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Waking up properly: is there a role of thermoregulation in sleep inertia?

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SUMMARY We assume that alertness should be highest at the end of a sleep episode: it is not. There is always sleep inertia upon awakening, which can last minutes to hours, and whose underlying physiological mechanisms are largely unknown. Previously, we had found a functional relationship between the degree of distal vasodilatation (as measured by the distal-proximal skin temperature gradient (DPG) and sleepiness (as measured by subjective ratings), promoting rapid sleep onset. This led us to hypothesize that the dissipation of sleep inertia (sleepiness) would be associated with reverse thermoregulatory mechanisms, i.e. distal vasoconstriction. In two sets of experiments with either a nocturnal sleep episode (study 1) or an afternoon nap (study 2) we could show that vasodilatation of hands and feet increased after lights off and that this was reversed after lights on. The time course of the DPG was significantly and positively correlated with subjective sleepiness (KSS), reflecting similar temporal relationships in both studies 1 and 2. The extremities cooled at a rate very closely parallel to the decay of sleepiness [time constants for the exponential decline calculated for study 2: DPG, 0.286 ± 0.048 h versus KSS, 0.332 ± 0.050 h; NS], indicating redistribution of heat from the shell to the core during dissipation of sleepiness. There was no statistical evidence that the time course of sleep inertia and its thermophysiological correlates depend on sleep structure prior to awakening. The symmetry between the thermoregulatory processes initiating sleepiness and those dissipating it is striking. In order to directly test our hypothesis, further studies with thermophysiological interventions (e.g. cooling the extremities) are needed.

KEYWORDS blood redistribution, core body temperature, distal and proximal skin temperatures, sleep inertia, vasoconstriction, vasodilatation

INTRODUCTION

It would seem obvious that we should be less tired after a good night's rest than before we go to sleep. The paradox is that alertness and performance are actually impaired immediately after waking up, due to the phenomenon of sleep inertia (Dinges 1992; Ferrara and De Gennaro 2000; Lubin *et al.* 1976). Not much is known about the physiological underpinnings (but see Balkin *et al.* 2002; Kuboyama *et al.* 1997). Sleep inertia is exacerbated after recovery sleep following sleep deprivation, but occurs after nighttime sleep in non-sleep-deprived individuals, as well as after daytime naps (Horne and Reyner 1999; Jewett *et al.* 1999; Lumley *et al.* 1986; Naitoh 1981). Sleep inertia can last minutes to hours, partially depending on the task and the dependent variables used to measure it (Achermann *et al.* 1995; Ferrara and De Gennaro 2000; Jewett *et al.* 1999). Careful studies have measured an asymptotic dissipation of sleepiness over a period of at least 1 h (Achermann *et al.* 1995; Folkard and Åkerstedt 1992; Jewett *et al.* 1999). This has repercussions in some situations, such as physicians on night call, where rapid decisions are required by a brain that is still sleepy (Gaba and Howard 2002). If we knew what mechanisms were responsible for this delay in waking up properly, the appropriate countermeasures could be applied in situations requiring immediate response and full responsibility.

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We have previously shown that heat loss, via selective vasodilatation of distal skin regions (measured by the distal minus proximal skin temperature gradient (DPG), seems to be a crucial process for the circadian regulation of core body temperature (CBT) and sleepiness (Aschoff 1956; Kräuchi and Wirz-Justice 1994, 2002; Kräuchi *et al.* 1998, 2000). Warm feet and hands (i.e. increased DPG) before lights off promote a rapid onset of sleep, suggesting a link between thermoregulatory and arousal (sleepiness) systems (Kräuchi *et al.* 1999, 2000). Therefore, in two separate studies, of a night's sleep episode (11 PM–7 AM) or an afternoon nap (4–6 PM), we aimed to see whether sleep inertia was associated with the reverse thermoregulatory mechanism of distal vasoconstriction.

METHODS

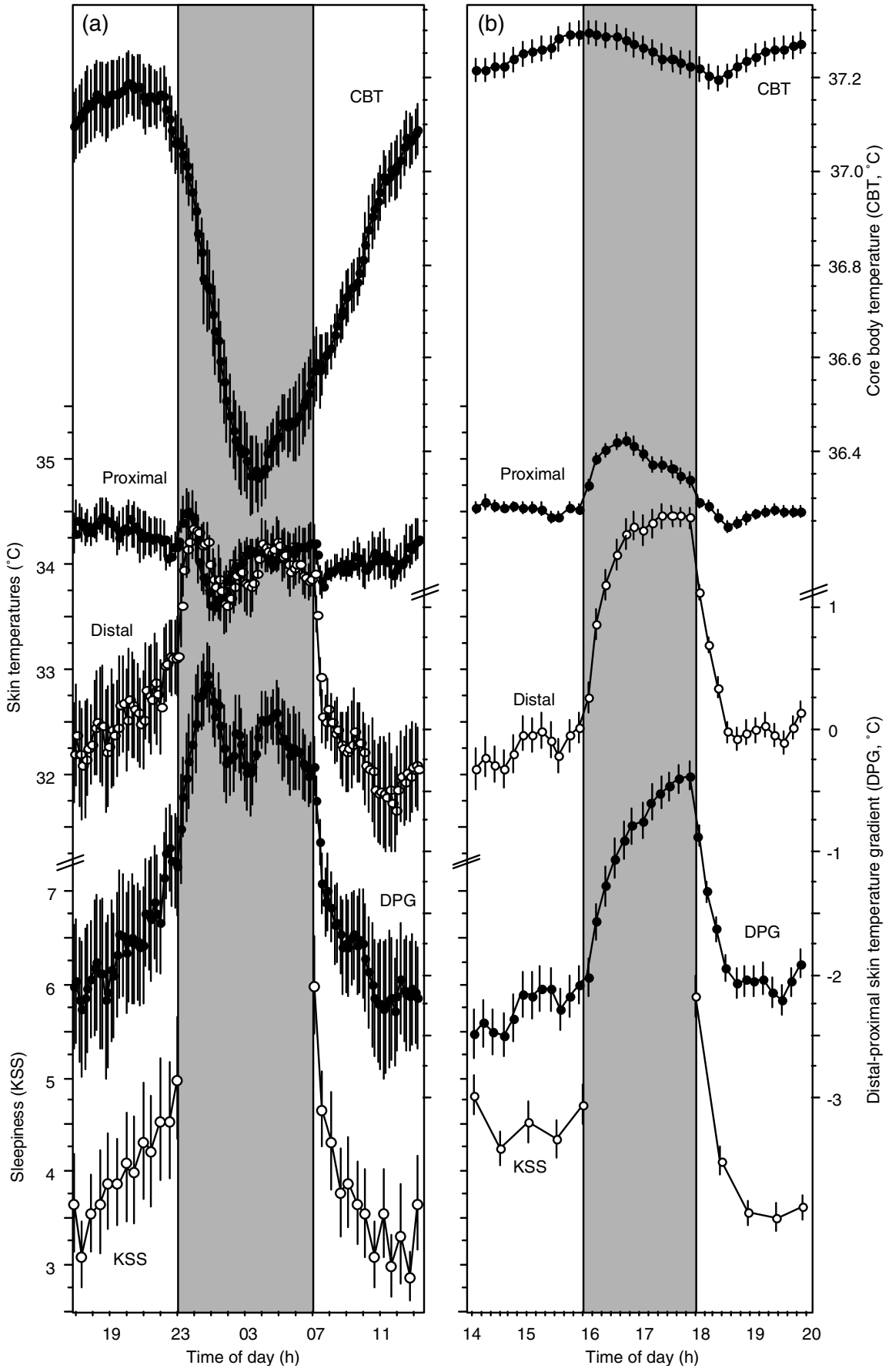
In both studies, rectal temperature (CBT, inserted 10 cm past the sphincter), distal (average: hands and feet) and proximal (weighted average: forehead × 0.093, thigh × 0.347, infraclavicular region × 0.266 and stomach × 0.294) skin temperatures were continuously recorded (20-s intervals) using thermocouples, in subjects kept under controlled conditions of a constant routine protocol (CR; constant supine posture, room temperature 22 °C, <8 lx dim light, humidity 60%, light bedcover, 100 kcal sandwiches and 100 mL water at 1-h intervals; for details see Kräuchi *et al.* 2000). The constant routine protocol was interrupted by scheduled sleep episodes (0 lx). Sleep was polysomnographically recorded by a digital recording system and sleep stages were visually scored on a 20-s basis according to standard criteria (for details see Knoblauch *et al.* 2002). In study 1 (start of CR at 07.00 hours), data were analyzed 6 h before, 8 h during and 6 h after a nocturnal sleep episode (nine men; age: 24 ± 3 years; BMI: 22.5 ± 2.1 kg m^{-2}). In study 2 (start of CR at 12.00 hours), data were analyzed 2 h before, during and after an afternoon nap (eight men, eight women; age: 25 ± 4 years; BMI: 22.1 ± 3.2 kg m^{-2}). Both data sets were taken from larger intervention studies (for details see Kräuchi *et al.* 2003; Wirz-Justice *et al.* 2002), whereby only data from the placebo condition were taken for the present analysis. The DPG provided a measure of selective distal vasodilatation (Rubinstein and Sessler 1990), and the Karolinska Sleepiness Scale (KSS; Åkerstedt and Gillberg 1990) assessed subjective sleepiness as an index of sleep inertia. Statistical analysis of the time course was carried out for each variable using one- or two-way ANOVAS for repeated measures on factor 'time' with Greenhouse-Geisser (G-G) statistics. *P*-values were based on corrected degrees of freedom, but the original degrees of freedom are reported. For both studies, the intra-individual association between DPG, CBT, and KSS was calculated using a multiple linear regression model for repeated measures, with between-subject differences taken into account (Glantz and Slinker 1990). In study 2, a nonlinear regression model with exponential decay calculated time constants of the sleep inertia period for 2 h after lights on. The following model was used to calculate the best fit to decelerating values of KSS and DPG: $Y_{(t)} = Y_{\text{floor}} + (Y_{\text{initial}} - Y_{\text{floor}})e^{(-1/ct)}$ [c = time constant (h), t = time (h), Y = KSS or DPG] (modified from Jewett *et al.* 1999). Statistical analyses were performed using the statistical packages JMP 5.0.1.2 and StatView 5.0.1 (both SAS Institute Inc.).

RESULTS

In study 1 of nocturnal sleep (Fig. 1a), DIST, DPG and to a lesser extent PROX rose rapidly at lights off, as earlier described in detail (Kräuchi *et al.* 2000), and fell immediately at lights on (ANOVA for repeated measures with factor time, forty 30-min bins; CBT: $F_{(39,312)} = 34.49$, $P = 0.0001$; PROX: $F_{(39,312)} = 2.62$, $P = 0.0500$; DIST: $F_{(39,312)} = 8.98$, $P = 0.0017$; DPG: $F_{(39,312)} = 10.71$, $P = 0.0001$; KSS: $F_{(23,184)} = 4.56$, $P = 0.0088$). In addition to these rapid processes, there was an underlying circadian modulation of all these variables as previously described in a constant routine protocol during 36 h of sleep deprivation (Kräuchi and Wirz-Justice 1994, 2002). In the evening, DIST and DPG increased, whereas PROX and CBT decreased. In the morning the inverse occurred. KSS exhibited a close temporal relationship with DPG, as indicated by a significant linear correlation (Fig. 2a). However, KSS was not significantly associated with CBT ($r = -0.065$, NS; analysis not shown). As the circadian decline in sleepiness and DPG in the morning overlaps the decline in sleep inertia after lights on, these two aspects cannot easily be separated when sleep occurs at the usual bedtimes. For this reason the sleep inertia process was not further analyzed in detail. In order to study effects of sleep inertia at a circadian phase with relatively stable CBT levels (and minimal melatonin and cortisol secretion), we analyzed in detail data from a second study with a nap scheduled between 4 and 6 PM.

In the nap study (Fig. 1b), DIST, DPG and to a lesser extent PROX increased rapidly immediately after lights off, whereas CBT declined slowly (one-way ANOVA for repeated measures with factor time, twelve 30-min bins; CBT: $F_{(11,165)} = 5.96$, $P = 0.0019$; PROX: $F_{(11,165)} = 34.49$, $P = 0.0001$; DIST: $F_{(11,165)} = 34.49$, $P = 0.0001$; DPG: $F_{(11,165)} = 25.49$, $P = 0.0001$; KSS: $F_{(7,105)} = 17.49$, $P = 0.0001$). DIST and DPG peaked at the end of the nap, PROX 50 min after lights off, and CBT reached a minimum 30 min after lights on. Sleepiness ratings were highest in the first assessment 1 min after lights on and reached lowest values after 60 min. DIST and DPG reached minimum values 100 min after lights on. PROX declined after the maximum within the nap and reached a minimum 40 min after lights on. DPG declined in an

Figure 1. (a) Influence of an 8-h nocturnal sleep episode (study 1, 11 PM – 7 AM, shaded area, lights off) on the time course of CBT (10-min bins), proximal and distal skin temperatures and DPG (10-min bins), and subjective sleepiness ratings (KSS, 30-min intervals) under constant routine conditions without posture changes. Data represent mean ± SEM ($n = 9$). (b) Same procedure for study 2 (exception: temperatures in 5-min bins), for a 2-h afternoon nap (4–6 PM; $n = 16$).


(a)
(b)
CBT
Proximal
Distal
DPG
KSS
Skin temperatures (°C)
Sleepiness (KSS)
Core body temperature (CBT, °C)
Distal-proximal skin temperature gradient (DPG, °C)
Time of day (h)
Time of day (h)
19
23
03
07
11
14
15
16
17
18
19
20
35
34
33
32
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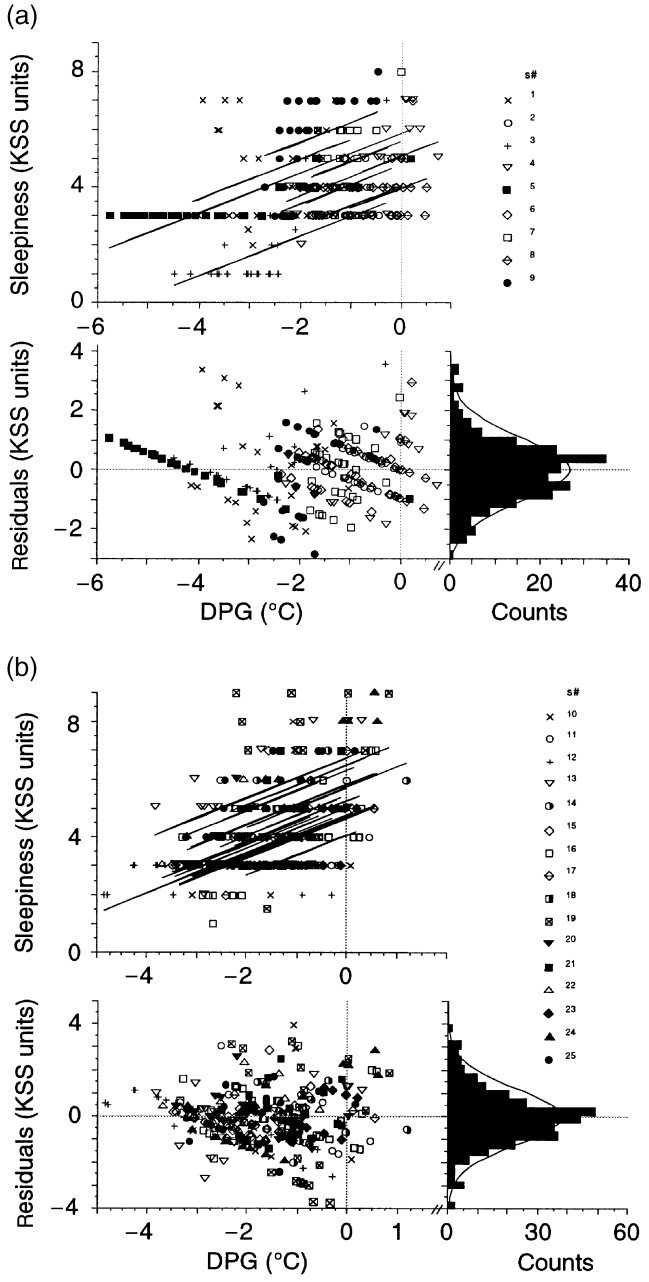

Figure 2. (a) Correlation analysis of DPG with KSS for study 1 using a multiple linear regression model for repeated measures, with between-subject differences taken into account (correlation coefficient: $r = 0.428$, $P = 0.0001$, $n = 9$, total 234 data pairs). Upper panel: scattergram of 234 data points (each subject separately) together with fitted regression lines for each subject separately; lower left panel: scattergram of residuals for each subject separately; lower right panel: histogram of residuals with superimposed normal distribution. Mean residuals = 0.00 KSS units ± 1.04 SD and normal distribution of the residuals (Shapiro–Wilk's $W = 0.976$, NS) indicate an appropriate fit to the chosen regression model. (b) Same procedure for study 2. Correlation coefficient: $r = 0.568$, $P < 0.0001$, $n = 16$ subjects with four experiments each at weekly intervals, total 320 data pairs. Mean residuals = 0.00 KSS units ± 1.20 (SD) and normal distribution of the residuals (Shapiro–Wilk's $W = 0.979$, NS) indicate an appropriate fit to the chosen regression model.

exponential 'cooling-out' function with similar time constants as for the exponential decline of KSS (0.286 ± 0.048 h versus 0.332 ± 0.050 h). The intra-individual time course of DPG after lights on was significantly correlated with KSS (Fig. 2b), whereas the time course of CBT was not ($r = 0.001$, NS; data not shown). KSS values 90–120 min after lights on were significantly lower than pre-nap values (30–0 min before lights off; ΔKSS units: 1.2 ± 0.2, $P < 0.0001$), reflecting the homeostatic reduction of sleepiness by the nap with no thermophysiological correlate (Kräuchi *et al.* 2000).

In a post-hoc analysis, we analyzed the influence of sleep stages before awakening on the dissipation of sleepiness and DPG after lights on. For classification, the last sleep stage during the 3 min (nine 20-s epochs) preceding lights on was taken into account (wake was rated if all 20-s were rated as awake). Of a total of 64 naps, seven ended with wake, 11 naps with sleep stage 1, 34 naps with sleep stage 2, six naps with sleep stage 3, one nap with sleep stage 4 and five naps ended with rapid-eye movement sleep (REMS). Due to the low numbers of naps ending in REMS or slow wave sleep (SWS, stages 3 + 4), no comparisons with these sleep stages were possible. Statistical comparisons with reasonable statistical power were possible between naps ending in non-rapid eye movement sleep (NREMS) versus wake or sleep stage 1 (WAKE + 1; $n = 10$ subjects with complete data pairs were found). Two-way ANOVAS for repeated measures (two repeated factors, time: five levels and sleep stage: two levels) revealed no differences in the time course between NREMS and WAKE + 1 of DPG and of KSS [see Fig. 3; DPG: time, $F_{(4,36)} = 32.70$, $P = 0.0001$; sleep stage: $F_{(1,9)} = 1.02$, NS; time × sleep stage, $F_{(4,36)} = 0.55$, NS; KSS: time, $F_{(4,36)} = 25.75$, $P = 0.0001$; sleep stage: $F_{(1,9)} = 0.05$, NS; time × sleep stage, $F_{(4,36)} = 0.68$, NS].

DISCUSSION

These data reveal a close functional relationship between the dissipation of sleepiness and distal vasoconstriction at the cooling-out rate of the extremities. In both studies, the extremities had been markedly warmed up during the rest period and cooled after lights on. In study 1 the underlying circadian modulation overlaps the changes taking place during the rest period, which could clearly be separated in study 2 during an afternoon nap. Sleep inertia was measured by subjective ratings of sleepiness, with the advantage of rapid and 'non-invasive' measurement with small alerting or fatiguing effects. However, the extent and time course of sleep inertia found is dependent on the tools used – results differ for speed and accuracy of performance, cognitive tasks, or self-ratings of sleepiness (Achermann *et al.* 1995; Ferrara and De Gennaro 2000; Jewett *et al.* 1999). Therefore, all our conclusions are limited to subjective sleepiness ratings, not necessarily similar for other aspects of sleep inertia.

In order to understand the relationship between thermoregulation and sleepiness/sleep regulation, it is necessary to account for at least five effects which usually occur closely

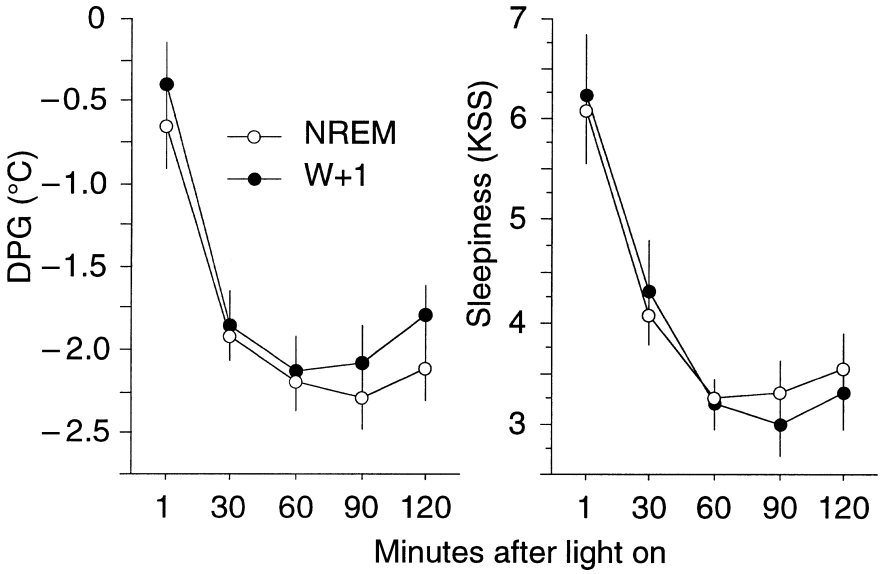

Figure 3. Time course of DPG separated according to sleep stage before awakening from a 2-h afternoon nap (4–6 PM). Averaged DPG (left panel) and KSS (right panel) during 2 h after awakening from sleep stages 2–4 (NREMS) or sleep stage 1 as well as already awake (WAKE + 1); $n = 10$ subjects with such a data pair were found. When in the four naps more than one sleep stage NREMS or WAKE + 1 occurred, data were combined. The dissipation of DPG and KSS did not significantly depend on whether subjects were in sleep stages NREMS or WAKE + 1 preceding lights on.

together at bedtime under normal conditions and which promote sleep induction: the endogenous circadian rhythm of thermoregulatory processes, the onset of melatonin secretion, hemodynamic changes induced by lying down, effects of reducing environmental light intensity *per se*, and responses to mental and body relaxation after lights off. In the evening, the circadian regulation of CBT begins with an increase in distal and a decrease in proximal skin temperatures, leading to heat loss and a subsequent decrease in CBT (Kräuchi and Wirz-Justice 1994; Kräuchi *et al*. 2000). It has been suggested that opening of arterio-venous shunts in distal skin regions is the main mechanism of body heat loss in the evening (Kräuchi *et al*. 2000). The onset of melatonin secretion occurs simultaneously, and it is known that exogenous melatonin promotes distal vasodilatation (Kräuchi *et al*. 1997, 2000). The postural change of lying down itself increases proximal, and most markedly distal skin temperatures, leading to heat loss and then a decrease in CBT (Kräuchi et al. 1997). Many studies attributing the decline in CBT to sleep have not recognized that this decline is mostly masking – the postural-induced effects can last for 1–2 h (Kräuchi et al. 1997). The masking effect was minimized in our studies by the posture-controlled constant routine protocol begun hours before measurement. Light in the evening (depending on intensity) can suppress melatonin secretion and hence delay its onset, as well as delaying the rise in distal skin temperature and sleepiness and the fall in CBT (Cajochen *et al*. 2000; Kräuchi *et al*. 1998). However, our constant routine protocol with low environmental light levels (< 8 lx) before lights off (0 lx) minimized this kind of masking as well. A further effect, not previously disentangled, is that the cognitive signal of lights off induces immediate relaxation prior to onset of sleep stage 2: proximal and most markedly distal skin temperatures increase on relaxation, again resulting in a decrease in CBT (Kräuchi *et al*. 2001). Thus, all five factors (circadian melatonin onset, down-regulation of CBT in the evening, lying down, reducing light intensity and relaxation) increase DPG concomitantly with increased sleepiness, followed by a decrease in CBT, each to a different extent and with different velocities.

Relaxation after lights off redistributes heat within the thermophysiological two-compartment system of the body (Aschoff 1956). Heat moves from the core to the shell by precapillary vasodilatation in both proximal and distal skin regions, leading, however, to only minor and slow changes in CBT (Kräuchi *et al*. 2000). At first glance, this finding is paradox, but can be explained by the marked decrease in heart rate that occurs concomitantly at lights off (Kräuchi *et al*. 2001), which leads to a reduced cardiac output. This impedes fast cooling of the core. By 2 h after lights off the two compartments have equilibrated, as indicated by similar distal and proximal skin temperatures (DPG *ca*. 0). Therefore, distal vasodilatation induces efficient body heat loss only when the cardiovascular system maintains a sufficient convective body heat exchange via blood circulation.

At lights on, all the changes occurring at lights off are reversed. Building up the thermophysiological two-compartment system of the body (core/shell) again takes time. This could explain the finding that changes in sleepiness are not always correlated with changes in CBT. However, the close intra-individual correlation between the exponential time course of DPG and sleepiness (decay of sleep inertia) supports a functional relationship between the dissipation of sleepiness and distal vasoconstriction of the extremities. Important support for this comes from analyses revealing that similar relationships hold after naps taken at different circadian phases (unpublished data). In addition, the dissipation of sleepiness and DPG did not differ with respect to the sleep stage preceding lights on (WAKE + 1 or NREMS). Thus, in contrast to others (e.g. Ferrara and De Gennaro 2000), our results support the notion that the sleep stage at awakening does not significantly influence the severity of sleep inertia nor the time course of its dissipation (Jewett *et al*. 1999). However,

for a definitive test of this hypothesis, further studies with enough statistical power are needed to differentiate the effect of all sleep stages on sleep inertia.

Our findings suggest that a 2-h relaxation episode would be sufficient to induce distal vasodilatation and hence sleep inertia when 'waking up', whether sleep occurs or not. In other words, all behaviors that help to induce distal vasodilatation (such as a hot bath, lying down, relaxation techniques such as meditation, autogenous training and yoga) will be followed by a period of sleep inertia. In fact, a recent study measuring sleep inertia (but no thermophysiological correlates) after a rest period in bed without sleep, supports our conclusion (Gottselig *et al.* 2003). The independence from sleep *per se* would be underlined by a change in terminology from 'sleep inertia' to 'relaxation inertia'.

Taken together, the symmetry between the thermoregulatory processes initiating sleepiness (Kräuchi *et al.* 1999, 2000) and those dissipating is striking, and provide a physiological rationale for a 'power nap' being short: redistribution of blood to the extremities is only partial after 10–20 min. This may lead to less distal vasodilatation on wake-up and less sleep inertia. A simple test of our hypothesis would be cold water applied directly to the extremities on waking, which should increase distal vasoconstriction and, in turn, alertness. The practical applications are evident, and are indirectly supported by studies which have rapidly stimulated alertness by cooling the forehead with cold air (Horne and Reyner 1999), or cold water (Hayashi *et al.* 2003), which is known to induce distal vasoconstriction via the trigeminus reflex (Brown *et al.* 2003).

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