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Functional link between distal vasodilation and sleep-onset latency?

KURT KRÄUCHI, CHRISTIAN CAJOCHEN, ESTHER WERTH, AND ANNA WIRZ-JUSTICE
Chronobiology and Sleep Laboratory, Psychiatric University Clinic, Wilhelm Klein Strasse 27, CH-4025 Basel, Switzerland

Kräuchi, Kurt, Christian Cajochen, Esther Werth, and Anna Wirz-Justice. Functional link between distal vasodilation and sleep-onset latency? *Am. J. Physiol. Regulatory Integrative Comp. Physiol.* 278: R741–R748, 2000.—Thermoregulatory processes have long been implicated in initiation of human sleep. The purpose of this study was to evaluate the role of heat loss in sleep initiation, under the controlled conditions of a constant-routine protocol modified to permit nocturnal sleep. Heat loss was indirectly measured by means of the distal-to-proximal skin temperature gradient (DPG). A stepwise regression analysis revealed that the DPG was the best predictor variable for sleep-onset latency (compared with core body temperature or its rate of change, heart rate, melatonin onset, and subjective sleepiness ratings). This study provides evidence that selective vasodilation of distal skin regions (and hence heat loss) promotes the rapid onset of sleep.

core body and skin temperatures; melatonin; heart rate; sleepiness; sleep electroencephalogram

A TEMPORAL RELATIONSHIP BETWEEN circadian phase of the core body temperature (CBT) rhythm and the initiation of sleep has long been recognized. In humans living under entrained and free-running conditions, sleep is typically spontaneously initiated on the declining portion of the CBT curve (7, 8, 34). Furthermore, an induced decrease of CBT after the administration of melatonin (Mel) or benzodiazepines, or after a postural change from an upright to a supine position, is associated with an increase in subjective sleepiness and reduced sleep-onset latency (11, 19, 22). Such findings have suggested a functional link between the decline in CBT, subjective sleepiness, and the ability to initiate sleep (6).

CBT declines when heat production is reduced and/or heat loss is increased (for review see Ref. 22). Therefore, it is possible that one of these two thermoregulatory processes is more intimately linked to sleep initiation than the resultant CBT itself. To our knowledge, there is no study in which the role of these two processes in regulating sleep initiation has been investigated under the controlled postural conditions of a constant routine (CR) protocol before lights out. Not only are these "unmasking" conditions crucial for studying differential thermoregulatory effects on sleep initiation, but also the measurements themselves must be noninvasive. For example, although the classical method of indirect calorimetry would give close insight into heat production, the technique of a ventilated hood system induces changes in heat loss, and both the hood and the hum produced by the ventilator are not conducive to a naturalistic sleep (26). We have therefore chosen more comfortable indirect measures of heat production and heat loss: changes in heat production across 24 h are correlated with the circadian rhythm in heart rate (26), and heat loss via distal skin regions is correlated with skin blood flow and the distal-to-proximal skin temperature gradient (DPG) (29).

In this study, we aimed at finding the best predictor for sleep-onset latency among a variety of prospective candidates: distal and proximal skin temperatures, CBT and its rate of change, heart rate, onset of nocturnal Mel secretion, and subjective sleepiness ratings.

MATERIALS AND METHODS

To increase the power of the analysis, data from two intervention studies designed to challenge the relationship between thermoregulation and phase shifts were combined (5, 20, 24, 33). The experimental manipulations had different thermoregulatory sequelae and thus yielded a broad variance, enabling extraction of the best predictor variables for sleep-onset latency.

Subjects. Twenty healthy male subjects [age 26 ± 4 yr (SD), body mass index 22.97 ± 1.43 kg/m^2] gave signed informed consent to participate in the studies and were instructed to refrain from alcohol, drugs, and more than one cup of coffee per day. The experimental protocols were accepted by the Human Research Committee of the Department of Medicine, University of Basel, Switzerland. The subjects had no self-reported sleep disorders, no extreme phase type, no shift work or transmeridian travel within 1 mo before the study, and all were nonsmokers. Medical disorders were screened by history and physical examination. One week before and during the study subjects were instructed to maintain regular bedtimes between 2400 and 0800. Adherence to a regular sleep-wake schedule during the week immediately before admission was verified with a wrist actigraph (Gähwiler Actigraph, Zürich, Switzerland); only subjects who maintained the regular schedule as instructed were admitted to the study. Before the experiment, each subject spent one adaptation night in the sleep laboratory. Two subjects were excluded due to technical problems. A complete dataset from 18 subjects was statistically analyzed.

Design. In two separate studies using a modified CR protocol of 10–16 h wakefulness followed by the usual timed

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nocturnal sleep period, immediate and possible circadian effects of various zeitgebers were assessed. In the first protocol, the acute effects of Mel (5 mg po at 2040), bright light (5,000 lx from 2100 to 2400), the combination of both (Mel + bright light), and placebo were measured on the treatment day and possible circadian phase shifts on the posttreatment day. Data from the acute Mel and Mel + bright light treatment days were included in a global analysis (23), but omitted here for reasons of possible confounding effects of the pharmacological doses of 5 mg Mel. Data from eight subjects each with six CRs and six nights were included (for details see Refs. 5 and 20). In the second protocol, after a baseline CR (including 2 nights), 10 subjects ate a single large carbohydrate (CHO)-rich meal (1,600 kcal, 75% CHO, 11% protein, 14% fat) either in the morning (0830) or in the evening (2130) for 3 consecutive days, followed by a posttreatment CR (including 2 nights; total 8 CRs, including 8 nights; for details see Refs. 24 and 33). The CR protocol provided the controlled conditions (<8 lx light intensity, room temperature 22°C, humidity 60%, supine position, light bed cover, 100-kcal sandwiches, and 100 ml water at 1-h intervals) to examine thermoregulatory variables under minimal masking due to behavior or environment (for details see Ref. 21).

Measurements. Rectal (CBT, probe inserted 10 cm into the rectum), proximal [right infraclavicular area; midthigh on the right musculus rectus femoris; 1 cm above the navel, stomach; midforehead; later combined according to Ref. 21 (forehead × 0.093 + thigh × 0.347 + infraclavicular area × 0.266 + stomach × 0.294)], and distal (hands, center of the the back of the left and right hand; feet, middle of the left and right foot instep; all later averaged) temperatures and heart rate were continuously measured (for details see Ref. 21) in 2-min intervals (later collapsed into 30-min bins) together with sleep-onset latency (time between lights off and the first occurrence of stage 2 sleep, assessed by polysomnographic recordings) (5). The DPG was calculated as the difference between distal minus proximal skin temperatures (adapted from Ref. 29); 30-min bins of heart rate were smoothed by weighted (1,2,1)-moving average before statistical analysis. During the CRs, subjective sleepiness was assessed at one-half-hour intervals on the Karolinska sleepiness scale (12) together with collection of saliva for measurement of Mel using a highly specific direct double-antibody RIA (32).

Statistical analysis. The statistical packages StatView 4.5 (Abacus Concepts, Berkeley, CA) and STATISTICA 5.1 (StatSoft, Tulsa, OK) were used. Sleep-onset latency was defined as the dependent variable. Before statistical analysis, sleep-onset latency and Mel were log transformed. Correlations for each single-predictor variable with the dependent variable were calculated at different times of day using a multiple linear regression model for repeated measures. All data were pooled to estimate a single regression equation (13). Backward stepwise regression analysis was performed to identify the important predictor variables for sleep-onset latency. The between-subjects differences were taken into account using dummy-coded subjects as forced variables in the model (13). One-way repeated-measures ANOVA (rANOVA) with factor time was calculated for each variable. Huynh-Feldt (H-F) statistics were used to adjust the covariance matrix for violations of sphericity. H-F *P* values were based on corrected degrees of freedom, but the original degrees of freedom are reported. Reversed Helmhert contrasts [P(H-F) < 0.05] were calculated to localize the time point of appearance of the first significant change in a variable model. Planned comparisons using protected least-significant difference (PLSD) tests were perfomed for determination of peak and trough values after lights off.

RESULTS

In Fig. 1, the mean time course of all predictor variables is shown for the baseline conditions ($n = 18$, all baselines per subject were averaged, $n = 2–4$, i.e., all CRs with interventions were excluded). No significant differences in any variables were found between the two experiments allowing data combination.

All variables exhibited a significant time course (for statistics, see Table 1). Interestingly, distal and proximal skin temperatures showed an inverse pattern before lights off, whereas directly afterward both skin temperatures sharply increased to a comparable peak level after ~1 h and remained together on a higher level throughout the entire night. After this peak, both skin temperatures declined to a first trough 3 h after lights off. Calculation of the DPG balanced out these parallel changes in the two skin temperature compartments and showed a rather smooth time course throughout the experiment without any abrupt rise related to lights off. The rate of change of CBT (ΔCBT) showed a small but significantly faster decline 1 h after lights off (Δ 0.043°C/30 min; Table 1).

Mel and heart rate showed the earliest (at 2030 and 2045) significant changes in the mean values followed by DPG and ΔCBT (at 2115 and 2130), and then skin temperatures and CBT (at 2215). Subjective ratings of sleepiness showed the first significant change at 2130, 1 h after Mel increase (measured at a level below 1 pg/ml). Due to the masking effects (e.g., sleep, food), it is not possible to determine (e.g., by cross-correlation analysis) the exact temporal relationship between all these parameters. During the CR, the time course of heart rate nicely reflected the protocol, i.e., heart rate regularly increased by ~2 beats/min after intake of a 100-kcal sandwich together with 100 ml water (the smoothed curve was used for analysis; Fig. 1).

Figure 2 shows the correlation coefficient of each variable with sleep-onset latency as it evolved throughout the evening and night. Correlations were calculated for each 30-min bin using a multiple linear regression model for repeated measures, with the between-subjects differences taken into account (13). Of all variables, DPG exhibited the highest correlations with log(sleep-onset latency) in the 1.5-h period before lights off, whereas log(Mel) and subjective ratings of sleepiness showed weaker but significant correlations (Fig. 2, *bottom*). Heart rate, CBT, and ΔCBT did not significantly correlate with log(sleep-onset latency) (Fig. 2, *top*). On the basis of these findings, the data between 2230 and 2400 were averaged to find the best predictor variables for sleep-onset latency.

Table 2 summarizes the results of the backward stepwise regression analysis. Log(sleep-onset latency) showed the highest correlations with DPG, all other potential predictor variables [heart rate, log(Mel), CBT, ΔCBT, Karolinska sleepiness scale] were not included in the regression model.

Figure 3 illustrates the result of the backward stepwise regression analysis, which extracted DPG as the main predictor variable for log(sleep-onset latency).

The scattergram of all 128 data points [log(sleep-onset latency) vs. DPG; 8 points per 10 subjects and 6 points per 8 subjects] is depicted in Fig. 3*A* and the fitted log(sleep-onset latency) for each subject with the same slope in Fig. 3*B*. In Fig. 3*C*, the residuals (fitted observed values) of log(sleep-onset latency) values are plotted against the original log(sleep-onset latency) values. The residual analysis (see histogram in Fig. 3*D*) revealed a mean value of 0.000 ± 0.214°C (SD) and normal distribution of the data (Shapiro-Wilk's $W = 0.9881$, $P < 0.89$), indicating an appropriate fit to the chosen regression model.

Figure 4 presents characteristic raw data plots of two individuals before and after timed manipulations to illustrate the finding of the backward stepwise regression analysis. These subjects were selected for their differences in thermoregulatory responses and the concomitant differences in sleep-onset latency. In *subject 7*, bright light administration in the late evening inhibited the rise in Mel, DPG, and sleepiness and reduced the decline in CBT: the sleep-onset latency was rather long (59 min). *Subject 15* ate a large CHO-rich meal before bedtime, immediately increasing heart rate, CBT, DPG, and sleepiness: in this case, sleep-onset latency was short (4.3 min). The use of these "naturalistic" interventions to modify temperature induces a broad intraindividual variance with different thermoregulatory effects that are a prerequisite for separating out crucial predictor variables for sleep-onset latency (see above).

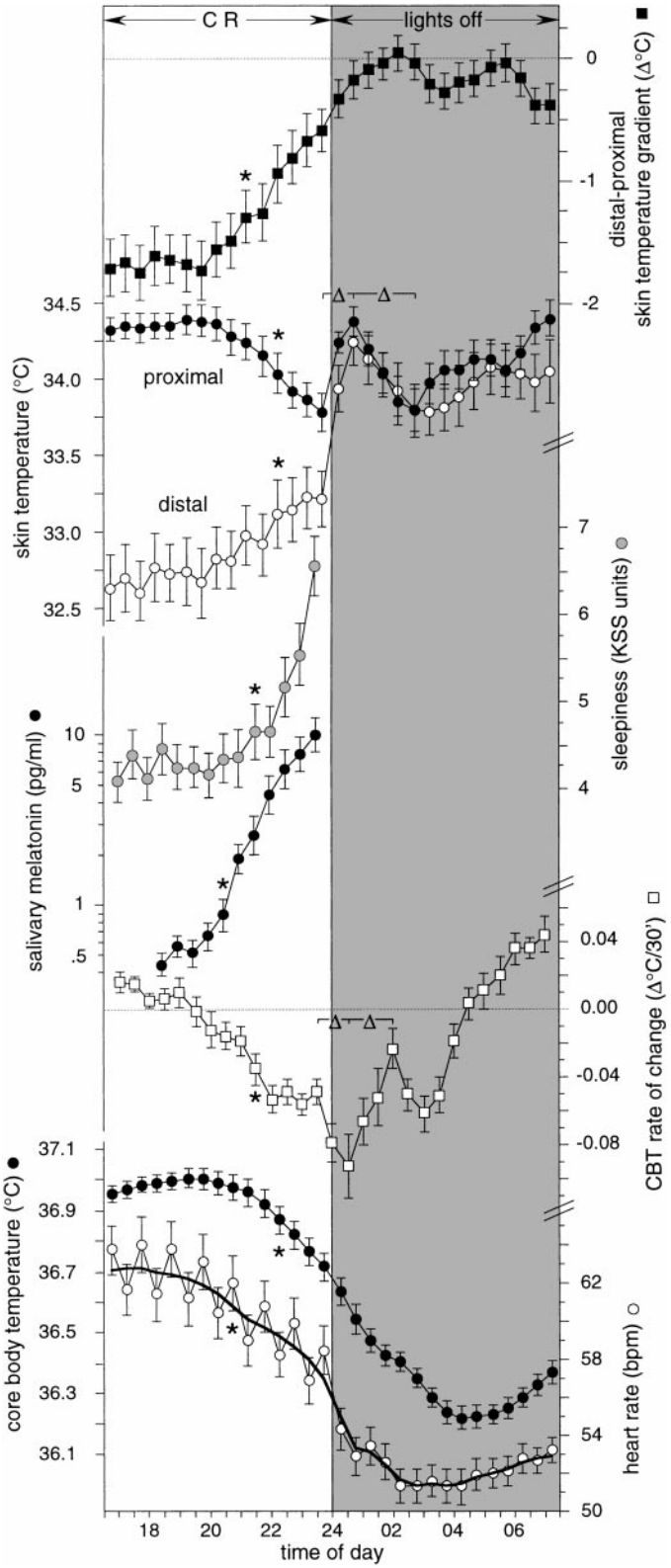

Fig. 1. Time course of heart rate [black line represents weighted (1,2,1)-moving average], core body temperature (CBT), and its rate of change, salivary melatonin, sleepiness, distal and proximal skin temperatures, and the distal-to-proximal skin temperature gradient (DPG) in a baseline 7.5-h constant routine (CR) followed by a 7.5-h sleep period. Data from first 2.5 h (1400–1630) of CR, which represent postural adjustments, were discarded. Continuously measured data are plotted in 30-min bins. Mean values of $n = 18$ subjects (±SE, vertical bars). Statistics in Table 1. *Time of appearance of a value significantly different from previous values ($P < 0.05$, reversed Helmhert contrasts). △Significant differences ($P < 0.05$, protected least-squares difference tests) between trough and peak values before and after lights off. KSS, Karolinska sleepiness scale; bpm, beats/min; Δ, difference.

DISCUSSION

The present data confirm and extend earlier findings that warm feet precede falling asleep (e.g., 10) and support the hypothesis that circadian changes in thermoregulation and sleep propensity ("sleep pressure") are functionally related.

Under baseline CR conditions, the thermoregulatory cascade and induction of sleepiness in the evening starts with the rise in Mel secretion (Fig. 1). The highly sensitive Mel assay revealed that the endogenous nocturnal rise in Mel secretion can be documented at levels <1 pg/ml. Mel secretion seems to be the hormonal signal timing the rise in blood flow in distal skin regions (measured by DPG) and hence heat loss (see below) (22). Administration of exogenous Mel during the day when endogenous Mel is low decreases CBT via selective vasodilation in distal regions and also induces sleepiness (20). This pharmacological dose mimics what occurs naturally when Mel secretion begins in the evening. When this nocturnal rise in blood flow in distal skin regions begins, heart rate declines, and this is correlated with the decline in heat production (22, 26).

Table 1. *One-way repeated-measures ANOVA of each variable for baseline (untreated) conditions*

Variable	df	*F*	*P*(H-F)	Time of First Significant Change	Peak		Trough	
					at	Δ°C	at	Δ°C
Distal								
Skin temperature	17,29	20.7	0.0001	22 15	0:45 h	0.734	2:45 h	0.835
Proximal								
Skin temperature	17,29	4.7	0.009	22 15	0:45 h	0.546	2:45 h	0.645
DPG	17,29	28.6	0.0001	21 15				
CBT	17,29	107.0	0.0001	22 15				
ΔCBT	17,28	13.8	0.0001	21 30	0:30 h	0.043	2:30 h	0.069
Heart rate	17,29	69.1	0.0001	20 45				
Mel	17,10	51.6	0.0001	20 30				
KSS	17,14	11.4	0.0001	22 30				

$n = 18$ subjects, data of baseline constant routines ($n = 2–4$) were averaged per subject before analysis. Peak is appearance of first peak after lights off; Δ°C (Peak) is difference between 30-min value before lights off and first peak value; Trough is appearance of first trough after lights off; Δ°C (Trough) is difference between first peak and first trough value. H-F, Huynh-Feldt; DPG, distal-proximal skin temperature gradient; CBT, core body temperature; ΔCBT, rate of change in core body temperature; Mel, salivary melatonin; KSS, Karolinska sleepiness scale.

As a consequence of the negative heat balance, CBT then decreases. A characteristic of endogenous circadian thermoregulation is the opposite phase relationship between proximal and distal skin regions in the circadian time course (at least for normal ambient temperatures; see below) (2). It is assumed that the timing of these diverse rhythms are under control of the circadian pacemaker in the suprachiasmatic nuclei (18).

Multivariate analysis of the data allowed evaluation of each putative step in this thermoregulatory cascade with respect to its role in circadian regulation of sleep propensity. Earlier studies had suggested that the process of normal sleep initiation is most likely to occur when CBT is declining at its maximum rate (6, 19). Our data partially confirm this, but have extracted a more powerful predictor. DPG was more strongly significantly correlated with sleep propensity (measured by sleep-onset latency) than rate of change in CBT. The highest correlation of all predictor variables with sleep-onset latency was found with the DPG during the 1.5-h period before lights off.

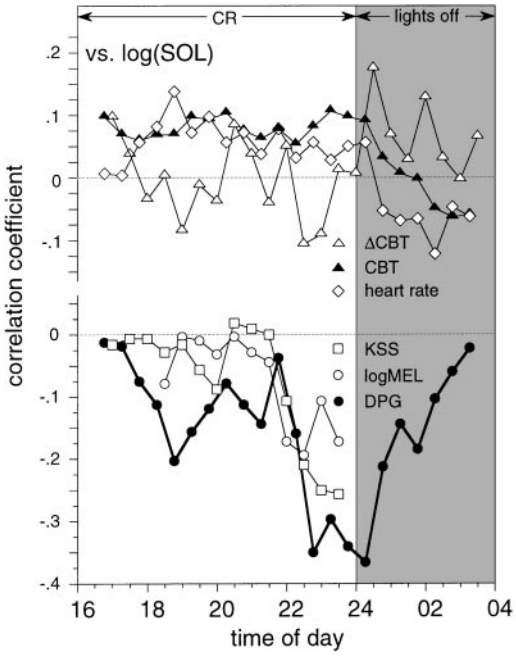

Fig. 2. Correlation coefficents vs. time of day of each predictor variable with sleep-onset latency (SOL). Correlations for each single predictor variable with dependent variable were calculated at different times of day using a multiple linear regression model for repeated measures, with the between-subjects differences taken into account (10). Correlation coefficients below $r = -0.2$ and above $r = +0.2$ were significant ($P < 0.05$). Note: among all predictor variables, DPG showed highest correlation coefficients during the 15-h episode of scheduled wakefulness before lights off. Mel, melatonin.

Under normal conditions, the maximal rate of change in CBT does indeed occur at this time of day when heat loss and, in turn, the difference between heat loss and heat production is maximal. However, the temporal relationship between heat loss and the maximal rate of change in CBT can be dissociated, as exemplified by one intervention in our experiments: a large CHO-rich meal (1,600 kcal) given 2 h before lights off (characteristic example, *subject 15* in Fig. 4). Because diet-induced thermogenesis lasts several hours (28), CBT was still increased at lights off, with a low rate of change, as was heart rate (indicating increased heat production). However, sleep-onset latency was not thereby large; on the contrary, it was short (4.3 min) (33). The reason we suggest for this discrepancy is that a large meal markedly augments heat loss via increased distal skin blood flow to adjust for the increase in body heat content, and it is the heat loss that is relevant for the propensity to fall asleep.

Previous studies with other manipulations of heat balance, e.g., exercise and passive body heating and

Table 2. *Result of the backward stepwise regression analysis according to Glantz and Slinker (13)*

Variable	df	Sum of Square	Mean Square	*F*	*r*	*P*	std b
Subjects	17	6.925	0.407				
DPG	1	0.952	0.952	17.63	−0.353	0.0001	−0.406
Residuals	109	5.832	0.054				
Total	127	13.71					

r, intraindividual correlation coefficient; std b, standardized regression coefficient.

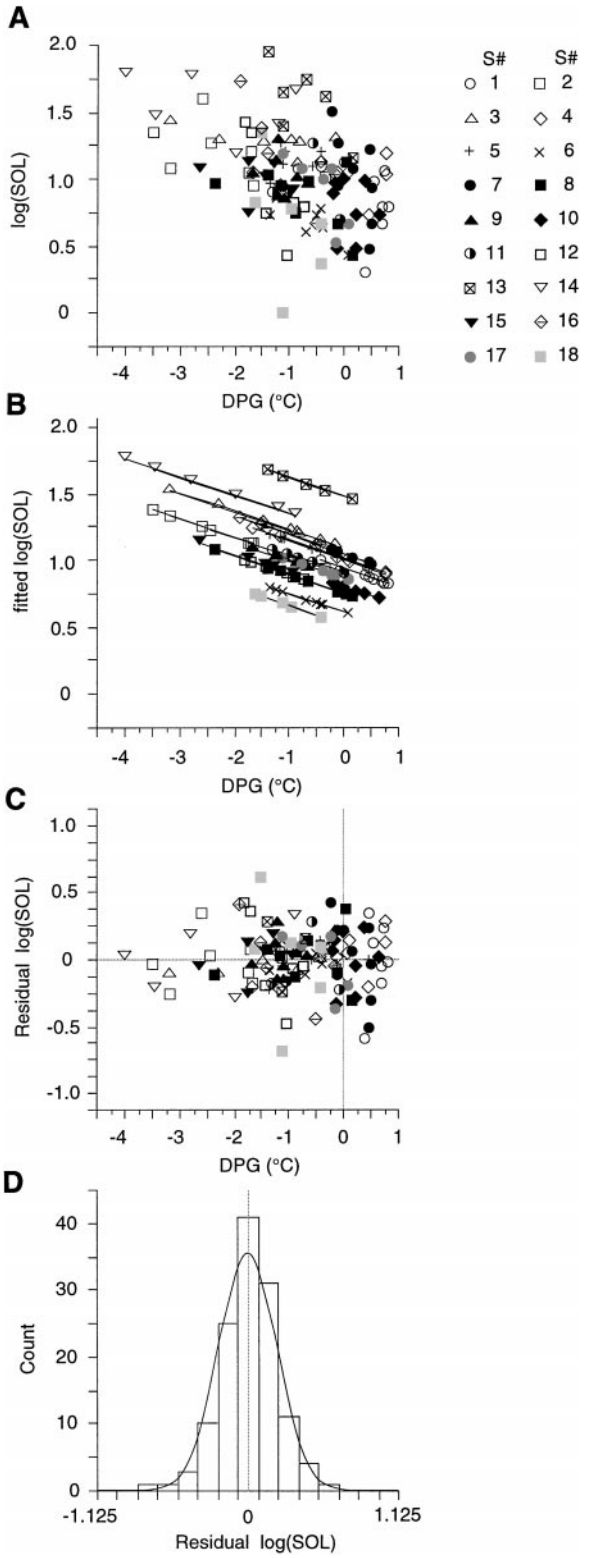

Fig. 3. Correlation analysis of DPG (pooled values between 2230 and 2400) with log(SOL) using a multiple linear regression model for repeated measures, with between-subjects differences taken into account (see Table 2) (13). *A*: scattergram of 128 data points (each subject separately); *B*: scattergram of fitted data points for each subject (S) separately; *C*: scattergram of residuals for each subject separately; *D*: histogram of residuals with superimposed normal distribution [mean = 0.000 ±(SD) 0.214°C].

cooling, laid the foundation for the general idea that there are links between thermoregulation and sleep (for example, see Ref. 17). These studies are, however, not conclusive with respect to sleep-onset latency perhaps because the protocols were not controlled with respect to lighting conditions, meals, activity, body posture, and the time after intervention, all of which determine whether heat loss is greater than heat production (for reviews, see Refs. 14 and 17). Under our controlled experimental conditions, an increase of distal vasodilation, and hence heat loss (see below), goes hand in hand with induction of sleepiness and, in turn, with reduced sleep-onset latency. The exact temporal relationship between heat loss, heat production, and sleepiness remains to be established for these other interventions and may prove interesting.

How is blood flow and hence heat loss in distal and proximal skin regions regulated? The inverse circadian time courses can be explained by the different vascular regulation of blood flow in these skin regions. Distal skin regions (e.g., fingertips and toes, earlobes, eyelids, and lips) are the major sites for vasomotor heat loss (1). They contain both capillaries and are rich in arteriovenous anastomoses (AVAs) with mainly thermoregulatory functions (15). AVAs efficiently adjust blood flow through the skin (15), i.e., blood can be rapidly transported from the core to the skin. In contrast, proximal skin regions (e.g., thorax or abdomen) contain exclusively capillaries with mainly nutritive functions (15). Skin blood flow through capillaries is a slow process (15). Therefore, the circadian time course of blood flow through capillaries in the proximal skin regions follows the time course of CBT, at least under unmasking CR conditions when sleep, large meals, and exercise are greatly restricted (26). Distal skin temperature, or the distal-CBT gradient, have a long history of use as indexes of peripheral blood flow (cited in Ref. 29). The advantage of the DPG we used in this study is that the reference temperature (proximal skin region) is a skin site exposed to the same ambient temperature as the distal skin region. This is important as a kind of "internal standard" because skin blood flow is greatly dependent on ambient temperature. Indications of the sensitivity of the DPG have come from challenge tests, for example, core body cooling induced peripheral vasoconstriction, thereby reducing heat loss via distal skin regions (9, 25). Thus DPG provides a rather selective measure for thermoregulatory skin blood flow through AVAs (and consequent heat loss), while adjusting for (i.e., subtracting) changes in capillary blood flow (represented by skin temperature changes at proximal regions) (29).

Information about the more subtle effect of "lights off" and sleep initiation per se on CBT regulation also emerges from this CR situation. Although the time course of skin temperature in proximal and distal regions is opposite during wakefulness, it can follow similar patterns when both capillaries and AVAs are similarily constricted or dilated, e.g., after postural changes or sleep onset (21, 26). At lights off (sleep onset transition; Fig. 1, Table 1), it can be seen that both

distal and proximal skin temperatures increase (~0.5–0.9°C). Local thermal influence can be ruled out as a cause of this increase because the bed covers remained more or less the same during the entire protocol. There were no changes in posture throughout the protocol, which would have led to redistribution of heat over the body. The only thing that changed at 2400 was that the lights were switched off with the implicit permission to fall asleep. It has been recognized for many years that sensory (e.g., loud noises, puffs of air) and emotional (e.g., mental arithmetic, pain) stimuli lead to a significant increase in cutaneous sympathetic nerve activity and, in turn, to reduced peripheral blood flow (16, 27). The opposite occurs with relaxation (31). A study very relevant to ours was carried out more than 20 years ago in the monkey (3). Lights on triggered peripheral vasoconstriction as reliably as a disturbing stimulus or noise, lights off was invariably followed by peripheral vasodilation even when repeated at short intervals. These experiments demonstrated how changes in arousal level rapidly changed autonomic nervous control of peripheral vasomotor tone. The authors concluded "peripheral vasodilation and a drop in deep body temperature appear to be two of the first physiological events leading to nocturnal sleep in both man and monkey. . ." (3).

We have shown that an increase in light intensity from 8 to 5,000 lx at 2100–2400 induces a selective decrease in distal skin temperature (reduced DPG) together with a slower decline in CBT and a long sleep-onset latency (e.g., *subject 15* in Fig. 4; 59 min). These changes were dependent on the inhibition of Mel secretion. After lights off, these effects were reversed: there was a large increase in distal skin temperature as well as DPG and a drop in CBT, and, presumably, Mel secretion resumed. The subject went to sleep only after this distal vasodilation had attained a sufficient value.

In contrast, when light intensity is reduced from 8 to 0 lx at lights off (as occured under baseline conditions), this should have had no effect on Mel secretion. Therefore, we can separate the vasodilatory effect of Mel per se and the initiation of sleep after lights off. It is possible that after lights off a decrease in sympathetic tone occurs (decreased arousal at sleep onset transition) (3), leading to precapillary vasodilation in both proximal and distal skin regions. This general increase in skin temperatures is dependent on ambient temperature; only in a cold and neutral environment has an increase in skin temperatures been found (14). Our study at room temperature (22°C) under constant conditions induced only slight changes in CBT, because the rapid and effective blood exchange from the core to the periphery through AVAs was not additionally activated after lights off.

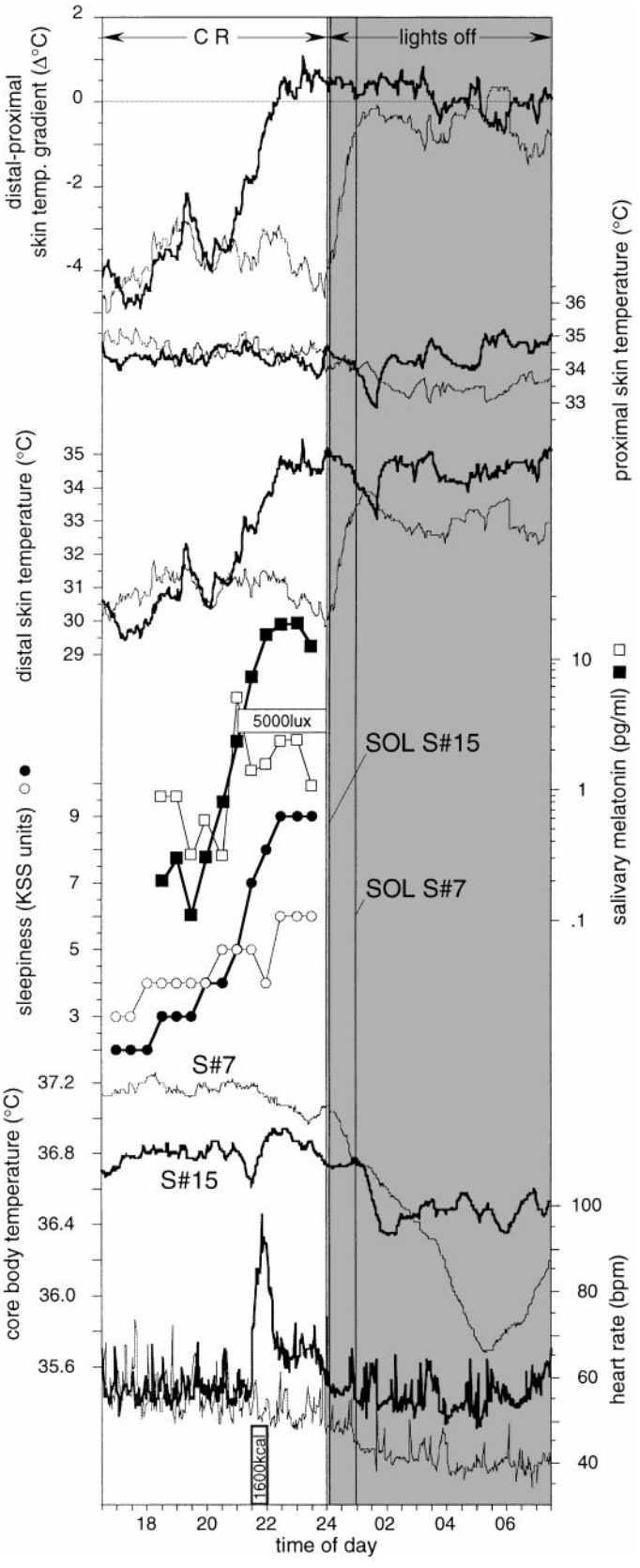

Fig. 4. Individual time course of raw data for heart rate, CBT, subjective sleepiness, salivary melatonin, distal and proximal skin temperatures, and DPG in a 7.5-h CR followed by a 7.5-h sleep period in 2 subjects (S7 and S15). Continuously measured data are plotted in 2-min intervals. S7 (thin line) was treated with bright light (5,000 lux) between 2100 and 2400, S15 (thick line) ate daily a single 1,600-kcal carbohydrate (CHO)-rich meal (in form of spaghetti con salsa pomodori) for 3 days; last meal between 2130 and 2200. In S7, light treatment reduced melatonin secretion, distal skin temperature rise, and CBT decline. Sleep onset (SOL = 59 min, vertical line) occurred only after vasodilation of distal skin regions. In S15, a large evening CHO meal increased heart rate and CBT. Sleep was rapidly initiated (SOL = 4.3 min, vertical line).

Under normal conditions, diverse events (onset of Mel secretion, lying down, lights off, relaxation) prepare the body for nocturnal sleep and all induce vasodilation. Their timing is usually coincident with the circadian decline in CBT, which represents the output of the circadian pacemaker [process "C" in the two-process model of sleep regulation (4)]. Therefore, both these "helpful masking effects" and the circadian regulation of CBT induce similar thermoregulatory changes, i.e., heat loss, which may represent the physiological correlate for "natural" sleepiness at night. Because a total sleep deprivation during a CR protocol also increases sleepiness, but without any significant thermoregulatory changes (26), this suggests that homeostatically regulated sleepiness and sleep propensity [process "S" in the two-process model of sleep regulation, (4)] is different from the thermoregulatory-related sleepiness.

Taken together, by using the controlled conditions of a CR protocol combined with diverse thermoregulatory manipulations, multiple physiological factors before sleep onset and their temporal course could be dissected out. This study provides evidence that vasodilation of distal skin regions (and hence heat loss) promotes the readiness for sleep (sleep propensity). Heat loss initiation via the onset of Mel secretion may be the mechanism underlying the circadian regulation of sleep propensity ["opening the sleep gate" (30)]. Although CBT globally correlates with sleep-onset latency, it is not the key factor. The best predictor for a short sleep-onset latency is vasodilated distal skin regions.

Perspectives

Although the connection between thermoregulation and sleep has long been known, it required the stringent conditions of a CR protocol before lights out to dissect out the time course of thermoregulatory events leading to sleep onset. Our "naturalistic" interventions segregated out distal vasodilation, and hence peripheral heat loss, as a key mechanism. Since Mel has previously been considered the trigger for opening the circadian-dependent "sleep gate," its ability to initiate distal vasodilation whenever it is given, provides evidence that this may be the "gate's" physiological correlate. The role of Mel in the regulation of AVAs, and hence heat loss, needs to be clarified. Knowing the importance of initiation of heat loss for sleep to occur provides a hypothetical framework for a more general question whether distal vasodilation is a physiological "final common pathway" also for the soporific actions of classical benzodiazepines, phytotherapies (e.g., valerium), or the old traditional physical remedies such as a warm bath or bed socks, and the importance of a cool bedroom to facilitate subsequent body heat loss.

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Address for reprint requests and other correspondence: K. Kräuchi, Chronobiology and Sleep Laboratory, Wilhelm Klein Strasse 27, CH-4025 Basel, Switzerland (E-mail: kurt.kraeuchi@pukbasel.ch).

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