Effects of daytime melatonin infusion in young adults

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Van den Heuvel, Cameron J., David J. Kennaway, and Drew Dawson. Effects of daytime melatonin infusion in young adults. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E19–E26, 1998.—Daytime oral melatonin typically exerts soporific and thermoregulatory effects; however, it is not clear whether these effects reflect the normal physiological response to endogenous nocturnal melatonin production. We infused melatonin at doses that produced physiological and supraphysiological steady-state levels in 24 young adults during two daytime bed rest protocols. From 1000 to 1630, subjects were infused intravenously with saline or melatonin in counterbalanced order. Each group of eight subjects received melatonin (and saline) infusions at one dose rate: 0.04 µg·h⁻¹·kg⁻¹·body wt⁻¹ (low), 0.08 µg·h⁻¹·kg⁻¹ (medium), or 8.0 µg·h⁻¹·kg⁻¹ (high). Low and medium melatonin infusions produced plasma and saliva levels within the normal nocturnal range observed in young adults. These levels were not associated with any changes in rectal, hand, forehead, or tympanic temperatures or with subjective sleepiness. High melatonin produced supraphysiological plasma and saliva levels and was associated with a significant attenuation in the daytime increase in rectal temperature, significantly increased hand temperature, and greater sleepiness. It is not yet clear whether the thermoregulatory and soporific effects of daytime supraphysiological melatonin administration are equivalent to the physiological responses to endogenous melatonin.

core temperature; thermoregulation; sleepiness; intravenous administration; soporific effects; physiology

IT HAS BEEN KNOWN for over 20 years that, in individuals entrained to a normal light-dark cycle, melatonin typically shows a circadian profile with low diurnal and high nocturnal levels (27). Since this first observation that the secretion of melatonin is elevated at the time people normally sleep, there has been considerable interest in the possible physiological role of melatonin in regulating sleep.

In one of the first reported studies of melatonin administration to humans, doses of 1.25–25 mg/kg injected intravenously at 4 PM for 5 days resulted in significant electroencephalogram deactivation and induction of sleep 15–20 min after administration (2). The reported hypnotic effects in this study were said to be stronger at the higher melatonin doses. Interestingly, the subjects were wakened easily after 45 min with no adverse or hangover effects, suggesting that melatonin has a relatively short half-life and a mode of action different from traditional sedatives.

From the early 1970s, studies typically used lower doses of daytime melatonin to better examine the “physiological” effects of the hormone. Lerner and Nordlund (20, 21) found significant increases in subjective sleepiness in subjects ingesting 1-mg melatonin capsules. Similarly, 12 volunteers who received 2-mg oral doses of melatonin at 1700 for 4 wk reported significant increases in self-rated fatigue at night (4). These results indicated that the soporific effects of melatonin might be apparent at much lower doses than those used in previous research. However, large interindividual variations in first pass metabolism of oral melatonin (1, 19) and the associated variability in circulating supraphysiological melatonin levels may limit the interpretation of results from previous studies.

Despite nearly 20 years of research, human studies have been unable to clearly define whether melatonin has a physiological role in regulating normal nocturnal sleepiness. The aim of this study, therefore, was to examine the effects of physiological melatonin levels on body temperatures and subjective sleepiness in young adults. Melatonin was infused at various rates with the aim of reproducing the salient features (i.e., dose and duration) of nocturnal physiological melatonin production as well as maintaining supraphysiological levels during the day, when endogenous melatonin production is low.

METHODS

Subjects. Twenty-four subjects (12 male, 12 female) aged 19–28 yr gave informed consent and volunteered to attend the laboratory for two nonconsecutive sessions between 0700 and 1900. The study was approved by members of the Ethics of Human Research Committee at The Queen Elizabeth Hospital, who used ethical guidelines from the National Health and Medical Research Council of Australia. Subjects were screened for medical, psychiatric, and sleep disorders by use of a battery of questionnaires, a clinical interview, and a 7-day sleep diary. Exclusion criteria for the present study included demonstration of any concurrent medical or psychiatric illness, occult sleep disorder, or regimen in which subjects were taking any medication known to affect thermoregulation, melatonin production, or sleep. Female subjects were studied during the follicular phase of their menstrual cycles, which has previously been shown as the phase of the cycle when women are most sensitive to daytime melatonin (8).

Experimental protocol. Subjects were required to abstain from caffeine, alcohol, and medications for ≥24 h before and during each experimental session. On presentation at 0700, subjects were cannulated in each forearm by medical staff. Between 0700 and 0800, subjects were fitted with a montage of thermistors for the measurement of body temperature: 1) on the back of the nondominant hand (YSI-4499E, Yellow Springs Instruments, OH), 2) in the middle of the forehead...
used: low (0.04 µg·h⁻¹·kg⁻¹) and medium (0.08 µg·h⁻¹·kg⁻¹) in the auditory canal adjacent to the tympanic membrane (Sheridan Catheter, Argyle, NY), and 4) 10 cm into the rectum (Steri-Probe 491B, Cincinnati Sub-Zero Products, Cincinnati, OH).

All thermistors were connected to a Mini-logger ambulatory data recorder (Mini Mitter, Sun River, OR) that allowed simultaneous sampling, storage, and display of temperature data at 2-min intervals in each experimental session.

Between 0800 and 1900, subjects lay quietly awake on a bed and could watch TV or read but were not allowed to move from the supine position except for short toilet trips as required (when possible, subjects were asked to use a bed pan). Subjects were fed a standard hospital meal between 1230 and 1300 and between 1730 and 1800 and were allowed one to two glasses of water per session.

At 1000, in each session, a 500-ml infusion bag connected to a digital infusion pump (IVAC, Phoenix Medical, Adelaide, SA, Australia) was connected to the cannula on the subject's dominant arm. In one condition, subjects received 0.9% saline, and in the other, melatonin (Sigma Aldrich, Castle Hill, New South Wales, Australia) dissolved in 0.9% saline. The order of presentation of treatments was counterbalanced for all subjects. Each subject was randomly assigned to one of three groups, with the constraint that each group consisted of four males and four females. Each of the three resulting groups received infusions at a different dose rate. The melatonin doses were administered according to the body weight of subjects at entry into the study, with the following dose rates for all subjects. Each subject was randomly assigned to one of three groups, with the constraint that each group consisted of four males and four females. Each of the three resulting groups received infusions at a different dose rate. The melatonin doses were administered according to the body weight of subjects at entry into the study, with the following dose rates used: low (0.04 µg·h⁻¹·kg⁻¹), medium (0.08 µg·h⁻¹·kg⁻¹), and high (8.0 µg·h⁻¹·kg⁻¹). Saline infusions were delivered at the same rate as melatonin to ensure subjects received equal infusion volumes across conditions.

Infusion solutions were prepared by The Queen Elizabeth Hospital Pharmacy Production Unit within 72 h of the start of each session and were refrigerated until required. Each infusion solution was covered by black plastic before and during the study to protect the melatonin from possible degradation by light and to ensure blinding of the subjects to the treatment. Double blinding was ensured by data coding during the data collection and entry phases of the study.

Plasma and saliva melatonin measurement. The cannula on each subject's nondominant side was used to sample 10 ml of blood at 0700, 1000, 1300, 1600, and 1900 in each session. Blood samples were stored in heparinized tubes for up to 2 h at 4°C and then centrifuged at 1,500 rpm for 10 min. Plasma was prepared and frozen at −20°C for later assay. One subject in the low-dose group had severely hemolyzed blood samples in one session, which were not assayed.

Saliva was collected while subjects chewed on a small piece of paraffin film for 2 min at hourly intervals between 0700 and 1000 and between 1700 and 1900 and at half-hourly intervals during the infusion period (i.e., 1030–1630). The saliva samples were stored at −20°C for later assay. The concentration of melatonin in 500 µl of plasma and in 200-µl saliva samples was determined using the Bühlmann melatonin radioimmunoassay kit (Bühlmann Laboratories, Allschwil, Switzerland), which measures melatonin by a double-antibody assay based on the Kennaway G280 anti-melatonin antibody (28). Melatonin was extracted from plasma samples before assay using reverse solid-phase columns, whereas saliva samples were assayed directly.

Subjective sleepiness. Coincident with each saliva collection, subjects were presented with a Linear Sleepiness Rating (LSR) sheet. The LSR was adapted from a standard 100-mm visual analog scale (10), which rates subjective alertness on a scale from very wide awake to very sleepy. The LSR generates a score between 0 and 100, with higher scores indicating higher levels of sleepiness.

Statistical analysis. Melatonin levels across time were compared using a two-way repeated-measures ANOVA (Super-ANOV A for the Macintosh, v4.5) with both within-group (saline vs. melatonin) and between-group (low vs. medium vs. high) factors. Subjective sleepiness scores were grouped into preinfusion (0800–1000), 1st one-half (1030–1300), 2nd one-half (1330–1630), and postinfusion (1700–1900) groups and expressed relative to saline condition scores. Temperature data across each session were binned into 2- to 2.5-h averages and expressed relative to a baseline average obtained between 0800 and 1000. Relative sleepiness and body temperature measures both within and between treatment groups were then compared using two-way repeated-measures ANOVA. Fisher's protected least squares difference tests were performed when required to determine where significance occurred.

RESULTS

Plasma melatonin. Plasma melatonin levels in each condition at the start of the study (0700) were significantly elevated but decreased to basal daytime levels (range = 5–22 pM) by the start of the infusion period (1000). Repeated-measures ANOVA revealed a significant interaction for condition by dose, such that plasma melatonin increased significantly above saline condition levels in all dose groups (P < 0.05), and mean melatonin levels were significantly different from each other (P < 0.05). Mean plasma levels (average of samples between 1300 and 1630) were elevated to 125 ± 32 and 232 ± 38 pM after infusion of melatonin at the low- and medium-dose rates, respectively. The high-dose melatonin infusion resulted in levels of the hormone that were >100-fold higher than in the medium-dose condition (34.5 ± 12.4 nM). Mean melatonin levels across the same period after saline infusion were 12 ± 2, 14 ± 3, and 9 ± 3 pM for the low-, medium-, and high-dose groups, respectively. Plasma profiles of melatonin in each condition are shown in Fig. 1.

Saliva melatonin. At the start of the study, saliva melatonin levels in each condition were elevated, but they decreased to basal daytime levels (range = 18–45 pM) before commencement of the infusions. Repeated-measures ANOVA did not detect any significant differences between melatonin levels after low-dose melatonin infusion compared with saline control levels. Mean saliva melatonin levels (average of samples from 1030 to 1630) were 51 ± 12 pM during the low melatonin infusion compared with 33 ± 11 pM during the saline infusion. However, there were significant increases in saliva melatonin after medium and high melatonin infusions compared with levels after the corresponding saline infusions (P < 0.05). Saliva melatonin levels were elevated to 65 ± 13 pM after infusion of melatonin at the medium-dose rate compared with levels during saline infusion of 27 ± 9 pM. The high-dose melatonin infusion resulted in saliva levels of melatonin ~20 times greater than the level observed with medium infusion. Mean saliva melatonin during high-dose infusion was 576 ± 67 pM compared with levels during
saline control infusion of 28 ± 4 pM. Saliva profiles of melatonin in each condition are shown in Fig. 2.

Analysis of the ratio of saliva to plasma (S/P) melatonin levels, as a proportional measure of free to bound melatonin in the body, was performed at both 1300 and 1630 with data from the medium and high melatonin dose groups. The ratio was not calculated for the low-dose group, as saliva levels did not increase above saline control levels. The proportion of melatonin in saliva relative to that in plasma, at both 1300 and 1630, decreased significantly with increasing doses of melatonin (P < 0.05). The ratio at 1300 was 10-fold higher in the medium group (35.1 ± 10.0%) than in the high-dose group (3.5 ± 0.9%). At 1630, a similar pattern of lower S/Ps with increasing melatonin dose was observed, where the medium-dose ratio was 33.1 ± 13.0% and the high-dose ratio was 3.5 ± 0.9%.

Body temperatures. Rectal core temperatures in all conditions increased significantly across the day (P < 0.05). To decrease interindividual variability in measures of core and peripheral temperature, data were binned into groups of 2–2.5 h: 0800–1000, 1000–1200, 1200–1400, 1400–1630, and 1630–1900. For analysis, data in each condition were also expressed relative to the preinfusion baseline temperatures (i.e., 0800–1000). Rectal core temperature showed a significant main effect of condition by time only after high-dose melatonin (P < 0.05). The daytime increase in core temperature was significantly attenuated from 1030 and remained lower until 1900 relative to the saline condition (P < 0.05 for all time groups). The mean decrease in rectal temperature between 1030 and 1630 was 0.17 ± 0.01°C. The rectal temperature data are shown in Fig. 3.

Hand skin temperature increased significantly and earlier than in the saline condition for the 2-h period immediately after the start of the high-dose melatonin
show that core temperature changes plateau at the supraphysiological levels of melatonin achieved with high-dose infusion.

Subjective sleepiness. Subjective sleepiness did not change significantly across time in any dose group (see Fig. 6) and was not significantly affected by melatonin infusion at the low- or medium-dose rates. However, melatonin infused at the high-dose rate significantly increased subjective sleepiness during the 1st half of the infusion period (i.e., 1030–1300, P < 0.05). The mean increase in LSR scores relative to saline for the 1st one-half of the high infusion period was 22.2 ± 3.7 units compared with nonsignificant increases across the same period of 5.4 ± 4.0 and 5.0 ± 3.4 units for the low and medium conditions, respectively.

Fig. 3. Time course of rectal core temperature (means ± SE) for all infusion dose rates (low, A; medium, B; and high, C). All data are expressed relative to mean temperature in preinfusion period (0800–1000). In each condition, rectal temperature increased significantly with time, and there was a significant difference between melatonin (C) and saline (●) conditions only at high melatonin dose rate (P < 0.05). Increase in rectal temperature was significantly attenuated by high-dose melatonin from 1000 until end of study at 1900 (P < 0.05).

Fig. 4. Time course of hand skin temperature (means ± SE) for all infusion dose rates (low, A; medium, B; and high, C). Data were expressed relative to mean temperature in preinfusion period (0800–1000). There were no significant changes with time at any melatonin dose rate. A significant difference between melatonin (C) and saline (●) conditions occurred only at high melatonin dose rate (P < 0.05), where hand temperature increased significantly between 1000 and 1200 relative to saline condition (P < 0.05).
Effects of gender on experimental variables. Each dose group (n = 8) consisted of four male and four female subjects. However, there were no significant effects of gender on any measured variable (melatonin levels, body temperature, or sleepiness) in this study.

DISCUSSION

The present study examined the effects of a prolonged daytime infusion of melatonin on temperature and sleepiness in healthy young adults. Low and medium melatonin infusion rates raised the daytime levels of plasma and saliva melatonin into the nocturnal physiological range observed in young healthy adults (for example, see Refs. 6, 28, 30, and 33). However, these dose rates had no significant effects on core or peripheral temperatures or subjective sleepiness. Infusion at the high-dose rate (100-fold higher than the medium dose) induced a significant attenuation of the daytime increase in rectal temperature observed within 30 min of the start of the infusion. A mean difference of 0.17 ± 0.01°C in rectal temperature was maintained during the infusion, and it remained lower than temperature in the saline control condition for ≥2.5 h after the infusion. Hand skin temperature during the high-dose infusion was increased significantly at an earlier time than in the saline condition. During the first 2 h after the start of the high melatonin infusion, hand temperature was 0.64 ± 0.29°C higher than in the saline condition. In addition, high-dose melatonin infusion significantly elevated subjective sleepiness for the first half of the infusion period. Although no effect of gender was observed on any experimental measure, caution should be taken in interpreting any lack of difference as caused by the small number of each gender (n = 4) in each dose group.

Together, the results suggest that melatonin must be elevated to supraphysiological levels during the day to elicit core hypothermic and soporific effects. It follows that the effects on thermoregulation and sleep observed with daytime oral melatonin administration, when levels are elevated into the supraphysiological range, may not be the same as the physiological response to the endogenous nocturnal rise of melatonin. However, it is of primary interest that high melatonin levels correlated significantly with the decline in core body temperature and were associated with significantly increased sleepiness. This supports the results of Kräuchi et al. (17), who found that both a postural change at 1000 from upright to supine and 5 mg of oral melatonin at 1300 suppressed rectal temperature and increased foot temperature in young men (17). The thermoregulatory changes after both interventions were associated with increased sleepiness.

Most previous studies examining the soporific and core hypothermic effects of exogenous melatonin have typically shown the administration of oral melatonin capsules (see Refs. 4, 7, 9, 12, 13, and 22). These studies are confounded by large interindividual variations in first-pass metabolism and the rapid elimination half-life of oral melatonin (1, 12, 19, 29), resulting in an early peak and rapid decline, as well as achieved circulating melatonin levels that vary up to 300-fold. Although the area under the curve (AUC) after oral administration of 0.1–0.3 mg of melatonin may be quantitatively similar to the AUC of endogenous nocturnal melatonin (13), it has been shown that plasma concentrations after ingestion of melatonin doses of ≥0.5 mg peak at supraphysiological levels (12). It is also possible that there are time-of-day differences in melatonin pharmacokinetics, although the results are unclear from the few studies in which identical doses were administered at different times of the day (33). Together, these confounded results have limited the interpretation of findings from previous studies with regard to the physiological effects of exogenous daytime melatonin.
In the attempt to assess the physiological role of melatonin, not only appropriate level but also the duration of the elevated melatonin levels may be important in signaling to various brain or peripheral effector systems. If this is the case, then oral melatonin administration studies have one general drawback: increasing the dose will increase duration but result in circulating levels far above those observed endogenously and may evoke pharmacological effects rather than mimic physiological responses to the hormone. To achieve daytime circulating plasma concentrations at or above the equivalent levels observed at night in healthy young adults, doses of 1–5 mg are typically used. Oral melatonin produces a profile characterized by high initial levels and a subsequent rapid decline, and even slow-release preparations produce supraphysiological levels in the distribution phase after administration (14–16). In these studies in which oral preparations were used, therefore, peak plasma levels typically exceed normal nocturnal levels by 100- to 1,000-fold and have a short duration of 2–3 h. In the present study, infusing melatonin achieved constant circulating levels during the day that were similar to both normal nocturnal levels (low- and medium-dose rates) and those achieved immediately after oral administration of 4–5 mg of melatonin (high-dose rate).

Previous research has indicated that 1–5 mg of oral melatonin can significantly lower core body temperature and increase sleepiness when administered to young adults during the day (7, 13, 22). The present data suggest that melatonin maintained at supraphysiological, but not physiological, levels during the day attenuates the daytime increase in core temperature by an average of 0.17°C. The change in core temperature was at least partially achieved by an acute increase in peripheral heat loss, as inferred from an increase in hand skin temperature during the first 2 h after the start of the high melatonin dose infusion. However, the relationship between changes in body temperatures may not be a straightforward one, because melatonin maintained a significant difference in rectal temperature, but not hand temperature, until the end of the study. Subjective sleepiness, which was elevated by high melatonin for the first one-half of the infusion, also decreased to control levels despite continuing high melatonin levels. These results suggest that hand temperature and sleepiness may respond to the onset of melatonin during an infusion but not be affected by the duration of the pulse.

No significant changes in temperature of the forehead or tympanic membrane occurred at any melatonin dose, suggesting that if melatonin actually exerts discernible effects at these sites, these measures may be relatively insensitive to small temperature changes. It would therefore appear that the effects on core body temperature are dose related and do not appear until circulating levels reach a threshold that is above the physiological range. At this stage we cannot clearly define what the melatonin threshold for significant core temperature effects is.

It has been suggested recently (33) that melatonin administered before endogenous onset may produce an immediate advance of the circadian pacemaker, which is responsible for the acute effects on body temperature and sleep propensity. The authors suggest that a phase shift of up to 10 h would be required, if the “shift hypothesis” were to explain the soporific and thermal-regulatory effects of daytime melatonin administration. However, the phase-response curve for melatonin administration suggests that melatonin is unable to shift the pacemaker by more than 1–2 h per day (31) and therefore makes this explanation of melatonin's effects unlikely. Furthermore, if melatonin is acting at the level of the circadian pacemaker, the present results suggest that it does so only at supraphysiological levels. Taken together, these evidence supports a direct effect of melatonin on sleep and temperature control centers, yet it is likely that this effect represents a pharmacological and not a physiological role of the hormone.

The present results are supported by previous studies that have reported soporific and hypothermic effects of daytime melatonin administration that resulted in supraphysiological blood levels, but not at doses that increased melatonin levels into the nocturnal physiological range (13, 32). In a recent study by our group (12), it was apparent that, even at oral daytime doses of 0.1 and 0.5 mg, which produced supraphysiological peak (+5D) plasma melatonin levels in eight subjects of 536 ± 421 and 3,054 ± 3,022 pM, respectively, melatonin did not produce significant changes in core temperature. It remains a possibility that the absence of thermoregulatory effects when melatonin levels are increased into the nocturnal range may reflect a time-of-day effect in responsiveness to melatonin. If this is the case, it would seem that the sensitivity to melatonin is lowered during the day (when melatonin is not produced), and thus that large, supraphysiological doses are required to elicit an effect on temperature and sleepiness. Whereas this has yet to be systematically studied, there is some evidence that evening melatonin administration at doses of 0.3–1.0 mg can significantly increase sleep propensity (33). Furthermore, a melatonin infusion at night that restored physiological levels of the hormone can reverse the core hyperthermic effects of light-induced suppression of endogenous melatonin (25). It remains to be seen whether exogenous melatonin administered in the presence of endogenous melatonin production at night can exert additional effects on body temperature regulation and thus indicate whether or not the thermoregulatory and soporific effects of melatonin are saturated at physiological levels. This is particularly important, given that nocturnal melatonin administration has been suggested as a potential therapy for age-related sleep disturbance (11).

Whereas melatonin has previously been thought to diffuse passively into all tissues and compartments in the body, the ratio of saliva to plasma melatonin was not constant across the achieved plasma melatonin concentrations. The reported melatonin S/P is ~0.30.
ing the possibility that sensitivity to melatonin infusion
role melatonin can play both endogenously and thera-
Future studies should aim to investigate not only the
determinant of the effects of melatonin in the body (23).
transbuccal administration, or nasal insufflation) at a
istered melatonin (e.g., by bolus melatonin injection,
findings supports the results of Laakso et al. (18),
which found that the proportion of endogenous melatonin
found in saliva decreases with increasing plasma lev-
els. A similar conclusion has been drawn from measure-
ments of saliva melatonin concentrations with and
without saliva flow stimulation (28). If so, then the
precision of estimates of plasma melatonin derived
from saliva would likely decrease significantly with
increasing doses of melatonin.
Finally, it may be possible to affect temperature and
sleepiness differently by changing the profile of admin-
istered melatonin (e.g., by bolus melatonin injection,
transbucual administration, or nasal insufflation) at a
constant melatonin level. It is possible that the shape of
the melatonin signal (i.e., rapid or slow onset) as well as
its dose, timing, and duration may be an important
determinant of the effects of melatonin in the body (23).
Despite some evidence, therefore, that endogenous
melatonin may not play a significant role in the regula-
tion of nocturnal body temperature and sleep propen-
sity changes, it has demonstrated utility in the treat-
ment of jet lag and some sleep disorders and as an
entraining signal for the circadian system (3, 5, 24).
Future studies should aim to investigate not only the
role melatonin can play both endogenously and therapeutically but also the mechanisms by which the hor-
more achieves these effects. Furthermore, investigat-
the possibility that sensitivity to melatonin infusion
changes across the day may help in understanding
more clearly the endogenous role of melatonin.

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