

Melatonin Treatment for Age-Related Insomnia

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Older people typically exhibit poor sleep efficiency and reduced nocturnal plasma melatonin levels. The daytime administration of oral melatonin to younger people, in doses that raise their plasma melatonin levels to the nocturnal range, can accelerate sleep onset. We examined the ability of similar, physiological doses to restore nighttime melatonin levels and sleep efficiency in insomniac subjects over 50 yr old. In a double-blind, placebo-controlled study, subjects who slept normally ($n = 15$) or exhibited actigraphically confirmed decreases in sleep efficiency ($n = 15$) received, in randomized order, a placebo and three melatonin doses (0.1, 0.3, and 3.0 mg) orally 30 min before bedtime for a week. Treatments were separated by 1-wk washout periods.

Sleep data were obtained by polysomnography on the last three nights of each treatment period. The physiologic melatonin dose (0.3 mg) restored sleep efficiency ($P < 0.0001$), acting principally in the midthird of the night; it also elevated plasma melatonin levels ($P < 0.0008$) to normal. The pharmacologic dose (3.0 mg), like the lowest dose (0.1 mg), also improved sleep; however, it induced hypothermia and caused plasma melatonin to remain elevated into the daylight hours. Although control subjects, like insomniacs, had low melatonin levels, their sleep was unaffected by any melatonin dose. (*J Clin Endocrinol Metab* 86: 4727–4730, 2001)

AGING ALTERS THE regulation of sleep in many individuals (1–3): about 30% of people over age 50 yr exhibit insomnia characterized by decreased total nocturnal sleep time; frequent nocturnal awakenings with difficulty falling back asleep; and early morning awakening. These alterations are associated with increased daytime sleepiness, attention or memory deficits, and changes in mood.

Administration of the pineal hormone melatonin, which in humans and most other species is secreted only at nighttime (4), can facilitate daytime sleep onset in normal young subjects (5–9). Effective doses include those that elevate plasma melatonin to levels normally occurring at nighttime (5) (*i.e.* 60–200 pg/ml) as opposed to daytime levels of less than 3–10 pg/ml. This suggests that endogenous melatonin might participate in the mechanisms that generate normal nocturnal sleep. Because older people not preselected for unusually good health (10) typically exhibit major reductions in nocturnal plasma melatonin levels (11–14), we hypothesized that age-related insomnia might arise from or be related to a potentially correctable melatonin deficiency (15, 16).

Following a pilot study (15), which suggested that a single oral dose of melatonin (0.3 mg) given to elderly insomniacs 30 min before bedtime could improve their sleep, we undertook a larger study to determine whether depressed nocturnal melatonin levels and insomnia are associated in individual older people; various melatonin doses, each given for a week, can restore sleep in this population; and melatonin's ability to restore sleep is, as has been suggested (17), related to the production of hypothermia.

Experimental Subjects and Methods

Subject selection

We invited men and women over 50 yr of age, who stated either that they had developed chronic insomnia or that they continued to sleep normally, to participate in the study. The subjective criteria for insomnia included latency to sleep of 30 min or more, two or more nighttime awakenings, or total period of nighttime sleep less than 6 h. The self-reports were confirmed by continuous 1-wk recordings of the motor activity; insomnia was defined as exhibiting less than 85% sleep efficiency (*i.e.* the ratio of total sleep time to sleep period) or having a total sleep time of less than 6 h during at least three of the seven nights of the evaluation period. Those qualified as normal sleepers had no subjective complaints of sleep alterations and had actigraphically defined sleep efficiencies not less than 90% and total sleep times of at least 7 h per night.

Those who met the defined exclusion and inclusion criteria became study subjects. Each then chose a convenient bedtime, typically his or her habitual time of lights off, and agreed to maintain this bedtime for the entire 9-wk test period. The study was a randomized, placebo-controlled clinical trial, approved by the committee on the use of humans as experimental subjects of the Massachusetts Institute of Technology. All subjects gave written informed consent to their participation. Community-dwelling subjects were recruited through advertisements in local newspapers and posters. Subjects of any ethnic/racial background were accepted, provided they met the screening criteria. The medical examination included detailed medical, psychiatric, and medication histories; a basic physical examination, including cardiorespiratory and neurological status; blood pressure and temperature measurements; and routine blood and urine laboratory tests.

Inclusion criteria consisted of complaints of chronic insomnia and increased daytime sleepiness (or frequent napping), which gradually developed with advancing age (after subjects reached 40 yr of age) and were present for at least 1 yr before the recruitment, with subjective symptoms consistent with psychophysiological insomnia as defined according to the International Classification of Sleep Disorders (307.42-0). Objective, polysomnographic (PSG) criteria for insomnia included sleep efficiency of less than 85% or latency to sleep onset more than 30 min. Exclusion criteria consisted of major psychiatric diagnosis on Axis I of DSM IV; regular use (once a week or more) of hypnotics, melatonin, stimulants, or other medications that may affect melatonin levels (*e.g.* β blockers, drugs that affect prostaglandin synthesis, or drugs that activate hepatic melatonin metabolism) and unwillingness or inability to discontinue the occasional use of these medications for at

Abbreviations: PSG, Polysomnographic; REM, rapid eye movement sleep.

least 4 wk before beginning the protocol; acute or unstable chronic conditions, including but not limited to insulin-dependent diabetes, uncontrolled thyroid disease, kidney, prostate, or bladder conditions causing excessively frequent urination (more than three times per night), congestive heart failure, angina, other severe cardiovascular disorders, hepatitis, asthma or severe respiratory allergies, stroke, cancer if less than 1 yr since end of treatment, conditions associated with chronic pain such as fibromyalgia, and neurological disorders such as Parkinson's disease, Alzheimer's disease, and epilepsy; more than "moderate" alcohol use, as defined by the Quantity-Frequency-Variability Index; unwillingness or inability to maintain a regular sleep/wake cycle during the entire period of the study; sleep apnea/hypopnea index >10; and periodic limb movements in sleep more than 10 per hour on PSG recording. Subjects in the two groups were matched for age and gender; all described themselves as middle class.

Treatments and data analysis

Subjects were blind to all the experimental treatments. They received a placebo on alternate (odd numbered) weeks throughout the study, starting with the first "run-in" week, thus providing washout periods between and after active treatments. During the second week and thereafter on each even-numbered treatment week, subjects received, in gelatin capsules, melatonin (0.1 mg, 0.3 mg, or 3.0 mg; Nestle, Lausanne, Switzerland) mixed with microcrystalline cellulose or the placebo (*i.e.* the cellulose) daily, administered double blind according to a randomized study design for 4 d at home and then for 3 d as inpatients in the MIT Clinical Research Center. Melatonin or placebo capsules were ingested half an hour before each subject's fixed bedtime. Each subject's actual times of ingestion and of bedtime, as well as their subjective assessments of sleep quantity and quality at home, were monitored by having them leave telephone messages immediately after ingesting a capsule, by sleep reports, and by continuous wrist actigraphy.

On the last three inpatient nights of each treatment week (days 5–7), subjects' sleep was monitored polysomnographically, and core body temperature was measured continuously using a rectal probe. Cortical activity was recorded following the 10–20 system of the International Federation at locations C3, C4, O1, A1, and A2, with reference/ground placed at Cz. Electrocardiography was monitored using a standard lead II configuration. Electrooculographic activity was monitored using electrodes placed at LOC and ROC. Electromyographic activity was monitored using electrodes placed lateral to the apex of the chin. Nasal and oral air flow, monitored using Pro-Tech transducers (Pro-Tech Services Inc., Woodinville, WA), respiratory muscle movements, and electromyographic recording on the anterior tibialis muscles of the left and right legs were monitored only during the diagnostic session to exclude primary sleep disorders. Subjects were able to sleep comfortably in a sound-attenuated, temperature-controlled private room with adjacent private bathroom, from individualized bedtime to 0700 h. Sleep stage variables were determined by visual scoring of the polygraph records according to the conventions established in the Rechtschaffen and Kales manual (1968).

All visual scoring was carried out without the knowledge of the subject's treatment condition. Major variables assessed were latencies to sleep onset, slow wave sleep, and rapid eye movement sleep (REM); sleep period (*i.e.* time from falling asleep to the final awakening in the morning); total sleep time (*i.e.* the amount of actual sleep time during sleep period); sleep efficiency, the ratio of total sleep time to sleep period (%); number of awakenings; time being awake after sleep onset; duration of each sleep stage (1, 2, 3, 4, and REM). All visual scoring was carried out without knowledge of the subject's treatment condition. PSG data were scored for the first (adaptation) and second (experimental) nights; those of the second night were included in the analyses. Core body temperature was automatically recorded every minute during the inpatient nights using disposable general-purpose rectal probes (YSI, Inc., Yellow Springs, OH) connected to a Mini-Logger (resolution 0.05 C, accuracy \pm 0.1 C; Mini-Mitter Co., Sunriver, OR). The data thereby obtained were downloaded to a personal computer for further analysis; data from the second night were analyzed.

After the second inpatient night, blood samples were drawn hourly for 24 h for measurement of plasma melatonin. A catheter with a saline lock was implanted in a forearm vein, and blood samples (3 ml each) were drawn every 15–60 min from 1700 h to 1700 h. The frequency of

blood sampling was determined by the anticipated rate of changes in circulating melatonin levels, which is greater at the onset and offset of nocturnal melatonin secretion. Because melatonin production is sensitive to environmental illumination, lighting conditions were strictly controlled. From 0900 h to 1800 h, light intensity was kept at 300 lux, and from 1800 h to bedtime at 20 lux; subjects slept in complete darkness, and light intensity in the bathroom was kept at 10 lux through the night. Melatonin concentrations were measured, using a Buehlmann Laboratories RIA kit (ALPCO, Windham, NH), in duplicate 0.5-ml aliquots from plasma samples collected before 2100 h and after 0700 h and in 0.2-ml aliquots of plasma samples collected between 2100 h to 0700 h.

The limit of sensitivity of the melatonin assay is 0.5 pg/ml. Intraassay coefficients of variation were 6.3% at 9 pg/ml and 6.1% at 22 pg/ml; the corresponding interassay coefficients of variation (for control samples) were 9.7% and 12.7%, respectively. All data were analyzed by mixed-models ANOVA. Summary outcome measures were analyzed using mixed-models ANOVA (SAS v6.12 proc mixed; SAS Institute Inc., Cary, NC; Proc Mixed Software). Each model included effects for insomniac/normal sleep, melatonin dose, and the interaction; the model allowed for possible period and carry-over effects that might arise as a result of the cross-over design. From the final model, estimates (and SE) of the three treatment differences *vs.* placebo were calculated; treatment differences were calculated separately for insomniacs and normal sleepers if the interaction remained in the final model. *P* values were not adjusted for multiple comparisons or tests. The data on sleep efficiency contained one extreme outlying value (29.7% while ingesting placebo by an insomniac subject), and the analysis was conducted with and subsequently without this value to confirm that it did not overly influence the analysis; results presented exclude this value. Area under the curve was transformed to the natural logarithmic scale for analysis. Core body temperature was summarized as the minimum overnight value. For peak melatonin levels, only descriptive statistics were generated. The melatonin time-concentration (on the natural logarithmic scale) curves were modeled similarly, with an additional factor of time in the model; contrasts were used to make comparisons between time points.

Thirty subjects completed the study. Eleven of the 15 subjects initially classified as insomniac, based on subjective and actigraphic data, did in fact demonstrate insomnia (*i.e.* sleep efficiency of less than 85%) on overnight PSG recordings obtained after ingesting the placebo. Fourteen of the 15 subjects originally classified as having normal sleep were also found not to be insomniac on PSG recordings.

Results

No significant increases in sleep efficiency were observed after subjects with normal sleep received any dose of melatonin (Fig. 1A and Table 1). In contrast, the sleep of insomniac subjects was significantly improved by all three melatonin doses, with the 0.3-mg dose causing the greatest effect ($P < 0.0001$) (Fig. 1B and Table 1). This change in overnight sleep efficiency was principally due to increased sleep efficiency during the middle portion of the nocturnal sleep period ($P = 0.018$) and, secondarily, to improvement during the latter third of the night (Fig. 2). The sleep efficiencies of insomniac subjects were normal during the first third of the night and were unaffected by melatonin during this interval. Melatonin had no behaviorally significant, dose-related effects on total sleep time; number of awakenings; latency to sleep onset; latency to REM sleep; or percent time spent in any of the sleep stages in insomniacs or normal sleepers.

Compared with their daytime levels, endogenous plasma melatonin concentrations (*i.e.* when subjects received the placebo) were significantly increased 2 h before bedtime ($P = 0.0008$), tended to peak about 4–5 h after bedtime, and remained elevated for about 8 h (Fig. 3). The group median (interquartile range) of peak endogenous melatonin concentrations was 25 (17–39) pg/ml; this compares with 100 pg/ml in normal young subjects and with 35 pg/ml in aged subjects,

as reported earlier (13). No significant correlations were observed between an individual's endogenous melatonin levels and his or her sleep efficiency in the overall group of subjects tested or in subgroups with normal sleep or insomnia.

A significant increase in circulating melatonin levels was detected within an hour of ingesting the hormone; median (interquartile range) peak levels, observed on average within 2 h of treatment, were 84 (59–120) pg/ml, 220 (124–299) pg/ml, or 1370 (957–2440) pg/ml after administration of the 0.1-, 0.3-, or 3.0-mg doses, respectively (Fig. 3). Ten hours after bedtime plasma melatonin levels after ingestion of the 0.1- or 0.3-mg doses were not significantly different from those observed after placebo treatment. However, melatonin levels after ingestion of the 3-mg dose remained significantly elevated through much of the following day (Fig. 3). Administration of the 0.1- or 0.3-mg melatonin doses failed to

modify the physiologic nocturnal decline in core body temperature; however, the 3-mg dose significantly lowered the group minimum core body temperature ($P < 0.0001$) (Fig. 4).

Discussion

The results of this study demonstrate, for the first time, that physiologic doses of melatonin that raise plasma melatonin to levels within its normal nocturnal range (*i.e.* 60–200 pg/ml) can significantly improve sleep in people suffering

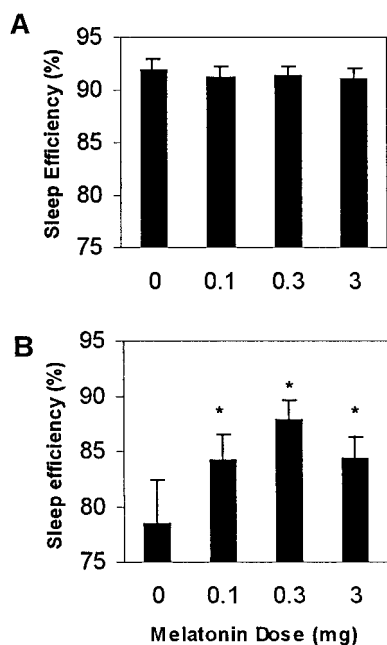


FIG. 1. Sleep efficiency in subjects with normal sleep (A) and age-related insomnia (B) following melatonin or placebo treatment. *, $P < 0.05$.

TABLE 1. Sleep parameters following melatonin (0.1-, 0.3-, and 3.0-mg doses) or placebo (0.0 mg) treatment in subjects with normal sleep or suffering from age-related insomnia

Diagnosis dose (mg)	Normal sleep				Insomnia			
	0.0	0.1	0.3	3.0	0.0	0.1	0.3	3.0
Sleep period (SP, min)	443 (41)	450 (35)	449 (42)	452 (39)	490 (56)	484 (52)	484 (54)	472 (59)
Total sleep time (TST, min)	408 (39)	411 (40)	410 (42)	413 (41)	390 (91)	402 (45)	409 (49)	398 (56)
Sleep efficiency (TST/SP, %)	92 (4)	91 (3)	91 (3)	91 (4)	78 (15)	84 (8)	88 (7)	84 (8)
Sleep latency (min)	9 (7)	10 (7)	5 (4)	7 (6)	11 (10)	10 (6)	10 (8)	10 (7)
REM latency (min)	74 (48)	60 (17)	70 (36)	61 (20)	99 (80)	68 (29)	54 (27)	52 (22)
Awake (% SP)	8 (4)	9 (4)	9 (4)	9 (4)	21 (16)	17 (9)	12 (7)	16 (8)
Stage 1 (% TST)	16 (7)	17 (5)	19 (6)	16 (7)	22 (9)	21 (8)	18 (9)	20 (8)
Stage 2 (% TST)	46 (12)	46 (8)	44 (9)	45 (8)	45 (9)	44 (8)	45 (13)	45 (9)
Stage 3 (% TST)	15 (7)	13 (6)	16 (9)	14 (7)	11 (6)	13 (6)	13 (7)	13 (5)
Stage 4 (% TST)	7 (5)	5 (4)	5 (4)	6 (5)	5 (6)	5 (4)	5 (4)	4 (4)
Stage REM (% TST)	17 (6)	20 (7)	18 (6)	19 (5)	17 (5)	17 (5)	19 (7)	18 (5)

Data are expressed as group mean (SD). SP, interval between first and last epoch of sleep (*i.e.* time in bed less latency to sleep); TST, amount of actual sleep time during SP (*i.e.* equal to SP less awake time); Sleep efficiency, percent of time spent asleep during SP (*i.e.* TST/SP [%]); Sleep latency, duration of time from bedtime to the onset of sleep; REM latency, interval from the time of sleep onset to the first appearance of REM sleep; awake, percent of time spent awake during SP; stage (1-REM), percent of total sleep time spent in one sleep stage (*i.e.* stage 1–4 or REM).

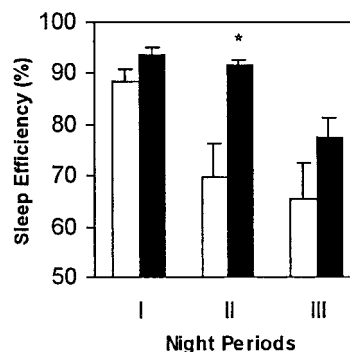


FIG. 2. Sleep efficiency in insomniacs during three consecutive parts (I, II, and III) of the night, following placebo (light bar) or melatonin (0.3 mg, dark bar) treatment. *, $P < 0.05$.

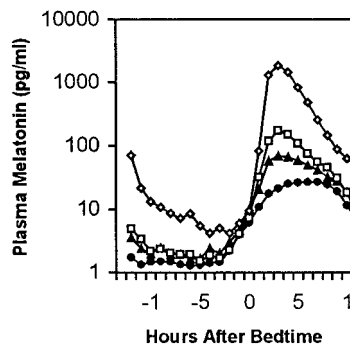


FIG. 3. Mean group ($n = 30$) plasma melatonin profiles after melatonin or placebo treatment 30 min before bedtime. *Inset*, daytime melatonin levels; *circle*, placebo; *triangle*, 0.1 mg; *square*, 0.3 mg; *diamond*, 3 mg.

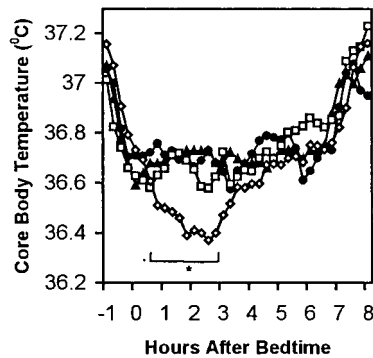


FIG. 4. Core body temperature profiles following melatonin or placebo treatment. Circle, placebo; triangle, 0.1 mg; square, 0.3 mg, diamond, 3 mg. *, $P < 0.05$.

from age-related insomnia; that bedtime melatonin treatment does not modify sleep efficiency or alter sleep architecture in older people in whom sleep already is normal; and that the major effect of the melatonin treatment we provided is observed during the midportion of the nocturnal sleep period. This study in aged insomniacs also found that, similar to ours and others' observations in young healthy individuals (5–9), pharmacological doses of melatonin do not increase the sleep-promoting effects of melatonin above those achieved by physiological doses and might even be less effective. Moreover, the pharmacological dose that we used (3 mg) was associated with a significant decline in core body temperature, but the physiological doses (0.1 and 0.3 mg) had no such effect. This confirms that although nocturnal hypothermia is induced when plasma melatonin is raised to supraphysiological levels, this decline is not a prerequisite for melatonin to promote sleep (5).

Even though, as shown previously (11–14), older people as a group clearly exhibited low nocturnal melatonin levels, no correlation was observed between each individual's endogenous nocturnal melatonin and his or her sleep quantity or quality. Earlier studies (18–20) addressing this issue produced conflicting results. There are several possible explanations for the fact that, while increasing circulating melatonin to "youthful" levels, can correct age-related insomnia, some elderly subjects with low levels continue to exhibit normal sleep. For example, the redundancy of the mechanisms controlling sleep might allow some individuals but not others to compensate for a low melatonin signal; or some individuals might manifest low nocturnal levels when young and might thus need less when older. This latter explanation is compatible with the very great interindividual variability in nocturnal melatonin levels that young individuals exhibit (21, 22); the variability within this group is much greater than that between the age groups (13). In view of this high variability and lack of an established method to assess an individual's sensitivity to melatonin, the definition of low melatonin or melatonin deficiency remains vague.

These data affirm the wisdom of using the lowest fully effective dose of a hormone to treat deficiencies in its plasma levels and of making the treatment's target the normalization of plasma hormone levels. Thus, as in young volunteers attempting to fall asleep (5–9), elderly insomniacs responded to a physiologic melatonin dose (0.3 mg) with a statistically significant

improvement in sleep quality and without subsequent alterations in the normal circadian pattern of circulating melatonin levels. A supraphysiological dose (3.0 mg) of melatonin was somewhat less efficacious; moreover, it not only elevated nocturnal plasma melatonin levels well beyond their normal range but also continued this elevation well into the following day and produced significant hypothermia. Hence, patients with age-related insomnia associated with low nocturnal melatonin levels (e.g. less than 60 pg/ml) might benefit from melatonin treatment using physiological doses administered at bedtime.

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