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Thermophysiologic Aspects of the Three-Process-Model of Sleepiness Regulation

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Sleepiness can be defined as a physiologic need for sleep and the behavioral measure of the subject's tendency to fall asleep at a certain time (sleep propensity) [1,2]. Sleepiness, and its converse alertness, are regulated and important determinants of vigilance and performance [3]. A better understanding of the mechanisms regulating sleepiness could lead to new strategies for sleepiness reduction and improved performance. Here we focus on the normal daily regulation of sleepiness and its relation to thermophysiologic processes.

In the last century, Kleitman [4] proposed that body temperature represents the underlying mechanism regulating performance. The speed of thinking and performance depends on the level of metabolic processes in neurons in the cerebral cortex. Raising the speed of performance through an increase in core body temperature (CBT) causes indirect acceleration of thought processes. In studies that have manipulated CBT through external means (eg, altering ambient temperature, cold water immersion), cognitive function improved by increasing CBT slightly above the normal temperature of approximately 37°C, whereas decreasing CBT below normal induced a decline in cognitive function [5–7]. In a forced desynchrony protocol, in which the contributions of circadian phase and time awake can be assessed, a CBT increase of 0.15°C was associated with increased subjective alertness and improved neurobehavioral performance [8]. Alertness and vigilance are a prerequisite for good performance. Thus, when alertness and vigilance are increased as a function of

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warmer CBT, performance is also indirectly improved. Thermoregulation is a complex phenomenon and involves an intimate coupling between the central (core) and peripheral (shell) body compartments that exchange body heat. CBT and skin temperatures often change in parallel, depending on the location where they are measured. This aspect, which is the focus of this article, has not been sufficiently considered in studies dealing with the relationship between thermophysiology, sleepiness, and sleep.

Circadian regulation of the core and the shell

A circadian rhythm of CBT was described in the middle of the nineteenth century, when it was shown that oral temperature followed a daily rhythm that included a maximum temperature in the early evening and a minimum in the early morning hours, with a maximum–minimum range of 0.9°C [9]. For a long time, muscular activity (exercise) and digestive processes were considered the most important factors for the generation of the CBT rhythm [10]. However, Aschoff and his colleagues [11–13] systematically explored the underlying causes and showed that the circadian rhythm of CBT is determined by changes in heat production (measured by indirect calorimetry or indirectly by heart rate [14]) and heat loss. They concluded that heat production undergoes a circadian rhythm that is phase advanced with respect to the circadian rhythm of heat loss (ie, when heat production surpasses heat loss, CBT increases) and that the lag arises because of the body's inertia and because transport of heat takes time. That both heat production and heat loss are regulated results in a much finer tuning of the CBT rhythm than if only one of these components was 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 liver, intestines, kidneys, the heart in the abdominal/thoracic cavity, and the brain, which together produce about 70% of the entire resting metabolic rate of the human body [13]. However, this heat is generated in only 8% 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. In other words, heat has to be transferred from the core to more peripheral parts of the body (ie, the extremities) with better heat transfer conditions [13]. These distal parts of the body have ideal (round) surface shapes, which are good properties for heat transfer to the environment. Under thermoneutral conditions, blood is the main medium for transporting heat from the core to distal skin regions (convectively), driven and distributed by the cardiovascular system. Therefore, in thermophysiologic terms, the human body consists of two compartments: the heat-producing core, and the heat-loss regulating shell [13].

The core (especially the brain) is homeostatically regulated around a set point of about 37°C, whereas the shell is not. Shell temperature depends largely on ambient temperature changes and can be considered poikilothermic, similar

to the body of a lizard. From this point of view, humans have bodies that are homeothermic and poikilothermic. In a hot environment the shell is small; in a cold environment it is large, and thus acts as a buffer to protect the core from dangerous cooling [13]. This regulation occurs very rapidly before CBT has enough time to change. This so-called "feed-forward regulation" [15] with respect to CBT is an important property of the thermophysiologic "core/shell" principle. Another feed-forward regulation serves the counter-current heat exchange in the extremities (ie, legs and arms). In a cold environment, venous blood returns by way of inner blood vessels located near the arteries that prewarm the back-streaming blood, thereby efficiently protecting the core from cooling out [16]. In contrast, in a warm environment the venous blood streams back by way of outer veins near the skin surface, thereby enhancing additional heat loss by way of the lower extremities [16]. Furthermore, it is known that when shunts (ie, arteriovenous anastomoses [AVAs], exclusively found in distal skin regions) between arterioles and venules are open, the blood streams back also by way of these outer veins, thereby enhancing the heat-loss function of opened AVAs [17]. Blood flows more rapidly through AVAs (about 10,000 times more blood volume per second) than through capillary blood flow [17] directly from arterioles to the dermal venous plexus, which enables an efficient heat exchange. All these autonomically regulated mechanisms of shell size occur through constriction or dilatation of blood vessels (arterioles and AVAs) in distal skin regions [17]. There is now substantial evidence indicating that homeostatic control of CBT is mediated by a hierarchically organized set of neuronal mechanisms, with the anterior hypothalamic-preoptic areas at the top of the hierarchy [18]. In addition to the homeostatic principle, a rostral projection from the circadian pacemaker (localized in the suprachiasmatic nuclei [SCN]) to the preoptic areas serves the circadian modulation of CBT [19].

The mechanisms for changing shell size according to changing ambient temperature also take place over 24 hours when the underlying endogenous circadian CBT rhythm is regulated under constant ambient temperature. Distal skin temperature rises in the evening, whereas heat production [14], proximal skin temperature, and CBT decline; in the morning the inverse occurs [14], as is described later. A crucial role for the circadian regulation of heat loss is played by the nocturnally secreted pineal hormone melatonin. Melatonin selectively augments distal skin blood flow, most likely through opening AVAs, either by central or peripheral mechanisms (or both), while leaving proximal skin blood flow and cerebral blood flow unaffected [20]. Until now, no direct evidence exists for the existence of melatonin receptors (Mt1 or Mt2) in distal blood vessels in humans. Melatonin initiates not only distal vasodilatation but also sleepiness, acting therefore as the hormonal trigger between body heat loss and induction of sleep in the evening (opening of the sleep gate) [21–25].

The following sections will discuss the relationship between thermophysiology, sleepiness, and sleep, as elucidated in a series of studies performed under constant routine conditions. This protocol provided the necessary controlled environmental conditions to study the relationship between thermoregulation,

sleepiness, and sleep [14,26] whereby external influences (“masking effects”) are minimized (eg, constant room temperature, 22°C; humidity, 60%; light, less than 8 lux; constant bed rest in supine body position; no sleep allowed; food and fluid intake in small isocaloric portions at hourly intervals).

Sleepiness in relation to skin temperatures and core body temperature

Three major processes are involved in the daily time course of sleepiness (Fig. 1). First, there is a homeostatic increase of sleepiness (process H) dependent on time spent awake which dissipates during sleep [27,28]. Neither the central localization nor the neurobiologic mechanisms of the sleepiness/sleep homeostat have been discovered. Second, a circadian process (C), driven by the circadian pacemaker in the SCN, produces a maximal drive for sleepiness during the subjective night in all diurnal species [27,28] and an alerting signal during the subjective day. Third, a process of sleep inertia (I) describes the

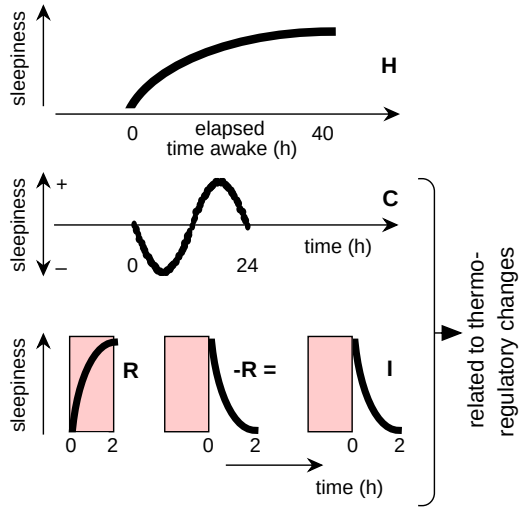

Fig. 1. Schematic illustration of the three-process model of sleepiness regulation. Process H represents the homeostatic component of sleepiness which increases with time elapsed awake, regulated by a sleep homeostat. H describes an exponential curve. The circadian component of sleepiness (C) is driven by the SCN producing a waking signal (-) during the subjective day and a sleepiness signal (+) during the subjective night. The sleep inertia process (I) describes a fast process that is active immediately after sleep and disappears in the following 1 to 2 hours in an exponential manner (gray area represents previous sleep duration). The exponential process R describes a relaxation-induced sleepiness, which starts immediately after lights-off or lying down (*gray area*). -R represents the inverse process of R occurring after lights-on or standing up (therefore, -R = I). Note: Processes C, R, and -R (I) are coupled with thermophysiologic changes (distal vasodilatation), whereas H is not coupled.

phenomenon of low vigilance on awakening even though sleepiness should be lowest at the end of a sleep episode [29,30]. The underlying neurobiologic and physiologic mechanisms for sleep inertia are unknown. All three processes have been mathematically described by the three-process model for sleepiness [29,31], which is a further development of the two-process model of sleep regulation [27,28].

The relationship between sleep and thermoregulation is tightly coupled to the question: "Why do we sleep?" From a thermophysiologic point of view, the proposed answer has been: "We sleep to conserve energy." This answer was derived from the observation that all living organisms, whether nocturnal or diurnal, sleep or rest when their metabolism (heat production) is low. However, this statement does not seem to be true, at least not for humans. In the past, one important observation had not been taken into account: not only did heat production decline in the evening, but also changes in heat loss occur via accelerated distal skin blood flow. Thus, the relationship between thermophysiology and sleep is rather the opposite: we sleep at times when distal skin blood flow starts to increase. The following summary of our studies concerning thermophysiology, sleepiness, and sleep deals with the question: "How are the three processes involved in sleep regulation related to thermophysiologic changes?"

Circadian and homeostatic aspects of sleepiness and its relation to changes in body temperatures

Numerous studies have indicated that the circadian profile of subjective and objective sleepiness is a mirror image of the endogenous CBT rhythm, with maximum sleepiness occurring around the CBT minimum [7]. From a homeostatic perspective, sleepiness should increase steadily with increased elapsed time awake; however, this is not the case. In the evening humans are often in a productive and alert state, especially evening chronotypes. From a homeostatic point of view this is a paradoxical phenomenon, explained by the fact that the circadian drive for alertness from the SCN is at its maximum right before humans usually fall asleep, thereby counteracting the homeostatic drive for sleep in the evening [32–34]. This so-called "wake maintenance zone" (or "forbidden zone to sleep") occurs at the circadian phase where the inner heat conductance is at its minimum: distal vasoconstriction is high in spite of the elevated CBT. Thus, the sleepiness/sleep homeostat interacts with the circadian clock in an additive or nonadditive way (which is still a matter of debate [35]), and determines the actual state of an individual's sleepiness. Usually humans choose their bedtimes shortly after the SCN-alerting signal has declined and the "sleep gate" has been opened [25], which occurs at the time of the maximum decline rate of CBT and the maximum increase rate of body heat loss [24].

Fig. 2 shows the results of a constant routine study illustrating circadian and homeostatic aspects of sleepiness together with the circadian patterns of CBT, distal, and proximal skin temperatures [14]. To illustrate the homeostatic component of sleepiness, an exponential curve (H) has been added to the

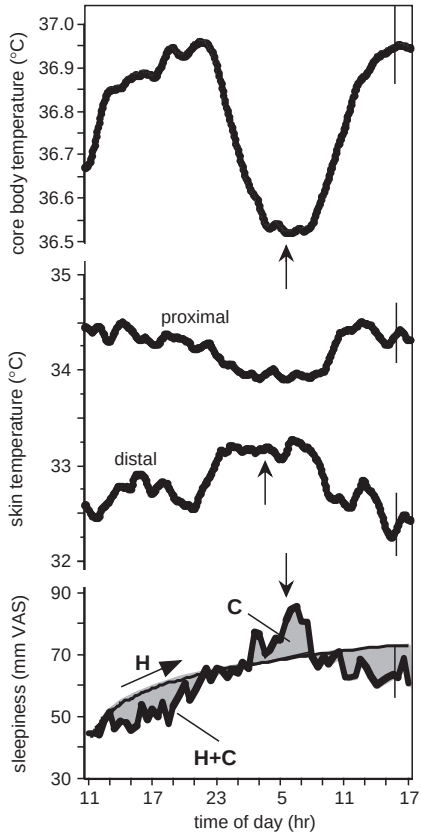

Fig. 2. Mean time course of CBT (rectal) and skin temperatures are shown in addition to subjective ratings of sleepiness (100 mm visual analog scale [VAS]). Seven men were studied in a constant routine protocol for 35 hours (sleep not allowed). Proximal indicates weighted mean of following skin regions: infraclavicular, stomach, forehead, and thigh, and distal indicates mean of hands and feet. The vertical bar at the right of the curves indicates plus and minus averaged SEM of all time points. To emphasize the homeostatic rise of sleepiness, an exponential curve (*thick line H*) has been added. The residuals (*gray areas*) indicate the circadian component C. Vertical arrows indicate circadian phase positions of the parameters derived from the mean of up- and downwards midrange crossing values. Note: The circadian rhythm of sleepiness is in phase with CBT; both are phase delayed compared with distal skin temperature. (*Data from* Kräuchi K, Wirz-Justice A. Circadian rhythm of heat production, heart rate, and skin and core body temperature under unmasking conditions in men. Am J Physiol 1994;267:R819–26.)

original subjective sleepiness rating (H + C). The residuals (C) describe the underlying circadian component of sleepiness (*gray areas*). The circadian regulation of sleepiness is in phase with CBT and phase delayed with respect to distal skin temperature, confirming other studies [36]. The fact that sleepiness is phase delayed relative to distal skin temperature explains the finding that increased distal skin temperature before nocturnal sleep is a better predictor for

short sleep-onset latency than the decline in CBT [26,37]. Therefore, the circadian component of sleepiness is related to thermophysiologic changes most closely coupled to distal skin vasodilatation. Interestingly, beside their circadian time courses, CBT, distal, and proximal skin temperatures are not changed in the course of a 35-hour sleep deprivation, indicating no or very small influence of increased sleep pressure (process H) on the thermophysiologic system during constant routine conditions. Thus, the thermostat seems to be sleep-pressure compensated or independent of the sleep homeostat. This phenomenon can be explained by two counteracting processes, resulting in no effect on the thermoregulatory system. That is, with increasing elapsed time awake, distal vasodilatation should also increase when sleepiness increases. However, to stay awake, distal vasoconstriction is induced, counteracting the former process and resulting in no changes.

Influence of sleep on the thermoregulatory system

Very early studies concluded that when subjects remained still and quiet in bed, neither sleep nor waking affected CBT [38]. However, more recent studies found a reduction of CBT during a nocturnal sleep episode [38]. This so-called "sleep evoked effect" on CBT has been replicated in several studies, also under constant routine conditions (CBT reduction of 0.3°C during an 8-hour night sleep episode) [39]. However, is this reduction of CBT really induced by sleep per se? To separate the true influence of sleep on the thermoregulatory system from behavioral changes related to sleep (eg, lying down, relaxation) we performed a constant routine for many hours before the start of a nocturnal sleep episode [26]. As described previously, proximal skin temperature and CBT decline before lights off, and the distal skin temperature increase was followed by an increase in sleepiness (Fig. 3a). After lights off, an additional phenomenon can be observed: distal and proximal skin temperatures increase rapidly to a similar level because of relaxation-induced withdrawal of the sympathetic vasoconstrictor tonus in precapillary muscles (see Fig. 3a).

When sleep is not allowed at this circadian phase, distal skin temperatures remain about 0.8°C lower than proximal skin temperatures (see Fig. 2). 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 [40]; CBT declines very slowly under normal environmental conditions [13]. When the data were adjusted with respect to the timing of sleep stage 2 onset, no additional thermoregulatory changes occur thereafter (Fig. 3b) [41]. This analysis indicated that a long-lasting redistribution of heat from the core to the shell begins immediately after lights-off before the onset of sleep [41,42]. In contrast to a previously claimed hypothesis [43,44], slow-wave sleep, which dominantly occurs at the beginning of a sleep episode [27,28] has therefore minor, if any, thermoregulatory functions. Taken together, the process of relaxation (R) begins immediately after

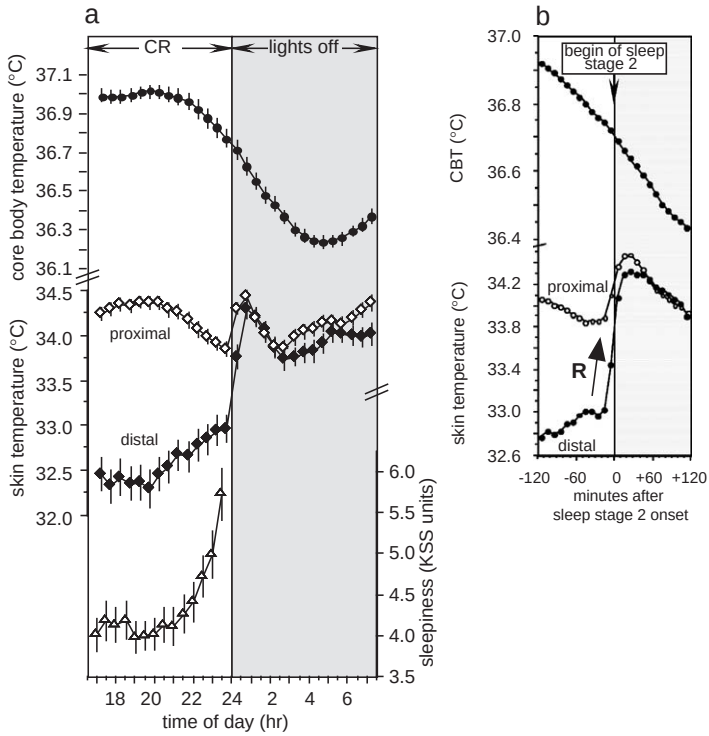

Fig. 3. (*a*) Mean curves (± SEM; N = 18 men) of CBT, skin temperatures, and subjective ratings of sleepiness before and during nocturnal sleep aligned to lights-off. Note: Distal and proximal skin temperatures show an inverse time course before lights-off, but increase in parallel to a similar level thereafter. (*Data from* Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. Functional link between distal vasodilation and sleep-onset latency? Am J Physiol 2000;278:R741–8.) (*b*) Mean time courses of CBT and skin temperatures (N = 36 men), adjusted to onset of sleep stage 2. Note: skin temperatures have already increased before sleep stage 2 onset, indicating a relaxation-induced effect (R). KSS, Karolinska sleepiness scale. (*Data from* Kräuchi K, Cajochen C, Werth E, et al. Thermoregulatory changes begin after lights off and not after onset of sleep stages 2. Sleep 2001;24:165–6.)

lights-off before sleep starts; it is not sleep that induces thermoregulatory changes but rather the relaxation process per se. Because sleep is a very relaxed state, especially deep sleep, a complete loss of the core/shell principle occurs at this time. Therefore, a logical question is: "What happens to the core/shell principle after waking up from a sleep episode?"

Sleep inertia is related to thermoregulatory after-effects of relaxation

To answer that question we analyzed data of a controlled constant routine study 2 hours before, during, and 2 hours following an afternoon nap from 16 to18 hours (Fig. 4) [45]. This circadian phase around the CBT maximum was chosen to separate thermophysiologic changes induced during and after a

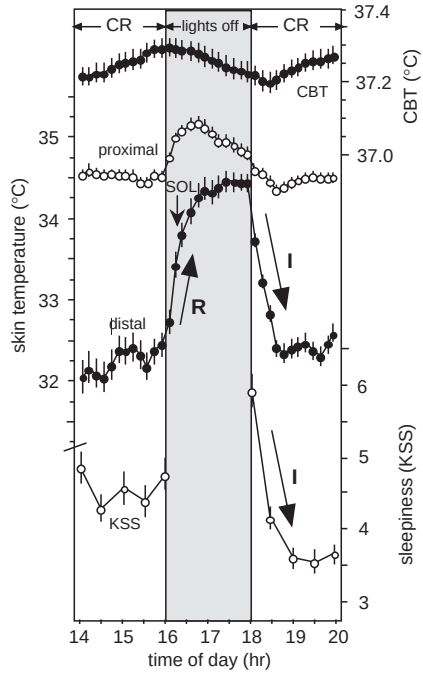

Fig. 4. Mean curves (± SEM; N = 8 men and 8 women) of CBT, skin, and subjective ratings of sleepiness 2 hours before, during, and after a nap between 4 PM and 6 PM. Note: Subjective ratings of sleepiness and distal skin temperatures showed a similar time course after lights on. -R equals I. KSS, Karolinska sleepiness scale; SOL, sleep stage 2 onset. (*Data from* Kräuchi K, Brunner DP, Cajochen C, et al. Time course or rectal temperature and heart rate during baseline and recovery sleep. J Sleep Res 1994;3(Suppl.1):132.)

sleep episode from the endogenous circadian thermoregulatory changes in the evening. However, very similar results were also found after a nocturnal 8-hour sleep episode (see Fig. 3) [26] with the confounding circadian changes in thermophysiology. In both experiments, immediately after lights-off, distal and proximal skin temperatures increased rapidly (before onset of sleep stage 2) to nearly a similar level at the end of the nap, whereas CBT declined marginally and slowly (see Fig. 4).

Proximal skin temperature peaked 50 minutes after lights-off, distal skin temperature later at the end of the nap, and CBT declined slowly to reach its lowest value (−0.08°C) 30 minutes after lights-on. Sleepiness ratings were highest in the first assessment right after lights-on and declined thereafter within about 1 hour, very similar to the time course of distal skin temperature. Proximal skin temperature declined after the maximum within the nap and reached its lowest value 40 minutes after lights-on. The distal skin temperature and sleepiness ratings declined after lights-on could be fitted to an exponential ‘‘cooling-out’’ function with a similar time constant. This indicates a close

temporal association between subjective sleepiness ratings and distal vasodilatation after lights-on. Sleep inertia on waking showed a similar rate of dissipation to the cooling-out rate of the extremities, which had been warmed up by the redistribution of blood during the dark period. Thus, as the readiness to fall asleep is correlated with distal vasodilatation, so is the waking-up process (or disappearance of sleep inertia) correlated with distal vasoconstriction. Taken together, the symmetry between the thermoregulatory processes initiating sleepiness [26,37] and those dissipating it is striking and provide a physiologic rationale for a "power nap" being short: redistribution of blood to the extremities is incomplete after less than 20 minutes of scheduled sleep or relaxation. 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 rapidly increase distal vasoconstriction and, in turn, alertness. In the following section the simple behavior of lying down to go to sleep will be revisited from a thermophysiologic point of view.

Lying down-induced sleepiness is related to relaxation-induced effects

A further relaxation effect can be induced by changes in body position (eg, from upright to a supine position). We have shown that distal and proximal skin temperatures increase rapidly after lying down, together with increased sleepiness ratings and decreased CBT (Fig. 5a) [46]. The opposite pattern was found in another study after a change from supine to upright body position (Fig. 5b) [46]. Here again, distal and proximal skin temperatures change in the same direction as during and after a sleep episode, indicating that relaxation-induced sleepiness may be differently regulated by the thermostat than by the circadian process of sleepiness, where distal and proximal skin temperatures show inverse patterns.

Changes in distal skin temperatures seem to be the crucial thermophysiologic correlate for relaxation-induced sleepiness, and not the decrease in CBT or changes in proximal skin temperature. The same conclusion can be drawn from experiments involving eating ice (200 g), where CBT and distal skin temperature decline and sleepiness decreases [47]. Thus, it is the increase in distal skin temperature that is associated with an increase in sleepiness, whereas the decrease in distal skin temperature is associated with a decrease in sleepiness (ie, alerting effect). This leads to the question: "Which mechanisms are involved in the coupling between distal vasodilatation and sleepiness induction?"

Putative mechanisms involved in coupling sleepiness and distal vasodilatation

Changes in acral skin blood flow are easily demonstrable by distal skin temperature, most prominently in fingertips, and are a commonly used indicator for sympathetic reflex responses to various stimuli. However, skin temperatures are a function of inner and outer heat transport and transfer conditions, leading

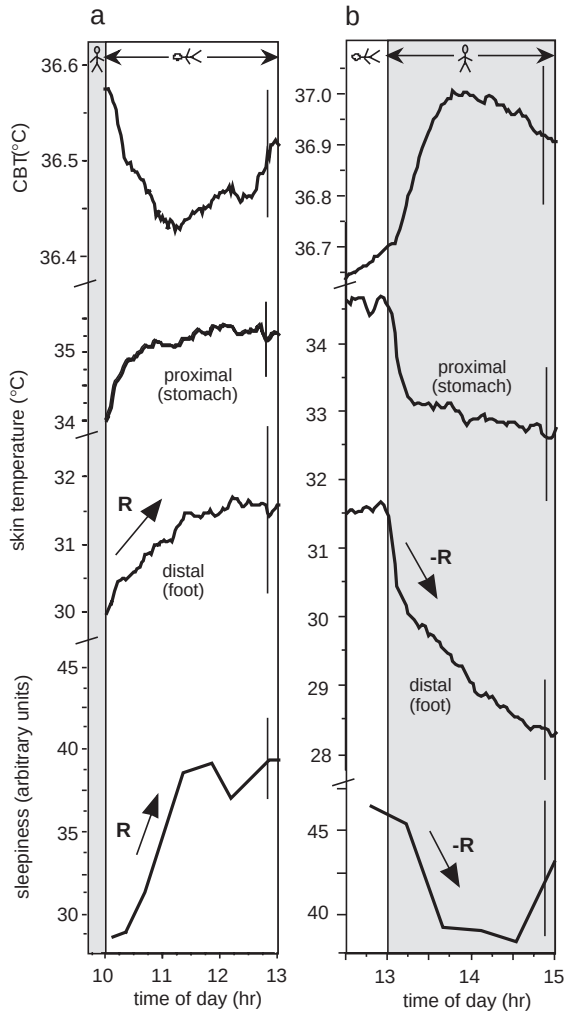

Fig. 5. (*a*) Mean curves (N = 8 men) of CBT, skin temperatures, and subjective ratings of sleepiness immediately after lying down from an upright position. The vertical bar at the right of the curves indicates plus and minus averaged SEM of all time points. Note: Distal and proximal skin temperatures increased together with subjective ratings of sleepiness. (*b*) Mean curves (N = 9 men) of CBT, skin temperatures, and subjective ratings of sleepiness after standing up from a supine position. The vertical bar at the right of the curves indicates plus and minus averaged SEM of all time points. Note: Distal and proximal skin temperatures decreased together with subjective ratings of sleepiness. (*Data from* Kräuchi K, Cajochen C, Wirz-Justice A. A relationship between heat loss and sleepiness: effects of postural change and melatonin administration. J Appl Physiol 1997;83:134–9; and Kräuchi K, Werth E, Wüst D, et al. Interaction of melatonin with core body cooling: sleepiness is primarily associated with heat loss and not with a decrease in core temperature. Sleep 1999; 22(Suppl 1):285–6.)

to a nonlinear relationship between skin blood flow and skin temperature; only a certain range of blood flow skin temperatures can be used as a good indicator for skin blood flow [13]. In many studies, the relationship between distal skin blood flow and sleepiness has been challenged by diverse interventions [48]. For example, distal skin temperature can be strongly affected during hypnosis, when images used for suggesting cold and warmth include experiences of physical temperature and physiologic stress or relaxation [49]. Furthermore, thermal biofeedback training in raising hand temperature increases not only finger-skin temperature [50] but also promotes a rapid sleep onset [51]. Therefore, sympathetic nerve activity seems to be the most important mechanism determining blood flow through arterioles by way of adrenergic constrictor nerves, and is also a good indicator for the arousal system. There is now emerging evidence from physiologic and neuroanatomic studies to indicate that changes in body temperatures may trigger somnogenic brain areas (eg, medial preoptic area [52], ventrolateral preoptic area [53]) to initiate sleep, either indirectly through nerve afferents activated by cold and warm receptors located in the dermis and in the core, or directly through changes in core blood temperature leading to changed spinal cord and brain temperatures [54]. However, the interrelationship between thermoregulatory and sleepiness/sleep regulatory mechanisms is rather complex. Recent studies have indicated that the medial preoptic area controls sleep and temperature through independent, but overlapping, neuronal circuits [53,55,56]. However, the disadvantage of these animal studies is that the behavior of an animal cannot be independently controlled for sleep, which is crucial to separate the influence of the three components of sleepiness regulation (C, H, and I). There is good reason to believe that future studies in humans using imaging techniques (eg, functional MRI) will shed more light on how thermoregulatory and sleepiness/sleep regulatory mechanisms are related in the human brain.

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References

[1] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(6):540–5.
[2] Åkerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. Intern J Neurosci 1990;52:29–37.
[3] Folkard S, Åkerstedt T. Trends in the risk of accidents and injuries and their implications for models of fatigue and performance. Aviat Space Environ Med 2004;75(3 Suppl):A161–7.
[4] Kleitman N. Sleep and Wakefulness. Chicago: The University of Chicago Press; 1987.

[5] Coleshaw SR, van Someren RN, Wolff AH, et al. Impaired memory registration and speed of reasoning caused by low body temperature. J Appl Physiol 1983;55:27–31.
[6] Giesbrecht GG, Arnett JL, Vela E, et al. Effect of task complexity on mental performance during immersion hypothermia. Aviat Space Environ Med 1993;64:206–11.
[7] Johnson MP, Duffy JF, Dijk DJ, et al. Short-term memory, alertness and performance: a reappraisal of their relationship to body temperature. J Sleep Res 1992;1:24–9.
[8] Wright Jr KP, Hull JT, Czeisler CA. Relationship between alertness, performance, and body temperature in humans. Am J Physiol Regul Integr Comp Physiol 2002;283:R1370–7.
[9] Gierse A. Quaeniam sit ratio caloris organici [MD Thesis] [What is the cause of organic heat?]. Halle; 1842 [in German].
[10] Hardy JD. Physiology of temperature regulation. Physiol Rev 1961;41:521–606.
[11] Aschoff J. The circadian rhythm of body temperature as a function of body size. In: Taylor R, Johanson K, Bolis L, editors. A Comparison to animal physiology. Cambridge, England: Cambridge Univ Press; 1982. p. 173–89.
[12] Aschoff J, Heise A. Thermal conductance in man: its dependence on time of day and of ambient temperature. In: Itoh S, Ogata K, Yoshimura H, editors. Advances in climatic physiology. Tokyo: Igako Shoin; 1972. p. 334–48.
[13] Aschoff J. Temperaturregulation. In: Gauer OH, Kramer K, Jung R, editors. Energiehaushalt und Temperaturregulation [Energy budget and temperature regulation]. Physiologie des Menschen. München: Urban & Schwarzenberg; 1971. p. 43–112 [in German].
[14] Kräuchi K, Wirz-Justice A. Circadian rhythm of heat production, heart rate, and skin and core body temperature under unmasking conditions in men. Am J Physiol 1994;267:R819–26.
[15] Mrosovsky N. Rheostasis. The physiology of change. New York: Oxford University Press; 1990.
[16] Aschoff J, Wever R. Kern und Schale im Wärmehaushalt des Menschen [Core and shell in human energy budget]. Naturwissenschaften 1958;45:477–85 [in German].
[17] Hales JRS. Skin arteriovenous anastomoses, their control and role in thermoregulation. In: Johansen K, Burggren WW, editors. Cardiovascular shunts. Alfred Benzon Symposium 21. Copenhagen, Denmark: Munksgaard; 1985. p. 433–51.
[18] Satinoff E. Neural organization and evolution of thermal regulation in mammals. Science 1978;201:16–22.
[19] Moore RY, Danchenko RL. Paraventricular-subparaventricular hypothalamic lesions selectively affect circadian function. Chronobiol Int 2002;19:345–60.
[20] van der Helm - Van Mil AH, van Someren EJ, van den Boom R, et al. No influence of melatonin on cerebral blood flow in humans. J Clin Endocrinol Metabol 2003;88:5989–94.
[21] Cajochen C, Kräuchi K, von Arx MA, et al. Daytime melatonin administration enhances sleepiness and theta/alpha activity in the waking EEG. Neurosci Lett 1996;207:209–13.
[22] Cagnacci A, Kräuchi K, Wirz-Justice A, et al. Homeostatic versus circadian effects of melatonin on core body temperature in humans. J Biol Rhythms 1997;12:509–17.
[23] Cajochen C, Kräuchi K, Wirz-Justice A. Role of melatonin in the regulation of human circadian rhythms and sleep. J Neuroendocrinol 2003;15:432–7.
[24] Campbell SS, Broughton RJ. Rapid decline in body temperature before sleep: fluffing the physiological pillow? Chronobiol Int 1994;11:126–31.
[25] Lavie P. Melatonin: role in gating nocturnal rise in sleep propensity. J Biol Rhythms 1997; 12(6):657–65.
[26] Kräuchi K, Cajochen C, Werth E, et al. Functional link between distal vasodilation and sleep-onset latency? Am J Physiol Regul Integr Comp Physiol 2000;278:R741–8.
[27] Daan S, Beersma DG, Borbély AA. Timing of human sleep: recovery process gated by a circadian pacemaker. Am J Physiol 1984;246:R161–83.
[28] Borbély AA. A two-process model of sleep regulation. Hum Neurobiol 1982;1:195–204.
[29] Åkerstedt T, Folkard S. A model of human sleepiness. In: Horne J, editor. Sleep '90. Bochum, Germany: Pontenagel Press; 1990. p. 310–3.
[30] Dinges DF. Are you awake? Cognitive performance and reverie during the hypnotic state. In: Bootzin R, Kihlstrom J, Schachter D, editors. Are you awake? Washington, DC: American Psychological Association; 1990. p. 159–75.

[31] Folkard S, Åkerstedt T. A three-process model of the regulation of alertness-sleepiness. In: Broughton RJ, Ogilvie RD, editors. Sleep, arousal, and performance. Boston: Birkhäuser; 1992. p. 11–26.
[32] Dijk DJ, Duffy JF, Czeisler CA. Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. J Sleep Res 1992;1:112–7.
[33] Ebbecke U. Schüttelfrost in Kälte, Fieber und Affekt. Klin Wochenschr 1948;39/40(15.Okt.):609–13.
[34] Edgar DM, Dement WC, Fuller CA. Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. J Neurosci 1993;13(3):1065–79.
[35] Achermann P, Borbely AA. Mathematical models of sleep regulation. Front Biosci 2003;8:s683–93.
[36] Gradisar M, Lack L. Relationships between the circadian rhythms of finger temperature, core temperature, sleep latency, and subjective sleepiness. J Biol Rhythms 2004;19(2):157–63.
[37] Kräuchi K, Cajochen C, Werth E, et al. Warm feet promote the rapid onset of sleep. Nature 1999;401:36–7.
[38] Aschoff J. Circadian control of body temperature. J Therm Biol 1983;8:143–7.
[39] Barrett J, Lack L, Morris M. The sleep-evoked decrease of body temperature. Sleep 1993;16:93–9.
[40] Somers VK, Dyken ME, Mark AL, et al. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med 1993;328(5):303–7.
[41] Kräuchi K, Cajochen C, Werth E, et al. Thermoregulatory changes begin after lights off and not after onset of sleep stage 2. Sleep 2001;24(Abstr Suppl):165–6.
[42] Lack L, Gradisar M. Acute finger temperature changes preceding sleep onsets over a 45-h period. J Sleep Res 2002;11(4):275–82.
[43] Sewitch DE. Slow wave sleep deficiency insomnia: a problem in thermo-downregulation at sleep onset. Psychophysiol 1987;24(2):200–15.
[44] McGinty D, Szymusiak R. Keeping cool: a hypothesis about the mechanisms and functions of slow-wave sleep. Trends Neurosci 1990;13(12):480–7.
[45] Kräuchi K, Cajochen C, Wirz-Justice A. Waking up properly: is there a role of thermoregulation in sleep inertia? J Sleep Res 2004;13:121–7.
[46] Kräuchi K, Cajochen C, Wirz-Justice A. A relationship between heat loss and sleepiness: effects of postural change and melatonin administration. J Appl Physiol 1997;83:134–9.
[47] Kräuchi K, Werth E, Wüst D, et al. Interaction of melatonin with core body cooling: sleepiness is primarily associated with heat loss and not with a decrease in core temperature. Sleep 1999;22(Suppl 1):285–6.
[48] van Someren EJW. Sleep propensity is modulated by circadian and behavior-induced changes in cutaneous temperature. J Therm Biol 2004;29:437–44.
[49] Kistler A, Mariauzouls C, Wyler F, et al. Autonomic responses to suggestions for cold and warmth in hypnosis. Forsch Komplementärmed 1999;6:10–4.
[50] Freedman RR, Morris M, Norton DA, et al. Physiological mechanism of digital vasoconstriction training. Biofeedback Self Regul 1988;13(4):299–305.
[51] Lushington K, Greeneklee H, Veltmeyer M, et al. Biofeedback training in hand temperature raising promotes sleep onset in young normals. J Sleep Res 2004;13(Suppl 1):460.
[52] Szymusiak R, Steininger T, Alam N, et al. Preoptic area sleep-regulating mechanisms. Arch Ital Biol 2001;139(1–2):77–92.
[53] Saper CB. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. Annu Rev Neurosci 2002;25:433–69.
[54] van Someren EJ. More than a marker: interaction between circadian regulation of temperature and sleep, age-related changes, and treatment possibilities. Chronobiol Int 2000;17:313–54.
[55] van Someren EJ, Raymann RJ, Scherder EJ, et al. Circadian and age-related modulation of thermoreception and temperature regulation: mechanisms and functional implications. Ageing Res Rev 2002;1:721–78.
[56] Kumar VM. Body temperature and sleep: Are they controlled by the same mechanism? Sleep Biol Rhythms 2004;2:103–24.