-hour suppression of REM sleep and a subsequent rebound of REM sleep. Holmes and Sugden (49) observed a minor somnogenic effect in rats following the intraperitoneal (i.p.) injection of melatonin (2.5–10 mg/kg body weight), but a lower dose (0.833 mg/kg i.p.) was reported by Mendelson et al. (50) to reduce sleep in rats. Recent results, reported by Tobler et al. (51), showed that 3 mg/kg i.p. melatonin injections had no effects on sleep in rats. Such inconsistencies may be explained by the extremely high pharmacological concentrations of melatonin in blood, cerebrospinal fluid (CSF) and brain tissue possibly produced by the doses used, and the fact that the relationship between the sleep–wake cycles of the animal studied (i.e. nocturnally active rats and crepuscular cats) and the serum melatonin rhythm is very different from that in diurnally active humans. In both animal species the melatonin rhythm is similar to that of humans in that melatonin levels are higher at night (when diurnal animals normally sleep), even though the animals are active at night. Thus, melatonin may have a different biological meaning in nocturnal and diurnal species.

Our volunteers experienced no untoward changes in mood and performance following treatment with either dose of melatonin, as assessed subjectively or using a battery of mood and performance tests. Although these parameters were not measured at the same time points

TABLE 3. *Duration of sleep stages (% of TST) after administration of placebo, 0.3 mg melatonin or 1.0 mg melatonin*

	Stage 2 (% of TST)			Stage 3 (% of TST)			Stage 4 (% of TST)		
Subject no.	Placebo	0.3 mg	1.0 mg	Placebo	0.3 mg	1.0 mg	Placebo	0.3 mg	1.0 mg
1	65	58.5	62.2	15.1	7.3	6.5	2.1	3.3	3
2	56.3	60.5	53.2	4.8	3.7	3.3	10.2	7.4	6.5
3	58.9	64.8	65	9	7.4	6.5	18.3	1.7	9.9
4	53.2	60.1	50.9	6.3	4.8	3.4	6.3	0.7	0
5	67.5	61.2	66.4	12.1	12.7	10.8	12.1	1.3	2.1
6	64.6	73.3		0	0.5		0	0	
7	59.1	71.9	68.9	12.2	9.5	9.9	0.5	0.4	1.5
8	55.1	57.4	63.4	8.1	10.5	9.3	17.3	0.3	0.1
9	51	54.4	49.3	5	6.6	7.7	9.5	5.8	8.2
10	61.3	62.8	71.6	9.2	6.9	6.7	1.7	1.7	2.4
11	54.1	51.2	66.3	9.6	5.3	7.1	4.5	12.8	0.1
12	65.6	70.2	75.2	6.5	1.9	1.8	0.4	0	0
Mean	59.3	62.2	62.9	8.16	6.43	6.6	6.9	2.9	3.1
SE	1.58	1.98	2.44	1.16	1.01	0.82	1.89	1.12	1.02

TST, total sleep time; SE, standard error.

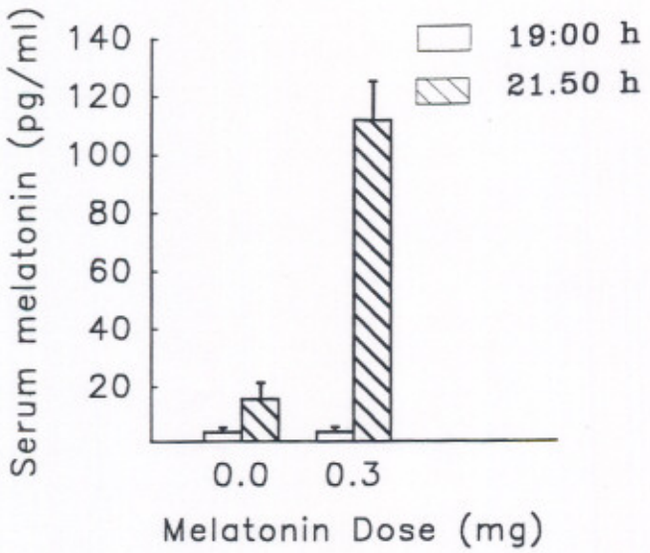

FIG. 3. Serum melatonin levels (pg/ml) before and after the administration of a 0.3-mg oral dose of melatonin or placebo at 2100 hours (n = 12).

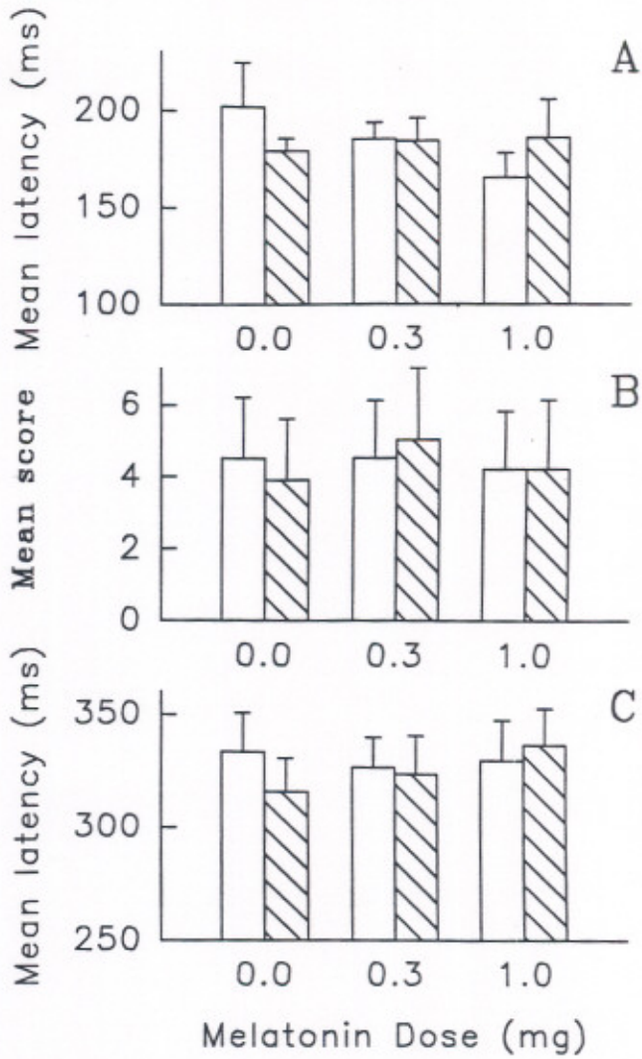

FIG. 4. Mood and performance on the morning following melatonin treatment: A) Simple Reaction Time; B) Profile of Mood States (POMS; Fatigue/Inertia Scale); C) Four Choice Reaction Time, measured at 0730 (open bars) or 0930 hours (striped bars).

as those used for assessing sleep at home, the subjects' self reports, comparing normal sleep at home with melatonin-induced sleep, revealed that sleep after melatonin treatment either more nearly resembled habitual sleep or did not differ from that after placebo. Moreover, our results demonstrate that sleepiness was not increased nor reaction time impaired on the morning following treatment with melatonin. This advantage of the melatonin treatment used may be related to the fact that, as we showed previously (42), 6–8 hours after the administration of a physiologic' dose of melatonin (mixed with the microcellulose in a gelatin capsule), the serum hormone concentration returns to the baseline level. It is interesting to note that treatment with benzodiazepines is reported to suppress melatonin production both in laboratory animals and in humans (52–55). The therapeutic sedative–hypnotic action of benzodiazepines may therefore disturb mechanisms that modulate natural sleep. This could underlie the benzodiazepine abstinence syndrome, including drug-withdrawal insomnia. Treatment of such symptoms with low doses of melatonin could have positive therapeutic consequences.

Among normal healthy humans, the daily nocturnal increment in blood melatonin concentrations correlates with the habitual hours of sleep (3). Moreover, an evening increase in urinary excretion of the melatonin metabolite, 6-sulfatoxymelatonin, has been shown to be concurrent with an increment in fatigue and sleep propensity (14,16). The data presented here (Fig. 1) affirm the correlation between the habitual onset of evening sleepiness, evaluated subjectively, and the onset of the nocturnal increase in serum melatonin concentration. The complexity of the wake–sleep transition and the dependency of the sleep–wake cycle on social factors are illustrated by the fact that among the students studied, habitual bedtime was not strictly correlated with the onset of melatonin production. According to their self reports, bedtime varied more than the perceived onset of evening sleepiness. These data are congruent with our observation that an increase in serum melatonin levels within the physiological range, either during the daytime or late in the evening, is not an imperative signal for sleep, but a gentle promoter of general relaxation and sedation, the elements of sleepiness that, in favorable conditions, significantly facilitate sleep onset. However, when a person is so motivated, he or she can overcome these feelings and be both alert and productive for some time. This behavioral pattern

resembles the natural evening quite wakefulness that normally precedes physiological sleep onset.

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Note: R.J.W. discovered the ability of low oral doses of melatonin, which elevate serum melatonin levels only to their normal nocturnal range, to promote sleep onset and maintenance, and the Massachusetts Institute of Technology patented this discovery. This patent has been licensed to a company, Interneuron Pharmaceuticals, Inc., which was co-founded by R.J.W. R.J.W. and I.Z. serve as scientific advisors to Interneuron Pharmaceuticals, Inc.

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