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Melatonin and Sleep

Sleep-Promoting and Hypothermic Effects of Daytime Melatonin Administration in Humans

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Summary: Sleep-promoting and hypothermic effects of orally administered melatonin during the daytime were assessed using a placebo-controlled, double-blind, cross-over design. Following a 7-hour nighttime sleep opportunity, healthy young male subjects (n = 8) were given either a placebo or one of three doses of melatonin (1 mg, 10 mg, and 40 mg) at 1000 hours. Sleep was polygraphically assessed in a 4-hour sleep opportunity from 1200 to 1600 hours. All doses of melatonin significantly shortened the latency to sleep onset. Melatonin also significantly increased total sleep time and decreased wake after sleep onset (WASO). Sleep following melatonin administration contained significantly more stage 2 and less stage 3–4, while stage 1 and rapid eye movement (REM) sleep were unaffected. In addition to the sleep-promoting effects, melatonin completely suppressed the normal diurnal rise of core body temperature. These data suggest that melatonin may be an effective method of promoting sleep for individuals attempting to sleep during their subjective day, such as shiftworkers and individuals rapidly traveling across multiple time zones. **Key Words:** Melatonin—Sleep—Humans—Core body temperature.

The pineal hormone melatonin is synthesized and secreted primarily at night in dim light (1,2). In seasonally breeding animals, melatonin is responsible for communicating the annual circadian changes in photoperiod that determine reproductive timing (3). Melatonin also plays a significant role in the circadian system. In mammals, melatonin serves as a chemical messenger of the primary circadian pacemaker, the suprachiasmatic nuclei (SCN), communicating an hormonal message of "darkness" (4,5). Melatonin is thought to function through high-affinity, pharmacologically specific receptors (6,7) located in both the periphery (8) and the CNS (for reviews see 9–12).

Melatonin receptors are concentrated in the SCN (13), where melatonin functions in a feedback loop and has direct phase-shifting properties (14). Melatonin administered to animals (15) and to humans shifts circadian rhythms according to a phase–response curve (PRC) (16,17). The "chronobiotic" actions of melatonin may be useful for treating individuals with sleep-schedule disorders. For instance, evening melatonin administration advances sleep and wake times of individuals with delayed-sleep-phase syndrome (18–22). Melatonin has also been shown to alleviate some symptoms of jet-lag after rapid transmeridian travel (23–27). Furthermore, preliminary research suggests that melatonin can facilitate circadian adjustment to shiftwork (28–30). Melatonin can also entrain free-running circadian rhythms in animals (31). In humans, melatonin has been used to treat blind (32–37) and sighted individuals (38,39) suffering from non 24 hour sleep–wake syndrome. Finally, anecdotal reports suggest that melatonin may eventually be used to regulate the sleep–wake cycles of children with various developmental and neurological deficiencies (40,41).

Although current research suggests that melatonin may be a useful treatment for circadian rhythm related sleep–wake disorders, it is not yet established whether melatonin will be useful for treating sleep disorders of non-circadian etiology. Melatonin does not have significant anxiolitic properties, diminishing its potential usefulness in treating insomnia with a strong anxiety component such as psychophysiological insomnia. On the other hand, melatonin may have sleep-promoting properties based on other mechanisms. To better predict the clinical applications of exogenous melatonin,

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it is important to know whether it has robust hypnotic effects independent of its chronobiotic effects.

Since it was first isolated in 1958, hypnotic-like effects have been reported following high doses (reviewed by 42). These early investigations, however, often lacked rigorous control. Subsequent research has demonstrated sleep-inducing effects in diurnal animals (43,44). In nocturnal rodents, one study showed activating effects of melatonin at a relatively low dose given at night (45), while others have shown sleep-inducing effects with the same dose (Stratton and Oakley, personal communication) and with higher doses (46). In humans, there is considerable debate over the sleep-promoting effects of exogenous melatonin. While melatonin has been reported to have some characteristics of traditional hypnotic drugs, its sleep-promoting effects are not as consistent (see 47 for review).

Most of the discrepancy in the literature can be accounted for by time of day. Melatonin given at night (after 2230 hours) has not uniformly demonstrated sleep-promoting effects (48,49), even at very high doses (50). The data for daytime and evening administration, however, are much more consistent. When administered from early afternoon (51–54) to late evening (55–59), melatonin shortens sleep-onset latencies. Daytime melatonin administration also increases subjective feelings of fatigue and sleepiness (54,60–62) and can impair performance (51,54,60,62).

Because melatonin may have time-of-day effects and because it lacks the large dose–response effects of traditional hypnotics, some have concluded that it is not an hypnotic. The observation that melatonin most consistently facilitates sleep latency from early afternoon to late evening has led some to suggest that its sleep-promoting effects are due to an immediate phase advance of the sleep-propensity rhythm. In most cases, such as when melatonin is administered in the late evening, this alternative explanation is consistent with the known chronobiotic effects of melatonin.

In summary, it is not established whether melatonin can promote sleep independent of its chronobiotic effects. Furthermore, since daytime administration has been assessed primarily in short-duration naps, no investigation has demonstrated that daytime melatonin improves other measures of sleep, such as sleep consolidation and total sleep time (independent of its effects on sleep latency). These dependent measures are also improved with traditional hypnotic drugs.

The current investigation used a placebo-controlled, double-blind, cross-over design to investigate the ability of three different doses of melatonin (1 mg, 10 mg, and 40 mg) to promote sleep in a moderate-duration daytime sleep opportunity. This investigation was conducted during the daytime so that exogenous melatonin could be evaluated in the absence of elevated endogenous melatonin levels and also to avoid the ceiling-effect problem associated with testing nighttime sleep in normal subjects. Melatonin was given at 1000 hours, near the peak phase-delay portion of the melatonin PRC (Lewy et al., in preparation). Therefore, significant sleep effects from 1200 to 1600 hours would not be predicted by a chronobiotic effect of melatonin.

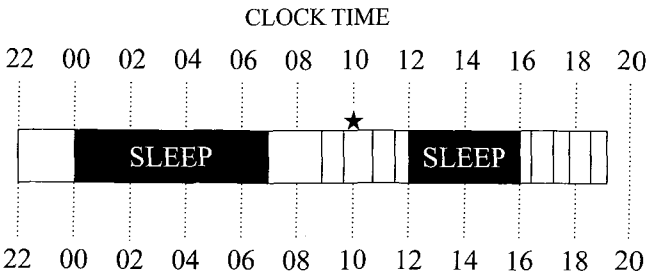

FIG. 1. Schematic depiction of one test session. The night before each trial, subjects slept from midnight until 0700 hours (black bar). The following morning, subjects were administered placebo or melatonin at 1000 hours (star) and allowed to sleep from 1200 until 1600 hours (black bar). Assessment blocks, including temperature monitoring, were given at 0900, 1030, 1630, and 1730 hours (white bars).

METHODS

Subjects

Eight healthy male volunteers (ages 18–30) participated for a total of 4 days each. All subjects passed an extensive screening process prior to participation. Subjects completed self-report questionnaires concerning medical history, food and chemical sensitivities, rest–activity schedules, and morning/eveningness preferences. They were also screened for chronic smoking, heavy caffeine use, and unstable work–rest schedules. Finally, subjects were given a physical examination to ensure that they were in good health at the time of the study. This investigation was approved by the Bowling Green State University Human Subject Review Board.

Melatonin

The four treatment conditions were 1 mg, 10 mg, and 40 mg of crystalline melatonin (Sigma Chemical Co., St. Louis, MO) and placebo. All doses were mixed in gelatin capsules with 400 mg of psyllium (psyllium fiber, General Nutrition Centers, Pittsburgh, PA). Subjects received one dose of melatonin each treatment trial, with a 4–7-day washout period between trials. The order of dose administration was counterbalanced according to a Latin-Square design.

TABLE 1. *Polygraphic data (mean ± SEM) for daytime sleep episodes*

Sleep parameter	Placebo	1 mg	10 mg	40 mg	*F* ratio
Sleep latency	4.83 (0.85)	2.94 (0.35)[a]	2.63 (0.40)[a]	3.19 (0.42)[a]	$F_{(3,21)} = 4.83$, $p < 0.01$
Latency to 10 minutes sleep	11.03 (2.08)	9.06 (2.54)	5.75 (1.90)	5.06 (1.46)	$F_{(3,21)} = 2.20$, $p < 0.12$
Latency to slow-wave sleep	32.99 (3.45)	35.43 (3.33)	56.13 (26.94)	49.98 (19.36)	$F_{(3,21)} = 0.75$, p = NS
Latency to REM after sleep onset	41.45 (14.00)	42.19 (12.08)	29.31 (9.31)	36.10 (13.14)	$F_{(3,21)} = 0.48$, p = NS
Total sleep time	203.91 (8.18)	219.62 (8.32)	226.50 (3.09)[a]	226.70 (1.81)[a]	$F_{(3,21)} = 3.41$, $p < 0.03$
Total WASO	29.59 (7.61)	15.53 (8.32)	7.38 (3.19)[a]	6.57 (1.43)[a]	$F_{(3,21)} = 3.47$, p = 0.05
Percentage of stage 1 sleep	15.81 (2.22)	15.83 (2.36)	15.80 (1.93)	16.35 (3.39)	$F_{(3,21)} = 0.02$, p = NS
Percentage of stage 2 sleep	33.23 (3.24)	46.51 (3.60)[a]	43.74 (4.26)[a]	40.53 (5.01)	$F_{(3,21)} = 6.54$, $p < 0.01$
Percentage of stages 3–4 sleep	24.50 (2.80)	13.91 (2.95)[a]	16.46 (3.95)[a]	16.25 (4.42)[a]	$F_{(3,21)} = 5.70$, $p < 0.01$
Percentage of stage REM sleep	26.46 (3.17)	23.75 (2.04)	24.00 (1.45)	26.86 (2.29)	$F_{(3,21)} = 0.78$, p = NS

SEM, standard error of mean; REM, rapid eye movement; WASO, wake after sleep onset.
[a] Tukey post hoc comparison significantly different from placebo ($p < 0.05$).

Procedure

Subjects arrived in the laboratory at 2200 hours the night before each test session; at that time they read and signed the informed voluntary consent forms. (See Fig. 1 for a graphic depiction of a test session.) From 2400 hours until 0700 hours, subjects were allowed to sleep, with the lights out, in a comfortable bed. Upon arising, subjects were fed a light breakfast. At 0730 hours electrode leads for physiological recording were attached. The electrode montage consisted of three electroencephalogram (EEG) sites (Fz, Cz, and Oz), electrooculogram (EOG), submental electromyogram (EMG), electrocardiogram (ECG), linked mastoid references, oral/nasal air thermisters, and isoground. At 1000 hours, subjects ingested a pill consisting of either 1 mg, 10 mg, or 40 mg of melatonin or placebo. Subjects were in bed for bio-calibration of the polygraph by 1145 hours. At 1200 hours, lights were turned down to less than 20 lux and subjects were instructed to attempt to sleep. At 1600 hours, lights were turned back up to 100 lux. Prior to and subsequent to sleep, subjects sat upright in a comfortable chair in constant light (<100 lux). Assessment blocks were given at 0900, 1030, 1630, and 1730 hours and included core body-temperature measurement, pulse rate, blood-pressure assessments, and performance testing. Following the last assessment block, electrode leads were removed and subjects filled out end-of-session questionnaires about side effects.

Dependent measures

Sleep

Sleep records were hand-scored into 30 second epochs by a trained polysomnographic technician using conventional criteria (63). The technician scoring sleep was also blind to treatment condition. Primary outcome measures for sleep included sleep latency, total sleep time, and wake after sleep onset (WASO). Additional dependent measures included: latency to persistent sleep, latency to stage 2 sleep, latency to slow-wave sleep, latency to REM sleep, the amount and percentage of each stage of sleep, sleep-spindle density (the number of sleep spindles per epoch of stage 2 sleep), amount of movement time, amount of wake time, and number of awakenings.

Temperature

Tympanic temperature was assessed at 0900, 1030, 1630, and 1730 hours using a FirstTemp tympanic temperature probe (Intelligent Medical Systems, Carlsbad, CA). Because it differs less than 0.2°C from deep body temperature in warm- and cold-exposed subjects, tympanic temperature in humans is considered a reliable index of core body temperature (64).

RESULTS

One-way repeated measures analyses of variance (ANOVA) were used to test the effects of melatonin on most parameters of sleep. Two-way (treatment condition × time) repeated measures ANOVAs were used to test the effects of melatonin on sleep duration and core body temperature. Where appropriate, probability values using Geisser-Greenhouse corrections for degrees of freedom are reported. Table 1 contains the mean parameters of sleep for each condition.

Sleep

Sleep latency

Sleep latencies with placebo were quite short (4.83 ± 0.83), suggesting underlying sleepiness (discussed below). Nevertheless, all three doses of melatonin facilitated the induction of daytime sleep, as indicated by significantly shorter latencies to sleep onset. Tukey post hoc comparisons revealed that, compared to placebo, all doses of melatonin facilitated sleep onset (see Table 1).

Melatonin also shortened the latency to 10 minutes of continuous sleep. Although the two highest doses reduced this latency to approximately half of placebo, this effect did not achieve statistical significance. As revealed in Table 1, the 10-mg and the 40-mg doses tended to increase the latency to stage 3–4 sleep and shorten the latency to REM sleep.

Total sleep

Sleep-promoting effects of exogenous melatonin were also demonstrated in a significant one-way ANOVA for total sleep time. Post-hoc comparisons revealed that, compared to the average total sleep time in the placebo condition, the 10-mg and the 40-mg doses achieved statistical significance ($p < 0.05$) while the 1-mg dose did not ($p = 0.07$). To better demonstrate the effect of melatonin on total sleep time, these data were analyzed further in a two-way repeated measures ANOVA (treatment condition × hour of sleep opportunity). Significant melatonin-induced increases in sleep duration were reflected in a significant treatment × time interaction ($F_{(9,63)} = 2.33$, $p < 0.03$). As depicted in Fig. 2, differences between melatonin and placebo were more apparent in the latter part of the sleep episode, especially in the 4th hour when the 10-mg (56.21 ± 1.11) and the 40-mg (56.84 ± 1.17) doses increased sleep by as much as 43% over sleep in the placebo condition (39.83 ± 7.45). Although the 1-mg dose (51.56 ± 5.14) increased sleep in this hour by nearly 30%, this increase was not as statistically reliable ($p = 0.07$).

Wake time

Melatonin improved measures of sleep consolidation, reducing the overall amount of time subjects were awake in bed. Melatonin significantly decreased total WASO. Post-hoc comparisons revealed that the 10-mg and the 40-mg doses achieved statistical significance ($p < 0.05$) while the 1-mg dose did not ($p = 0.07$), even though the 1-mg dose yielded a 47.5% reduction in WASO from placebo (see Table 1). As expected from the sleep latency and WASO data, melatonin also significantly reduced total wake time ($F_{(3,21)} = 3.90$, $p = 0.02$).

Sleep architecture

Melatonin significantly changed daytime sleep architecture. Compared to placebo, the 1-mg and 10-mg doses significantly increased the percentage of stage 2 sleep. The increase in stage 2 sleep in the 40-mg condition did not achieve statistical significance ($p = 0.08$). Melatonin-induced increases in stage 2 were accompanied by comparable decreases in the combined stages of 3–4 sleep. Compared to placebo, reductions in the percentage of stages 3–4 sleep were significant

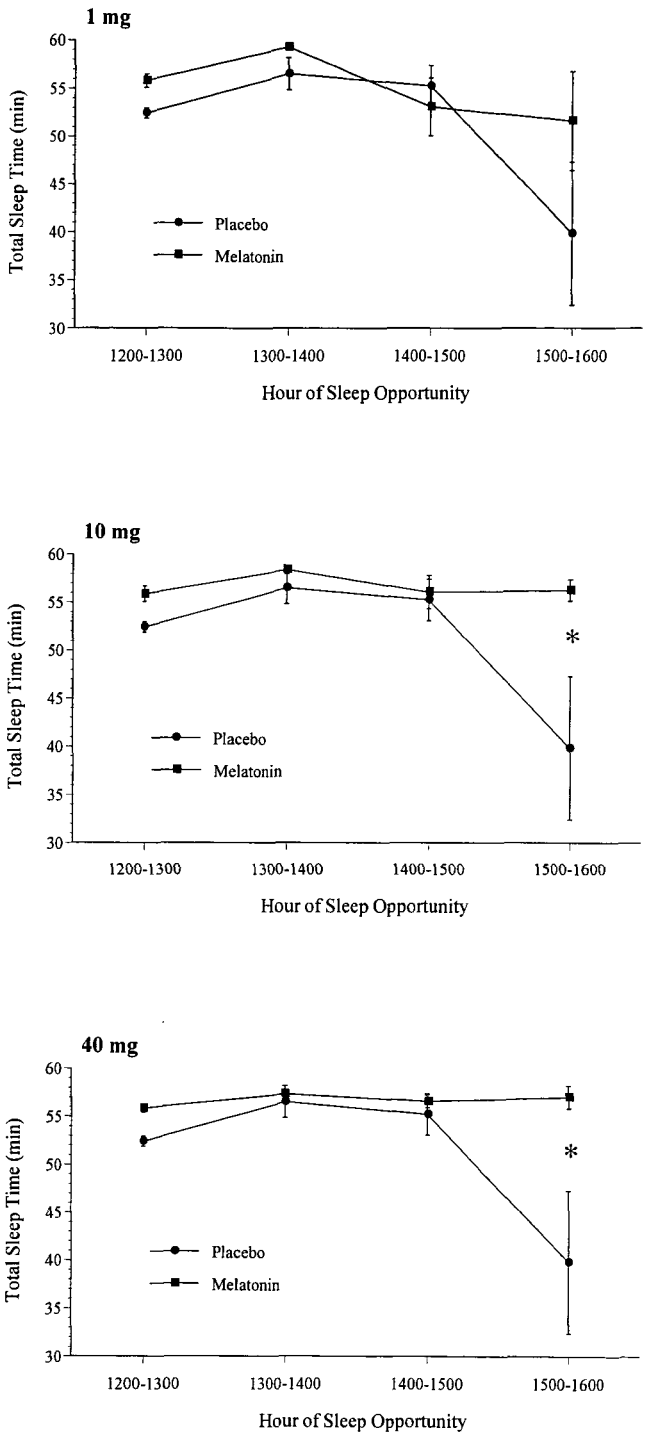

FIG. 2. Mean total sleep by hour of sleep episode. Although a statistically significant effect on sleep latency is apparent in the first hour, the increase in total sleep time over placebo occurred primarily in the last hour of the sleep episode. Asterisks indicate significant post hoc comparisons ($p < 0.05$).

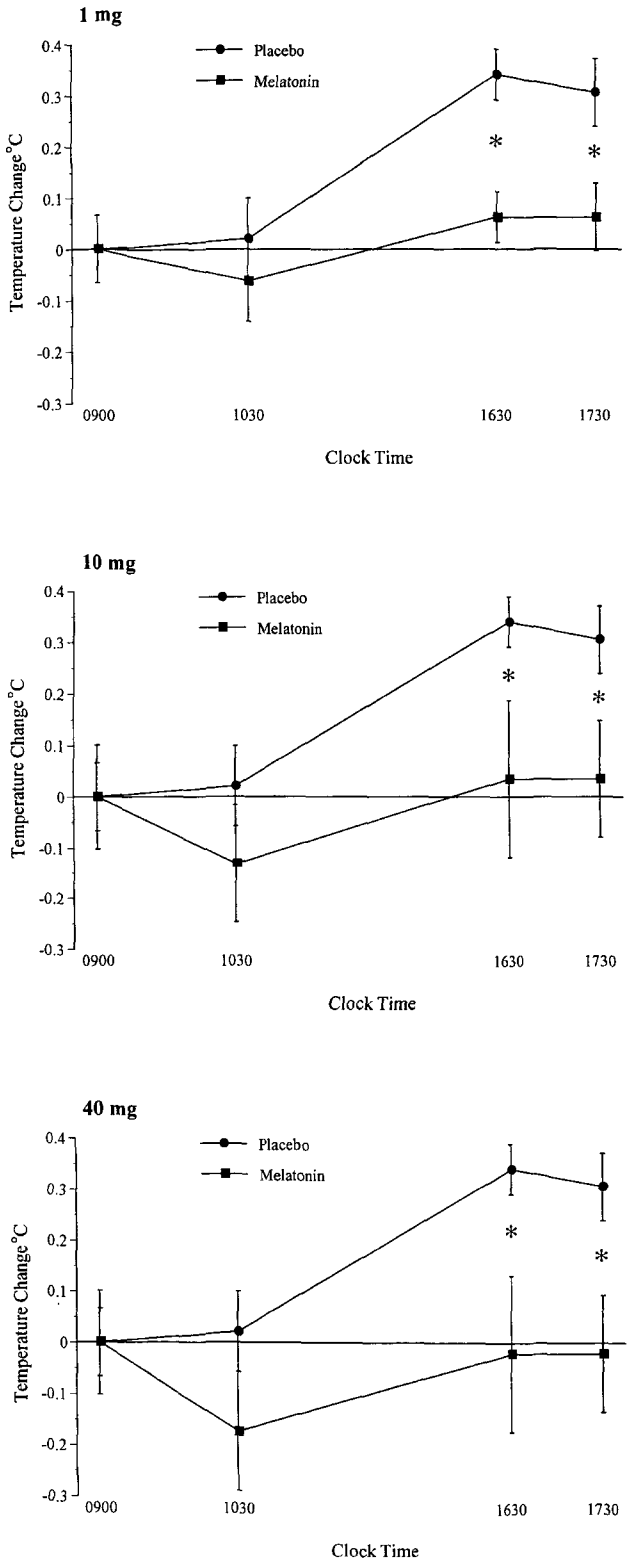

FIG. 3. Mean tympanic temperature, relative to baseline, in degrees Celsius. Body-temperature data are presented as differences from baseline (0900 hours). All doses of melatonin significantly attenuated the daytime rise in body temperature for at least 7.5 hours after administration. Asterisks indicate significant post hoc comparisons ($p < 0.05$).

for all doses. The percentages of stage 1 sleep and rapid eye movement (REM) sleep were unaffected by melatonin (see Table 1).

Temperature

Melatonin yielded significant and long-lasting hypothermic effects. Temperature data (depicted in Fig. 3) were analyzed as differences from baseline (0900 hours) using a two-way (treatment condition × time of day) repeated measures ANOVA. Significant melatonin-induced suppression of body temperature was revealed by a significant main effect for dose ($F_{(3,21)} = 9.48$, $p < 0.01$). Compared to placebo, all doses of melatonin significantly reduced temperature ($p < 0.05$). Body temperature in the placebo condition increased across the day so that by 1730 hours, temperature had risen 0.31°C ± 0.07 from baseline (0900 hours). Melatonin attenuated this increase in a dose-dependent manner, so that temperature following the 1-mg dose had increased over baseline to only 0.06°C ± 0.09. Temperature following the 10-mg dose peaked at 0.03°C ± 0.11. The 40-mg dose completely suppressed the daytime rise in body temperature, so that over 7 hours after administration mean temperature levels had not come back to baseline −0.02°C ± 0.09.

DISCUSSION

Sleep

Melatonin significantly facilitated subjects' ability to initiate and sustain sleep in a moderate-duration daytime sleep episode. All three doses of melatonin (1 mg, 10 mg, and 40 mg) shortened sleep latency to about half that of placebo. This finding is consistent with previous research reporting that melatonin, given from early afternoon to late evening, can shorten sleep latency measured behaviorally (54,65) and objectively with a polygraph (51–53,55,59).

The results of the present investigation demonstrate that daytime melatonin administration can promote other measures of sleep. Melatonin increased total sleep time and decreased WASO. Previous investigations, using either short daytime naps (54,56) or nighttime sleep (48–50,55,58,59), have not demonstrated a melatonin-induced increase in total sleep time independent of sleep latency. Therefore, the present investigation is the first to demonstrate that exogenous melatonin can sustain polygraphically recorded daytime sleep independent of its effect on sleep latency. These findings suggest that previous investigations testing melatonin either in short daytime naps or at night were unable to discriminate treatment effects because of a ceiling effect of sleep in the placebo condition.

The short sleep latencies in the present investigation may have been partially due to subjects being in bed 15 minutes prior to lights out. However, the short sleep latencies, together with the high amount of total sleep time in the placebo condition, suggest that these subjects were quite sleepy, a common finding in undergraduates. This was in spite of the initial screening procedures and the 7-hour sleep opportunity in the laboratory the night before each daytime test session. Sleep opportunities were restricted to 7 hours on these nights to standardize sleep times across subjects and conditions without allowing the subjects to become sleep satiated. As polysomnograph (PSG) recordings were not done during these nights, however, the actual amount of sleep subjects had prior to the testing day was not documented and was at least somewhat less than 7 hours.

Sleep architecture

Melatonin-induced sleep contained a higher percentage of stage 2 and less stages 3–4 sleep. One study (nighttime sleep) has reported melatonin-induced reductions in stage 4 sleep (57), but most report no affect on stages 3–4 sleep (55,48–50). Therefore, more research is needed to determine the conditions under which melatonin will affect slow-wave sleep. Increases in visually scored stage 2 sleep at the expense of stages 3–4 sleep are characteristic of traditional hypnotics, such as the benzodiazepines.

With nighttime administration, a previous study of normal subjects reported increased REM sleep latency with 5 mg but not 1 mg of melatonin given 15 minutes prior to bedtime (48). In another study of insomnia subjects, however, the same investigators found the reverse; 1 mg, but not 5 mg, increased REM sleep latency (49). Therefore, the trend in the present investigation towards shorter REM-onset latencies contrasts both with the previous findings and with the effects of some benzodiazepines.

Temperature

Melatonin attenuated the daytime rise in temperature for more than 7 hours, consistent with prior reports of a hypothermic effect of melatonin (54,60,62, 66–69). Body temperature was not assessed during the sleep period, when the hypothermic effects of melatonin may have been greatest (61). Nevertheless, there was a strong trend for a dose–response relationship between melatonin and temperature, replicating our previous work (61). Dollins and colleagues have also demonstrated dose-dependent hypothermic effects from 0.1 mg to 10 mg (54) but not between 10 mg and 80 mg (60).

It is plausible that the sleep-promoting effects of melatonin are mediated by its hypothermic effects (70). Melatonin is able to affect body temperature centrally and peripherally. Both the SCN and the thermoregulatory center of the brain are located in the anterior hypothalamus, suggesting chemical, structural, and functional relationships between the two (71). There are both afferent and efferent projections between the anterior preoptic area of the hypothalamus and the pineal gland. Additionally, there are melatonin receptors in the area of the brain responsible for thermoregulation, the anterior preoptic area of the hypothalamus (72). Melatonin may also alter body temperature peripherally by affecting blood vessels. This is suggested by the presence of putative melatonin receptors located in arteries such as the circle of Willis and the caudal artery of the rat, arteries involved in thermoregulation (73). Similarly, post-mortem examinations of humans reveal intense melatonin binding in most brain arteries. Therefore, there are several ways that melatonin can affect body temperature.

In summary, previous reports of melatonin-induced reductions in sleep latency can be alternatively explained by chronobiotic effects, specifically by an immediate phase advance of the SCN. In the current investigation, melatonin was administered at 1000 hours (near the peak of the phase-delay portion of the melatonin PRC) and sleep was tested from 1200 to 1600 hours. Therefore, the demonstrated sleep-promoting effects are not easily explained by the phase-shifting action of melatonin. This, combined with the finding that melatonin-induced sleep contained significantly more stage 2 sleep at the expense of stages 3–4 sleep, suggests that melatonin produces effects on sleep and sleep architecture similar to known hypnotic drugs. Furthermore, melatonin shares several other characteristics of traditional hypnotic drugs, including the induction of subjective feelings of sleepiness, shortened sleep-onset latency, increased total sleep time, and improved sleep consolidation. However, the sleep-promoting effects of melatonin are not as robust or consistent as those reported by benzodiazepines; even at extremely high doses, melatonin does not appear to have significant anxiolitic or sedating properties.

Besides its chronobiotic effects, melatonin is most consistently a hypothermic. Given the close relationships among melatonin, body temperature and sleep propensity (for a review see 70), it is likely that the sleep-promoting effects of melatonin reported in this and in other investigations are at least mediated by its effects on body temperature. This suggests that besides being used to treat circadian-rhythm related sleep disorders associated with a phase disturbance, melatonin may also be useful for treating sleep disorders associated with low circadian amplitudes. For example,

melatonin may promote sleep in the elderly by causing a robust decline of nocturnal core body temperature.

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