A relationship between heat loss and sleepiness: effects of postural change and melatonin administration

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Kräuchi, Kurt, Christian Cajochen, and Anna Wirz-Justice. A relationship between heat loss and sleepiness: effects of postural change and melatonin administration. *J. Appl. Physiol.* 83(1): 134–139, 1997.—Both the pineal hormone melatonin (Mel) and postural changes have thermoregulatory sequelae. The purpose of the study was to evaluate their relationship to subjective sleepiness. Eight healthy young men were investigated under the unmasking conditions of a constant routine protocol. Heart rate, rectal temperature (T_{re}), skin temperatures (foot, T_{fo}; and stomach), and subjective sleepiness ratings were continuously recorded from 1000 to 1700. Mel (5 mg po) was administered at 1300, a time when Mel should not phase shift the circadian system. Both the postural change at 1000 from upright to a supine position (lying down in bed) and Mel administration at 1300 reduced T_{re} and increased T_{fo} in parallel with increased sleepiness. These findings suggest that under comfortable ambient temperature conditions, heat loss via the distal skin regions (e.g., feet) is a key mechanism for induction of sleepiness as core body temperature declines.

core body temperature; distal skin temperature; proximal skin temperature; heart rate

IN HUMANS, the pineal hormone melatonin (Mel) is secreted nocturnally when core body temperature (CBT) declines and sleepiness increases (3, 9). The rhythms of Mel secretion and CBT are driven by the circadian pacemaker and undergo parallel phase shifts after the appropriate timing of a light pulse (21). The nocturnal secretion of Mel partially contributes to the nocturnal decline in CBT and, thus, to the circadian amplitude of CBT (5). Administration of exogenous Mel induces hypothermia in humans, as measured by reduced CBT (3). This reduction of CBT can come about by two processes: decrease in heat production and/or increase in heat loss.

The endogenous circadian rhythm of CBT is characterized by a nocturnal decline of CBT that is a consequence of reduced heat production and vasodilation at distal skin regions (16). We have recently shown that administration of Mel in the early evening phase-advances the circadian system in parallel with an earlier regulation of the endogenous nocturnal decline in CBT (15). Administration of exogenous Mel in the daytime, when it is not usually secreted, induces sleepiness in addition to its hypothermic effect (6, 8, 25, 28). The endogenous nocturnal onset of Mel is itself accompanied by an increase in sleepiness (6, 28).

We wish to introduce here a further phenomenon: the postural change of lying down causes a decline in CBT that can be considered as preparatory for sleep (2, 14). This "postural hypothermia" can occur at any time of day (14, 19). Under the usual entrained conditions, all three effects (nocturnal decline of CBT, onset of Mel secretion, and lying down) are synchronized around bedtime; thus, the three effects in concert coordinate sleepiness to aid sleep onset.

The purpose of this study was to separate the phase-advancing from the thermoregulatory effects of Mel and investigate their relation to sleepiness. This was not possible in our previous experiment with evening administration of Mel (6, 15), because the acute hypothermia and the phase advance of the circadian system occurred together. Mel was therefore administered at 1300, when it is not endogenously secreted and, according to its phase-response curve, should not phase-advance the circadian system (17). The acute effect of Mel on thermoregulatory processes and their relationship to the soporific effect of Mel (28) could be studied without any confounding thermoregulatory effects related to circadian phase shifts.

MATERIALS AND METHODS

Subjects

Eight male students were screened for general medical or psychiatric disorders by history and physical examination [age: 25 ± 4 yr (SD) (range: 21–31 yr); height: 182 ± 6 cm (170–188 cm); body mass: 75 ± 12 kg (60–96 kg), body mass index (BMI; weight/height^2): 22.44 ± 2.63 kg/m^2 (18.94–27.16 kg/m^2)]. They had no sleep disorders (Pittsburgh Sleep Quality Index <5), no extreme phase type (Torsvall-Åkerstedt morning-evening preference questionnaire), no shift work or transmeridian travel within 1 mo before the study, no medication or drug use, and all were nonsmokers. The experimental protocol was accepted by the Human Research Committee of the Department of Medicine, University of Basel. The nature and purpose of the study were explained to the subjects before they gave their written consent. All subjects completed the study without any complaints. Before the study, the subjects were asked to maintain a regular sleep-wake cycle for at least 1 wk. This was verified by daily sleep diaries and ambulatory monitoring of the subjects' motor activity (Gähwiler Actigraph, Zürich; data not shown). During the study, the amount of caffeine was limited to one morning cup of coffee per day, and no alcohol consumption was allowed.

Experimental Protocol

The double-blind placebo-controlled study was performed according to a crossover design. Each subject participated in two consecutive treatment periods that comprised 1 day with placebo capsule (mannite po) and 1 day of treatment with a Mel capsule (5 mg po), in randomized order with a 1-wk washout period in between. The capsule was adminstered at 1300. The subjects reported at 0900 to the chronobiology laboratory; there the electrodes and thermocouples were attached. From 0900 to 1000, the subjects were in a sitting or standing body position and could adapt to the new environment. To eliminate masking effects on the parameters measured, the constant routine (CR) procedure has been devel-

oped (7, 19). The classic 40-h CR of continous wakefulness controls for, for example, posture, activity, food intake, and external conditions (7, 19). In this study, the CR was reduced to a 7-h version (15): subjects remained supine and awake in bed in a sound-attenuated chronobiology room (temperature 22°C, humidity 60%, light <10 lux) from 1000 to 1700 under a light cover. Water (100 ml) and isocaloric sandwiches [50 kcal: 50% carbohydrate, 25% protein, and 25% fat (foods used: tuna fish, turkey, or cheese, with lettuce on brown bread)] were administered at hourly intervals to meet energy and water requirements. The subjects were cared for by trained personnel and remained awake during the entire CR without information about time of day. To ensure wakefulness, the subjects were not allowed to close their eyes at any time. Reading, writing, talking, and playing games were allowed during the experiment (providing they were not overstimulating). To find an objective measure of sleepiness, the waking electroencephalogram (EEG) was recorded for 6 min every 45 min throughout the CR (see Ref. 6) directly after subjective sleepiness ratings.

Data Acquisition

Thermometry. Temperature data were continuously recorded by a computerized system (System Hofstetter, SHS Allschwil, Switzerland) in 2-min intervals and collapsed off-line into 30-min intervals. Rectal temperature (T_{re}) as a measure of CBT was registered by a thermocouple (polyoxymethylene probe: 2-mm diameter, copper-constantan, accuracy ≤0.01°C; Interstar, Cham, Switzerland; Therm, type 5500–3, Ahlborn, Holzkirchen, Germany) inserted 10-cm into the rectum. Skin temperatures were also registered by thermocouples (silver disk: 1-cm diameter, copper-constantan, model P 224, Prof. Schwamm, Ahlborn; accuracy ±0.01°C; Therm, type 5500–3, Ahlborn) fixed to the skin with thin air-permeable adhesive surgical tape (Fixomull, Beiersdorf, Hamburg, Germany). The temperatures were measured on three body sites: 1 cm above the navel ["stomach" (T_{st}); proximal skin region]; middle of instep and sole of the left foot [averaged later to foot temperature (T_{fo}); distal skin region].

Heart rate. Electrocardiograph leads were placed on the lateral thorax at approximately the sixth intercostal space and on the manubrium of the sternum. The analog signal was amplified by a Nihon-Khoden 18-channel polygraph. A computerized system (System Hofstetter, SHS Allschwil, Switzerland) digitized this signal and detected heart rate by the length of the R-R interval. Data were averaged into 2-min intervals and later collapsed into 30-min blocks.

Subjective ratings. Throughout the CR, sleepiness was self-rated at intervals of 20–40 min on a bipolar 100-mm visual analog scale (VAS; 0 mm = extremely alert, 100 mm = extremely tired) and on the Karolinska Sleepiness Scale (KSS; Ref. 12). After linear transformation of the KSS to a scale of 0–100 [(KSS-1) × 12.5], both scales were combined for an average sleepiness measure. The time course of average sleepiness (arbitrary units) was calculated by analysis of variance (ANOVA; see *Data Analysis*). Additionally, self-ratings (bipolar VAS) of thermal comfort were recorded (0 mm = feeling cold, 100 mm = feeling hot). During the entire study, subjects rated themselves in the neutral thermal zone (VAS values ~50 mm), indicating a comfortable ambient temperature (not significant by ANOVA, data not shown).

Salivary Mel. Saliva was collected for 4 min every 45 min, directly after the subjects rated their sleepiness. Mel in the treatment group was assayed by radioimmunoassay (11).

Data Analysis

Raw data from each subject were inspected visually, and data segments that were affected by removal or malfunctioning of the temperature sensors or electrocardiograph electrodes, for instance, were removed. These missing data (<1%) were replaced by values derived from a linear interpolation procedure.

To reduce short-term fluctuations and the number of time segments, all data were averaged in 30-min blocks. The statistical differences between the 30-min blocks of the CR period were analyzed by one-way ANOVA for repeated measures. Huynh-Feldt (H-F) statistics were used to adjust the covariance matrix for violations of sphericity. H-F's P values were based on corrected degrees of freedom, but the original degrees of freedom are reported. When the F-ratio proved significant, Duncan's multiple-range post hoc tests were applied to locate significant differences between the means. Results are reported in detail when significance level was $P < 0.05$.

Two kind of analyses were calculated separately: *1*) the effect of postural change (time course during the 3-h period after lying down; a one-way ANOVA for repeated measures was performed for 6 × 30-min blocks), and *2*) effect of Mel administration (the time course during the value of the 4-h period after Mel intake; a two-way ANOVA for repeated measures was performed for 10 × 30-min blocks).

To relate changes in subjective ratings of sleepiness with CBT and T_{fo} (30-min blocks), Pearson's product-moment correlations (r) were calculated. This analysis was based on preadministration adjusted values (relative changes) of the lying-down period (6 time points) and the Mel-induced effects (8 time points). Mel-induced effects were calculated by subtracting placebo values of corresponding time points. Fisher's z-transformation was used to permit pooling the correlation coefficients of the eight subjects.

RESULTS

Lying-Down Effect (Preadministration Period Between 1000 and 1300)

None of the measured variables differed statistically between treatment and placebo days in the period between 1000 and 1300 (two-way ANOVA, data not shown) and were therefore averaged. For statistics, see Table 1. Compared with the initial estimation at 1020, the subjects felt significantly more tired at 1120, and sleepiness remained higher thereafter (Fig. 1*A*, *a*). After subjects lay down, T_{re} decreased significantly below the initial value at 30–150 min, reaching a minimum 60–90 min after the postural change (Fig.

Table 1. *One-way ANOVA results, lying-down effect, in six 30-min blocks from 1000 to 1300*

Variable	Time [$F(5, 35)$]	P
T_{re}, °C	4.45	<0.05
T_{fo}, °C	5.33	<0.05
T_{st}, °C	7.58	<0.02
Heart rate, beats/min	7.83	<0.0001
Sleepiness, au	3.41	<0.05
Salivary melatonin,* pg/ml	0.75	NS

Time, six 30-min blocks of time from 1000 to 1300; ANOVA, one-way analysis of variance for repeated measures; T_{re}, rectal temperature; T_{fo}, skin temperature of foot; T_{st}, skin temperature, stomach region; au, arbitrary units; NS, not significant. *Salivary melatonin was measured only in the treatment group [$F(3, 21)$].

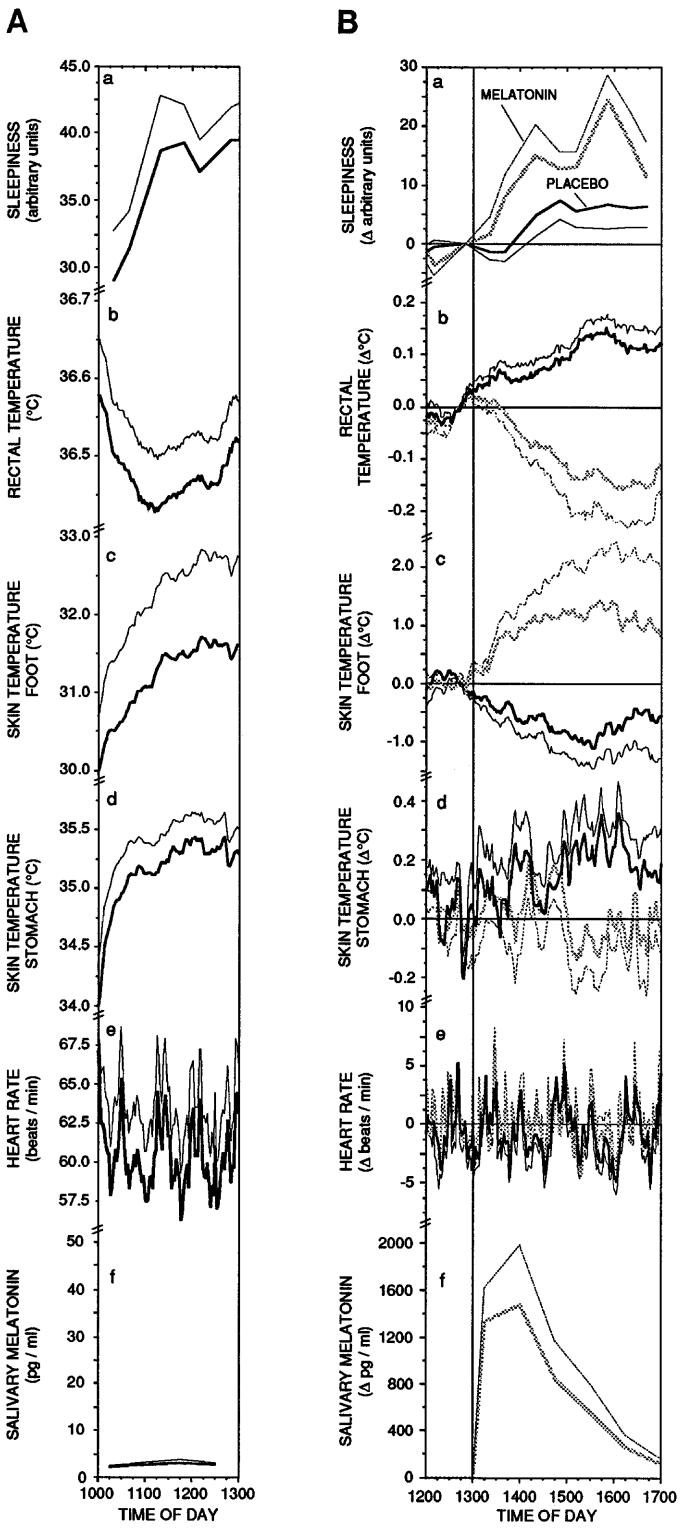

Fig. 1. *A*: time course of subjective sleepiness ratings (*a*) and physiological variables (*b-f*) during lying-down period (1000–1300). Values for each subject were averaged over both experimental days. Thick lines, mean values; thin lines, SE; $n = 8$ subjects. See Table 1 for statistics. *B*: time course of subjective sleepiness ratings (*a*) and physiological variables (*b-f*) 1 h before and during 4 h after administration of 5 mg melatonin (gray lines) or placebo (solid lines), respectively. Data are adjusted to preadministration values at 1230–1300 (zero line). Capsules were administered at 1300 (vertical line). Thick lines, mean values; thin lines, SE; $n = 8$ subjects. See Table 2 for statistics.

Table 2. *Two-way ANOVA results, melatonin vs. placebo, in ten 30-min blocks from 1200 to 1700*

	Treatment		Time		Treatment × Time	
Variable	$F(1,7)$	P	$F(9, 63)$	P	$F(9, 63)$	P
T_{re}, °C	11.70	<0.02	1.05	NS	8.38	<0.01
T_{fo}, °C	10.04	<0.02	0.20	NS	4.02	<0.05
T_{st}, °C	2.88	NS	0.41	NS	1.67	NS
Heart rate, beats/min	0.01	NS	1.79	NS	1.56	NS
Sleepiness, au	21.03	<0.05	5.23	<0.01	2.86	<0.05
Salivary melatonin,* pg/ml			7.13†	<0.01		

Treatment, melatonin vs. placebo; time, 10 × 30-min blocks from 1200 to 1700; treatment × time, interaction term. *Salivary melatonin was measured only in the treatment group; one-way ANOVA for repeated measures; †$F(7, 49)$.

1*A*, *b*). The value at 1230–1300 was significantly higher than the minimum value, but not different from the initial value at 1000–1030, indicating a U-shaped time course. Skin temperatures of both foot and stomach increased significantly after subjects lay down (Fig. 1*A*, *c* and *d*), with first appearance of increased values above the initial value at 1100–1130 and 1030–1100, respectively. Heart rate decreased significantly below the initial value after 30 min and remained at this lower level until 1300 (Fig. 1*A*, *e*). This variable is more subject to fluctuations induced by the protocol (e.g., eating snacks, urinating, and so forth). Salivary Mel was below the limit of detection throughout the lying-down period between 1000 and 1300 (Fig. 1*A*, *f*).

Effect of Mel Administration (Postdrug Period Between 1300 and 1700)

To show the effects more clearly, the average preadministration value of each variable between 1230 and 1300 was subtracted from each 2-min sample (Fig. 1*B*). For a summary of statistics, see Table 2.

A two-way ANOVA for subjective sleepiness ratings revealed significant main effects (treatment, time) and an interaction (treatment × time). Compared with placebo, Mel increased sleepiness significantly at 1340, 1420, 1510, 1550, and 1620 (Fig. 1*B*, *a*).

The reduction of T_{re} after Mel administration is shown in Fig. 1*B*, *b*. Two-way ANOVA showed a significant main effect for treatment and a significant interaction (treatment × time). Post hoc comparisons revealed no difference between the values before capsule intake (1200–1300). Mel administration significantly reduced T_{re} below the placebo values in the period 1330–1400 and thereafter.

Figure 1*B*, *c* shows an increase in T_{fo} after Mel administration. A two-way ANOVA showed a significant main effect for treatment and a significant interaction (treatment × time). Post hoc comparisons revealed that Mel administration increased T_{fo} significantly above the placebo values at 1330–1400 and thereafter.

The same analysis of T_{st} revealed no significant interaction. However, resampling data in 2 × 2-h blocks after 1400 revealed a significant decrease of T_{st}

between 1500 and 1700 after Mel administration [treatment × time: $F(3,21) = 3.08$, $P < 0.05$; placebo vs. Mel, 1500–1700, $P < 0.05$] (Fig. 1*B*, *d*).

Heart rate after Mel administration did not differ from placebo, either in the main effect or in the interaction (two-way ANOVA for repeated measures) (Fig. 1*B*, *e*). Again, the small protocol-induced variations could be seen.

A one-way ANOVA for salivary Mel revealed a significant time course. Compared with the preadministration values, Mel administration increased all salivary Mel levels after 1315 (Fig. 1*B*, *f*). Even 4 h after Mel intake, at 1700, when endogenous Mel levels are normally undetectable, the mean salivary Mel level was still >100 pg/ml.

Relationship Among Changes in Sleepiness, CBT, and Skin T_{fo}

The individual increase in sleepiness either induced by lying down or by Mel is significantly correlated with changes in skin T_{fo} (z-transformed $r = 0.551$, $n = 14$, $P < 0.05$) and tended to correlate with CBT (z-transformed $r = -0.459$, $n = 14$, $P < 0.1$). The correlation coefficients (in absolute values) did not statistically differ from each other. The time course of changes in T_{re} and T_{fo} were significantly intercorrelated (z-transformed $r = -0.616$, $n = 14$, $P < 0.05$).

DISCUSSION

This experiment permits a comparison of two phenomena: a "natural" and a "pharmacological" increase in sleepiness accompanied by heat loss and a decrease in CBT. The change in posture from upright to a supine position increased skin temperatures and decreased T_{re}. This time course after lying down from 1000 to 1300 is in clear contrast to the endogenous time course of T_{re} and T_{fo} previously found in a 35-h CR protocol (16). Although recognized decades ago (2, 14), the effect of postural changes on CBT is still somewhat neglected in studies on thermoregulation. Generally, lying down induces a drop in T_{re} that lasts ~2 h (22, 24). When a person lies down, the rise in cutaneous blood supply accelerates the return of cooled venous blood from the legs, resulting in an enhanced core cooling through convective heat exchange, which leads to a decrease in CBT (24). Thus a fall in T_{re} after lying down can be attributed to heat loss due to reflexive skin vasodilation (24).

Parallel to these effects, heart rate showed a general declining trend. The superimposed peaks, as shown in Fig. 2*E*, are induced by the protocol, e.g., saliva sampling, food intake, and quiet periods during the waking EEG (see MATERIALS AND METHODS). The change from an upright to a supine position induced elevation of skin blood flow rate due to deactivation of central and local sympathetic and humoral vasoconstriction reflexes (22). Therefore, the decline in heart rate after lying down may have been directly induced by reduced sympathetic outflow (22). After ~2 h, a new relative steady-state condition of thermal balance was attained, and the normal circadian profile characteristic of a CR returned. Earlier studies have shown that heat production measured by indirect calorimetry does not change with changes in posture (23). Therefore, the usual circadian relationship throughout the 24 h between changes in heat production and changes in heart rate (16) seems not to be true for postural changes. However, it is possible that heat production, as measured by indirect calorimetry, is not sensitive enough to measure small posture-induced changes in heat production.

It is noteworthy that during this period after lying down sleepiness increased with the same time course as temperatures changed. This finding is of methodological importance. Studies of thermoregulation, with or without drug administration, should not use the first 2–3 h of data collection, because this dynamic adaptation period could mask the real changes. This is of special importance for studies investigating the relationship between thermoregulation and sleep, where lying down and turning lights off occur in temporal proximity.

The most striking result of the present study was that Mel (5 mg po) at 1300 showed a hypothermic response comparable to that found in our earlier study at 1800 (15). However, in contrast to that study, no effects on heart rate were observed. Mel induced a fast increase in T_{fo} in parallel with a decrease in T_{re}. T_{st} was also decreased, with significantly reduced values 2–4 h after Mel administration. How can these results be interpreted?

Mel at 1800 induces hypothermic effects together with a phase-advance of the circadian system; both effects overlap and are, therefore, not separable (15). The causal relationship between the two effects are still not clarified. Mel at 1800 induces a downregulation of CBT comparable to the endogenous nocturnal decline in CBT at ~2100 (16). In a CR, the time course of the nocturnal decline of CBT can be clearly followed. First, heat production declines and vasodilation occurs at distal skin regions, followed by changes in CBT (16). The proximal skin regions, however, show vasoconstriction, as demonstrated by reduced proximal skin temperatures due to passive blood flow reduction. It is well known that distal skin regions of the body are the major sites for vasomotor heat loss (1). These skin regions are rich in arteriovenous anastomoses that adjust blood flow through the skin and therefore play a central role in thermoregulation (4). It is assumed that arteriovenous anastomoses are not present in the skin of the thorax or abdomen (4). The proximal skin regions are known to play only a minor role in thermoregulation (1). It is, therefore, possible that Mel acts not only via specific Mel receptors in the circadian clock localized in the suprachiasmatic nuclei (20, 27) but also directly on putative Mel receptors of arteriovenous anastomoses. Vascular Mel receptors with a specific function in heat loss have been recently described in rats (26); whether they also occur in humans is not known.

We have shown that the circadian variation of heat production and the circadian variation of heart rate are

positively correlated (16). The earlier decline in heart rate induced by Mel administration at 1800 can be interpreted as an indication of an earlier reduction of heat production, due to the phase-advance of the circadian system. To our knowledge, Mel administration at 1300 should not cause a phase advance (17). The lack of effect of Mel at 1300 on heart rate suggests there is no phase-advance of the evening decline. Thus, we interpret this as having successfully separated the pharmacological effect of Mel on heat loss from any circadian phase-shifting effect.

In parallel to the hypothermic effect, Mel induced sleepiness ~40 min after its administration. This effect on subjective sleepiness was confirmed by objective measures: increased power density in the θ/α band (5.25–9 Hz) of the waking EEG (data summarized in Ref. 6). The close relationship between heat loss and sleepiness was already recognized in 1944 by Ebbecke (10). He described general relationships between affective states and changes after heating up and cooling down of the body. The "Heizaffekt" (heating mood) with increasing CBT (relative increase of heat production over heat loss) is a feeling of alertness and a refreshed state. Conversely, the "Entwärmungsaffekt" (deheating mood) with reduction of CBT (relative increase of heat loss over heat production) is a feeling of relaxation, comfort, and tiredness. This alternation of heat distribution between the shell (heat loss) and core (heat conservation) seems to be closely related to induction of sleepiness and alertness, respectively. We found significant intercorrelations between changes in subjective ratings of sleepiness and T_{fo} or CBT, verifying this relationship. However, the causality between these parameters remains to be elucidated.

Recently, a sleep-controlling mechanism in the preoptic area of the anterior hypothalamus (POAH) has been postulated (13, 18). The POAH is also the neural basis of critical thermoregulatory mechanisms in mammals and contains a high concentration of warm- and cold-sensitive neurons that can control both autonomic and behavioral thermoeffector activities (13). These studies support a role for the POAH as important for mediation of both sleep and thermoregulation. On the basis of this concept, one can speculate that heat loss induced by Mel or lying down activates afferents to the POAH and induces sleepiness via the POAH. The hypothesis that Mel directly modulates central thermoregulatory centers is less likely, because only few Mel receptors have been found in the POAH itself (20, 27).

Further evidence for a strong relationship between CBT and sleepiness stems from the forced desynchrony protocol, where the circadian rhythms of CBT and alertness are in phase, with highest sleep propensity occurring at the CBT minimum (9). Hypothermia seems to be at least functionally related to sleepiness. Whether Mel administration can still induce sleepiness when peripheral heat loss is reduced is presently under investigation.

Our study suggests that heat loss via the distal skin regions is a key mechanism for induction of sleepiness as CBT declines, at least under normal room temperatures. This finding may suggest simple strategies to manage sleepiness.

We thank Drs. I. Tobler and D. Dinges for comments on an earlier version of the manuscript. We also thank C. Hetsch, M. F. Dattler, and G. Balestrieri for their skillful assistance in data acquisition.

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Received 18 July 1996; accepted in final form 12 March 1997.

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