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Effect of inducing nocturnal serum melatonin concentrations in
daytime on sleep, mood, body temperature, and performance

(vigilance/fatigue/hypnotic/circadian)

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ABSTRACT We examined effects of very low doses of melatonin (0.1–10 mg, orally) or placebo, administered at 1145 h, on sleep latency and duration, mood, performance, oral temperature, and changes in serum melatonin levels in 20 healthy male volunteers. A repeated-measure double-blind Latin square design was used. Subjects completed a battery of tests designed to assess mood and performance between 0930 and 1730 h. The sedative-like effects of melatonin were assessed by a simple sleep test: at 1330 h subjects were asked to hold a positive pressure switch in each hand and to relax with eyes closed while reclining in a quiet darkened room. Latency and duration of switch release, indicators of sleep, were measured. Areas under the time-melatonin concentration curve varied in proportion to the different melatonin doses ingested, and the 0.1- and 0.3-mg doses generated peak serum melatonin levels that were within the normal range of nocturnal melatonin levels in untreated people. All melatonin doses tested significantly increased sleep duration, as well as self-reported sleepiness and fatigue, relative to placebo. Moreover, all of the doses significantly decreased sleep-onset latency, oral temperature, and the number of correct responses on the Wilkinson auditory vigilance task. These data indicate that orally administered melatonin can be a highly potent hypnotic agent; they also suggest that the physiological increase in serum melatonin levels, which occurs around 2100 h daily, may constitute a signal initiating normal sleep onset.

Serum melatonin levels in normal humans are very low during most of the day but increase significantly to a mean of 80 pg/ml (range, 0–200) between 0200 and 0400 h (1 pg/ml = 4.31 pmol/liter) and remain elevated during the normal hours of sleep, falling sharply to daytime values around 0900 h (1). The physiological significance of the nocturnal increase in serum melatonin could derive from acute effects of the hormone [e.g., its ability to reduce core body temperature (2), alter thermoregulation (3), modify brain levels of monoamine neurotransmitters (4), stimulate prolactin secretion (5), or induce sleepiness (6, 7)].

Alternatively, the nocturnal increase in serum melatonin could constitute a time signal, affecting the temporal characteristics of other circadian rhythms. Oscillations in the concentration of circulating melatonin could directly affect circadian rhythms (8, 9) or could provide humoral communication of information about environmental lighting (and thus about time of day), which entrains endogenous physiological and behavioral rhythms (e.g., those associated with photoperiodism or seasonality; ref. 10). Some studies also suggest a role for melatonin in human development. The decrease in amplitude of the melatonin rhythm, which occurs late in the 1st decade of life, has been proposed as a factor contributing to pubescence (11), while further decrease, which occurs after the 6th decade, may contribute to disruptions in circadian rhythmicity reported by the elderly (12).

The acute effects of exogenous melatonin on human behavior have been studied only sporadically and have used melatonin doses that raise serum melatonin levels well beyond their normal nocturnal range. Thus, Lieberman et al. (13) found that a dose (240 mg over a 2-h period) that raised melatonin levels several thousandfold impaired mood and performance. More recently, we found similar behavioral changes after a considerably lower dose of the hormone (10 mg), which still raised serum levels to 40–50 times the normal nocturnal level (i.e., 4072 pg/ml; ref. 14).

The present study was designed to determine whether much lower daytime doses, which elevate serum melatonin levels significantly but keep these levels within the normal nocturnal range, are also sufficient to produce short-term behavioral effects. If so, this would suggest a similar role for the normal nocturnal increase in serum melatonin levels. We gave the melatonin at midday (9 or more h before the nocturnal increase) and measured mood, performance, sleepiness, and (indirectly) sleep onset.

METHODS AND MATERIALS

Twenty healthy male volunteers [mean age, 23.05 ± 4.22 (SEM) years; range, 18–24 years] participated. Before admission to the study, each subject gave his informed consent, had a physical examination to ensure that he was in good health, and completed two 1.5-h training sessions to become familiar with testing procedures and the performance test battery. Subjects were also screened for depressive symptoms by using the Hamilton psychiatric rating scale for depression (15) with a special addendum for seasonal affective disorder (16); any with a history or findings of depression were excluded. All subjects were paid for their participation in the experiment.

The study was double blind and placebo controlled. A repeated-measures, within-subjects, 5 × 5 Latin square design was used. The subjects participated in five 8-h (0930–1730 h) testing sessions. At least 5 days elapsed between successive test sessions. Capsules containing 0.1, 0.3, 1.0, or 10 mg of melatonin or placebo were administered orally (p.o.) at 1145 h each test day. Treatment order was determined by the balanced Latin square design.

Oral temperatures were measured hourly and blood was sampled at regular intervals via an indwelling venous catheter for subsequent serum melatonin measurement. Serum samples were separated by centrifugation and stored at −20°C.

Abbreviations: p.o., orally; RT, reaction time; POMS, profile of mood states; SSS, Stanford sleepiness scale.
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until they could be assayed by radioimmunoassay for melatonin (17).

Throughout test sessions, subjects were required to sit at an assigned computer workstation with eyes open. The task order and time of testing were held constant across test days. All instructions, performance tasks, and mood questionnaires were automated to reduce the possibility of experimenter-induced bias. The performance tasks used were coded in-house and included measures of (i) auditory vigilance (18), (ii) four-choice reaction time (RT) (19), (iii) simple RT, and (iv) symbol digit (modalities) substitution (20). Mood questionnaires included the profile of mood states (POMS; ref. 21) and the Stanford sleepiness scale (SSS; ref. 22).

Details of the tasks and their administration are published elsewhere (14). The mood questionnaires were completed at 1030 h and at hourly intervals beginning at 1200 h. The simple and four-choice RTs and symbol digit substitution tasks were completed at 1030, 1300, 1500, 1600, and 1700 h. The auditory vigilance task was administered at 1200 and 1400 h. Subjects were allowed to leave their workstations during lunch (a standard lunch was served between 1100 and 1130 h), toilet breaks (<5 min), and during the half-hour sleep test.

Subjects participated in a sleep test between 1330 and 1400 h. They were asked to recline (on either a bed or reclining chair) and relax with their eyes closed in a quiet, darkened room. In each hand they held a 1-in (2.54 cm) plastic tube that bore a positive pressure switch. They were asked to rest their hands, palm up, alongside their body and to depress the switches with the last segment of their index fingers. Release of the switch on either tube was recorded as a pen deflection on an event recorder. An investigator remained in attendance with the subjects to ensure that they followed instructions. An event-timer solenoid was randomly activated to reduce the possibility that the soft click of the switch would be misconstrued by the subjects as a significant event. After 30 min, the subjects were asked to stop relaxing and/or were awakened. They were then asked (i) if they fell asleep, (ii) if so, how long it took to fall asleep, and (iii) to respond to the SSS.

Latency to switch release was measured from the beginning of instruction presentation to the first full minute of switch release. Total switch release time was measured as the total length of time a recording pen was deflected (the smallest interval of pen deflection measured was 1 min; accuracy, 0.25 min). One subject failed to release a switch during a sleep test session but was identified as asleep by his prolonged snoring. Sleep onset for this subject was recorded as occurring after 2 min of continuous snoring. When questioned later, the subject reported that he had indeed fallen asleep.

The after-treatment-dependent measures were each assessed by using a repeated-measures, within-subjects, 5 × 5 Latin square analysis. Orthogonal planned comparisons (23) 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 (i) placebo vs. all melatonin treatments, (ii) 0.1 vs. 0.3, 1.0, and 10 mg of melatonin, (iii) 0.3 vs. 1.0 and 10 mg of melatonin, and (iv) 1.0 vs. 10 mg of melatonin. Pairwise comparisons were subsequently calculated for these measures (repeated-measures \( t \) tests for the sleep test and melatonin data and ANOVAs for the other measures) because inspection of the data suggested that the planned comparisons provided an insufficient basis for interpreting results. Only main effects that resulted in significant contrasts and interaction effects are reported. There were some missing data due to difficulties with equipment. Group means were therefore substituted for the 1700-h (0.1 mg), 1300-h (1.0 mg), 1700-h (1.0 mg), and 1000-h (10 mg) measures for subjects 15, 03, 16, and 15, respectively, on most performance measures. Blood samples were not drawn during placebo testing of subject 01 due to difficulties with catheterization, and group means were substituted for the data. Group means of serum melatonin levels were also substituted for six other missing data points. The Greek symbol \( \Delta \) is used to indicate "an average change of."

RESULTS

Serum Melatonin Levels. Mean serum melatonin levels are illustrated in Fig. 1. The mean (SEM) areas under the time–melatonin concentration curve (AUC) between 1000 and 1730 h for the placebo and 0.1-, 0.3-, 1.0-, and 10-mg treatment conditions were 87.7 (51.1), 213.2 (25.02), 459.9 (62.7), 1599.0 (141.7), and 21,000.4 (3752.3), respectively. Serum melatonin AUC differed significantly among the five treatment conditions (\( F_{(4,60)} = 34.34; P < 0.001 \) and all planned contrasts were significant \( P < 0.001 \). All pairwise comparisons were also significant \( P < 0.001 \). The order and treatment-by-order effects were not significant.

Melatonin Treatment Effects. Significant melatonin treatment effects were found for oral temperature (\( F_{(4,60)} = 7.90; P < 0.001 \)); sleep test sleep-onset latency (\( F_{(4,60)} = 6.65; P < 0.001 \)); sleep duration (\( F_{(4,60)} = 7.80; P < 0.001 \)); self-reported sleep-onset latency (\( F_{(4,60)} = 10.52; P < 0.001 \)); postsleep test SSS responses (\( F_{(4,60)} = 3.11; P < 0.05 \) (Fig. 2); POMS vigor–activity (\( F_{(4,60)} = 4.16; P < 0.05 \)) and fatigue–inertia (\( F_{(4,60)} = 3.05; P < 0.05 \) (Fig. 3) responses; SSS responses (\( F_{(4,60)} = 2.79; P < 0.05 \)); number of correct responses on the Wilkinson auditory vigilance task (\( F_{(4,60)} = 3.42; P < 0.05 \)); and four-choice RT response latency (\( F_{(4,60)} = 3.84; P < 0.01 \)). Table 1 summarizes the planned comparison results and Table 2 contains the mean (SEM) levels measured. The treatment-by-order interaction effects were nonsignificant for all measures except the SSS (\( F_{(4,60)} = 4.68; P < 0.001 \)). There were no significant differences among the baseline (1000 h) oral temperature, SSS, or POMS measures. An order effect was found among the four-choice RT response latency baseline measures (\( F_{(4,60)} = 15.13; P < 0.001 \)), but the treatment and treatment-by-order interaction effects were nonsignificant.

As Table 2 indicates, response levels for some measures did not consistently increase or decrease relative to serum melatonin levels. For example, self-reported SSS responses were greatest and POMS vigor–activity scale responses were smallest after ingesting 0.3 mg, rather than higher doses, of melatonin. Pairwise comparisons were calculated to aid in interpretation of these data. Mean oral temperature measures were significantly less, relative to placebo, after ingesting 1.0 and 10 mg of melatonin (\( \Delta \) –0.24°F and –0.37°F, respec-

FIG. 1. Mean (SEM) serum melatonin profiles of 20 subjects sampled at intervals after ingesting 0.1, 0.3, 1.0, and 10 mg of melatonin or placebo at 1145 h.
Fig. 2. Mean (SEM) sleep-onset latencies (A), sleep durations (B), self-reported sleep-onset latencies (C), and posttest SSS responses (D) after ingestion of melatonin or placebo at 1145 h (n = 20). 

Precisely; °F = (°C × 9/5) + 32. Oral temperatures measured after ingesting 1.0 (Δ −0.16°F) and 10 (Δ −0.29°F) mg of melatonin were also less than those measured after ingestion of 0.1 mg of melatonin. Ingestion of 10 mg of melatonin also decreased oral temperature relative to the 0.3- and 1.0-mg doses (Δ −0.21°F and −0.13°F, respectively). SSS responses indicated greater feelings of sleepiness, relative to placebo, after ingesting 0.3, 1.0, and 10 mg of melatonin (Δ +0.51, +0.47, and +0.46, respectively). POMS responses showed a decrease in self-reported feelings of vigor-activity, relative to placebo, after ingesting 0.3, 1.0, and 10 mg of melatonin (Δ −2.77, −1.90, and −1.95, respectively). Feelings of vigor-activity were also decreased after ingesting 0.3 mg relative to 1.0 mg of melatonin (Δ −1.33). POMS responses indicated an increase in self-reported feelings of fatigue-inertia, relative to placebo, after ingesting 0.3, 1.0, and 10 mg of melatonin (Δ +2.14, +1.56, and +2.28, respectively). Sleep test sleep-onset latencies were shorter, relative to placebo, after ingesting 0.1, 0.3, 1.0, and 10 mg of melatonin (Δ −7.45, −9.03, −11.02, and −10.32 min, respectively). The duration of sleep (i.e., switch release) experienced during the sleep test was greater, relative to placebo, for the 0.1-, 0.3-, 1.0-, and 10-mg melatonin doses (Δ +8.20, +10.04, +12.09, and +10.47 min, respectively). Sleep test self-reported sleep latencies were smaller, relative to placebo, for the 0.1-, 0.3-, 1.0-, and 10-mg melatonin doses (Δ −7.60, −10.60, −13.27, and −10.65 min). Subjects also indicated that they slept more quickly after ingesting 1.0 mg, relative to 0.1 mg, of melatonin (Δ −5.67). Responses to the postsleep test SSS indicate that subjects felt sleepier after ingesting 1.0 and 10 mg of melatonin than after ingesting placebo (Δ +0.70 and +0.95, respectively). Post-sleep test SSS responses also indicate that 1.0 mg of melatonin caused greater feelings of sleepiness than 0.1 mg (Δ +0.70). Fewer Wilkinson auditory vigilance task correct responses were recorded, relative to placebo, after subjects ingested 1.0 and 10 mg of melatonin (Δ −4.75 and −5.67, respectively). Correct four-choice RT response latencies were greater (i.e., longer) after ingesting 10 mg, relative to placebo, and 0.1 mg of melatonin (Δ +17.21 and +14.46 ms, respectively). All of the pairwise comparison results reported above were significant at the P < 0.05 level.

Order and Time Effects. Significant order effects were found on the Wilkinson auditory vigilance, simple RT, four-choice RT, and symbol digit substitution tasks. These results indicate that subjects tended to respond more accurately (symbol digit substitution responses and RT response latencies) with practice and less frequently (Wilkinson auditory vigilance) on subsequent test days. These changes are of little interest because (i) significant treatment-by-order interactions were not found on these measures, (ii) the Latin square is balanced to compensate for order effects, and (iii) similar results have been observed previously (14).

There were consistent patterns of variance over time among the mood scale measures. Subjects' SSS (F(5,75) = 17.50; P < 0.001) and POMS fatigue-inertia (F(5,75) = 8.04; P < 0.001) responses indicate that they felt sleepiest and most fatigued and that they felt the least vigorous [POMS vigor-activity scale (F(5,75) = 12.79; P < 0.001)] at 1400 h, 2.25 h after melatonin ingestion (Fig. 3). Oral temperatures were consistently low at 1200 and 1400 h (means, 96.85°F and
Table 1. Mean differences of planned comparisons following significant overall F tests

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Mean Difference (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 vs. 0.1, 0.3, 1.0, and 10</td>
<td></td>
</tr>
<tr>
<td>Oral temperature, °F</td>
<td>-0.21** (0.06)</td>
</tr>
<tr>
<td>SSS</td>
<td>0.42** (0.10)</td>
</tr>
<tr>
<td>Profile of mood states</td>
<td></td>
</tr>
<tr>
<td>Vigor–activity scale</td>
<td>-2.02** (0.59)</td>
</tr>
<tr>
<td>Fatigue–inertia scale</td>
<td>1.75** (0.40)</td>
</tr>
<tr>
<td>Sleep test</td>
<td></td>
</tr>
<tr>
<td>Sleep-onset latency, min</td>
<td>-9.46** (3.85)</td>
</tr>
<tr>
<td>Sleep duration, min</td>
<td>10.20** (3.04)</td>
</tr>
<tr>
<td>Self-reported sleep latency, min</td>
<td>-10.53** (3.85)</td>
</tr>
<tr>
<td>SSS responses</td>
<td>0.61** (0.48)</td>
</tr>
<tr>
<td>Wilkinson auditory vigilance,</td>
<td></td>
</tr>
<tr>
<td>correct responses</td>
<td>-3.72* (0.30)</td>
</tr>
<tr>
<td>Four-choice RT</td>
<td></td>
</tr>
<tr>
<td>correct response latency, ms</td>
<td>10.06** (13.25)</td>
</tr>
</tbody>
</table>

Values in table are an average of the subsequent melatonin doses (mg) minus the first dose listed in the heading. All comparisons were F tests calculated with 5 and 15 degrees of freedom; n = 20 (see text for details of missing value substitutions). * P < 0.05; ** P < 0.001.

97.09°F, respectively). Mean four-choice RT response latencies were the greatest at 1300 h (i.e., 377.77 ms) and decreased to 360.15 ms at 1700 h. Significant treatment-by-time interactions were found in oral temperature (\( F_{(24,360)} = 1.60; \) P < 0.05) and number of correct responses on the four-choice RT task (\( F_{(12,180)} = 1.92; \) P < 0.05).

**DISCUSSION**

Ingestion of melatonin (0.1–10 mg) at 1145 h resulted in correspondingly increased circulating melatonin levels. Serum melatonin concentrations observed after the 0.1- and 0.3-mg doses were within the normal dynamic range for nocturnal melatonin concentrations (1). Sleep test results indicate that acute administration of melatonin (0.1–10 mg, p.o.) at midday decreased objective and self-reported sleep-onset latencies by an average of 9.46 and 10.53 min, respectively, relative to placebo. Sleep duration was increased by an average of 10.2 min during the 30-min sleep test, relative to placebo, by ingestion of melatonin. Pairwise comparison of SSS scores, after the sleep test, indicates that the 0.3- and 1.0-mg doses of melatonin increased self-reported feelings of sleepiness, relative to placebo, and that feelings of sleepiness after the 1.0-mg dose were greater than those after the 0.1-mg dose. These results indicate that ingestion of an acute dose of melatonin, sufficient to increase circulating melatonin to levels within the normal nocturnal physiologic range, has hypnotic effects. The acute nature of the hypnotic effect of melatonin suggests that it may constitute a direct physiologic effect of the hormone independent of its action as a circadian zeitgeber time signal (24–26). This hypothesis is supported by the recent independent observation that melatonin (5 mg, p.o.) administered at 1200, 1700, or 1900 h exerted a direct hypnotic effect, increasing sleep propensity within 90–120 min of ingestion (27). The phase shifts in circadian rhythms in sleep (27) or endogenous melatonin secretion (28, 29) previously seen after a single acute dose of the hormone, as used here, were of insufficient magnitude to support the hypothesis that the hypnotic effects found in the current study could be caused by melatonin acting as a zeitgeber time signal. Such a hypothesis would suggest that a 9-h phase shift in sleep onset can occur after a single acute dose of melatonin at midday; this seems highly improbable.

The observed significant decreases in oral temperature after ingestion of 1.0 and 10 mg of melatonin are consistent with previous reports (2, 14). Alterations in mood and performance measures after melatonin ingestion, relative to placebo (e.g., increase in feelings of sleepiness and fatigue; increase in four-choice RT latency; decrease in feelings of vigor, decrease in number of correct responses on the Wilkinson auditory vigilance task), are also consistent with previous reports in both direction and magnitude of measure (13, 14). The direction and magnitude of response change, relative to placebo, among the melatonin doses administered.
were consistent on both the mood and performance measures. It thus seems likely that failure to find significant differences in mood or performance between placebo and the lower melatonin doses (0.1 and 0.3 mg) is due to the limited sensitivity of the measures used rather than an absence of effect.

The results of this study are consistent with the observations of Vollrath et al. (6), who report a decrease in daytime latency of sleep onset in subjects given 1.7 mg of melatonin nasally and with those of Lavie and colleagues (27) described above. Nickelsen et al. (30) reported that 50 mg of melatonin, administered p.o. at 0900 or 1900 h, caused nonsignificant decreases in sleep latency but increased feelings of sleepiness only after the administration at 0900 h. Others (31, 32) reported that evening ingestion of melatonin (1 and 5 mg) did not influence sleep onset or duration but did cause an increase in rapid eye movement (REM) sleep-onset latency. Therefore, the sedative-like effects may be significantly influenced by the time of its administration. Alternatively, the experimental designs used in the negative studies might have precluded observing the hypnotic effect seen here (e.g., by not allowing subjects to modify their sleep times or by forbidding afternoon napping; refs. 28 and 29). It should be noted that the pattern of physiologic and performance responses observed here resembles that observed for drugs in the benzodiazepine family (33–35).

In summary, administration of a small melatonin dose (0.1–0.3 mg, p.o.) during the daytime, which raises serum melatonin concentrations to within the normal nocturnal range, or of slightly higher doses (1.0–10 mg, p.o.) was shown to cause hypnotic effects relative to placebo. These effects include a decrease in objective and self-estimated sleep-onset latency, an increase in sleep duration, and sleepiness upon waking. Self-reported feelings of sleepiness and fatigue were increased and feelings of vigor diminished. Oral temperature and the number of correct responses on the Wilkinson auditory vigilance task were found to decrease significantly after ingestion of 1.0 and 10 mg of melatonin. These results are similar to those reported after ingestion of benzodiazepines and suggest that melatonin may find use as a hypnotic drug. They also suggest that the normal physiologic secretion of melatonin may be an important and direct-acting factor in bringing about sleep onset.

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