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The human sleep–wake cycle reconsidered from a thermoregulatory point of view

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Abstract

Sleep is typically initiated on the declining portion of the circadian rhythm of core body temperature (CBT) when its rate of change, and body heat loss, is maximal. Distal vasodilatation plays a primary role in the circadian regulation of body heat loss and is strongly associated with sleepiness and sleep induction. In contrast, sleep (i.e. non-REM sleep and slow-wave activity, SWA) has no or only a minor thermoregulatory function. Two lines of evidence support this statement. First, detailed analyses of thermoregulatory changes before and after lights off show clearly that they start before stage 2 sleep begins. Second, accumulation of sleep pressure with increasing time awake, increases subjective sleepiness and SWA during the succeeding recovery night, but does not influence the thermoregulatory system. Taken together, the circadian modulation of sleepiness and sleep induction is clearly associated with thermoregulatory changes, but the thermoregulatory system seems to be independent of the sleepiness/sleep regulatory system. A simplified model is presented which attempts to explain the relationship between these two systems. It is based on the main hypothesis that all thermoregulatory effects which lead to an increase in the core/shell ratio (e.g. a reduced shell by increased distal skin temperature) lead to increased sleepiness and, as a consequence, to increased sleep propensity. However, the sleepiness/sleep regulatory system feeds back onto the thermoregulatory system only indirectly via sleep-related behaviors (e.g. relaxation, lying down).

Keywords: Thermoregulation; Distal and proximal skin temperatures; Core body temperatures; Heat loss; Sleepiness; Slow-wave activity; Psychomotor vigilance; Model

1. Introduction

The idea that temperature and sleep are interrelated is based on evolutionary history. Sleep, specifically the stage rapid-eye-movement (REM) sleep, developed in association with endothermy [1,2]. All species, independent of temporal niche, usually sleep during the circadian trough of their core body temperature (CBT) rhythm [2,3]. Early studies in humans revealed a close temporal relationship between sleep onset and the CBT rhythm [4–6]. When the sleep–wake cycle is synchronized with the geophysical light–dark cycle, the maximum of CBT occurs in the early evening, and the minimum in the second half of the nocturnal sleep episode. Sleep is then typically initiated on the declining portion of the CBT curve when its rate of change, and body heat loss, is maximal [6–8]. In the morning when heat production is dominant over heat loss, CBT increases, as does the propensity to wake-up. In a time-free environment, the temperature peak advances to the first half of the nocturnal sleep episode [6]. Under these new phase relationships, sleep propensity (the need or pressure for sleep) is maximal close to the temperature minimum, and the tendency to wake-up still clusters on the rising limb of the CBT rhythm [6]. These preferred zones for falling asleep and for waking up have a profound effect on sleep duration — sleep length is maximal (circa 14 h) when sleep is initiated around the CBT maximum [6]. All these findings indicate that sleep propensity and sleep duration are tightly coupled with the thermoregulatory system. However, in contrast to the sophistication of sleep EEG (electroencephalogram) analyses, including spectral decomposition of the EEG-signal, the thermoregulatory system has not been adequately studied in parallel. In many studies, only CBT was measured, but it has to be borne in mind that CBT represents

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only about 70% of the body heat content, and information about changes in heat loss and heat production are mostly lacking.

There is substantial evidence indicating that homeostatic control of CBT is mediated by a hierarchically organized set of neuronal mechanisms, with the preoptic anterior hypothalamus (POAH) at the top of the hierarchy [9]. In addition to the homeostatic principle, a rostral projection from the circadian pacemaker localized in the suprachiasmatic nuclei (SCN) to the preoptic areas serves to produce the circadian modulation of CBT [10,11]. The double modulation of CBT by a homeostatic and a circadian process has been interpreted as an indication that the overt daily rhythm of CBT results from the concerted action of the two processes [12]. Thus, the circadian rhythm of CBT has been explained as a result of a regulated change in the thermoregulatory "set-point" by the SCN [13]. On the other hand, the two processes could have evolved separately, so that the thermoregulatory system and the circadian system could have independent control of the effector organs which regulate heat production and heat dissipation and, consequently, CBT [12]. Similarly to the thermoregulatory system, it has been shown that homeostatic–(not yet anatomically identified) and circadian–(SCN) driven processes also regulate sleep propensity [14,15]. This has been mathematically described in the two-process model of sleep regulation, whereby the precise relationship between homeostatic and circadian processes is still a matter of debate [14–17]. Many studies have shown that the level of slow-wave activity (SWA) monitored by the EEG is a robust measure of non-REM sleep intensity and may serve as an objective physiological indicator for accumulated sleep propensity during wakefulness and, therefore, of sleep homeostasis [18]. A close relationship between the duration of prior waking and SWA in the following sleep episodes has been demonstrated [19]. A sleep deficit elicits a compensatory response of increased SWA; excess sleep has the opposite effect [20].

A further measure showing a circadian and a homeostatic modulation is sleepiness, either subjectively rated or objectively measured by analysis of a waking-EEG [21,22]. Sleepiness can be defined as a physiological need for sleep or the subject's tendency to fall asleep at a certain time, and therefore represents a further index of sleep propensity [23,24]. In addition to the homeostatic and circadian regulation of sleepiness, a third process called 'sleep inertia' has long been known, which describes the phenomenon of low vigilance upon awakening even though sleepiness should be lowest at the end of a sleep episode [25,26]. A three-process-model of sleepiness regulation has also been mathematically described [27,28]. Within this framework, the main question that arises is: how are the homeostatic and circadian processes of CBT related to those of sleepiness and sleep propensity? Here we focus on changes in the thermoregulatory system occurring in routine daily life, and their relation to the sleepiness/sleep regulatory system (see below). This report briefly summarizes our own studies carried out over the last decade and does not constitute a complete review of the entire field. Finally, a simplified model is presented which attempts to explain the relationship between the thermoregulatory and the sleepiness/sleep regulatory systems.

2. Circadian thermoregulation: regulation of core and shell

The circadian rhythm of core body temperature (CBT) is a well-described physiological phenomenon. The first publication of a daily record of CBT in humans appeared in the middle of the 19th century in the form of a thesis by Gierse [29]. He showed that his own oral temperature revealed a maximum temperature in the early evening and a minimum in the early morning hours, with a maximum–minimum range of 0.9 °C. It was long assumed that behavioral activity and digestive processes were the most important factors for the generation of the CBT rhythm [30]. In the mid-20th century, Aschoff et al. systematically explored the causes of this rhythm [31,32]. They showed that the circadian rhythm of CBT is determined both by changes in heat production and changes in heat loss, and concluded that heat production undergoes a circadian rhythm which is phase advanced with respect to the circadian rhythm of heat loss (i.e. when heat production surpasses heat loss, CBT increases). The fact that both heat production and heat loss are concomitantly regulated results in a much more efficient tuning of the CBT rhythm than if only one of these components were regulated. Therefore, changes in CBT can only be explained by knowing the relationship between heat production and heat loss.

Under resting conditions, heat production depends mainly on the metabolic activity of inner organs such as the brain and organs in the abdominal/thoracic cavities such as the liver, intestines, kidneys and the heart. About 70% of the entire resting metabolic rate of the human body is produced by these inner organs [33]. However, this heat is generated in less than 10% of the body mass, which is surrounded by a small proximal skin surface whose shape is too flat for a good heat transfer to the environment. This means that, even in a comfortable thermoneutral environment, heat has to be transferred from the core to parts of the body with better heat transfer conditions, namely to the extremities such as fingers and toes [33,34]. These distal parts of the body have ideal (round) surface shapes for good heat transfer properties to the environment. Blood is the main medium for transporting heat (convectively) from the core to distal skin regions, driven and distributed by the cardiovascular system. The human body consists therefore of two compartments, the heat producing core, and the heat-loss regulating shell [33,34].

Core body temperature (especially in the brain) is homeostatically regulated around 37 °C, and the shell is rather poikilothermic and therefore largely dependent on environmental temperature. In a warm environment the shell is small; in a cold environment it is large. Thus the shell acts as a buffer to protect the core from dangerous cooling [34]. This autonomically regulated mechanism of shell size occurs via constriction or dilatation of peripheral blood vessels, mainly of arteriovenous anastomoses (AVAs) and pre-capillary arterioles in distal skin regions [35,36]. The proximal skin regions are only regulated via pre-capillary arterioles. Since blood flow through capillaries is very slow, proximal skin temperature can be passively influenced by CBT via heat conduction. Sympathetic nerve activity is crucial for regulation of the peripheral vascular system. Regulation of blood vessel diameters occurs very

rapidly before there is enough time for CBT to change. This so-called feed-forward regulation [37] with respect to CBT is an important property of the thermophysiological 'core-shell' principle [34].

Another feed-forward regulation serves the counter-current heat exchange in the extremities, i.e. legs and arms. This mechanism is extraordinarily efficient in birds, who can stand on ice without any cooling of their body. In a cold environment, venous blood returns via inner blood vessels located near the arteries which pre-warm the blood, thereby efficiently protecting the core from cooling [33]. In contrast, in a warm environment the venous blood streams back via outer veins near the skin surface, thereby enhancing additional heat loss via the lower extremities [33]. It is known that the regulation of arteriovenous anastomoses (AVAs) is also involved in this counter-current heat exchange. These vessels are exclusively localized as shunts between arterioles and venules in distal skin regions (e.g. finger tips) and, when they are open, the blood streams back mainly via outer veins, thereby enhancing the heat-loss function of opened AVAs [35,36]. Blood flows very rapidly through these shunts, about 10,000 times faster than via capillaries [35,36], and directly from arterioles to the dermal venous plexus, so enabling heat to be exchanged efficiently.

Taken together, in all these mechanisms of heat loss and heat conservation, the opening or closing of the AVAs in distal skin regions is crucial. Changes in shell size also take place when the underlying endogenous circadian CBT rhythm is regulated [31]. This has been studied under controlled environmental conditions [38], where external influences (masking effects) are minimized, in the so-called constant routine protocol (CR; [39]): e.g. constant room temperature (22 °C), humidity (60%) and light (<8 lx); constant bed rest in supine body position but no sleep allowed; and food and fluid intake in small isocaloric portions at equal intervals. It has been shown that distal skin temperature rises in the evening, whereas heat production, proximal skin temperature and CBT decline — in the morning the inverse happens [31,38,40]. This inverse circadian regulation of distal and proximal skin temperature is an index of a circadian regulation of the 'core/shell' ratio. The circadian rhythm in heat production (measured by indirect calorimetry), as well as by heart rate (a correlate of heat production), is phase advanced with respect to CBT and heat loss, confirming the findings of Aschoff and Heise [31]. However, the constant routine results, when sleep was not allowed, were obtained under more closely controlled conditions [38].

Furthermore, an important role for the heat loss effector system in the evening appears to be the nocturnally secreted pineal hormone, melatonin. Melatonin augments distal skin blood flow, most probably via opening AVAs, either by central or peripheral mechanisms, or both [41,42]. However, there is no direct evidence for the existence of melatonin receptors (MT1 or MT2) on distal blood vessels in humans. Melatonin initiates not only distal vasodilatation, but also induces sleepiness, acting therefore as a hormonal trigger between body heat loss and induction of sleep in the evening (opening of the sleep gate [43]; more details are provided elsewhere [42]). Although melatonin is not the main topic of this review, it leads to the question of how changes due to the thermoregulatory system are related to sleepiness and sleep induction.

3. Sleep induction in relation to core and shell temperatures

An elegant way to dissect out the contribution of homeostatic and circadian components of sleepiness and sleep-EEG measures is by scheduling subjects to non-24 h sleep–wake cycles (days much longer or shorter than 24 h, e.g. 28 h, 20 h), outside the range of entrainment [44,45]. In these so-called 'forced desynchrony' protocols, sleep occurs at many different circadian phases, while the sleep homeostat, which is responding to the time spent awake, can be assumed to be nearly in a steady state. This protocol has been developed to produce a predictable change in the phase relationship between the sleep–wake cycle and the endogenous circadian rhythm of CBT driven by the pacemaker in the SCN. A state of spontaneous internal desynchrony can unpredictably occur in about 20% of subjects when they live for weeks in a time-free ("free-running") environment [46]. However, both forced and spontaneous desynchrony protocols have the disadvantage that many thermophysiological effects taking place during the wake phase are hard to control, and so behavior masks what is really going on. For example, lying down always occurs near lights off and sleep initiation. This change of posture is of major importance in thermoregulation. We have shown that, after lying down, distal and proximal skin temperatures increase rapidly, together with increased sleepiness ratings and decreased CBT (Fig. 1a) [41]; these changes last at least 1.5 h [41], after which, a new thermoregulatory steady state is reached. This masking phenomenon has often been neglected in interpreting previous data on thermoregulation and sleep.

Furthermore, in another study the opposite pattern was found after a change from the supine to the upright body position (Fig. 1b) [47]. Distal and proximal skin temperatures followed the same direction after such postural changes, indicating that this kind of sleepiness seems to be regulated by the thermostat differently from the circadian process of sleepiness, where distal and proximal skin temperatures show inverse patterns. The conclusion from these studies is that changes in distal skin temperatures seem to be the crucial thermophysiological correlate of relaxation-induced sleepiness and not a change in proximal skin temperature.

The same conclusion can been drawn from experiments concerned with inner temperature — comparing the intake of an ice/water mixture (250 ml, 4 °C) with hot water (250 ml, 55 °C). Here, all temperatures – CBT, distal and proximal (data not shown) – declined and sleepiness decreased after ice intake, and the converse occurred after hot water intake [48] (Fig. 2). Thus, it is in fact the increase in distal skin temperature (and hence increase in heat loss), which is associated with an increase in sleepiness, whereas a decrease in distal skin temperature (heat retention) is associated with a decrease in sleepiness (i.e. an alerting effect). Furthermore, this study further shows that a decrease in CBT is not necessary for sleepiness induction.

Interestingly, although alertness follows a circadian time course similar to psychomotor vigilance, as measured by an

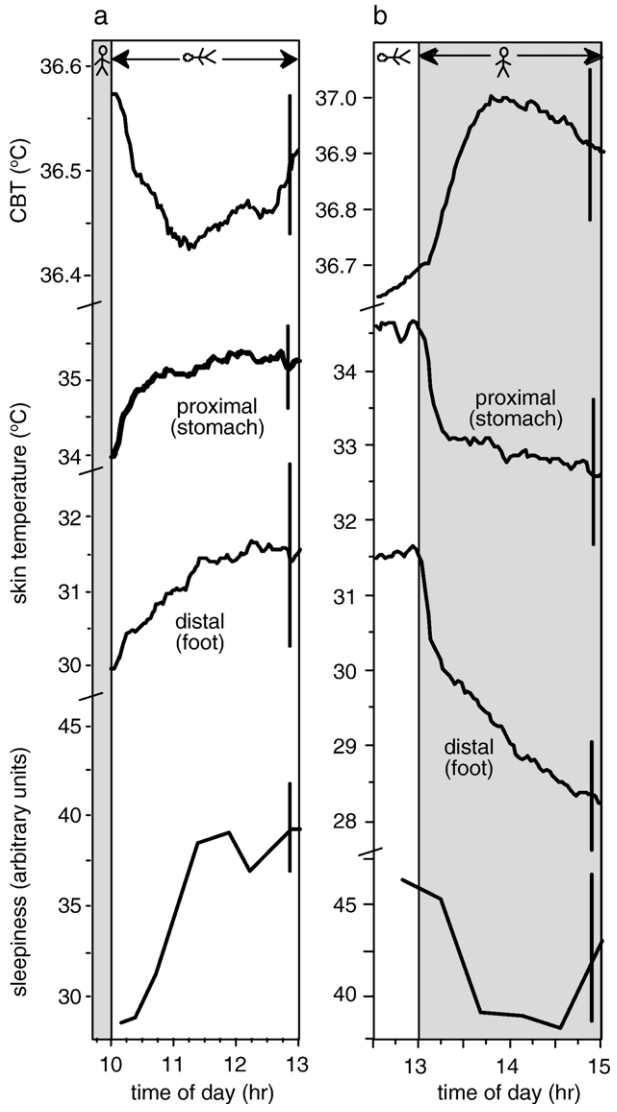

Fig. 1. Mean curves of core body temperature (CBT), proximal and distal skin temperatures, and subjective ratings of sleepiness. The vertical bars at the right of the curves indicate averaged s.e.m. of all time points (data redrawn from [47]). a) Effects of lying down from a standing position (N=8 men). Note: CBT decreased and skin temperatures increased together with subjective ratings of sleepiness. b) Effects of standing up from a supine position (N=9 men). Note: CBT increased and skin temperatures decreased together with subjective ratings of sleepiness.

acoustic reaction time test, they are not identical. The above experiments of mild core body cooling or warming actually leads to their dissociation. In spite of the alerting effect of mild core body cooling, reaction time lengthened. Alertness seems to be intimately linked to distal skin temperature, but psychomotor vigilance remained closely linked with CBT. Based on these findings it can be concluded that any factors modulating thermoregulation (induced e.g. by changes in body position, food and fluid intake) have also to be strictly controlled in experiments using psychomotor vigilance tests. It is possible that some controversial results could have arisen from uncontrolled thermoregulatory conditions.

The close relation between heat loss and sleepiness was recognized a long time ago. Ebbecke [49] described general relationships between affective states and changes after heating up and cooling down the body [10]. The 'Heizaffekt' ('heating affect') with increasing CBT and decreasing distal skin temperature (relative increase of heat production over heat loss) produces a feeling of alertness and a refreshed state. Conversely, the 'Entwärmungsaffekt' ('de-heating affect') with reduction of CBT and increasing distal skin temperature (relative increase of heat loss over heat production) produces

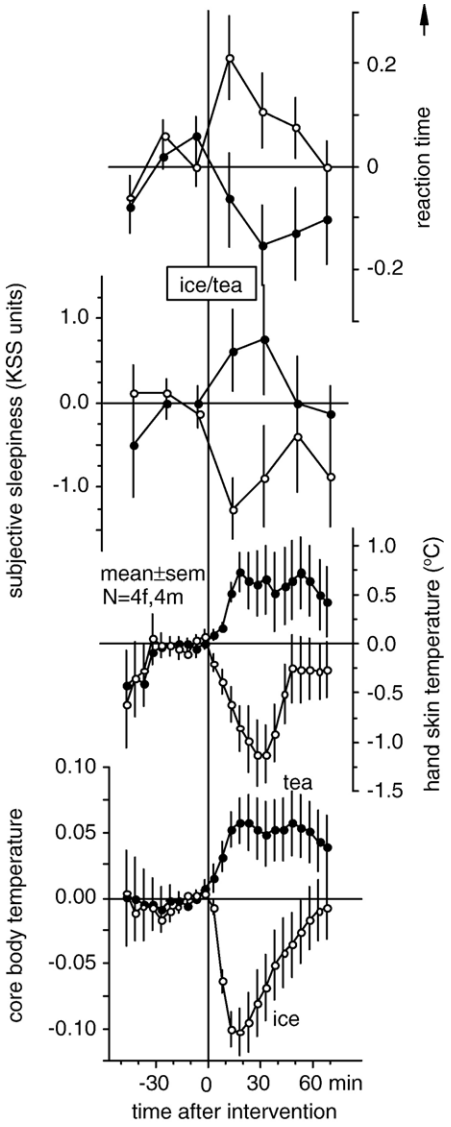

Fig. 2. Time courses (mean±s.e.m., N=4 women, 4 men) of core (rectal) body temperature, hand skin temperature, subjective sleepiness (Karolinska Sleepiness Scale), and reaction time ($-s^{-1}$) (acoustic reaction time test, 75 randomized acoustic signals of 60–100 db within 3 min) before and after ingestion of 250 ml crushed ice/water mixture (='ice') or 250 ml 55°C warm water (='tea') at 12:50 h within 5 min (randomized crossover design, 1–3 days between). Reaction time is presented in $-1/x$ transformed raw values. This transformation leads to normally distributed values (positive values indicate higher reaction time values). All data are expressed as relative changes to the mean of pre-ingestion values. For details see [48]. Note: Although sleepiness, reaction time and distal skin temperature follow more or less a similar circadian time course [51,93], mild core body cooling or warming leads to their dissociation: sleepiness being correlated with distal skin temperatures, but reaction time remaining negatively linked with CBT.

a feeling of relaxation, comfort and tiredness. This change in heat redistribution between the core and shell and vice versa seems to be related closely to the induction of sleepiness and alertness, respectively. Similar effects could also be expected for post-prandial sleepiness (post-meal dip) [50] or after an exercise bout. Thus, in order to understand the relationship between the thermoregulatory system and the sleepiness/sleep regulatory system, studies under controlled unmasking conditions before, during and after a sleep episode are needed.

4. Challenging the sleepiness/sleep regulatory system does not affect the thermoregulatory system

In order to control for masking conditions that affect both the thermoregulatory and the sleepiness/sleep regulatory system, we attempted to combine the advantages of the CR (unmasking conditions for the circadian CBT rhythm) with the forced desynchrony protocol (sleep occurring at different circadian phases). In a 40-h crossover study we compared under constant posture conditions a forced desynchrony protocol in a very much shortened form (10 cycles with 150 min of scheduled wakefulness and 75 min of scheduled sleep each cycle) with a CR (40-h sleep deprivation) [51]. This comparison allows, at least partially, a separation of homeostatic and circadian aspects. The nap protocol furthermore allows a systematic comparison of sleep and sleep inertia on thermoregulation at different circadian phases. Finally, a comparison of 8-h sleep episodes before and following the two protocols further allows an evaluation of the effect of high vs. low sleep pressure on the thermoregulatory system in relation to SWA decay kinetics. An overview of the study results is given in Fig. 3. This study supports our previous hypothesis that the circadian modulation of sleepiness is primarily related to the circadian regulation of distal vasodilatation (and hence to heat loss and CBT reduction), whereas the homeostatic regulated increase of sleepiness is nearly independent thereof [52].

The findings further suggest that this close relationship between distal vasodilatation and sleepiness also holds for the process of sleep inertia, thus confirming and extending our published data [53]. This means that both the evening increase in sleepiness, which leads to maximum sleep propensity in the middle of the night, and the exponential decline of sleepiness upon awakening, can be described as a function of changes in distal vasodilatation. In contrast, the homeostatic increase in sleepiness related to duration of prior time awake is not related to a thermoregulatory function. This homeostatic build-up process of sleepiness has been related to topographic EEG correlates in the frontal cortex [22]. Based on these different physiological correlates, two “kinds” of sleepiness can be postulated (thermoregulatory-related and -unrelated). That the circadian pattern of all measured body temperatures did not differ between the two protocols indicates they were independent of the homeostatic build-up of sleepiness (sleep pressure). This allows the conclusion that all the measured circadian patterns are not influenced by a masking process via the sleep homeostat and countermeasures taken by a subject to keep awake. The build-up process of sleep pressure over 40 h has in

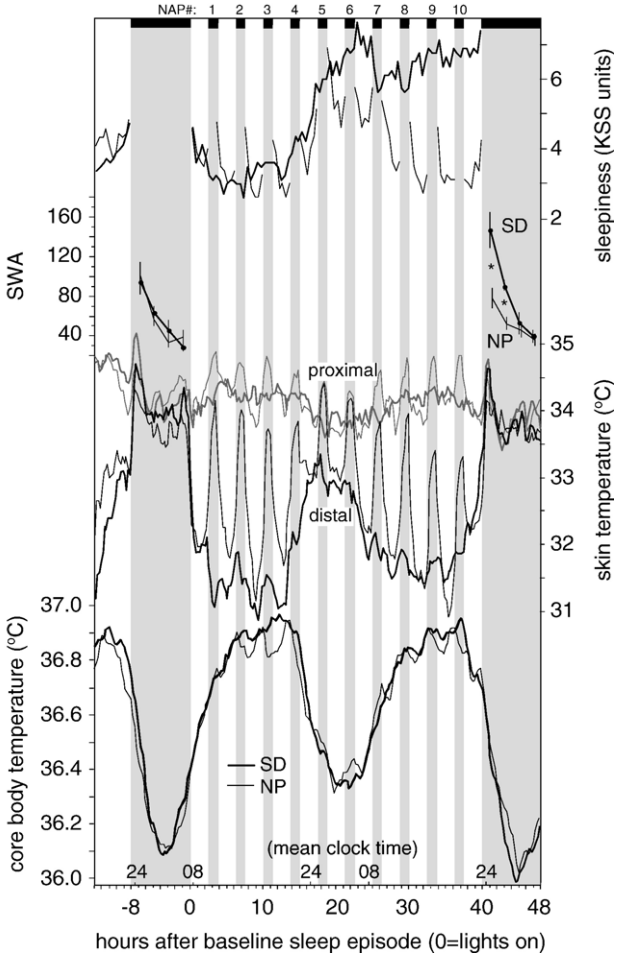

Fig. 3. Mean time course (N=8 healthy young men, constant posture protocol) of core body temperature, proximal and distal skin temperature, slow-wave activity (SWA) and subjective ratings of sleepiness (KSS) for the 40-h sleep deprivation (SD) and nap (NP; ten cycles of 75 min dark vs. 150 min light,<8 lx/cycle) protocols (data redrawn from [51]). SWA (μV^2/0.25 Hz, power density; for more details, see [20]) during non-rapid eye movement (NREM) sleep in the frequency range from 0.75 to 4.5 Hz was averaged per 2 hourly intervals throughout the nights (recording sites: Cz-A2 -derivation; for more details see [20]). Temperature data are binned in 15-min intervals. For better visualization s.e.m. values were omitted (mean s.e.m.-values/time bin did not differ between SD and NP, data not shown). The large black and grey areas indicate dark phase (nocturnal sleep) for both protocols; the black and grey areas between 0 and 40 h indicate dark phase (0 lx) for NP protocol only (light phase:<8 lx). Proximal = weighed mean temperature of following skin regions: infraclavicular, stomach, forehead and thigh; distal = mean of hands and feet. For more details, see [51]. Note: In contrast to the clear differences in sleepiness ratings and SWA at the end of the 40-h protocols and during the recovery sleep, the thermoregulatory system did not differ between the protocols.

fact no, or only minor, thermoregulatory consequences. This finding confirms our previous CR-study where we found non-significant changes in body temperatures (core, distal and proximal skin temperatures) at the same circadian phase 24 h after a sleep-deprivation episode [38]. This does not preclude the possibility that with greater amounts of sleep deprivation the thermoregulatory system will remain independent of sleep pressure.

As found in earlier studies [31,40], proximal skin temperature exhibited a circadian profile similar to CBT, whereas distal

skin temperature showed an inverse and phase advanced circadian pattern. As previously noted [38], the falling limb of the CBT rhythm in the evening is steeper than the rising limb in the morning. Similarly, the rising limb of the distal skin temperature (DIST) rhythm in the evening is also steeper (Fig. 3) than the falling limb in the morning. This indicates an asymmetrical regulation of heat loss and heat production in the evening and morning. Heat loss seems to be dominant in the evening, heat production in the morning [31,38].

We can also define the temporal relationship between the circadian rhythm of sleepiness and the thermoregulatory system. Sleepiness was significantly phase delayed by approximately 100 min with respect to the rhythms of DIST, and phase locked to the CBT rhythm with a negative correlation coefficient [51]. Since the circadian rhythm of DIST precedes both sleepiness and CBT, this could be the reason why DIST is a better predictor for sleepiness (and hence for sleep onset latency) than CBT [54,55]. Interestingly, sleepiness shows not only a close phase relationship to DIST and CBT but also a similar asymmetrical circadian pattern, with a faster rise in the evening than decline in the morning [51]. All these circadian phase relationships are similar in both protocols (high and low sleep pressure) and therefore independent of the sleep–wake cycle [51].

The phase relationship between the circadian rhythm of DIST and CBT may also provide a thermophysiological explanation of the so-called "wake maintenance zone" in the evening just before endogenous melatonin secretion and distal vasodilatation begin [43]. At this circadian phase the circadian system counter-regulates with high effort the homeostatically increased sleepiness and sleep pressure to maintain wakefulness [44]. In thermophysiological terms, the "wake maintenance zone" can be characterized as the most vasoconstricted state of distal skin regions in relation to CBT over the entire circadian cycle (i.e. low inner heat conductance with high CBT and low DIST) [34,56]. This can be seen at mean clock time around 20.00–21.00 h when CBT is at its maximum and distal skin temperature is at its minimum (Fig. 3). Sleepiness rises thereafter when distal skin temperature increases and CBT starts to decline.

5. Influence of sleep on the thermoregulatory system

The analysis of nocturnal recovery sleep after 40 h of sleep deprivation provided conclusive evidence that the increased SWA (particularly during the first 4 h) resulting from increased sleep pressure does not influence the thermoregulatory system (Fig. 3). Previous studies had claimed that high SWA has effects on the thermoregulatory system or even a thermoregulatory role [57–60], e.g. down-regulation of CBT for energy conservation. Others found the inverse, a relative increase of CBT during recovery sleep after a 40-h CR [61]. Unfortunately, none of these experiments used posture-controlled protocols. Our nap vs. sleep-deprivation protocol allowed not only comparisons between baseline and recovery sleeps following a complete 40-h CR with a controlled body position, but also a comparison of the recovery sleep following conditions of relative high (sleep-deprivation protocol) vs. low (nap protocol) sleep pressure [51]. This latter comparison controls for any possible confounding effect of the long period of 56 h lying in bed on the influence of SWA and on thermoregulation. In comparison to the nap protocol recovery sleep after a 40-h CR protocol shows a clear increase of SWA, most pronounced at the beginning of the sleep episode (Fig. 1). In contrast, the thermoregulatory system remains unaffected as seen by no differences in CBT and skin temperatures between these two conditions.

Furthermore, when we compare the thermoregulatory system during an 8-h sleep episode with an 8-h wake episode at the same circadian phase, we find differences in the thermoregulatory system; CBT is reduced during a sleep episode [13,62]. This so-called sleep-evoked effect on CBT has been replicated in several studies, also under controlled CR conditions before the nocturnal sleep episode (CBT-reduction of 0.3 °C during an 8 h night sleep episode) [63]. Is this reduction of CBT really induced by sleep *per se*? In order to dissect out the influence of sleep on the thermoregulatory system (measured not only by CBT, but also by distal and proximal skin temperatures) we analyzed the temperature data associated with the 8-h sleeps before and after the CR (Fig. 3). As described above, proximal skin temperature and CBT declined before lights off, and the distal skin temperature increase was followed by an increase in sleepiness (Fig. 3). After lights off, an additional phenomenon can be observed. Both distal and proximal skin temperatures increased rapidly to a similar level, due to behavioral relaxation-induced withdrawal of the sympathetic tone in pre-capillary muscles (Fig. 3). When sleep is not allowed at this circadian phase (16–24 h after lights on), distal skin temperatures remain about 0.8 °C lower than proximal skin temperatures (Fig. 3). During sleep, however, the core-shell difference is lost completely, as indexed by very similar levels of proximal and distal skin temperatures. However, the increase in skin temperatures after lights off does not lead to efficient heat loss, because cardiac output is decreased in parallel [47,64] — CBT declines very slowly under temperate environmental conditions [47].

In another study [65], data were analyzed before and during a late afternoon nap (lights off between 16.00 and 18.00 h) when the thermoregulatory system is nearly in a steady state (Fig. 4). Data were compared with respect to the time of lights off and with respect to the timing of sleep stage 2 onset. No additional thermoregulatory changes could be observed after beginning of sleep stage 2 (Fig. 4). This analysis of an afternoon nap indicates that a long-lasting redistribution of heat from the core to the shell begins immediately after lights off and *before* the onset of sleep, as found in other studies [47,51,52,64,66–68]. In contrast to previously claimed hypotheses [57–60], slow-wave sleep, which dominantly occurs at the beginning of a sleep episode [14,15] has therefore a minor, if any, thermoregulatory function. The process of relaxation begins before sleep starts — it is not sleep which induces thermoregulatory changes, but rather the relaxation process, preparing for sleep, *per se*. As sleep is a "very relaxed" behavioral state, especially deep sleep, a complete loss of the 'core-shell' principle occurs at this time.

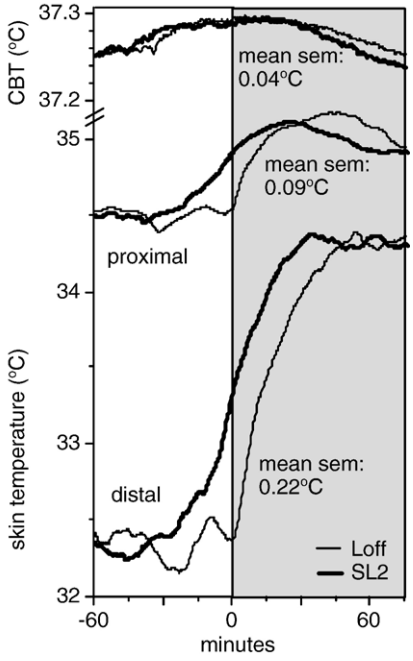

Fig. 4. Thin line: mean time course (20-s intervals; $N=8$ men, 8 women) of core body temperature (CBT) and proximal and distal skin temperatures before and during an afternoon nap (lights off at 16:00 h). Thick line: when the same data are adjusted to onset of sleep stage 2. The vertical line at 0 min indicates the time of lights off or onset of sleep stage 2, respectively. Light phase: <8 lx; dark phase: 0 lx. Note: Both distal and proximal skin temperatures increase immediately after lights off. However, skin temperatures have already increased before the onset of sleep stage 2, indicating an effect of behavioral relaxation immediately after lights off.

Taken together, these findings clearly disprove the long-held belief that sleep or, more precisely, non-REM sleep, causes CBT to decline [57–60]. Since 'lying down' and 'relaxation after lights off' evoke an increase in skin temperatures and a decline in CBT, these major masking effects have confounded prior studies and render their conclusions doubtful. This is not to deny the importance of such masking in real-life conditions, however.

In summary, it is reasonable to assume that the circadian pacemaker drives the circadian propensity for sleep via a circadian rhythm in heat loss (vasodilatation). A similar, but inverse mechanism is responsible for the sleep inertia upon awakening. These thermoregulatory mechanisms underlying circadian sleepiness and sleep inertia are not related to changes in 'homeostatic sleepiness', which results from being awake over longer periods.

6. A thermoregulatory model of sleepiness and sleep

The model (summarized in Fig. 5) represents an attempt to incorporate the above-described findings into the available knowledge of the human thermoregulatory and sleepiness/sleep regulatory systems. This very simplified model consists of four components. At the top, the endogenous self-sustaining circadian pacemaker, localized in the SCN of the hypothalamus, regulates circadian rhythms of a variety of physiological variables including CBT and the timing of sleep and wakefulness and, therefore, of sleepiness and alertness also [10,69–71]. It remains unclear whether the SCN controls the thermoeffector organs (e.g. blood vessel muscles in distal skin regions regulating heat loss) directly or indirectly via the "control center" of the thermoregulatory system (Fig. 5, left box), localized in the POAH [9,10,69–71]. This brain region is known to perform the integration of all information that is perceived via the feedback mechanisms from various thermoreceptors localized in the core and the shell of the body [9,10,69–71]. In order to keep CBT (the controlled variable) constant at a certain level ("set-point"), the POAH sends, as a consequence of the integrative information process, error-signals to the thermoeffector organs. The POAH has been declared the most important brain area for CBT homeostasis [9,10,60,69–71]. It is possible that the circadian modulation of CBT by the SCN could be performed at one of these diverse functional levels of the POAH, changing thereby the thermoregulatory "set-point".

Recently, it has been shown that the thermoregulatory system, as well as the sleep regulatory system, can feed back to the SCN [72], supporting the notion that the SCN belongs to a circadian regulating system, which includes recently discovered peripheral clock mechanisms (for review see [73]). In comparison to the thermoregulatory system, the sleepiness/sleep regulatory system represents a more-or-less "black box" anatomically. It is known that both sleepiness and sleep propensity (as quantified by EEG–SWA) are homeostatically regulated variables [14,15]. They can be considered as the controlled variables of the sleepiness/sleep regulatory system, perhaps regulated by the same "control center" [71]. Furthermore, accumulating sleepiness with elapsed time of wakefulness increases sleep propensity and, during sleep, when SWA decays, sleepiness is also reduced [25]. This inverse relationship (indicated by ± arrows in Fig. 5) has recently been demonstrated to have neurochemical and anatomical correlates in the brain [74]. It has been shown that the control of wakefulness and

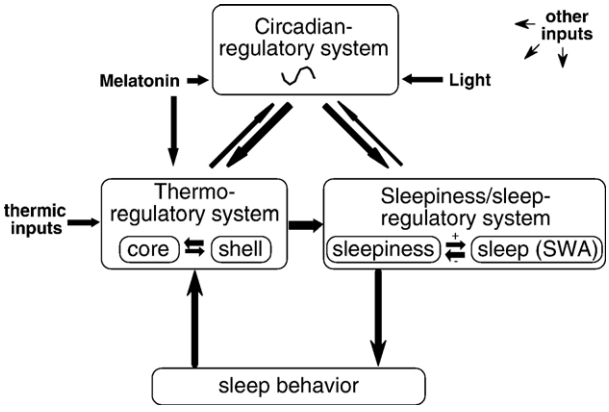

Fig. 5. Schematic illustration of the thermoregulatory model of sleepiness and sleep. Note: The model is based on the main hypothesis that all thermoregulatory effects which lead to an increase in the core/shell ratio (i.e. reduced shell, increased distal skin blood flow and distal skin temperature) should lead to increased sleepiness and, as a consequence, to increased sleep propensity. However, the sleepiness/sleep regulatory system feeds back to the thermoregulatory system only indirectly via sleep-related behaviors (e.g. relaxation, lying down). For more details, see text.

sleep emerges from the interaction of cell groups that cause arousal with other nuclei that induce sleep, such as the ventrolateral-preoptic-nucleus (VLPO) [74]. The VLPO inhibits the ascending arousal regions and is in turn inhibited by them, thus forming a reciprocally inhibitory "flip-flop" switch between awake and sleep [74]. Diverse neurotransmitter systems are involved in this feedback regulation, stabilizing either wake or sleep, e.g. orexin, serotonin, noradrenaline, histamine, GABA, galanin [74,75]. Therefore, the reciprocally inhibitory "flip-flop" switch mechanism needs an additional homeostatic process that accumulates during wakefulness and diminishes during sleep. The nature of the homeostatic drive for sleep is a focus of extensive research [74,76]. The recent finding that, in the basal forebrain, adenosine accumulates during prolonged wakefulness and falls during sleep, suggests a role for adenosine as a local somnogen in this region [74,76,77]. In spite of these promising results, further studies are needed to show whether this is the only mechanism or whether other neurochemical pathways are also involved. However, a more recent study showed that human brain adenosine concentrations are not only dependent on elapsed time awake but also on circadian phase [78].

Although the thermoregulatory and sleepiness/sleep regulatory systems are far from being fully understood, there are indications how they could interact [60,70,71,74,79,80]. Many studies have indicated that POAH regulates not only CBT but also sleep. Local warming of POAH triggers NREM-sleep onset in rats. Sleep, therefore, may be modulated by thermosensitve neurons in the POAH. In support of this hypothesis, warm-sensitive neurons in the POAH increase their discharge during transition from awake to NREM-sleep, starting several seconds before sleep onset (for reviews see [60,70,79]). Heat loss is thought to be initiated by activation of POAH warm-sensitive neurons. Thus activation of POAH warm-sensitive neurons could account for the coupling of sleep onset and of heat loss. Moreover, it could be demonstrated that peripheral thermal stimulation is capable of stimulating warm-sensitive neurons in the POAH, which in turn can promote sleep [60].

What is known about thermophysiological effects induced by sleepiness and sleep? Many studies have indicated a loss of thermoregulatory capacity with increasing sleep depth, most marked during REM-sleep. However, under thermoneutral conditions, in which we usually sleep, this impairment has no thermoregulatory consequences. In contrast to many animal studies, it could be shown that sleep *per se*, defined as the beginning of sleep stage 2, does not induce further thermoregulatory effects (Fig. 4). This view has been strengthened by the finding that increased SWA after sleep deprivation does not influence the thermoregulatory system (Fig. 3). The discrepancies between animal and human studies can either be explained by the circumstances that in animal experiments the masking effects induced by sleep behavior cannot be as strictly controlled as in humans, or that different species with different body size show different coupling between the thermoregulatory and sleep regulatory systems.

Since increased sleepiness, as accumulated during a 40-h sleep deprivation episode, did not have thermoregulatory sequelae (Fig. 3), no arrow can be drawn from the sleepiness/sleep regulatory system to the thermoregulatory system (Fig. 5). However, we do find thermoregulatory changes when we observe the entire sleep episode, including sleep-preparatory behavior. It was postulated some years ago that appetitive behavior preceding sleep is likely to be accompanied by physiological and neurochemical changes that provide a situation which will facilitate the onset of sleep [81] — a sort of "fluffing of the physiological pillow" [7,8]. Many appetitive behavior patterns preceding sleep (bottom box in Fig. 5) are known to promote sleep, but they also influence the thermoregulatory system, such as lying down (Fig. 1), relaxation (Fig. 4) and searching for a comfortable thermal environment — for example: using bed socks, bedcovers and so on [82]; switching lights off (permitting nocturnal melatonin to rise) [55]; suggestion of warmth [83]; autogenic training [84]; warm drinks (Fig. 2;) [48]; biofeedback [85,86]; Kneipp' bedsocks [65]; intake of melatonin [41,87]; and classical sleeping pills [88].

According to the above model, the thermoregulatory system is not directly influenced by the sleepiness/sleep regulatory system; it is the sleep-related behavior which feeds back to the thermoregulatory system and subsequently affects the sleepiness/sleep regulatory system. All these sleep behaviors have a common property — namely, they all increase distal skin blood flow (and distal skin temperature) and increase the 'core/shell' ratio; a withdrawal of the sympathetic nervous system to the skin seems to play a major role in this regulation [47]. Other kinds of thermal input (such as iced water intake; Fig. 2) also change the 'core/shell' ratio and consequently influence the sleepiness/sleep regulatory system. Of course, not everything in this model is new; many of its aspects have already been published in previous reviews [47,60,70,79,80,89]. What is new, however, is that we now have solid documentation of the lack of direct influence of sleep on the thermoregulatory system, in contrast to prior postulates. Future studies will disclose which afferent thermoreceptor systems [90–92] are crucial for sleep promotion, and it can be speculated that in the near future a new generation of selective substances will be developed for treating sleep-onset disturbances.

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