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Melatonin improves evening napping

Rachel Nave, Ron Peled, Peretz Lavie *

Sleep Laboratory, Bruce Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel

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Abstract

Twelve young adults were treated with either melatonin, 3 mg or 6 mg, or placebo, at two different times before an early evening nap (18.00–20.00 h) according to a balanced double-blind Latin square design. Polysomnographic monitoring revealed that both dosages of melatonin significantly shortened sleep latency and increased total sleep time in comparison to placebo, irrespective of the time of administration. Subjects also tended to assess their sleep as 'deeper' after melatonin treatment. Based on previous data and the present results, it was concluded that exogenous melatonin exerts hypnotic effects only when circulating levels of endogenous melatonin are low.

Keywords: Napping; Polysomnographic recording; Melatonin

1. Introduction

Studies investigating the possible hypnotic effects of melatonin have produced conflicting results. While there were early reports that variable doses of melatonin only produce subjective sensations of fatigue and sedation (Vollrath et al., 1981; Arendt et al., 1984, 1985; Anton-Tay et al., 1971; Lieberman et al., 1984; MacFarlane et al., 1991), or have no detectable effects on objective sleep measures (James et al., 1987, 1990), James et al. noted a tendency toward increased rapid eye movements (REM) latency. More recent reports indicate that low doses of melatonin may actually possess hypnotic effects (Tzischinsky and Lavie, 1994; Dollins et al., 1994). One possible explanation for these conflicting results is that in different studies melatonin was administered at different times in relation to the level of endogenous melatonin (see extensive discussion in Dawson and Encel, 1993). In studies showing no effect, melatonin was administered just before bedtime, close to the nocturnal rise in endogenous melatonin. Hypnotic effects were demonstrated, however, when melatonin was administered during the daytime, when there are no detectable levels of melatonin (Tzischinsky and Lavie, 1994; Dollins et al., 1994), or in patients with melatonin deficiency (Haimov et al., 1993). In the present study, we investigated the effects of exogenous melatonin on napping during the early evening hours, a time during which the sleep propensity is low (Lavie, 1986), and which is also prior to the nocturnal rise in endogenous melatonin. Previously, we found that melatonin administered at this time increased the propensity to sleep (Tzischinsky and Lavie, 1994).

2. Materials and methods

Twelve healthy young adults (mean age = 24.6 ± 2.7 years) were paid to participate after giving their informed consent. All were students living on campus, following more or less the same daily schedule. None had used any kind of drug or medication for at least 3 months before the study. The study comprised 5 experimental periods of 2-h nap attempts between 18.00 and 20.00 h, separated by at least one 7-day 'rest period'. During each of the experimental periods, subjects came to the lab at 15.45 h. At 16.00 h (T1) and then at 17.30 h (T2) they were given one of the following treatments: placebo and placebo, placebo and 3 mg melatonin (or in the reverse order), placebo and 6 mg melatonin (or in the reverse order), according to a double-blind Latin

* Corresponding author. Sleep laboratory, Gutwirth Bldg, Technion City, Haifa, Israel 32000.

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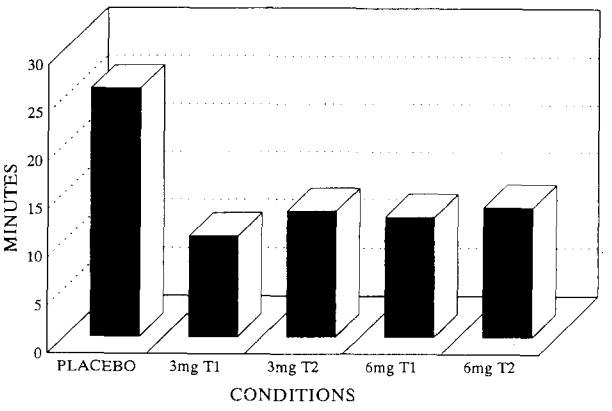
square design. The reason for administering melatonin at two different times before bedtime was that, in our experience with clinical trials, melatonin is most effective when administered 2 h before the desired bedtime (Tzischinsky et al., 1992). Furthermore, our laboratory findings indicated that daytime administration of melatonin may have delayed hypnotic effects (Tzischinsky and Lavie, 1994).

The subjects were requested to refrain from daytime sleep for 2 weeks before the start of the study, as well as during its 5-week duration. To control for the subjects' behavior during the study, actigraphic recordings were collected 3 days before each of the experimental periods. The subjects were requested to avoid major physical exertion on the day before coming to the laboratory.



T1=16:00 T2=17:30
*MISSING=120 MIN.

Fig. 1. Stage 2 sleep latency in the melatonin and placebo conditions.

2.1. Statistical analysis

In order to establish the effects of different doses of melatonin in comparison to placebo administered 2.0 h or 0.5 h before bedtime, we performed a Latin square design analysis of variance (ANOVA) for total sleep time in minutes, minutes of sleep in stages 1, 2, 3/4 and REM, and sleep latency (until sleep stage 2). A significant ANOVA was followed by four preplanned specific contrasts: (1) Placebo vs. melatonin treatment (placebo vs. 3 mg – T1, 6 mg – T1, 3 mg – T2, 6 mg – T2). (2) Melatonin administered at 16.00 h. Melatonin administered at 17.30 h. (3) 3 mg vs. 6 mg administered at 16.00 h. (4) 3 mg vs. 6 mg administered at 17.30 h.

3. Results

All subjects successfully completed the experimental protocol. Fig. 1 presents the sleep latency for each of the conditions. ANOVA revealed that sleep latency was significantly reduced in all drug conditions in comparison with placebo (Table 1) ($F(1, 32) = 8.9$; $P < 0.0054$). None of the other contrasts was significant. Table 1 also presents the means for stages 1, 2, 3/4, REM and total sleep time for each of the experimental conditions. A significant difference was found between placebo and all drug conditions with regard to total sleep time ($F(1, 32) = 18.95$; $P < 0.0001$). All the other three contrasts were not significant. Likewise, the same contrast was significant for stage 2 sleep time ($F(1, 32) = 8.90$; $P < 0.0054$). Since sleep was limited to 2 h, few subjects showed REM sleep. Therefore, REM latency could not be computed. To further demonstrate the effects of melatonin on sleep, Fig. 2 presents mean amounts of awake time in the 12 10-min epochs comprising the allocated nap time for each of the conditions. The persistent differences between the placebo and melatonin conditions are clearly evident.

3.1. Subjective assessment of sleep quality

Analysis of the post-nap sleep questionnaires revealed a borderline significant difference between the placebo and melatonin conditions only with respect to the subjective assessment of sleep depth ($F(1, 32) = 3.53$; $P < 0.06$). None of the other comparisons (mood or tiredness) or contrasts was statistically different between placebo and melatonin.

3.2. Actigraphic monitoring

The mean duration of total sleep time during the 3 days preceding each of the 5 experimental periods

Table 1
Minutes of sleep in each stage and stage 2 sleep latency over the 120 min of the experiment for the melatonin and placebo conditions

	Placebo	3 mg T1	6 mg T1	3 mg T2	6 mg T2
Stage 1	5.0 ± 3.1	5.9 ± 4.1	5.0 ± 2.5	5.6 ± 2.6	4.7 ± 2.6
Stage 2	41.3 ± 23.4	49.4 ± 19.3	51.7 ± 19.6	54.5 ± 13.5	51.5 ± 17.7
Stage 3/4	27.1 ± 19.4	31.5 ± 17.0	36.5 ± 18.2	33.0 ± 14.8	31.0 ± 17.9
REM	2.9 ± 5.8	11.7 ± 9.0	8.6 ± 8.3	6.2 ± 7.8	7.9 ± 9.0
TST	76.3 ± 38.3	98.5 ± 21.6	101.9 ± 22.9	99.3 ± 20.5	95.1 ± 33.0
SL [a]	25.8 ± 35.3	10.4 ± 10.5	12.4 ± 11.0	13.0 ± 10.0	13.4 ± 14.5

T1 = administration time at 16.00 h; T2 = administration time at 17.30 h; SL = stage 2 sleep latency; REM = rapid eye movements; TST = total sleep time.

[a] In two subjects who did not fall asleep in the placebo condition, sleep latency was considered as 120 min.

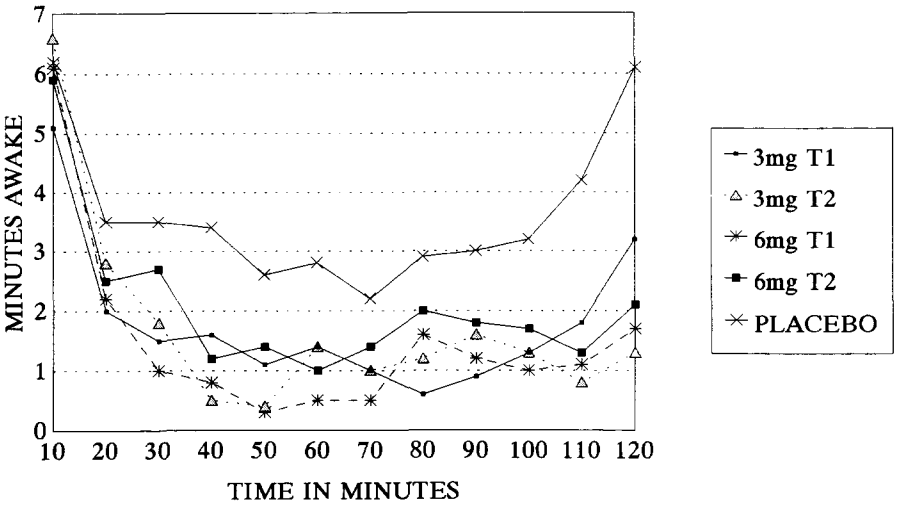


Fig. 2. Mean time awake in 10-min intervals in the melatonin and placebo conditions.

ranged from 476 ± 68 min to 422 ± 54 min. Analysis of variance revealed no significant differences between conditions.

4. Discussion

Our present results provide further evidence that melatonin possesses hypnotic effects when administered at times when circulating melatonin levels are low. Both dosages of melatonin administered either 2 or 0.5 h before bedtime significantly decreased sleep latency and consequently significantly increased total sleep time. Most of this increase was accounted for by increased sleep stage 2. Similar results have been obtained in two other laboratories, but have so far been published only in abstract form (Zhdanova et al., 1994; Hughes et al., 1994). Several mechanisms have been invoked to account for the hypnotic effects of melatonin. These include indirect effects via phase shifting of the circadian sleep-wake oscillator (Sack et al., 1991) or via thermoregulatory processes (Dawson and Encel, 1993). A direct effect of melatonin on somnogenic neural structures has also been postulated (Tzischinsky and Lavie, 1994). In view of the fact that circadian phase shifting by melatonin is generally achieved after repeated administrations, it is highly unlikely that the present results can be explained by a phase advance in the sleep-wake oscillator. Since we did not monitor core body temperature, we cannot determine if the improved sleep was indeed associated with changes in thermoregulation. Although further studies should be performed before these possibilities can be ruled out, a previous observation from our laboratory demonstrating a dissociation between the effects of melatonin on evening sleep propensity and on body temperature (Tzischinsky and Lavie, 1994) may exclude thermoregulation as a possible explanation.

In contrast to our original hypothesis that administering melatonin 2 h before bedtime would be more effective than 30 min before bedtime, we did not find any time-of-administration effect. Melatonin was equally effective in shortening sleep latency and increasing total sleep time when administered 2 h, or half an hour, before bedtime. Also, the observation that no differences were found between the two doses of 6 and 3 mg may suggest that the lack of a time-related effect could be due to the high levels of melatonin. Possibly even 3 mg of melatonin was excessive, and therefore any time-related effects were masked. Indeed, Dollins et al. (1994), using behavioral criteria for assessing sleepiness, reported significant daytime hypnotic effects of melatonin, with doses as low as 100 μg. In order to test this explanation, the present study should be repeated with lower doses of melatonin.

The present results, together with our previous findings on the effects of melatonin in elderly melatonin-deficient insomniacs (Haimov et al., 1993), and on daytime sleep propensity levels (Tzischinsky and Lavie, 1994; Dollins et al., 1994), indicate that melatonin may be of potential clinical use in patients in whom there are low levels of circulating melatonin. Thus, shift-workers, attempting to sleep during the day to compensate for nightwork, or to prepare themselves for night-shift, may benefit from melatonin. Likewise, travellers crossing multiple time zones may benefit from melatonin when its administration coincides with low levels of endogenous melatonin (Arendt et al., 1987).

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