Sleep Medicine Reviews (2007) **11**, 439–451

SLEEP MEDICINE reviews

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PHYSIOLOGICAL REVIEW

The thermophysiological cascade leading to sleep initiation in relation to phase of entrainment ☆

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KEYWORDS
Sleep induction;
Heat loss;
Heat production;
Temperature regulation;
Phase of entrainment;
Vasospastic syndrome;
Sleep onset insomnia;
Circadian rhythm

Summary This article reviews circadian thermoregulation in relation to sleep induction and phase of entrainment in the light of the comprehensive thermophysiological and chronobiological concepts of Jürgen Aschoff. The idea that temperature and sleep are interrelated is based on evolutionary history. Mammalian sleep developed in association with endothermy, and all species, independent of temporal niche, usually sleep during the circadian trough of their core body temperature (CBT) rhythm. The circadian pattern of CBT results from the balance between heat production and heat loss, the latter being relevant for sleep induction. Sleep under entrained conditions is typically initiated on the declining portion of the CBT curve when its rate of change and body heat loss is maximal. Body heat loss before lights off, via selective vasodilatation of distal skin regions, promotes sleepiness and the rapid onset of sleep. This thermophysiological effect represents the cement between the circadian clock and the sleep–wake cycle, and in turn determines phase of entrainment (Ψ) and sleep onset latency (SOL). These interrelationships have been recently studied in a particular subset of the general population, mainly women, who suffer from cold hands and feet (the so-called vasospastic syndrome, VS). Women with VS exhibit not only a lower capacity to lose heat during the daytime but also a prolonged SOL, a disturbed Ψ of the circadian clock with respect to the sleep–wake cycle and psychologically, a disposition to turn experienced anger inwards. This naturalistic model leads us to a more general conclusion that regulation of distal skin blood flow may have clinical relevance for insomnia, in particular sleep onset insomnia.

Introduction

The notion that thermoregulation and sleep are interrelated is based on the theory of evolution. There was a convergent evolution for REM sleep and endothermy in mammals and birds, indicating that these parallel developments must have

☆Dedicated to Anna Wirz-Justice in recognition of her contributions to the field made during her career at the Psychiatric University Clinics Basel.

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1087-0792/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.smrv.2007.07.001

occurred prior to separation of the emerging mammalian and avian lines.[1–4] Based on these observations, some researchers have even deduced causal relationships between induction of sleep (and Slow-Wave-Activity, SWA) and the reduction of core body temperature (CBT).[5–8] The reduction of CBT, which results in energy conservation due to reduced body metabolism, should be the reason why we sleep. However, there is no causality, at least not in humans. We could recently demonstrate that non-REM-sleep and SWA do not influence the thermoregulatory system.[9–11] Nevertheless, this does not mean that the sleep regulatory system and the thermoregulatory system are independent. A further, rather simple, but not meaningless relationship exists, in that all species, independent of whether nocturnal or diurnal in habit, usually sleep or rest during the circadian trough of their CBT rhythm. This observation offers another, inverse explanation, namely, that we rest and sleep when CBT is reduced after heat has been redistributed from the core to the outer layer of the body, the shell. Therefore, heat redistribution from the core to the shell could represent a crucial signal for sleep initiation. Because these thermoregulatory processes are well known to be modulated in a circadian manner, they could additionally serve as an entrainment mechanism for the sleep–wake cycle. Recent findings suggest that the CBT rhythm has internal non-photic zeitgeber properties for the entrainment of multiple peripheral pacemakers distributed all over the body.[12 (p. 404), 13] Based on this, one could consider that increased distal skin temperature in the evening, via enforced skin blood flow, provides a synchronising signal for peripheral circadian oscillators in the extremities. Thermoregulatory heat loss mechanisms could therefore be relevant for ensuring an appropriate phase relationship between the circadian system and the sleep–wake cycle. An important underlying assumption is that phase of entrainment largely determines normal, undisturbed sleep with the criteria of consolidation (sleep continuity) and short sleep onset latency (SOL).[14–16] An abnormal phase of entrainment could thus be a cause of sleep disturbances.[14–16]

Sleep is not an isolated phenomenon of the brain alone; sleep is also a behaviour involving the entire body.[17,18] A body that is asleep is in the most relaxed state of normal daily life, and this relaxed state in turn influences the thermoregulatory system, i.e., heat is redistributed from the core to the shell and down-regulates CBT to a lower level.[10,19] Usually this occurs in the evening, when we usually go to sleep, leading to a larger difference between the diurnal maximum and nocturnal minimum values of CBT than without sleep.[10,19–24] From a functional point of view, it is possible that such an increase of the overt daily amplitude could contribute to entrain a circadian oscillator.[25–27]

Organisms are active during the day (diurnal), night (nocturnal) or during twilight (crepuscular). Crepuscular animals, birds and insects can be matinal or vespertine, that is active in the morning or evening, respectively. There are two ways in which this can be manifested. First, by the well-known mechanisms of synchronising the endogenous pacemaker (e.g., light acting on the suprachiasmatic nuclei, SCN), which in turn entrains the rest–activity cycle, and second, by a route that does not directly involve the main pacemaker (so-called masking; e.g., activity, food intake).[27,28] The 'masking effect' was first described in experiments with animals.[29] Masking complements clock control as a way of helping organisms specialise in a temporal niche.[26] Masking in the first place obscures the behaviour of the pacemaker but may eventually influence the phase of the pacemaker via more indirect pathways (feedback mechanisms, e.g., via temperature).[13,27,28]

Regulation of circadian phase and phase of entrainment

The temporal structure of our daily life is under the control of three different clocks: the solar clock, providing light and heat during the day; the social clock, which determines our working and free day schedule[16]; and the biological (circadian) clock, which is essential for timing of physiological processes across the 24 h, such as activity and sleep, release of hormones and blood constituents, etc.[30,31] The central circadian clock is localised in the SCN of the hypothalamus; recently described peripheral clocks also belong to the entire "circadian clock system" (hereafter named 'circadian clock').[13,30–32] The circadian clock is entrained to environmental cycles through signals called zeitgebers (e.g., light; heat = temperature).[33–35] Without any zeitgebers the circadian clock 'runs free' with a certain free-running period (τ), which is dependent on prior light history.[34,35] In humans, individual τ's are more or less Gaussian distributed around a mean between 24 and 25 h.[16,34] In real life, however, the circadian clock is usually entrained to the 24-h day of the solar clock, mainly by light exclusively through the eyes to the SCN.[16,30,36,37] Heat as a zeitgeber has not been adequately tested in humans.

Entrainment of any oscillator, from mechanical to biological, works through similar principles.[15] The characteristics of, e.g., light as a zeitgeber depend on the fact that light shifts circadian phase by different amounts and in different directions depending on the timing of light exposure (for review see Ref. [15]). At some circadian phases, the oscillator is delayed and at others it is advanced, or it may not respond at all. These response characteristics, which can be drawn as a phase–response-curve, are dependent on number of additional factors: intensity, wavelength and duration of the light signal, as well as the inherent responsiveness of the circadian clock to the entraining stimulus via the eye. Together, these factors constitute what is called the 'strength of a zeitgeber' (or coupling strength of a zeitgeber to the circadian clock).[15,16,34] With increased strength of the zeitgeber the amplitude of the phase response curve is bigger, i.e., phase shifts are larger.[15,16,34]

Phase of entrainment in relation to sleep disturbances

In the entrained human circadian system under normal daily life situations, CBT exhibits a maximum in the late afternoon, and a minimum towards the end of the sleep episode. This phase relationship between the sleep–wake cycle and the CBT rhythm (phase of entrainment, Ψ) can be changed by means of zeitgebers, e.g., light. In general, Ψ is dependent on how much and in what direction the endogenous τ deviates from the 24-h solar cycle, that is, how much the daily light signal has to advance or delay the circadian clock.[15,16] Another determinant is the strength of the zeitgeber, e.g., the differences in amplitude of day–night light intensity. For example, in subjects with extreme long or short τ the difference in Ψ will become even more extreme when the strength of the zeitgeber is decreased.[16] Furthermore, individual Ψ also can differ because the retinal photoreceptor or phototransduction cascade responds differently, or additionally, because of the way the circadian clock controls its output (e.g., CBT, melatonin secretion, sleep–wake cycle) might be different.[14]

There are two kinds of Ψ which have to be differentiated: *external and internal 'phase of entrainment'*.[15,34] The external phase of entrainment (Ψ_{ext}) defines the phase relationship between the external entraining cycle (e.g., ambient light–dark cycle) to an output of the circadian clock (e.g., to the CBT rhythm, sleep–wake cycle) (for review, Refs. [15,34]). The internal phase of entrainment (Ψ_{int}) defines the phase angle between two outputs of the circadian clock, e.g., sleep onset time and phase of the CBT rhythm (e.g., time of CBT minimum, T_{min}). Figure 1 illustrates the different kinds of phase of entrainment (masking effects of zeitgebers will be explained below). The different thickness of the arrows from the SCN to the outputs CBT and sleep–wake cycle indicates different coupling strength from the circadian clock to the two outputs: strong coupling to CBT and weak coupling to the sleep–wake cycle. This indicates that a shift of the circadian clock does not shift the different Ψ's to a similar extent—the shifts are dependent on the coupling strength of the SCN to the outputs. When we speak of the sleep–wake cycle we usually mean the self-selected dark–light cycle (dark phase = sleep), however, this is not precise enough, it takes a certain time to fall asleep, i.e., SOL. SOL can be defined as Ψ_{int} between lights off and sleep onset. Therefore, it is of importance to separate times of lights off from sleep onset, since both can be differentially influenced.

The functional relevance of Ψ_{int} for sleep disturbances (or for "normal sleep") has been shown in many studies (for review see Refs. [14,16]).

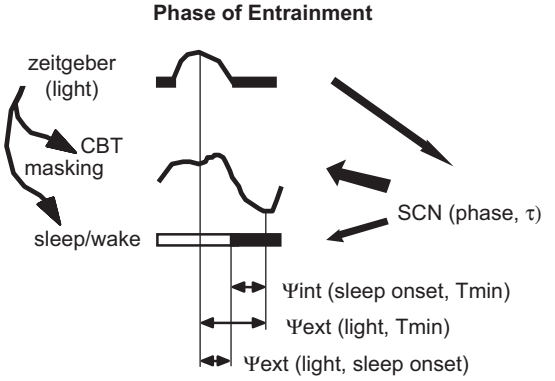

Figure 1 The schematic diagram shows different kinds of phase of entrainment. External phase of entrainment (Ψ_{ext}) indicates the phase angle (horizontal arrows at both ends) between an external zeitgeber rhythm (e.g., light, temperature) and an output rhythm (e.g., CBT, sleep–wake cycle) of the circadian clock (SCN). Internal phase of entrainment (Ψ_{int}) denotes the phase angle between two output rhythms. For example, Ψ_{int} (sleep onset, T_{min}) stands for internal phase of entrainment between the sleep episode (phase marker: sleep onset) and the CBT rhythm (phase marker: T_{min}). Straight arrows represent coupling to and from the circadian pacemaker. The thickness of an arrow indicates the strength of coupling. Shaped arrows symbolise masking effects. For further explanations, see text.

Experiments in which sleep was scheduled to occur at many circadian phases have demonstrated that a consolidated 8-h sleep episode can only be obtained at one specific Ψ_{int}. When the sleep–wake cycle is synchronised 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.[10,21,22] 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 trough advances to the first half of the nocturnal sleep episode.[38] Under these new phase relationships, sleep propensity (the need or pressure for sleep) is maximal close to the temperature minimum, but the tendency to wake-up still clusters on the rising limb of the CBT rhythm.[38] These preferred zones for falling asleep and for waking up have a profound effect on sleep duration—sleep length is maximal (ca.14 h) when sleep is initiated around the CBT maximum.[39] However, only when sleep is initiated ca. 5 h before the temperature minimum will sleep remain virtually uninterrupted for 8 h.[40–42] Additionally, when sleep is initiated at that circadian phase, SOL is also short.[43] Therefore, it can be assumed that Ψ_{int} of the sleep–wake cycle and the thermoregulatory system is a very important determinant for normal, undisturbed sleep with the criteria of consolidated sleep (sleep continuity) and of short SOL. An abnormal Ψ_{int} could be a cause for sleep disturbances.

Individuals show systematic differences in phase of entrainment. The following mechanism plays a crucial role for these differences. It is known that the shorter the τ, the earlier is the phase of the circadian system relative to the entraining light–dark cycle. Individuals may have different τ, for example, because of genetic differences. Those subjects who prefer to go to sleep and get up early (so-called "larks") tend to have a shorter τ than those who prefer to sleep later ("owls").[16,44–46] In some humans, the phase of entrainment is so extreme that it leads to syndromes known as advanced (ASPS) or delayed sleep phase syndrome (DSPS).[37,40,47] These patients regularly wake up as early as 4 a.m. or cannot fall asleep until 3 a.m., respectively. Furthermore, there are blind individuals complaining of a cyclic sleep disorder, in which they are able to sleep at night and remain awake throughout the day for some days at a time, but then at other times their nighttime sleep is disturbed. It has been documented that the timing of their circadian rhythms slowly drifts later week by week—their circadian clock is free-running, or relatively coordinated, but not stably entrained (for review, Refs. [37,40]). Transient misalignment between the circadian system and the environmental solar cycle is observed during 'jet lag', whereby an abrupt shift in environmental time occurs and the circadian clock takes several days to re-entrain to the new light–dark cycle.[48,49] In shift work, it is not the light–dark cycle that abruptly shifts, but the required sleep–wake cycle.[14] A further example of different phase of entrainment is seen in older adults. Older subjects wake up at earlier circadian phases than the young.[50,51] All these different subject groups exhibit changes in their Ψ irrespective of cause, which could subsequently lead to, e.g., reduced sleep continuity, longer SOL, early morning awakening, impaired daytime alertness, memory, and performance, as well as disturbed endocrine and gastrointestinal functions (for reviews see, e.g., Refs. [14,16,52]).

For determining Ψ, the circadian pattern of CBT (with its phase and amplitude) is one of the gold standard reference rhythms. Therefore, it is more than simple curiosity to want to elucidate the regulation of CBT.

The interplay between heat production and heat loss

Homeostatic regulation of CBT

In order to understand circadian regulation of the CBT rhythm, it is important to elucidate first how CBT is homeostatically regulated. There is substantial evidence indicating that homeostatic regulation of CBT is controlled by a hierarchically organised set of neuronal mechanisms, with the pre-optic-anterior-hypothalamus (POAH) as the most important control centre.[53,54] In addition to homeostatic regulation, a rostral projection from the circadian pacemaker localised in the SCN to the pre-optic areas serves the circadian modulation of CBT.[53] There is an old discussion as to how the circadian system interacts with the thermoregulatory system.[55,56] Aschoff generally assumed that CBT is primarily under homeostatic control and is secondarily modulated by the circadian system through daily oscillation in the thermoregulatoy "set-point".[55] The "set point" concept can be perceived or replaced by a series of thresholds of the thermal responses ('reciprocal cross-inhibition'[1,57,58]). Activation of heat combating responses (e.g., vasodilatation, hyperpnea, hot feeling, preference of cold environment, sweating)

means that CBT is above the reference temperature, and vice versa: activation of cold combating responses (e.g., skin vasoconstriction, piloerection, increased thermogenesis, feeling of cold, preference of warm environment, shivering) means that CBT is below the reference temperature.[59]

Of all thermoregulatory responses, the easiest to investigate in humans is thermal sensation and thermal comfort, simply by asking subjects if they feel cold or hot, or if they prefer cool or warm stimuli. A circadian modulation of thermal sensation and thermal comfort should occur if the thermoregulatory "set-point" does not change across the circadian time course, e.g., feeling of cold during night, when CBT is low. We have recently completed a study in healthy young women under the very controlled conditions of a constant routine protocol.[60] They exhibited no circadian pattern of thermal sensation and thermal comfort. The circadian rhythm of CBT can be therefore explained as a result of a slowly regulated change in the thermoregulatory "set-point", or in the thresholds for the diverse thermoregulatory effects, via the SCN.[55,57,59] In contrast, it has been recently shown that the interthreshold range between shivering and sweating does undergo a circadian time course with maximum during the night phase.[61] Taken together, both the thermoregulatory system and the circadian system control effector organs which regulate heat production and heat dissipation, and consequently CBT.[55,62]

Where is heat produced in our body? 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.[63,64] Daily energy expenditure can be divided into three main components: resting metabolic rate (RMR), diet- and exercise (activity)-induced thermogenesis, whereby the last two components represent the major masking components of the endogenous circadian CBT rhythm.[65] RMR is usually the largest component of daily energy expenditure, accounting for 50–70% of all energy expenditure during 24 h.[65–67] Recent findings have shown that mitochondrial carrier proteins (uncoupling proteins, UCP), which uncouple respiration from ATP production, are responsible for the majority of RMR.[65–67] UCP3 seems to be the important molecular determinant for the regulation of RMR.[66,67] About 70% of the entire RMR of the human body is produced by inner organs.[63,64] However, this heat is generated in less than 10% of the body mass, which is surrounded by a small proximal skin surface (only ca. 30 m^2 around the trunk) and whose shape is too flat for a good heat transfer to the environment.[63,64] 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[63,64]. These regions are our main thermoeffectors as they possess the physical and physiological properties to best serve the function of heat loss.

Distal skin regions (e.g., fingers and toes) have ideal (round) surface shapes (small radius) for good heat transfer to the environment—the surface to volume coefficient increases from proximal to distal skin sites.[68] This alone can explain that the extremities exhibit a lower skin temperature under moderate environmental conditions (room temperature ca. 15–30 °C) than the more proximal skin regions (e.g., forehead). The dependency of skin temperatures and CBT on environmental room temperature is shown in Figure 2. Similar curves would be found for a physical body with similar surfaces, shapes and thermal properties of a human body.

Figure 3 shows a comparison of 24 h mean skin temperatures together with the range of oscillations (calculated as the difference between

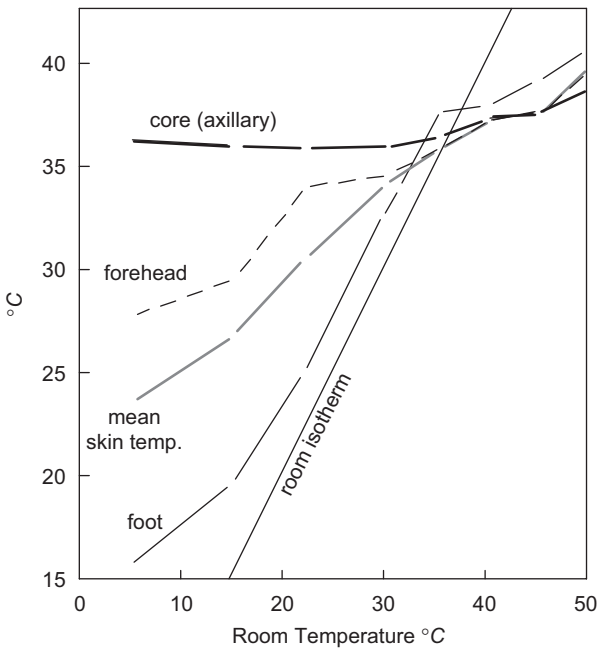

Figure 2 Core body temperature and skin temperatures (on the ordinate) of the naked human body at different ambient temperatures (on the abscissa) (redrawn from Aschoff[68]). Note: distal skin sites exhibit a larger dependency on room temperature than proximal skin sites. Room isotherm indicates the line when a measured body temperature would be equal to room temperature. For further explanations, see text.

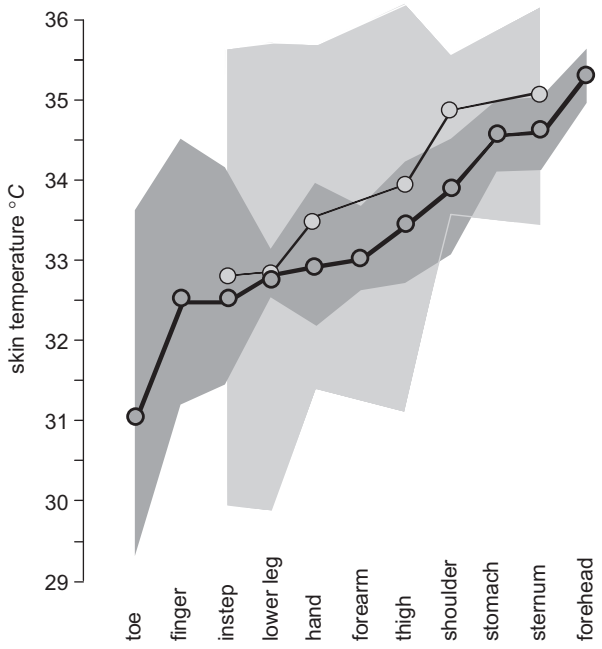

Figure 3 Profile of the 24-h mean values of different skin temperatures (dots) and range of oscillation measured as the difference between maximal and minimal values within a 24-h day (grey areas). Results of two studies are compared. Dark grey dots and dark grey area are results redrawn from the doctoral thesis of Schmidt[69] (average of eight healthy women, 22–26 yr, measured during their luteal phase for 28-h in the lab). Light grey dots and light grey area indicate results of a recently finished ambulatory study (biology diploma thesis of Gompper[70]) (average of 20 healthy women; 20–40 yr mean: 25 ± 4 S.D.; weekly mean during their luteal phase under normal life situations). Note: in both studies, distal skin sites exhibit lower 24-h mean skin temperature but larger range of daily oscillations than proximal skin sites. The ambulatory study (with zeitgeber) revealed similar 24-h mean values but larger daily oscillations than the laboratory study (without zeitgeber). For further explanations, see text.

maximal and minimal values within a 24-h day) measured on diverse body sites under controlled laboratory conditions (supine position in bed, naked, 28 °C room temperature[69]). As in Figure 2, the most distally placed probes measured the lowest 24 h mean skin temperatures. However, the range of oscillations between the daily minimum and maximum exhibited an inverse pattern—distal skin regions show the highest amplitudes and proximal sites the lowest. This finding can only be explained by an active regulation of heat loss in distal skin regions. It is interesting to note that data from a study we carried out 35 years later, with skin temperatures registered over 1 week under ambulatory normal life conditions,[70] showed also an increase in the range of oscillations between the daily minimum and maximum from proximal to distal skin regions and a decrease of the 24 h mean skin temperature values from proximal to distal sites. So, the older laboratory findings could be confirmed by the newer ambulatory study, the latter in addition showing an increase in the range of oscillations between the daily minimum and maximum values by a factor of 2–3. This indicates that the overt daily rhythm of skin temperatures is masked by daily life situations (e.g., large meals, activity, etc.) increasing therefore the daily amplitude, especially in distal skin regions.

Such an active regulation of increased amplitudes of skin temperature from proximal to distal sites can only be explained by a selective physiological regulation of heat loss in distal skin regions. Blood, the main medium for transporting heat from the core to distal skin regions, is driven and distributed by the cardiovascular system, and essentially regulated by arterio–venous–anastomoses (AVAs).[71,72] AVAs are shunts between arterioles and venules exclusively found in distal skin regions.[73] When they are open, blood, loaded with heat, flows very rapidly (about 10,000 times faster than via capillary blood flow[71,72]) and directly from arterioles to the dermal venous plexus enabling an efficient heat exchange. Additionally, blood streams back via outer veins, thereby enhancing the heat loss function of opened AVAs.[63,71,72] This regulation represents a further property of distal skin regions: the counter-current heat exchange in the extremities, i.e., legs and arms.[62–64] This mechanism is extraordinarily efficient, and can be particularly seen in birds, which can stand on ice without cooling out their body. In a cold environment, venous blood returns via inner blood vessels located near the arteries, which prewarm the back-streaming blood, thereby efficiently protecting the core from cooling out.[62–64] 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.[62–64] It is known that AVAs are also involved in the regulation of the counter-current heat exchange—when they are closed venous blood returns via inner blood vessels, and vice versa. The physiological mechanisms described above act usually in synchrony, and with support of the physical properties of the extremities they serve as a very efficient heat loss system.[62–64]

In summary, the human body consists of two compartments, the heat producing core, and the heat-loss regulating shell.[62–64] The autonomically regulated mechanisms of shell size occur via

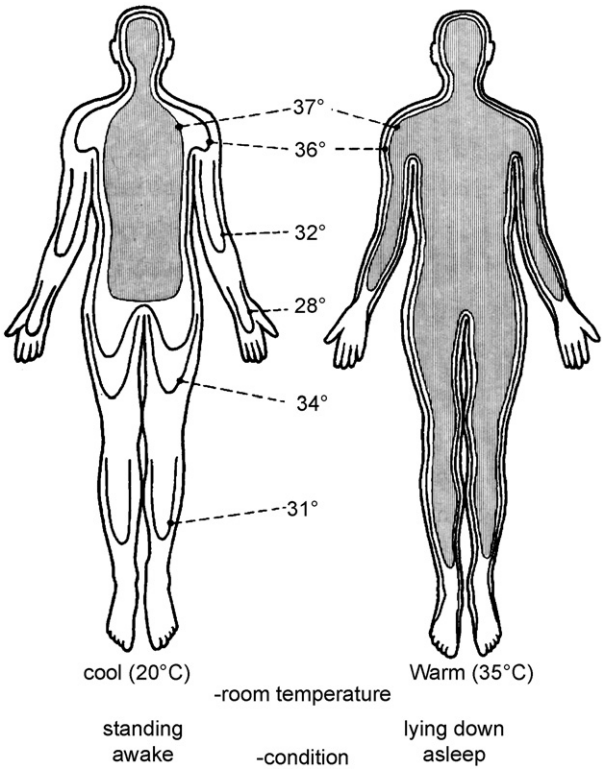

Figure 4 The schematic diagram shows a human body in a cool (20°) and warm (35 °C) environment, respectively (taken from Aschoff[62]). Similar distributions of the core and skin temperatures can be observed under waking and standing conditions (cool) and, under sleeping and lying down conditions (warm) in a thermoneutral environment. For further explanations, see text.

constriction or dilatation of peripheral blood vessels, mainly of AVAs and pre-capillary arterioles in distal skin regions.[62–64] The size of proximal skin regions is regulated in parallel to the extremities, however, to a much lesser extent—they contain no AVAs.[73,74] Sympathetic nerve activity is crucial for regulation of the peripheral vascular system. Regulation of blood vessel diameters occurs very rapidly before CBT has enough time to change. This so-called feed-forward regulation[75] with respect to CBT is an important property of the thermophysiological 'core/shell' principle.[38,76] The core, 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 cool environment it is large (see Figure 4). Thus, the shell acts as a buffer to protect the core from dangerous cooling.[38,76] Similar states of core to shell ratio can be observed under waking and standing condition (cool) and, under sleeping and lying down conditions (warm) in a temperate environment.

Circadian regulation of CBT

All the thermoregulatory mechanisms described above are also involved in the circadian regulation of CBT. The circadian CBT rhythm is a well-described thermophysiological phenomenon in many animals, as well as humans. The first publication of a daily record of CBT in humans already appeared in the middle of the 19th century by Gierse in the form of a thesis.[77] He could show 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 behavioural activity and digestive processes were the most important factors for the generation of the CBT rhythm.[78] In the mid-20th century, Aschoff and his colleagues systematically explored the causes of this rhythm.[55,79,80] They showed that the circadian rhythm of CBT is determined by both 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; Figure 5).

The time lag arises because of the body's inertia—transport of heat takes time, which in turn is determined by heat exchange from the core to the shell (i.e., inner conductance; Refs. [55,80]). We confirmed this phase relationship under the unmasking conditions of a constant routine proto-

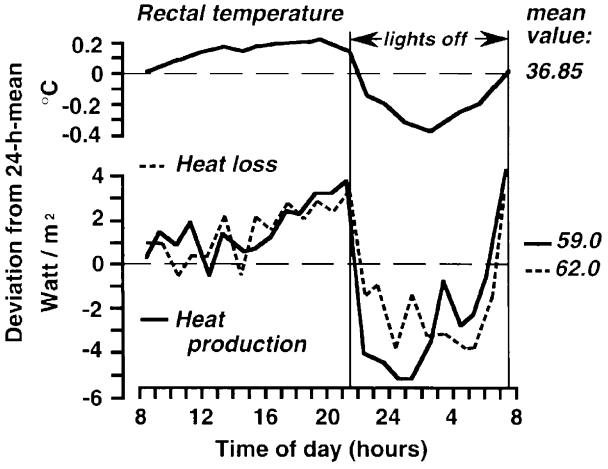

Figure 5 Circadian patterns of core body temperature (CBT), heat production and heat loss (redrawn from Aschoff, circadian control of body temperature[55]) (average of eight women, 22–26 yr, recorded during their luteal phase at an ambient temperature of 28 °C, naked, supine position in bed). Note: CBT declines when heat loss surpasses heat production. For further explanations, see text.

col, showing that the circadian pattern of CBT does in fact result from endogenous circadian rhythms of heat production and heat loss.[81] Therefore, the circadian time course of CBT can be explained by knowing the phase relationship between heat production and heat loss. Additionally, the relationship between the amplitudes of the circadian rhythms in heat production and heat loss is also an important determinant of phase and amplitude of CBT. Assuming similar circadian amplitude of heat production and heat loss, Aschoff and colleagues calculated a phase-angle difference between heat loss and heat production (another Ψ_{int}) of -21°, indicating that heat loss lags behind heat production by 1.4 h.[55,80,82] However, we have to keep in mind that masking effects induced by sleep and activity can change the shape (including amplitude) of the daily pattern of heat loss and heat production. It can be expected that under normal life situations their phase relationship, and hence that of CBT, can be affected even more. The evoked components of heat production and heat loss by activity and food intake could be of much higher magnitude than the endogenous circadian amplitude of heat loss and heat production.[55,80,82] Therefore, it seems rather plausible to assume that amplitudes of heat production and heat loss are not similar under normal daily life conditions. Moreover, it remains to be shown which of the thermoregulatory effector systems (or CBT itself) is crucial for the diverse Ψ_{int} (e.g., heat loss vs. freely chosen light–dark cycle; heat production vs. freely chosen light–dark cycle; CBT vs. freely chosen light–dark cycle, etc.) under conditions of different zeitgeber strengths. For that it is necessary to measure the thermoregulatory system more carefully with respect to heat loss and heat production, i.e., CBT and skin temperatures in relation to the light–dark cycle under the influence of different zeitgeber strengths (e.g., different *T*-cycle lengths with different light intensity).

Figure 6 shows masking effects induced by lights off and sleep in comparison to data 24-h later at a similar circadian phase without sleep.[11] This study was carried out under very controlled constant routine (CR)-conditions (constant semi-supine position, food and water intake in small portions, constant 23 °C room temperature and 60% humidity, <8 lx), which is absolutely necessary for dissecting out the diverse masking components on the circadian rhythm of CBT, distal and proximal skin temperatures. Many important effects can be seen. Directly after lights off at the beginning of the first night with sleep, proximal and—even more pronounced—distal skin temperatures increased rapidly. This occurs before sleep stage 2.[9,11] After the initial peak, an overall higher level of nocturnal proximal (+0.25 °C) and distal (+1 °C) skin temperature can be seen in comparison to skin temperature levels 24-h later when sleep is not allowed.[11] In contrast, CBT declined to a lower level (−0.25 °C) during sleep than without sleep, indicating heat redistribution from the core to the shell during the sleep phase. This redistribution occurs rather slowly, which has been explained by the reduced

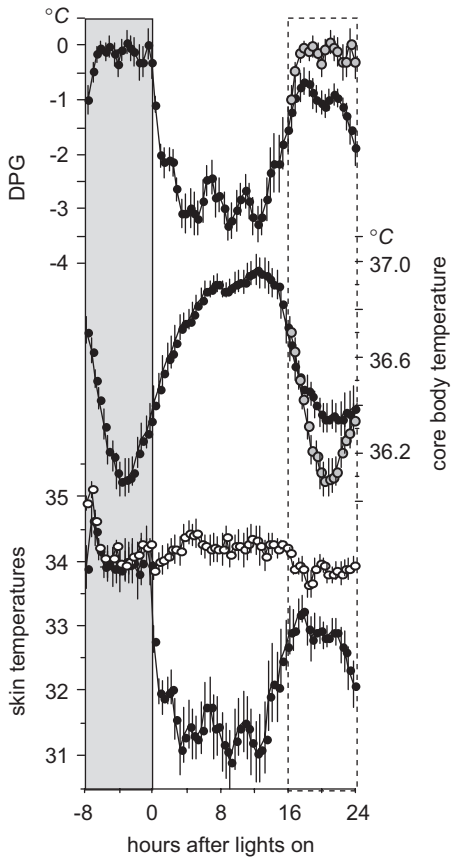

Figure 6 Time course (from the bottom up) of distal and proximal skin temperatures, core body temperature (CBT) and the distal–proximal temperature gradient (DPG) during an 8-h nocturnal sleep episode (at their habitual bed times after an 8-h constant routine protocol, CR) and during the following 24-h CR (redrawn from Ref. [11]) (mean ± S.E.M. of eight men, 21–29 yr, recorded in supine position in bed, 22 °C room temperature, humidity 60%, light bedcover; CR-conditions: <8 lx, 100 kcal sandwiches, and 100 ml water at 1 h intervals). The grey area indicates the nocturnal dark episode (0 lx) and the stippled lines define the 8-h sleep deprivation episode when the subjects usually sleep. In order to emphasise the thermoregulatory effects of a nocturnal sleep episode, data of CBT and DPG of the nocturnal sleep episode are double plotted on the data 24-h later without sleep (grey dots). Note: the 8-h sleep episode induces a fast increase of DPG and a slow reduction of CBT, indicating heat redistribution of heat from the core to the shell. For further explanations, see text.

cardiac output during sleep impeding a fast heat loss during the sleep episode, at least under more or less thermoneutral conditions.[83,84] Furthermore, under conditions without sleep, distal skin temperature shows an inverse pattern to proximal skin temperature, the latter following the circadian time course of CBT with a trough during night. This finding is a further indication that the circadian rhythm of distal skin blood flow is an actively regulated physiological process, whereas the circadian time course of proximal skin blood flow is not. The increase in distal skin temperature in the evening is clearly phase advanced compared with the decline in CBT confirming many previous studies. In the upper panel (Figure 6) the distal–proximal skin temperature gradient (DPG), a measure of distal skin blood flow,[85] indicates that during sleep the shell has completely disappeared (DPG around 0 °C), resembling therefore a state similar to that shown in Figure 4 of the human body in a warm environment. Of course, the core to shell ratio during sleep is also dependent on room temperature, however, to fall asleep a certain comfortable microclimate is necessary.

Relationship between thermoregulation and sleepiness/sleep regulation

We have shown that SOL is dependent on DPG level ca. 90 min before lights off. We usually choose our sleep times (lights off) when DPG levels are ca. −1 °C or higher (Figure 6). High DPG has been established as a good predictor for short SOL.[10,19,86]

Many appetitive behaviours preceding sleep are known to promote sleep, and they also influence the thermoregulatory system, such as lying down,[87–89] relaxation, searching for a comfortable thermic environment (using bed socks, bedcovers, etc.; Ref. [90]), switching lights off (permitting nocturnal melatonin to rise), suggestion of warmth,[91] autogenic training,[92] warm drinks (Figure 2; Ref. [93]) biofeedback,[94,95] Kneipp bedsocks,[96] intake of melatonin[88,97] and classical sleeping pills.[98] Such ''masking'' in real-life conditions, especially the naturally occurring 'lying down' and 'relaxation after lights off', evoke an increase in skin temperatures (mainly in distal sites) and a decline in CBT.[93,99] Metaphorically speaking a thermophysiological cascade is necessary to fall asleep. With each step the body loses its shell and goes a step nearer to falling asleep.

In a simplified model, the relationship between the thermoregulatory system and the sleepiness/sleep regulatory system has been explained by including a behavioural feedback loop from the sleepiness/sleep regulatory system to the thermoregulatory system.[93] The model is based on findings that in humans, homeostatic aspects of sleepiness regulation (i.e., build-up of sleepiness during wakefulness and its decay during sleep) are not related to the thermoregulatory system, whereas the circadian processes of sleepiness regulation and sleep inertia clearly are related to thermoregulation.[100,101] The disappearance of sleep inertia after sleep or a nap episode shows very similar kinetics as distal vasoconstriction.[100] Furthermore, relaxation-induced sleepiness (e.g., after lying down, at lights off, with thermal biofeedback training; see above) also evokes an increase in distal skin temperatures. Distal skin temperature (vasodilatation) of hands and feet seems to be the crucial variable for the association between thermophysiology, sleepiness and sleep. The reverse effect (vasoconstriction) occurs at lights on or a posture change from supine to standing. Therefore, in terms of thermophysiology, sleep inertia can be explained as the reverse of a relaxation process (i.e., decrease in distal skin temperatures).[100] Our results reinterpret the so-called sleep-evoked reduction of CBT as a consequence of relaxation-induced vasodilatation after lights off. Sleep *per se* has no further thermoregulatory effects.

With this understanding of thermophysiological mechanisms, we may develop the appropriate thermal strategies to treat sleep onset insomnia and alleviate sleep inertia. In recent years, we have carried out a series of studies with subjects having a so-called vasospastic syndrome (VS). Subjects with VS represent a sub-set of the general population (mostly women before menopause) with a diathesis of responding with spasm, in particular in the distal extremities (hands and feet), to stimuli like cold or emotional stress.[102] First, results have shown that women with VS exhibit not only long SOL but at the psychological level, turn their experienced anger inwards, indicating a possible role of problematic anger/aggression in the genesis of VS and sleep onset insomnia.[103] For this reason, women with VS are ideal subjects for studying the relationship between thermophysiology and sleep onset insomnia in humans ('model of nature').

In a recent survey, carried out in a random population of the Canton Basel-Stadt, we could show that it is primarily women who suffer from cold hands and feet, and that this characteristic was significantly associated with problems falling asleep and longer SOL (subjectively rated questionnaire).[104] This suggests a potential clinical relevance of the thermophysiological approach for sleep onset insomnia. At a next step, in a controlled

CR-laboratory study, we could show that women having both VS and sleep onset insomnia exhibit in comparison to controls a phase delay of the circadian system by ca. 1 h (circadian rhythms of distal and proximal skin temperatures, CBT and salivary melatonin secretion) and no differences in sleep times.[60] This finding indicates that subjects with low inner conductance during the day, i.e., subjects with VS, exhibit a changed Ψ_{int} between their circadian system and the sleep–wake cycle. Finally, in an ambulatory study measuring skin temperatures at 11 skin sites continuously over 1 week, we could not only confirm the laboratory finding but additonally could show a higher diurnal amplitude in VS with minimum distal skin temperatures in the early evening.[70] Thus, women with VS exhibit lower distal skin temperatures than controls before the nocturnal sleep episode, which could be responsible for their sleep onset insomnia.

Taken together, increased distal skin temperature (hands and feet), and thereby reduced shell size (i.e., lower inner thermal conductance[70]), seems to be the crucial variable for the association between thermophysiology, sleepiness and sleep induction. This thermophysiological effect further represents the cement between the circadian clock and the sleep–wake cycle, and in turn determines phase of entrainment and SOL.

Practice points

1. Mammalian sleep developed in association with endothermy, and all species, independent of temporal niche, usually sleep during the circadian trough of their core body temperature (CBT) rhythm.
2. Sleep under entrained conditions is typically initiated on the declining portion of the CBT curve when its rate of change and body heat loss is maximal.
3. Body heat loss before lights off, via selective vasodilatation of distal skin regions, promotes sleepiness and the rapid onset of sleep, i.e., there is a thermophysiological cascade to fall asleep.
4. All remedies used to promote sleep onset increase distal skin blood flow (e.g., bedsocks, hot water bottle, autogenic training, benzodiazepines).
5. Difficulties initiating sleep (DIS), i.e., a long sleep onset latency (SOL) may be related to a reduced capacity of heat loss regulation.
6. Subjects, mainly women, who suffer from cold hands and feet (the so-called vasospastic syndrome, VS), exhibit not only a lower capacity to lose heat during the daytime but also a prolonged SOL, a disturbed phase relationship between the circadian timing system and the sleep–wake cycle, and psychologically, a disposition to turn experienced anger inwards.

Research agenda

More research is needed to elucidate whether:

1. In different patient groups DIS is always correlated with VS before habitual sleep times.
2. There exists a causal chain from socially induced anger/aggression/stress problems to a physiological manifested vasospastic syndrome before habitual sleep times, and hence DIS.
3. Enhanced body heat loss via distal skin regions before lights off is able to reduce DIS.
4. Phase advancing the circadian clock by morning bright light and/or evening melatonin administration (changed 'phase of entrainment') reduces DIS.
5. Phase delaying the sleep–wake cycle (changed 'phase of entrainment') reduces DIS.

Acknowledgements

I am grateful to Anna Wirz-Justice for her helpful comments to the manuscript and her excellent continuing support. Our work is supported by the Swiss National Science Foundation (#3100A0-102182/1 & #3130-3054991.98/3100-055385.98), the Schwickert-Stiftung, the 6th European Framework Programme EUCLOCK (018741) and the Daimler-Benz-Stiftung project CLOCKWORK.

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