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The interrelationship between sleep regulation and thermoregulation

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1. ABSTRACT

The circadian distribution of vigilance states and body temperature changes are tightly coupled. The increase in heat loss at the end of the day is associated with increased ease to fall asleep. Experimental data show that warming the skin or the brain can increase sleep propensity, sleep consolidation, and the duration of sleep. Anatomical and neurophysiological studies show that the pre-optic-anterior-hypothalamus (POAH) is the main integrator of sleep and thermoregulatory information. It integrates information on vigilance states, body temperature, and environmental temperature and influences vigilance states and body temperature in response. Animals that display daily torpor may be a valuable model to investigate the relationship between sleep and thermoregulation. During torpor these animals seem to apply similar strategies and physiological processes as humans during entrance into sleep, but in a more extreme way, providing an excellent opportunity to investigate these processes in more detail. More systematic investigations are needed to further our understanding of the relationship between sleep and thermoregulation, and may provide the basis to treat sleep disturbances with thermal strategies.

2. INTRODUCTION

This review deals with the relationship between the thermoregulatory system and the sleep regulatory system. First a brief introduction into these two systems is given. In both, two interacting physiological principles, homeostasis and circadian regulation have to be separated. Subsequently the interaction of sleep and thermoregulatory mechanisms will be discussed. The last part concerns hibernation, a special condition displayed by a limited amount of mammalian species. The similarities and differences in the thermoregulatory system in the same animal in hibernation and in the state of endothermy are discussed.

In order not to go beyond the scope of this review some restrictions have to be made. Of the about 4’000 mammalian species we report for the most part findings from humans, rats, ground squirrels, and hamsters. As a consequence, this review is far from complete. A vast knowledge has been accumulated about the enormous variation in the nature of rest/sleep states and thermophysiology across the animal kingdom (1). Animals increase survival by obtaining a safe sleeping site, and have

used sleep to maximize energy savings by reducing body and brain energy consumption, and simultaneously conduct a variety of recuperative processes (1).

3. SLEEP REGULATION

Although the function of sleep is still unknown, it clearly has a restorative function on the brain. One of the cornerstones of our present knowledge is that this restorative function is under the control of a sleep homeostat. The basic concept of sleep homeostasis is relatively easy to understand: as waking duration increases, sleep pressure increases, and the amount and intensity of subsequent sleep is a function of prior waking duration. In mammals, the intensity of sleep is reflected in the activity of the slow-waves (<5 Hz) of the electroencephalogram (EEG) during non-rapid-eye-movement-sleep (NREMS) (2-4). Despite this relatively simple approach a significant portion of the variation observed in the amount of sleep and the activity of the slow-waves during NREMS is explained by the concept of sleep homeostasis, and in several mammalian species it was shown that the amount of slow-wave activity in NREMS depends on the duration of prior wakefulness (5-10). In addition, mathematical models simulating the sleep homeostatic response have been applied successfully in human (11), rat (12), and mouse (10, 13).

The other major player in the game of sleep regulation is the circadian clock, which resides in the suprachiasmatic nucleus (SCN) of the hypothalamus (14, 15) . Not only is the circadian clock involved in the timing of sleep (16), but it also seems to influence sleep propensity by supporting or inhibiting sleep at the appropriate time of day (11, 17). Many models of sleep regulation include the influence of the circadian clock (4).

Although circadian and sleep homeostatic mechanisms both influence the occurrence of sleep, it is generally assumed that homeostatic and circadian sleep regulatory processes can function independently (4). This notion is supported by the findings that sleep homeostasis is intact after circadian rhythmicity has been abolished by SCN lesion (18-20), and that circadian processes can be manipulated by light in the morning without changing NREMS slow-wave activity (21). In addition, slow-wave activity decreases over the course of a sustained sleep period, independent of circadian phase (16). However, recently it was shown that SCN neuronal activity is responsive to changes in sleep and EEG slow-wave activity (22, 23) suggesting a reciprocal influence of sleep pressure on circadian clock functioning.

Sleep homeostatic and circadian regulatory mechanisms together determine the occurrence and depth of sleep and both need to be taken into account to understand the interaction between sleep and thermoregulation. Furthermore, recent research has provided new insights into the relationship between thermoregulation and sleep on the basis of neuroanatomical studies showing significant interaction of the two systems on brain levels.

4. CIRCADIAN REGULATION OF BODY TEMPERATURE

From a thermophysiological point of view the human body consists of two compartments, the heat producing homeothermic core, and the heat-loss regulating poikilothermic shell (24-26). Core body temperature (CBT) comprises the temperature of the brain and the abdominal cavity, including inner organs (e.g. liver, heart, kidney). In most placental mammals CBT is regulated around 37°C. The brain is the main target for homeothermy allowing control of all behavioral and physiological processes over a broad environmental temperature range. Diverse afferent inputs from cold and warm sensitive neurons, are received and processed in the major thermoregulatory centre in the brain located in the preoptic anterior hypothalamus (POAH) (27). In this hypothalamic area the appropriate efferent responses controlling sweating, shivering and changes in vasomotor tone are activated to maintain CBT. These thermoregulatory defenses are characterized by thresholds triggering each response at a certain CBT-level and gain (slope of the effector intensity in relation to CBT). CBT is normally maintained within the so-called interthreshold zone of shivering and sweating (28, 29). Within that zone vasoconstriction and vasodilatation are the only autonomic thermoregulatory defenses keeping CBT within a narrow range (28, 29). In addition to autonomic thermophysiological defenses to cope with changing environmental temperature, many organisms possess effective behavioral strategies to reach thermal comfort. Thermal comfort in humans is defined as the state of mind that expresses satisfaction with the environment. Moreover, the so-called 'thermoneutral–zone' describes an ambient temperature range within which an organism keeps its CBT constant by subtle changes in cutaneous blood flow without the need to call upon heat-gain or heat-loss mechanisms (29). Humans in the thermoneutral-zone usually sense thermal comfort - all animals try to sleep in such a state.

CBT is regulated between thresholds but those thresholds are subject to circadian oscillations (30). Circadian rhythms in mammals are generated by the self-sustaining central pacemaker localized in the SCN, usually entrained (synchronized) to the 24-h solar day mainly by the zeitgeber light (14, 15). The regulation of CBT by homeostatic and circadian processes results from the concerted action of the two processes. A rostral projection from the SCN to the POAH enables the circadian modulation of the thermoregulatory system (31). In humans, the daily decline of CBT in the evening has been explained as the result of a regulated decline in the thermoregulatory thresholds of heat production and heat loss; the inverse happens in the morning. When heat production surpasses heat loss, body heat content increases, and vice versa. Depending on environmental temperature ca. 70-90% of body heat content is located in the body core, and therefore changes in CBT reflect to a great extent changes in body heat content. However, both heat production and heat loss are modified by activities, e.g., muscular exertion, fluid and food intake, which are not randomly distributed over the circadian cycle. These behaviors, therefore, induce so-called masking effects, and

may differentially modify the endogenous rhythm of CBT (32).

In order to disentangle circadian from masking effects on thermophysiological variables a so-called constant routine (CR) protocol was developed (33, 34). This protocol includes a constant supine position, food and water intake in small portions, constant room temperature, 60% humidity, and <8 lx., and keeps masking components on a low level. Using the CR protocol it was shown that the endogenous circadian time course of CBT is generated by both changes in heat production and heat loss (35). The time course of changes in heat production precedes that of heat loss and CBT varies as a resultant. This temporal relationship between heat production and heat loss seems to be the underlying mechanisms for the generation of a circadian rhythm in CBT, whereby the two regulatory mechanisms are not only separated in time but also in space in the body (36). Under resting conditions, ca.70% of daily body heat production depends on the metabolic activity of inner organs, whereas body heat loss takes place by changes in shell size through redistribution of heat from the core to the shell via blood flow mainly to the distal skin regions (37). Thermoregulatory changes in distal skin blood flow are autonomically regulated via constriction or dilatation of arteriovenous anastomoses (AVAs). AVAs are shunts between arterioles and venules, exclusively found in distal skin regions (e.g. toes, fingers) (38, 39). When they are open, blood loaded with heat, flows very rapidly and directly from arterioles to the dermal venous plexus enabling an efficient heat exchange from the core to the distal skin regions (38). Additionally, when AVAs are open blood flows back via outer veins, bypassing hereby the very efficient heat sparing mechanism of counter-current heat exchange (25, 40). In the cold, the shell is large (AVAs closed, blood returns via inner veins) and in a warm environment the shell is small (AVAs open, blood returns via outer veins) (25, 26, 40). Thus, the shell acts as a buffer to protect the core from cooling or heating. All peripheral tissues such as fat, skin, and in particular skeletal muscles of the legs and arms can contribute substantially to the size of the shell, provided that peripheral blood flow is low. Therefore, rates of blood flow through muscles and skin are the main determinants of shell size and hence of peripheral insulation. The distal skin regions, in particular fingers and toes, are our main thermo-effectors to loose body heat as they possess the physical and physiological properties to best serve the function of heat loss. They have ideal surface shapes (round, small radius) for good heat transfer to the environment—the surface to volume coefficient increases from proximal to distal skin sites. The distal skin temperatures provide therefore a good measure of shell size. The exact neural process by which the stability of CBT is achieved is still a matter of debate, however, sympathetic nerve activity seems to be crucial for regulation of peripheral vasoconstriction, but also specific vasodilatory systems have been described (41).

In studies carried out under the CR protocol, distal skin temperatures of hands and feet exhibit an inverse circadian rhythm in comparison with CBT (35). In addition, distal skin temperatures are phase advanced by about 100 min and their circadian amplitude is about three times higher than that of CBT (35, 42). In contrast, proximal skin temperatures (e.g. thigh, infraclavicular region, stomach, forehead) follow CBT with similar amplitude (43). This inverse relation between distal skin and proximal temperature rhythms reflect the differences in thermophysiological regulatory mechanisms mentioned above (43). The distal - proximal skin temperature gradient (DPG) provides therefore a selective measure of distal skin blood flow, and hence of body heat loss via the extremities (44).

Nocturnal secretion of the pineal hormone melatonin, which is under control of the SCN, plays a crucial role in the endogenous down regulation of CBT in the evening (45). Administration of melatonin in the afternoon, when endogenous melatonin levels are low, provokes exactly the same thermophysiological effects as observed naturally in the evening (46). Distal skin temperatures increased, whereas CBT and proximal skin temperatures declined (46). It is still a matter of debate whether melatonin induces distal vasodilatation in humans directly on receptors in blood vessels, indirectly via modulation of sympathetic nerve activity, or both (47). In parallel to these physiological effects of melatonin subjective ratings of sleepiness increased, as well as objective waking electroencephalographic -characteristics of sleepiness like increased activity in the theta and alpha range (48). Taken together, melatonin secretion in the evening belongs to the well-orchestrated circadian physiological concert controlled by the SCN (37), which down regulates CBT, increases sleepiness and promotes sleep.

5. RELATIONSHIP BETWEEN SLEEP- AND THERMOREGULATION

The most evident explanation whether and why the sleep regulatory and thermoregulatory systems could be interrelated is a teleological one: in the evolutionary past of mammals sleep was for energy conservation (1, 49-51). However, this explanation needs to be critically scrutinized for each species with respect to the extent of energy conservation during sleep. All species sleep or rest when their energy expenditure is low. This observation represents the starting point of all energetic explanations why we sleep. Human sleep evolved from sleep of remote smaller ancestors, and it is quit possible that earlier forms of sleep were linked to energy conservation. Rest or quiet wakefulness is a prerequisite for sleep in all species, including humans, and the survival benefit of energy conservation during sleep has been acquired in remote ancestors with a small body size (see below) (1, 49-51). There are two mechanisms how sleep can conserve energy. One is that sleep reduces energy expenditure indirectly by reducing activity. This mechanism would also be functional when animals only exhibit quiet wakefulness. In addition, sleep results in decreased energy expenditure below that of quiet wakefulness by a change in thermophysiology. Energy conservation may be particularly important in small animals and infants (50). Their high surface–to-body-mass ratio is ideal to lose heat and makes energy conservation achieved by sleep highly adaptive. When body size increases in the

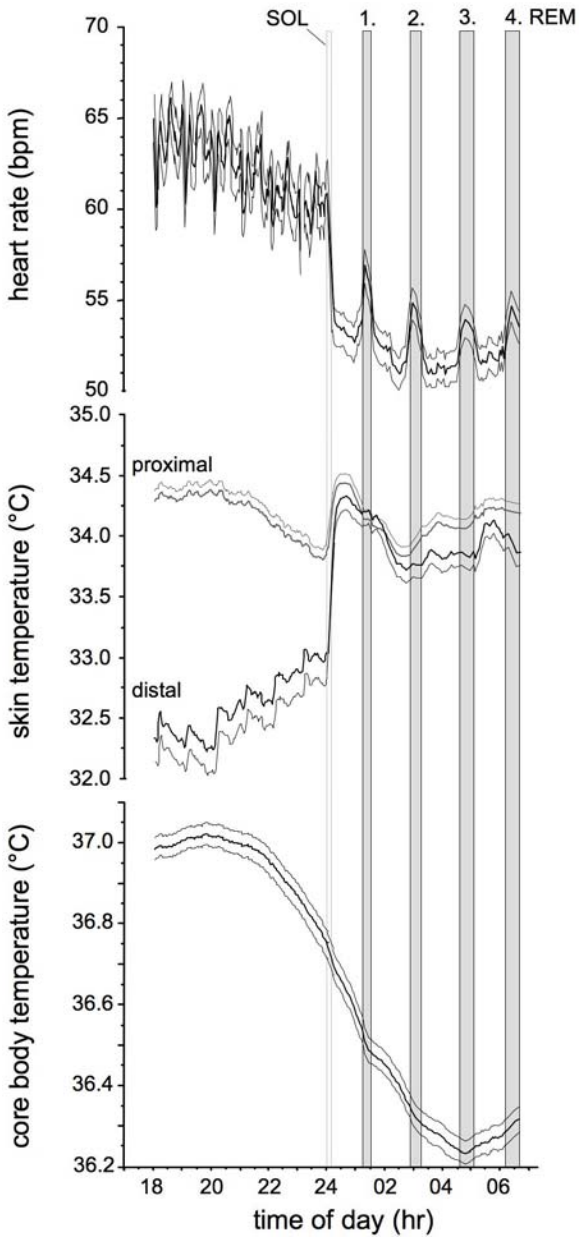

Figure 1. Time course of continuously measured data (5-min bins) of core body temperature (CBT), distal and proximal skin temperatures, and heart rate in a baseline 7.5-h constant routine followed by a 6.7-h sleep period divided in four percentilized NREMS-REMS cycles (20 intervals for NREMS, 4 intervals for REMS; data from (56)). Mean sleep onset latency: 12 min±4. Mean values (bold lines) of N=18 male subjects (±sem, thin lines). Heart rate: bpm, beats/ min. Note: Distal and proximal skin temperatures exhibit inverse time courses before lights off, but were nearly indistinguishable thereafter. Before lights off heart rate reflects the study protocol rhythm of one hourly food and water intake and declined sharply thereafter during sleep onset latency (SOL). Distal and proximal skin temperature increased largely during SOL but exhibited only small changes according to NREMS-REMS cycles (as CBT did in parallel). In contrast, heart rate was strikingly increased before and during each REMS episode.

course of development and sensory-motor systems mature, a parallel decrease in sleep time occurs. In spite of the well-recognized potential for energy conservation in small species, human sleep is only accompanied by a modest decline in energy expenditure below the level of quiet waking (52). Therefore, for larger species, including humans, the simple explanation 'sleep is for energy conservation' can be discarded (52). In the following we present two lines of studies, to clarify the relationship between sleep and thermoregulation. 1.) Correlative findings between the sleep and thermoregulatory system from contemporaneous measurements of sleep, EEG, and thermophysiological variables under thermal comfort conditions provide information about how the two systems are related. 2.) A more conclusive approach is to challenge the two systems investigating how they react to stimuli applied in one of the two systems.

6. CO-VARIATION OF SLEEP- AND THERMOPHYSIOLOGICAL- VARIABLES

6.1. Baseline conditions

It has been observed that subjects living under normal conditions choose their bedtime (lights off) at the maximal rate of decrease in their CBT rhythm (53, 54). However, in order to investigate the sleep and thermoregulatory system it is crucial to separate circadian from masking components of an overt diurnal pattern. This is much easier to accomplish in humans then in animals. In spite of this advantage the most often neglected factor in human research is the so-called laying down effect. A change from standing to a supine body position induces redistribution of heat from the core to the shell, increasing skin temperatures (mainly in lower legs and feet), and decreasing CBT; in parallel sleepiness is induced (46, 55). This effect lasts for about 1-2 hours (46, 55), which significantly confounds the endogenous time course of the different body temperatures in a classical sleep recording protocol where subjects lie down ca. 0.5 hour before lights off. After a normal 8-h nocturnal sleep episode the inverse happens: skin temperatures decline and CBT increases. Figure 1 summarizes the temporal relationship between thermophysiological variables and heart rate under the unmasking CR-conditions before habitual bedtime and for the following sleep episode starting 12±5 min after lights off (56). There were no changes in posture throughout the protocol. Local thermal changes can also be ruled out as a cause of these variations because the bed covers remained the same during the entire protocol. The only thing that changed at midnight was that the low intensity lights (<8lux with minor effects on melatonin secretion) were switched off with the implicit permission to fall asleep. Before lights off the previously described endogenous pattern of CBT down regulation is visible. In the evening, heart rate (an indirect measure of intra-subject variation of heat production) declined first, followed by the beginning of heat loss (indicated by the rise in DPG) and finally by a decrease in CBT. Subjective ratings of sleepiness increased together with DPG and salivary melatonin levels. The proximal skin temperature exhibited a similar pattern as CBT. Immediately after lights off, and before sleep stage 2

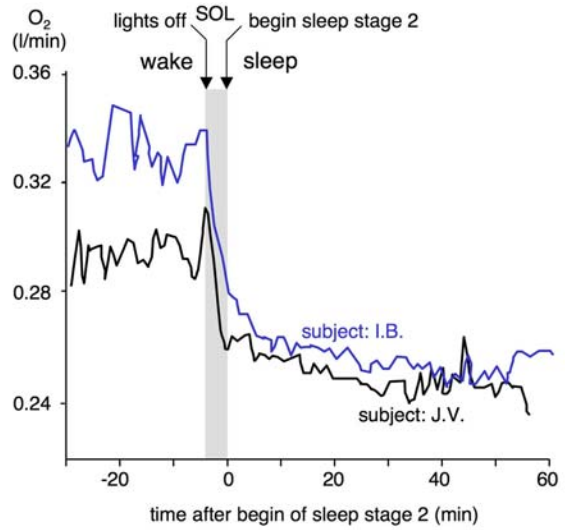

Figure 2. Time course of oxygen consumption (l/min) of two healthy young men before and after sleep initiation (redrawn data from (93)). Note: Oxygen consumption was largely declined after lights off already before sleep stage two began (SOL= sleep onset latency to sleep stage 2).

occurred, remarkable changes emerged. Both distal and proximal skin temperature increased, and heart rate and energy expenditure (Figure 2) declined (43, 56, 57). Additionally, an increase in sweating rate is often observed, depending on CBT (58).

The characteristic increase in distal skin temperature represents heat redistribution from the core to the shell. Similar findings after lights off before sleep onset have been described in the lower leg by measuring skin blood flow (59), foot skin temperatures (60) or finger skin temperatures in multi sleep latency tests distributed over a 45h CR protocol (61, 62). However, CBT exhibited a significant, but only slight increase in the rate of change after lights off (43, 56). This is in agreement with other CR studies reporting that CBT during quiet wakefulness is elevated by about 0.3°C compared to sleep at the same circadian phase (63) (Figure 3). In contrast to the fast changes in skin temperature, the decline in CBT is slow, which can be explained by the reduced cardiac output during sleep initiation impeding a faster heat loss during the sleep episode, at least under thermoneutral conditions (57). The decline in CBT is dependent on environmental temperature conditions, with a cooler environment inducing larger decreases (64). DPG around 0°C indicates that during sleep the thermoregulatory shell has nearly disappeared, resembling therefore a state similar to that of the human body in the awake state in a warm environment (e.g. 35°C). Heat redistribution from the core to the shell is completed within approximately one hour after lights off. Such a completely relaxed one-compartment body would be prone to fast cooling when sleep occurs in a cool environment. However, in normal life we protect our body during sleep by searching a sleeping berth in a comfortable thermal environment. When sleep is initiated outside the temporal niche, for instance by taking an afternoon nap, similar thermophysiological changes occur as seen in nocturnal sleep again starting directly after lights off and before beginning of sleep stage 2 (65). At the end of a sleep episode, the transition to waking is accompanied by an inverse thermophysiological pattern (65). It takes a certain amount of time to recover from sleep, a time span called sleep inertia. It has a similar, but inverse, time course in distal vasoconstriction, and from a thermophysiological point of view sleep inertia is the inverse process of sleep initiation (65). Furthermore, within this context it is noteworthy that similar thermophysiological effects as occur during sleep initiation can be observed without falling asleep. For instance relaxation techniques (66, 67), autogenic training (68), yoga (69), autosuggestion of warmth (70) and meditation (67) induce a withdrawal in muscular and cutaneous sympathetic nerve activity leading to increased distal skin blood flow, increased distal skin temperature, and to a reduction in heart rate, energy expenditure and CBT. Taken together, distal vasodilatation followed by a drop in CBT appears to be a thermophysiological event, which is primarily related to relaxing behavior occurring before sleep onset.

How is the NREMS-REMS cycle related to changes in thermophysiological variables? There are not many studies carried out in humans in which thermophysiological, sleep, and EEG -variables before and during sleep were measured in parallel. To our knowledge only one study reports brain temperature together with sleep-EEG data whereby no significant systematic changes regarding the NREMS-REMS cycle were found (71). In order to highlight the ultradian changes during the sleep episode the time courses of skin temperatures, CBT and heart rate data were percentilized according to four succeeding NREMS-REMS cycles (Figure 1). Changes in proximal and distal skin temperatures related to the NREMS-REMS cycle are very small; both increase approximately 0.2°C during NREMS, relative to REMS. These changes occur in parallel to minimal changes in CBT (ca. 0.02°C) (72, 73) (see Figure 1). In humans it is not known whether such changes also occur in the hypothalamus, the brain region where sleep and thermoregulation are integrated. However, heart rate is largely increased during REMS, relative to NREMS, and this increase starts a few minutes before REMS onset. Although this increase represents a robust change in cardiovascular regulation, it is reflected only in a minor increase in energy expenditure during REMS (74). In rodents, although less pronounced, similar changes in heart rate were found in rats (75) and the Djungarian hamsters (Figure 4). Brain temperature is determined by cerebral heat production, cerebral blood flow and the incoming ceratoid blood temperature. Parmeggiani and colleagues, who extensively studied thermophysiological alterations regarding the NREMS-REMS cycle, concluded that changes in brain heat production are practically not relevant for changes in brain temperature during the NREMS-REMS cycle (76). Rather the hypothesis was favored that changes in brain temperature over the NREMS-REMS cycle are caused by systemic hemodynamic alteration at the onset of REMS, at least in smaller mammals. Warm venous blood from the body returns to the heart where it is mixed

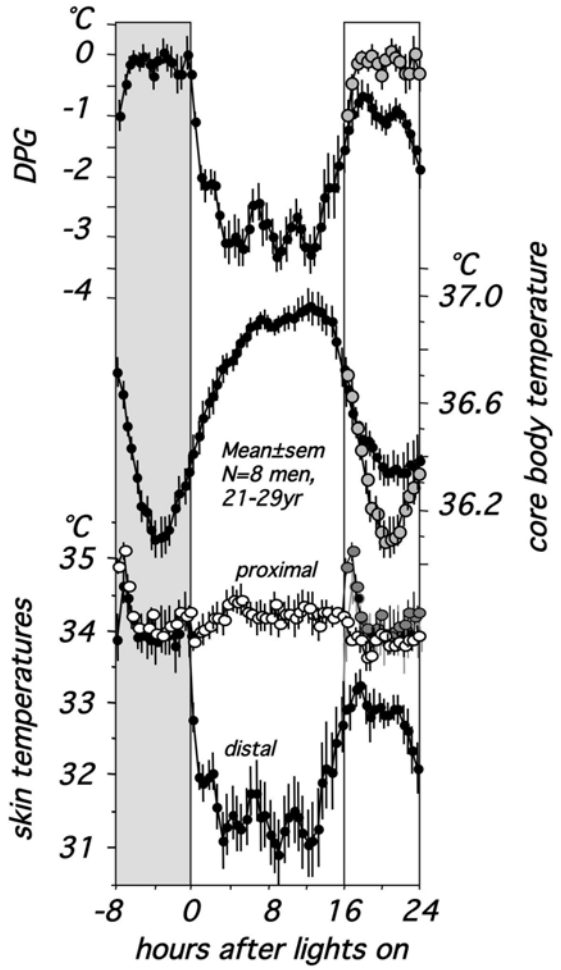

Figure 3. Time course (from the bottom up) of core body temperature (CBT) and the distal–proximal temperature gradient (DPG) during an 8-h nocturnal sleep episode (at their habitual bed times after an 8-h constant routine protocol, CR) and during the following 24-h CR (redrawn from (43)) recorded in supine position in bed, 22°C room temperature, humidity 60%, light bedcover; CR-conditions: <8 lux, 100 kcal sandwiches, and 100 ml water at 1 h intervals). The grey area indicates the nocturnal dark episode (0 lx) and the open area (16-24h) 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.

with cool venous blood from the systemic heat exchangers of the body, e.g. the fingers and toes in humans and the tail in rats. This mechanism affects carotid blood temperature and hence brain temperature and represents the most important determinant of changes in brain temperature regarding the NREMS-REMS cycle in primates. However, supporting data for this hypothesis are not available in humans. Selective brain cooling seems to be of less significance in humans, but is of importance in numerous mammals (76).

In animal research next to recording body temperatures, it is also possible to record brain temperature. The relation between sleep and brain temperature was already shown in 1965 when Kawamura and Sawyer demonstrated in the rabbit that NREMS is associated with a decrease in brain temperature, whereas REMS and waking are associated with an increase (77). This observation has been extended to several mammalian species (rat: (78-80); cat, sheep and rabbit: (81, 82); mole rat: (83); guinea pig: (84); Djungarian hamster: (85) (see also Figure 4). In an elegant study in the rat, where sleep-wake recordings were combined with recording of brain, intraperitoneal (i.p.) and skin tail temperature Alföldi *et al* (86) showed that body heat is redistributed when vigilance states change. At NREMS onset brain and i.p. temperature decreased, whereas tail temperature increased. The opposite occurred at NREMS to waking transitions. At NREMS–REMS transitions brain temperature increased dramatically, whereas i.p. and tail temperature did not change. The data indicate that at sleep onset heat is redistributed from the core to the shell and this corresponds well with data obtained in humans. Where rats thermoregulate by vasodilatation and vasoconstriction of blood vessels within their tail, humans thermoregulate in a similar way with the skin of their extremities. In humans most of these thermoregulatory changes are circadian in nature and start several hours before sleep onset, whereas in the rat they are directly sleep related and occur at the immediate onset of sleep. This difference is probably due to the ultradian sleep wake pattern in the rat, in which a delay of several hours would be non-functional.

In humans, the relation between sleep regulation and thermoregulation are best investigated in a CR protocol (see above), however, thermophysiological combined with EEG -measurements under natural living conditions are also necessary to investigate whether the described thermoregulatory changes are also present under masked conditions (43, 87). Applying a CR in rodents is not possible. On the basis of the relationship between brain temperature and vigilance states, Franken *et al* (88) were able to subtract the influence of vigilance state changes on brain temperature. From this 'mathematical CR' they concluded that approximately 90% of the variance in brain temperature in the rat is caused by changes in vigilance states. Similar analysis, based on brain temperature, core body temperature and motor activity or the amount of active wakefulness (instead of vigilance states) resulted in lower values (30-70%) (89-91). Differences in the estimates between the studies are probably caused by differences in the methods and variables used in the modeling. A recent study showed that vigilance state related changes in brain temperature remained intact after removing the SCN confirming that these changes are independent of circadian clock functioning (92).

Taken together, there are robust thermoregulatory effects induced by the relaxing sleep

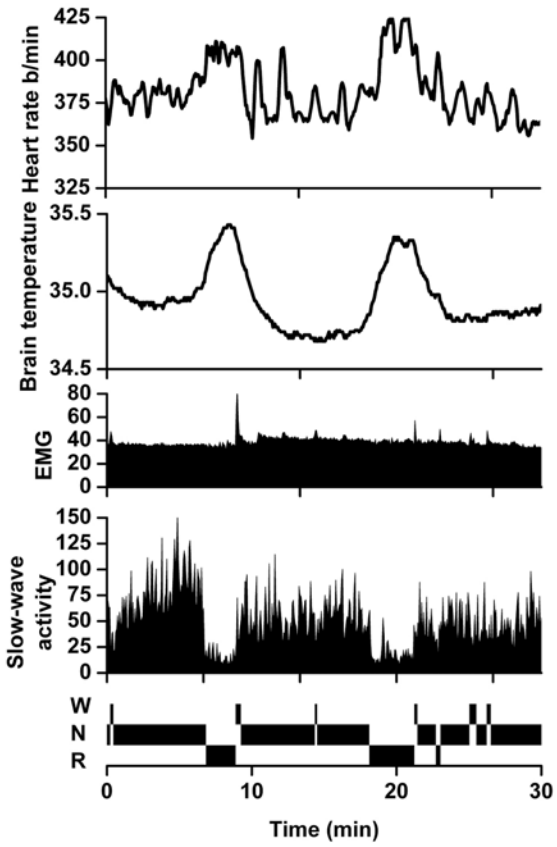

Figure 4. A 30 min record of heart rate, brain temperature measured at the parietal cortex, integrated EMG activity from the neck muscles, and EEG slow-wave activity (SWA, mean EEG power density between 0.75-4.0 Hz), and vigilance states (W=waking, N=NREMS, R=REMS), of a Djungarian hamster (*Phodopus sungorus*). Values are plotted for 4-s epochs. Note the decrease of heart rate and brain temperature at the entrance into NREMS sleep and the increase during REMS.

behavior before sleep stage 2 occurs, however, the NREMS-REMS cycle seems to have minor thermoregulatory function in larger animals like humans, but may still have thermoregulatory consequences in small rodents. The thermoregulatory mechanisms, which are active during the wake-sleep transition redistribute heat from the core to the shell, and induce a decline in heart rate, energy expenditure (74, 93-95) and CBT. Because relaxing behavior before sleep belongs inseparably to sleep, it is therefore in accordance with the notion that energy conservation was the function of sleep in our evolutionary past and the thermoregulatory effects occurring with relaxing behavior before sleep may be a remnant of that past.

6.2. Circadian changes

Subjects living under normal entrained conditions choose their bedtime (lights off) at the maximal rate of decrease in their CBT rhythm. However, when subjects live in a time free environment, self-selected bedtime is phase delayed and occurs close to the CBT minimum, which is an indication that the sleep-wake cycle and the circadian rhythm of CBT are separate but coupled oscillatory systems. Unfortunately, neither direct nor indirect measurements of heat loss and heat production were carried out in these studies in parallel. Therefore it is possible that not CBT is the crucial variable for sleep induction, but one of its determinants e.g. heat loss. Since heat loss is in fact closely linked to sleep initiation, it can be speculated that the phase relationship between heat production and heat loss changes under free-run conditions. With respect to the CBT rhythm heat loss probably phase delays under free-run conditions.

There is also a reproducible and robust circadian rhythm in sleep onset latency to sleep stage 2 (SOL2), which is closely related to the circadian CBT rhythm and thermoregulatory effects. In forced desynchrony studies it was shown that SOL2 is longest at the circadian maximum of CBT, ca. 1.5 h before CBT declines and melatonin secretion increases (16). This phase is called the "wake-maintenance zone" (96). At that circadian phase inner heat conduction is lowest as indicated by the largest difference between CBT and distal skin temperature, and by the largest negative DPG values. Thereafter SOL2 declines rapidly and is minimal around the CBT minimum, when inner heat conduction is largest. This is the case when distal skin temperature is highest and the difference between CBT and distal skin temperature is lowest and DPG is around 0°C. However, it remains to be determined whether thermal interventions at the wake-maintenance zone, such as lower leg warming, are successful to reduce SOL2, as melatonin administration is (97).

Under free-run conditions changes in the circadian phase of REMS propensity rhythm have also been observed. Under normal entrained conditions REMS exhibits a strong circadian pattern, with a peak located shortly after the CBT minimum (98-101). During synchronized free-run conditions the sleep-wake cycle is phase delayed by ca. 1 hour with respect to CBT and REMS propensity, and in parallel REMS-latency is shorter. The phase relationship between CBT and REMS propensity has also been studied under spontaneous and forced desynchrony conditions (16). Remarkably, the phase relationship between CBT and REMS-propensity rhythms did not change. The maximum REMS propensity was always located shortly after the minimum of the CBT rhythm. Interestingly, parallel changes in the CBT rhythm and REMS propensity were found after phase shifts of the circadian system while keeping the phase of the sleep-wake cycle constant. Such circadian phase advances were induced either by bright light exposure in the morning or melatonin administration in the evening (21, 102). Taken together the circadian rhythm of REMS propensity is closely phase locked with the through in the circadian rhythm of CBT, however, with a phase lag of ca. 1-2 hour.

A further interesting finding has been observed in subjects living in a time free environment on self-selected sleep-wake schedules. The duration of EEG recorded sleep episodes is highly correlated with the

circadian phase of the CBT rhythm at lights off and not primarily with the length of prior wakefulness. Maximal sleep length occurred when sleep was initiated at the CBT maximum and minimal sleep lengths at the rising part of the CBT rhythm (98-100, 103). Accordingly, in a 9.33h: 18.66h sleep-wake scheduled forced desynchrony protocol sleep efficiency was highest when sleep was initiated around the circadian maximum of CBT and minimal when sleep was initiated at the rising part of the CBT rhythm (16).

It is well accepted that SWA in NREMS is mainly determined by the prior waking duration. However forced desynchrony experiments reveal a somewhat neglected but significant circadian modulation of slow-wave-activity (SWA) at the beginning of a sleep episode (16). SWA is highest when CBT is at its circadian maximum and lowest shortly before CBT minimum (16). The exponential decline in SWA follows a similar time course with largest reduction of SWA when sleep starts at CBT maximum. The decrease in CBT at the beginning of a sleep episode is largest when circadian CBT is maximal and lowest around the CBT minimum, which could be correlated to the decline in SWA. However, conclusive interpretation is precluded because the decline in CBT after lights off is confounded by lying down induced masking effects shortly before the beginning of a sleep episode. Nevertheless, these findings provide evidence that SWA levels at the beginning of a sleep episode could be related to CBT or its down regulation.

Taken together, selected sleep timing, SOL2, REMS latency, REMS propensity, sleep duration, and initial SWA seem to be closely associated with CBT. In spite of the fact that these variables are not fully in phase with CBT, which precludes a direct link to CBT, it is quite possible that one of the determinants of CBT (e.g. heat production, heat loss) is directly interrelated. It still remains to be established whether these rhythms are independently governed by the SCN or causally linked directly to thermoregulatory measures. These correlative findings observed from sleep patterns under entrained, free-run and spontaneous or forced desynchronized conditions lead to the question how is sleep affected by thermoregulatory challenges?

7. INTERVENTION STUDIES

7.1. In humans

Effects of thermal interventions, either by warming or cooling, on sleep are not easy to investigate. A thermal intervention either applied passively (by baths, changes in air temperature, changes in the amount of clothing or bed covers, water-perfused suits, heated blanked, sauna), or actively (body exercise) induces significant changes in skin temperatures and CBT (50, 104-107). Another way to increase body temperature is by inducing fever. However, the induction of fever involves inoculation with pyrogens, cytokines or pathogens to facilitate fever, which themselves alter sleep (108). Fever is caused by the immune response in coordination with changes in sleep wake distribution, which renders disentanglement of the consequences of fever on sleep almost impossible. However, the response of sleep to the induction of fever shows large similarities with the response of sleep to warming (see below).

The intensity of a thermal intervention (temperature and duration of heat load, strength of exercise) is crucial, but also the skin region and time of day of application before or during sleep - obviously, only certain passive heat loads can be applied during sleep. It has been shown that sleep inhibits all ongoing thermoregulatory activities (105, 109, 110). The inhibition is modest in SWS and stronger in REMS that means sleep reduces the thresholds and gains of autonomic heat and cold defense mechanisms and expands the interthreshold zone (105, 109). As a consequence CBT and skin temperatures increase in a warm environment and decrease in cool environment to a higher extent. In contrast to small animals, the reduction of thermoregulatory effects during REMS in humans is small in scale (64, 111). In general, too strong thermal interventions induce arousals and awakenings, which in turn can change thermoregulatory effects (105). Maximal TST is found in the thermoneutral-zone whereas REMS is more irritable to strong thermal interventions than SWS. When a thermal load is given repeatedly the thermoregulatory system can adapt and the effects on sleep are changed e.g. arousing effects are reduced. For instance, before modern technology arrived the aborigines in the central Australian desert and nomadic Lapps in arctic Finland have experienced comparable degrees of cold exposure during the night (112, 113). Both showed thermoregulatory adaptation leading to lowered thermoregulatory thresholds for shivering. As a consequence CBT was more reduced during sleep and undisturbed sleep could occur at low environmental temperatures. However, many modalities of thermal interventions on sleep are not sufficiently studied in detail. Additionally, effects of thermal interventions on the diverse aspects of sleep can be different in controls (young vs. older) and sleep-disturbed subjects.

7.1.1. Modulating temperatures

In humans, body heat content and hence CBT can be effectively manipulated by body immersion in a warm or cold bath. Acute changes in environmental temperature induce counter-regulatory effects in the shell (vasoconstriction or vasodilatation) in order to protect the core. However, depending on the temperature gradient, after a certain time the core cools out or heats up. Body immersion changes CBT directly by external uptake or liberation of heat via conductive heat transfer. For instance, due to rapid conductive heat loss in a cold bath CBT drops faster compared with the decrease rate observed in air at the same temperature (114). Re-warming of the shell after cool bathing leads to a characteristic after-drop in CBT (115). Many studies show effects of positive heat load on sleep, however, no study examined the effects on sleep after a cold bath.

In general, passive body heating (bathing at 40-43°C for 30–90 min; CBT increase: 1.4-2.6°C) or active body heating via exercise, can have positive effects on

many aspects of sleep not only in healthy young adults (116-120), but also in older and sleep-disturbed subject (121-125). However, the experimental conditions are of importance for the outcome (104). It has been found that warm bathing in the evening decreased sleep onset latency (116), enhanced SWS (116-120), and sometimes reduced REMS, particularly in the first REMS episode (117, 118). Bathing performed in the morning or early afternoon had no effect on sleep architecture (116, 120). In these early studies skin temperatures, CBT and sleep polysomnography were often not continuously recorded in parallel and EEG spectral analysis was not performed.

In principal, the actual level of CBT at sleep onset or the subsequent decline in CBT could be related to the appearance of SWS after warm bathing (119, 126, 127), whereas the decline in CBT can be defined as the rate of change. Additionally, a phase delay of the overt CBT nadir during the night sleep episode and increased SWA have been described after evening hot full bathing (128, 129). All these CBT characteristics can be inter-correlated, e.g. directly after a positive heat load the velocity of CBT decline is increased, the CBT level is elevated before sleep onset and as a consequence the overt CBT nadir during subsequent sleep can be delayed. Moreover, not only CBT but also other thermoregulatory variables, e.g. skin temperatures, are possible important causal factors.

In a series of experiments the effects of tiny changes in skin temperatures of only 0.4-2°C within the thermal comfort zone without significantly altering CBT were investigated on several sleep parameters. This was accomplished by a sophisticated thermal suit allowing subtle thermal changes before and during sleep (121-123). It could be demonstrated that intermittent skin temperature elevation during the night sleep episode suppresses nocturnal awakenings and shifts sleep to deeper stages in young and, especially, in older healthy and insomniac subjects (122). In addition, EEG- spectral analysis showed enhancement of low-frequency cortical oscillations by skin temperature warming (122). Studies over the whole sleep episode are necessary to verify that the sleep-depth-enhancing effect of mild skin warming can indeed be sustained. Nevertheless, these findings emphasise the contribution of skin temperatures to these effects, primarily of “proximal skin” temperatures (including the trunk) but also more distal skin regions (legs and arms). However, in order to effectively separate proximal from distal skin regions (hands and feet) a method has to be developed which clearly separates the intermediate lower arm and lower leg from the proximal parts (e.g. trunk). Other studies using the same thermal suit, or bedsocks, to increase skin temperature within a similar range revealed that subtle skin temperature warming was associated with a rapid onset of sleep in young and older controls, older insomniacs and narcoleptics (121-125). In general, these studies demonstrate that subtle skin temperature warming is able to promote the rapid onset of sleep. More sophisticated studies with respect to skin regions are necessary to show which region exhibit strongest effects on sleep initiation and sleep architecture. Nevertheless, the increase in skin temperatures may have been the causal factor involved in the faster sleep onset and the increase of SWS in may older studies. Therefore, it is quite possible that thermal afferents provide a signal for the sleep inducing brain regions in the hypothalamus (130).

7.1.2. Modulating sleep pressure

In order to study the effects of sleep deprivation on the thermoregulatory system it is of importance to consider circadian time. All thermoregulatory variables, e.g. CBT, skin temperatures, heart rate, oxygen consumption, undergo manifest circadian variations. Additionally, each experiment needs to control for changes in behavior, e.g. changes in body position, locomotor activity, food intake, light intensity. With the CR-protocol (33, 34), it was shown that total sleep deprivation does not significantly change CBT, distal and proximal skin temperatures, heart rate and energy expenditure measured 24 hours later at the same circadian time (35). This finding indicates that sleep pressure, which is strongly increased by a total sleep deprivation, may not affect the thermoregulatory system under these circumstances. However, it is possible that the CR protocol, e.g. constantly lying down in bed, could have masked the sleep deprivation effect on the thermoregulatory system. Thermoregulatory effects induced by e.g. controlled exercise bouts could be affected by sleep deprivation (106). The interaction of different levels of sleep pressure with the thermoregulatory system has been investigated in a 40-h crossover study under constant posture conditions. A nap protocol (10 cycles with 150 min of scheduled wakefulness and 75 min of scheduled sleep each cycle) was compared with a classical CR (40-h sleep deprivation) (42). This comparison allowed, at least partially, a separation of homeostatic and circadian effects of sleep regulation in relation to the thermoregulatory system under the same postural conditions. The circadian pattern of CBT, distal and proximal skin temperatures did not differ between the two protocols indicating independency of the homeostatic build-up of sleepiness (sleep pressure) (42) (see Figure 5). It was concluded that all the measured circadian patterns are not influenced by a masking process via countermeasures taken by the subjects to remain awake. The build-up of sleep pressure over 40 h had in fact no, or only minor, thermoregulatory consequences during wakefulness. A comparison of nocturnal 8-h sleep episodes before and following the two protocols revealed that CBT, distal and proximal skin temperatures did also not differ in spite of the large difference in SWA. This study supports the 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 (131). For a final conclusion, however, longer sleep deprivations need to be tested whether the thermoregulatory system remains independent of sleep pressure.

7.2. In rodents

7.2.1. Modulating temperatures

In rodents, exposure to an ambient temperature outside the thermoneutral zone has prominent effects on temperature regulation and sleep regulation, particularly

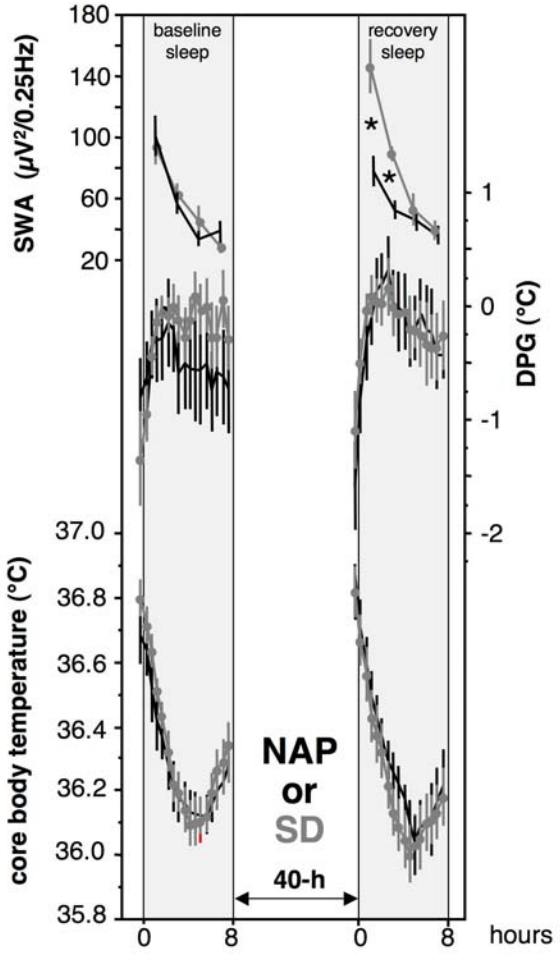

Figure 5. Time course (mean±sem; N= 8 men) of slow-wave activity (SWA, Cz-A2 -derivation), distal - proximal skin temperature gradient, and CBT during the baseline night and the recovery night (redrawn from (42)). NAP = 10 x 75/150 min sleep/wake cycles regularly distributed over 40 hours (black lines). SD = 40-hour sleep deprivation (grey lines). Dark phase: 0 lux; light phase: <8lux. Note that, in contrast to SWA, no significant differences were found in any body temperature measures between NAP and SD during baseline and recovery night. *Significant differences between the 2 protocols (p at least <0.05). Gray areas indicate the dark phase of nocturnal sleep.

when this exposure is acute. Outside the thermoneutral zone, thermoregulatory demands override sleep regulatory demands. REMS seems to be the most sensitive to changes in ambient temperature. In the rat daily amounts of REMS decreased when temperature decreased from 23ºC, (7-9% REMS), to -10ºC (0% REMS) (78, 86), indicating that REMS is incompatible with low ambient temperature in the rat. Cats and Djungarian hamsters were shown to enter REMS easier when brain temperature was relatively low. (82, 132), but also in these species REMS will probably disappear when temperature is lowered further. Low ambient temperature is now applied as a REMS deprivation tool (133) or to investigate REMS regulatory mechanisms (82, 134, 135).

Increasing ambient temperature is a method applied more frequently. The amount of REMS during the light period in rats showed an almost linear increase from approximately 5% at 23ºC to 11% at 29ºC (136). Above 30ºC REMS virtually disappeared (136). Maximum amounts of sleep are obtained around 30ºC, but rats prefer to sleep at lower ambient temperatures (137). In general increasing ambient temperature seems to increase NREMS pressure. Increasing ambient temperature to approximately 34ºC for 3 hours, with brain temperature of approximately 40ºC, resulted in more slow-waves during subsequent NREMS compared to sleep-matched controls (138). Under these warm conditions animals slept less compared to baseline, indicating that sleep demand was overruled by the high ambient temperature. The amount of REMS did not change compared to control and brain temperature was significantly decreased in the first 5 h of recovery.

In an experiment where ambient temperature was increased to 30ºC for 24 h, starting at dark onset, brain temperature on the cortex was significantly increased by 0.3ºC but hypothalamic temperature did not change (139). This treatment did not result in a change in the amount of the different vigilance states, but did result in an increase in SWA in NREMS in the dark period. A similar 24-h experiment where ambient temperature was increased to 32ºC and brain temperature on the cortex by approximately 1ºC resulted in increased NREMS and increased SWA in the dark period (140). The data indicate that increases in NREMS and sleep depth can be induced without increasing hypothalamic temperature.

Next to manipulation of ambient temperature one of the main interventions applied in animals is the manipulation of brain temperature. Heating the POAH for 1 h (1.0ºC above baseline), increasing hypothalamic brain temperature locally in combination with sleep-wake EEG recordings, in cats, resulted in increased NREMS and SWA in NREMS (141). Cooling during 1 h (2.0ºC below baseline) did not elicit a change in sleep or the sleep EEG.

In general, the data indicate that an acute increase in ambient or brain temperature can influence the occurrence of NREMS and SWA in the NREMS EEG, but the results depend on the level of temperature increase.

7.2.2. Modulating sleep pressure

Brain temperature is higher during sleep deprivation compared to baseline (85, 132, 140, 142-144). Subsequent recovery is characterized by a decrease in brain temperature below baseline and an increase in NREMS and SWA in NREMS (85, 140, 142, 143). These results were interpreted as the recovery from a heat load incurred during the sleep deprivation (145), and a clear negative correlation between brain temperature and the amount of NREMS was obtained (132, 142). However, there was no significant correlation between brain temperature and SWA in NREMS (132, 142) ruling out the possibility that brain temperature is determined by the depth of sleep directly (also illustrated in Figure 6)

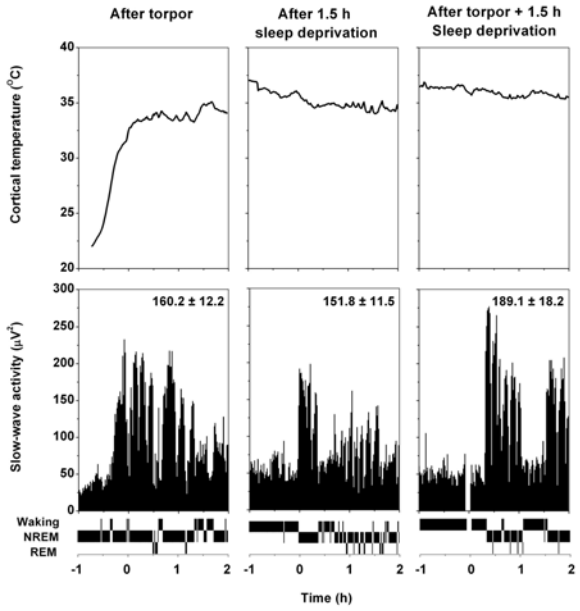

Figure 6. Representative records of brain temperature measured at the parietal cortex, slow-wave activity (SWA; mean EEG power density between 0.75-4.0 Hz), and vigilance states of the same Djungarian hamster emerging from torpor (left), in recovery after 1.5 h of sleep deprivation (SD, middle), and after torpor + 1.5 h SD (right). Data points represent mean values over 15 4-sec epochs (1 min). Hour zero defines the end of torpor (cortical temperature reaches 32ºC, (196)) or SD. Note that SWA values are higher after torpor or torpor combined with SD compared with SD alone. Note the lack of a relationship between the level of SWA during NREMS and the corresponding brain temperature. Values within the bottom panel are means (±SEM) SWA in the first 30 min after terminating of torpor or SD (as percentage of 24-h baseline, n=8, (176)) and were significantly different between torpor + SD and SD alone ($p<0.01$, 2-tailed paired t-test, after significant ANOVA for repeated measures).

In addition, in Djungarian hamsters, well adapted to a short photoperiod (winter) with brain temperature 1°C below long photoperiod (summer) levels, recovery sleep after a 4-h sleep deprivation is accompanied by an increased in brain temperature (132). This is in contrast to the long photoperiod where recovery sleep is accompanied by a decrease in brain temperature (85, 132). In this case a correlation between brain temperature and SWA in NREMS, supported the notion that brain temperature during recovery sleep is set to the same level in both photoperiods (132), suggesting that there may be an optimal temperature for high-amplitude NREMS slow-waves.

In other experiments increased ambient temperature was combined with sleep deprivation. However, two very similar experiments increasing ambient temperature to 32ºC during sleep deprivations of 2.5 h (140) and 3 h (143) did not give consistent results. The sleep deprivation of 2.5 h resulted in a short lasting increase in NREMS and SWA (140), but this was not found after the 3-h sleep deprivation (143). In contrast, after the 3-h sleep deprivation a short lasting increase in REMS was observed (143), which was not found after the 2.5-h sleep deprivation (140). It can be asked whether consistent results can be obtained with these relatively short sleep deprivation durations in the rat. A more systematic approach, with different ambient temperatures and slightly longer sleep deprivations, is needed to resolve these issues.

7.2.3. Brain temperature, the sleep electroencephalogram and temperature sensitive neurons

Not only vigilance states are influenced by changes in brain temperature, the EEG is influenced as well. Analysis of the EEG of the Djungarian hamster during entrance into the hypothermic state torpor (see VII Hibernation and daily torpor in relation to sleep), and the EEG of either rats, cats or humans which were actively cooled showed that, when brain temperature is decreased, the amplitude and frequency of the EEG is decreased as well (146-149). The relation between brain temperature and the frequencies of the EEG followed a Q10 of approximately 2.5 (148), meaning that when brain temperature decreased by 10ºC prominent frequencies in the EEG became 2.5 times slower. Significant changes in frequencies of the EEG related to day-night differences or menstrual cycling, can be observed as well (150). The effect may be relatively small, but can be significant, even for frequencies in the slow-wave range (151). Faster frequencies like the theta peak in rodents (6-9 Hz) (150, 151) and activity of faster frequencies (>10 Hz) (151) are influenced significantly by the daily modulation of brain temperature. Therefore, effects ascribed to some unknown circadian factor (143, 152) or through hormonal changes (153, 154) could also be caused by changes in brain temperature (151). Analyzing the EEG at equal core body temperature or brain temperature is important to prevent mixing of temperature effect with other factors (155).

In addition to the above mentioned manipulations and in relation to the function of the POAH in sleep and temperature regulation, animal research allows the recording of the electrical activity of neurons in the POAH with electrophysiological techniques. In general these kinds of measurements reveal, next to temperature insensitive neurons, the activity of two distinct types of neurons that either increase firing rate or decrease firing rate when temperature increases. The first group is called 'warm sensitive', whereas the latter is called 'cold sensitive'. Cold sensitive neurons, when observed, can be considered to be genuinely cold sensitive, because a biochemical process (i.e. neuronal firing) that decreases in speed when temperature is increased is quite unique. In contrast, a biochemical process that increases its speed when temperature rises is the normal condition and has been explained theoretically at the end of the 19th century (156, 157). Many processes (i.e. firing rate of SCN neurons (158); the frequency of prominent EEG waves (151); muscle contraction (159)) become twice to three times as fast when temperature is increased by 10ºC ($2<Q_{10}<3$)

indicating that it is a general property of living tissue ranging from cell to behavior.

In order to identify warm sensitive neurons, two definitions can be found in the literature. Either the increase in firing rate of the neuron needs to be more than double when temperature is increased by 10ºC (Q_{10}>2) (160), or the increase in firing rate needs to be more than 0.8 impulses/sec/1 ºC warming (161). Both definitions are inadequate because in both the risk of including false positives is large. The 'Q_{10} > 2' definition ignores that many biochemical processes have a Q_{10} between 2 and 3. Therefore, a Q_{10} > 3 needs to be reached before one can be relatively certain that the neuron is genuinely warm sensitive and that the firing rate change can be distinguished from the passive biochemical response of the surrounding neurons. In the second definition fast firing neurons have a large chance to be included, even when they follow the passive Q_{10} rule of doubling their activity when temperature is increased by 10ºC. Nevertheless, genuine warm sensitive neurons can be found in several areas of the brain (i.e. the POAH (162); the diagonal band (163)).

In addition, the firing rate of these temperature sensitive neurons is vigilance state dependent. In general, warm sensitive neurons increase their firing rate at NREMS onset. In contrast, cold sensitive neurons increase their activity during waking (162, 163). To be able to distinguish the vigilance state related changes in activity from temperature related changes it is important to add polysomnography to the electrophysiological recordings (164). Afferents from the lateral tegmental system and the locus coeruleus are probably involved in the vigilance state related changes in neuronal activity observed in the POAH (165). The changes in activity in the ensemble of neurons are thought to coordinate the changes in vigilance states in response to the thermoregulatory demands encountered.

8. HIBERNATION AND DAILY TORPOR IN RELATION TO SLEEP

When individual animals are subjected to prolonged unfavorable environmental conditions, they may respond by migration, adaptation or, if all else fails, death. All things considered, hibernation is one of the most extreme adaptive behaviors in endotherms. In general hibernating mammals are small with weights between 10 g and 1 kg (166). During the hibernation season the animals remain in their burrow, do not eat, and spend a considerable amount of time with body temperatures below euthermia. This torpid state is not due to a loss of thermoregulatory capacities, but is a regulated hypothermic state which is entered voluntarily and can be terminated by the animal itself. During deep torpor metabolic rate is only a fraction of that during normothermia (167) and body temperature can drop by more than 35°C (168).

In deep hibernators the torpid state lasts for several days or weeks. A group of smaller mammals (bodyweights between 5 and 50g (166)) adopted the strategy of daily torpor. Here body temperature is dropped during the rest phase for a couple of hours, but during the active phase it is back to euthermia. These animals usually do not build up a fat reserve, and their main energy supply, even during a period with regular bouts of daily torpor, is food in storage or collected during daily foraging. Both hibernation and daily torpor result in substantial energy savings (169-171). The ability of animals to enter torpor is therefore considered to be an adaptive mechanism which permits the conservation of energy during unfavorable environmental conditions.

It is unclear whether circadian rhythms continue during hibernation. In ground squirrels, normal 24-h rest-activity rhythms only slowly re-appeared a couple of days after termination of deep torpor, and this return correlates with the number of vasopressin containing neurons in the SCN (172). Also the distribution of sleep in hibernating ground squirrels between deep torpor bouts does not show a circadian modulation (173). Even Djungarian hamsters, which display daily torpor and are known to still have a functioning circadian clock under those conditions (174) display no day-night amplitude of sleep and wakefulness on days without torpor (175). In contrast, homeostatic responses to sleep deprivation are intact (6, 9, 176, 177). Also temperature regulation and other homeostatic regulatory processes are still functioning (178). Under certain circumstances a small circadian modulation of body temperature can be observed during hibernation (179). We may, however, conclude that the contribution of the circadian clock to sleep or temperature regulation is extremely reduced during torpor whereas the homeostatic regulation seems to be virtually intact.

8.1. Thermoregulation and metabolic rate

There is general agreement that the reduction in metabolic rate during torpor is considerable and important for survival. However, it is still a matter of debate how the animals reach the reduction in metabolic rate. The traditional view was that body temperature is reduced and that metabolic rate follows this reduction. The Q_{10} of metabolic rate between euthermia and torpor often is close to 2, typical for a passive biochemical reaction (156, 157). Therefore the main reduction in metabolic rate seemed to be explained by the temperature effect on biochemical processes in the body (180-182).

However, during torpor entry or during torpor at relatively high body temperatures Q_{10} values above 3 for metabolic rate were observed in some species. In these cases an additional physiological inhibition was needed to explain the reduction of metabolic rate (183-185). In those cases metabolic rate may be actively down regulated before torpor entry and the decrease in body temperature is the consequence of the reduction in metabolic rate (186-188). As an alternative hypothesis it has also been proposed that metabolic rate is a function of the difference between body temperature and ambient temperature, similar as during euthermia (186). As this difference is very small during torpor, metabolic rate is equally reduced.

Reduced pH is known to slow down metabolic processes and may inhibit metabolic rate during deep torpor (189-191). The respiratory quotient (RQ, the ratio between

CO_2 production and O_2 consumption) in ground squirrels drops during entrance into hibernation and rises during arousal (192), suggesting storage of CO_2, which may decrease pH. In the Djungarian hamster, at entrance into daily torpor, RQ increases whereas it decreases before emergence from daily torpor (192). Other candidates for metabolic rate reduction are changes in enzyme activity. During deep torpor in hibernating ground squirrels mitochondrial respiration is reduced by 50%, compared to non-torpid individuals (193, 194).

The present data support the notion that there is a difference in the mechanism of metabolic rate reduction between deep hibernators and animals that display daily torpor (195). Detailed analysis of metabolic rate, body temperature, and ambient temperature during complete torpor bouts suggests that during daily torpor the reduction in metabolic rate is largely determined by the decrease in body temperature, whereas in hibernators some kind of extra reduction in metabolic rate is applied.

At entrance into torpor the animals let body temperature drop below euthermic temperature. In general a reduction in body temperature below 30-32°C lasting at least 1-2 h is defined as torpor (174, 196). During torpor the animals remain in a curled up position and show no behavioral signs of accelerated cooling. Direct and indirect calorimetry did not show a significant change in thermal conductance during entrance into torpor (186) or a difference in conductance between torpor and euthermia (197), indicating that animals are not actively accelerating heat loss during entrance into torpor. Differences in decrease rate of body temperature have been observed between hamsters entering hibernation and freshly killed hamsters at the same ambient temperature. The latter cooled faster, a difference caused by a relatively slow drop in metabolic rate of the animals entering hibernation compared to the dead animals (198). In general animals entering torpor reduce metabolic rate slowly and passively let the body lose its heat.

When the ambient temperature is at a tolerable level (0-5°C for sustained torpor, 10-15°C for daily torpor) the threshold level for thermoregulatory responses is adjusted below the actual ambient temperature (199). However, for some unknown reason, torpor does not persist during the entire hibernation season. In hibernation, deep torpor is interrupted on a regular basis by a short (<24 h) euthermic period (200, 201). It appears that an internal oscillation brings the organism back to its higher rate of life. Above 0°C body temperature, torpor bout length correlates negatively with ambient temperature and metabolic rate of the animal during the hibernation bout (202, 203). Experiments where ambient temperature was fluctuated during sustained torpor, suggest that the arousal is not induced by a process accumulating in the course of the torpor bout, but that a separate arousal process exists which is more susceptible at higher temperatures (204). Although the mechanism of the arousal is still not known, its origin appears to be completely endogenous.

The question of the reason for these arousals, is important. Energy conservation is the function of hibernation, and it is very effective in doing so. Energy expenditure during the hibernation season is reduced to less than 15% of what the animals would have expended if they remained euthermic (167). However, the energetic costs of the periodic arousals constitute 64-90% of the total energy expenditure during the hibernation season (167, 205, 206). It has been proposed that arousals are required to eliminate metabolic waste products (207, 208), to replenish blood glucose levels (209), or to restore cellular electrolyte balance (210). All these hypotheses have not survived critical experimental testing.

At the beginning of the 1990's a new hypothesis, based on EEG observations proposed that animals terminate torpor and return to euthermia to restore a sleep debt (211, 212). NREMS was deepest at the beginning of a euthermic period and most of the euthermic period was spent in sleep (see also Figure 6 left panel). The putative restorative function of NREMS was thought to be incompatible with torpor.

8.2. Sleep and torpor

Animals in torpor appear to be sleeping. They remain in their nest, in a sleep-like posture, with elevated arousal thresholds. Based on several behavioral and physiological findings it is generally accepted that torpor has evolved as an extension of sleep. Sleep, daily torpor and hibernation were therefore considered to be homologous processes of energy conservation (213) characterized by a further decrease in body temperature, and an EEG which resembles euthermic NREMS. Analysis of the EEG when animals enter torpor shows that rodents are mainly in NREMS (196, 214). As temperature decreases the amount of REMS is reduced and disappears from the EEG below 25°C (196, 214, 215). As temperature decreases further the amplitude of the EEG decreases progressively (216) and prominent frequencies in the EEG slow down (148, 151, 217). As a result vigilance states cannot be determined reliably with EEG below 20°C. Recordings of neuronal activity in the hypothalamus of hibernators at brain temperatures between 10-20°C indicate that these animals keep alternating between long NREMS and short waking bouts (215). Below 10°C it is not possible to determine vigilance states with electrophysiological methods (215). These findings supported the hypothesis that NREMS is an adaptive behavior for energy conservation, which function is strengthened during torpor (79, 170, 218).

However, when the animals subsequently emerge from deep hibernation or daily torpor they immediately enter deep NREMS with high SWA (196, 211, 212) (Figure 6, left panel), suggesting that during torpor the function of sleep cannot be fulfilled completely return to euthermia is necessary to recover from a sleep deprivation incurred during hypothermia. By combining daily torpor with sleep deprivation experiments in the Djungarian hamster it was shown that torpor and sleep deprivation had an additive effect on subsequent sleep, confirming the 'sleep deprivation during torpor' hypothesis (176, 217, 219)

(Figure 6). In contrast, similar experiments in hibernating ground squirrels resulted in rejection of the hypothesis (9, 177, 220).

There appear to be fundamental differences between animals who have multiple day torpor bouts and animals who display daily torpor. The mechanism of metabolic rate reduction seems to differ (195). In daily torpor animals make use of the normal reduction in metabolic rate and body temperature which occurs during the start of the rest phase and at entrance into sleep. By reducing the set-point in body temperature the animals save energy, but are able to reverse back to activity within a reasonable short period of time. Hibernators who remain torpid for more than a day seem to apply additional mechanisms to reduce metabolic rate, beyond those used by animals who only display daily torpor. A second fundamental difference is the effect of hypothermia on subsequent sleep. This difference led to the rejection of the 'sleep deprivation during torpor' hypothesis in hibernators (220), whereas for animals who display daily torpor the hypothesis is still considered to be valid (217).

In rodents who display deep multiple day torpor like ground squirrels, circadian regulation of temperature and sleep seems to be reduced to a level that currently cannot be measured reliably. Homeostatic regulation, however, is intact. Although applied in an extreme way, animals that enter daily torpor seem to make use of the same processes, which reduce body temperature at the onset of sleep in humans. This similarity may provide an opportunity to investigate the relationship between body temperature and sleep in much more detail.

9. CONCLUSIONS

Sleep and temperature regulation are closely related. In the past it was thought that changes in CBT were the most prominent determinants of the influence of temperature on sleep initiation and depth of sleep. However, more recent studies suggest that the physiological changes related to heat loss, occurring in the periphery, are more important - sleep initiation is easier when the body is prepared to loose heat. From that point of view results from old experiments may need to be reinterpreted and more sophisticated experiments need to be carried out. Eventually this will lead to a deeper understanding of the relationship between sleep and body temperature regulation and, in addition, may lead to treatments of sleep disturbances via thermo therapeutic strategies.

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