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PHYSIOLOGICAL REVIEW

Thermoregulation as a sleep signalling system

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Summary Temperature and sleep are interrelated processes. Under normal environmental conditions, the rhythms of core body temperature (T_C) and sleep propensity vary inversely across the day and night in healthy young adults. Although this relationship has drawn considerable interest, particularly in recent years, it is still not known whether this relationship is causative or merely coincidental. As somnogenic brain areas contain thermosensitive cells, it is possible that the sleep/wake cycle may be directly affected by thermoregulatory changes themselves. That is, that changes in temperature may trigger, either directly or indirectly, somnogenic brain areas to initiate sleep. There is now an emerging body of evidence from both physiological and neuroanatomical studies to indicate that this may indeed be the case. This paper will examine the literature relating to this relationship and propose a model where thermoregulatory changes provide an additional signal to the brain regions that regulate sleep and wakefulness. The model attempts to explain how temperature changes before and after sleep onset act in a positive feedback loop to maintain a consolidated sleep bout.

Human thermoregulation

Thermoregulation refers to the processes required to maintain the body temperature within a narrow set range essential for cell functioning. One of the first models of temperature regulation was formulated by Aschoff in 1956[1] and incorporated the idea of a core and a shell. In such a model, the temperature of the core (T_C) is maintained within a specific range (around 37 °C). In contrast, the shell is dependent largely on environmental temperature with the extremities of the body, such as the hands and feet, varying over several degrees. For example, at room temperature (23 °C), distal skin is approximately 7–8 °C below the core. In contrast, at 35 °C the hands and feet are only 3–4 °C below the core. Core body temperature can only be held constant if heat uptake and heat production are balanced by heat loss from the body. This regulation of body temperature is achieved by the activation of several effector mechanisms to achieve heat production or heat loss.

For heat loss to occur, blood that carries heat from the core, is shunted from the muscles to the cutaneous vascular beds, primarily as a result of a decrease in sympathetic tone. Peripheral skin is considered the major site of heat loss, as it is rich in arteriovenous anastomoses, which are involved

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in the regulation of blood flow and are approximately 10,000 times faster than capillaries at shunting blood.[2] The augmented skin blood flow facilitates heat loss in several ways. First, the increased blood flow increases the heat transfer per unit of time, which also functions to reduce the normal arteriovenous (or counter-current) heat exchange. Second, the increase in skin temperature creates a positive thermal gradient with the environment and allows the conduction, convection and radiation of heat to occur.

The production of heat also occurs by several distinct mechanisms, the activation of which is dependent on environmental and behavioural conditions. At rest, approximately 56% of the heat generated comes from the organs and 18% from the musculature. Under constant routine conditions (when activity, food intake and sleep are strictly controlled), the daily variation in heat production co-varies with heart rate. To maintain thermal homeostasis under cold stress, metabolic heat production must be augmented by additional muscle activity, either voluntarily or via shivering. Voluntary muscle activity includes behavioural responses to the cold such as jumping on the spot or rubbing hands together.

Autonomic aspects of temperature regulation

Although temperature can be influenced by conscious actions, nearly all of the highly specific and subtle day-to-day processes involved in thermoregulation are unconscious and controlled by the autonomic nervous system.[3] Information about environmental temperature or the temperature of objects is registered by receptors in the skin. These thermoreceptors fall into two general categories: cold receptors or those that detect changes in temperature in the order of 20–30 °C, and warm receptors detect temperature changes above 30 °C.[4] Both types of receptors have firing rates that attenuate if temperature remains constant but will increase rapidly in response to a change in perceived temperature. At the level of the spinal cord and thereafter at each ascending hierarchical level, thermal information is processed and integrated. Information regarding the degree and nature of this integration has been obtained from single neuronal studies (for review see Ref. [5]) involving areas such as the hypothalamus, medial forebrain, and thalamus. It is thought that these multiple thermostats or integrators can communicate with, and facilitate or inhibit, other sites. Such integration results in the spatial and temporal information needed to drive the relevant effector mechanisms. Although thermal integration is known to occur at the level of the spinal cord, a group of neurones in the pre-optic area/anterior hypothalamus (PoAH) is now considered to be the predominant integrator of thermal information.[6] The importance of the PoAH in thermoregulatory integration can be seen from experiments performed on mammals where lesions in this area have resulted in impaired thermoregulatory responses to changes in ambient temperature.[7,8] In addition to receiving afferent inputs from thermoreceptors in the skin and spinal cord[7,9] the PoAH also receives afferent inputs from thermosensitive neurones in the PoAH itself.

Servocontrol or 'set point' model of temperature regulation

Although the exact mechanism by which the PoAH maintains precise control over body temperature is unclear, one of the more accepted models incorporates the idea of a set point and the concepts and terminology of servocontrol systems typically used in the field of engineering. In such a model, core body temperature is maintained within a specific range by comparing the moment-to-moment temperature with a desired value or set point by the PoAH. The PoAH then generates an error signal that is proportional to the difference between the set point and the measured temperature. Efferent pathways controlling various effector systems are then specifically activated so as to minimise the error and maintain homeostasis.

The circadian regulation of temperature

The principles of thermal homeostasis described above enable the body to respond appropriately to acute changes in the environment. In addition, thermal homeostasis has a temporal aspect that facilitates the prediction of environmental challenges, thereby allowing corrective responses to such challenges to occur in advance. This concept of predictive homeostasis is clearly represented in the thermal physiology of the circadian system.

In healthy individuals, (T_C) demonstrates predictable sinusoidal rhythmic variability over each 24-hour period with a peak around 2100 h and a minimum around 0500 h.[10] This variability is known as a circadian rhythm (*circadian*; from the Latin *circa* and *dies*, meaning 'around a day') and is

applied to any physiological process that occurs rhythmically and persists with an endogenous period of approximately 24 h in the absence of rhythmic environmental time cues. Research has found that both peripheral heat loss and heat production contribute to the circadian variability in T_C with increased peripheral skin temperature being the primary contributor to the evening decline in T_C and increased heat production being the major contributor to the morning increase in T_C. Due to time lag needed for heat loss from the periphery to reach the core (called thermal inertia), the increase in peripheral heat loss precedes T_C changes by approximately 25 to 100 min.[10]

Because the circadian period is so similar to the light/dark cycle, it was considered for some time that circadian rhythms were a reflection of the transition from day to night and night to day. However, the endogenous period of T_C was first demonstrated by Aschoff and Wever in 1962.[11] By measuring T_C in individuals removed from all external time cues (temporal isolation), it was discovered that the period of the T_C rhythm was slightly longer than the 24-hour day, which indicated that an internal pacemaker was likely to generate the rhythm of T_C.[12,13] In addition, the fact that the endogenous T_C period was clearly, albeit only slightly, different to 24 h (approximately 24.2 h)[14] led to the suggestion that the endogenous T_C rhythm must be normally synchronised or set to the earth's 24 h cycle by external time cues. In 1972, a group of cells were located in the anterior hypothalamus that, when removed, completely abolished the daily rhythms in drinking behaviour and activity of rodents.[15] It is now established that this group of cells, called the suprachiasmatic nuclei (SCN), is the primary integrator and endogenous oscillator (or pacemaker) of the circadian system in mammals.[16] Environmental information reaches the SCN from the retina via the monosynaptic retinohypothalamic tract and also from a multisynaptic pathway involving the geniculohypothalamic tract.[17] As environmental information is capable of influencing the temporal activation of the SCN,[18] the environment can act as a 'synchroniser' of circadian rhythms.[16] This capacity to influence the timing of a biological rhythm is called entrainment. Neural projections from the SCN innervate the PoAH as well as several brain structures known to regulate sleep and wakefulness (see Ref. [19] for review). It is through these connections that the circadian system is thought to influence T_C and the sleep/wake cycle.

Regulation of the sleep/wake cycle

While the rhythm of T_C is one of the most well recognised circadian rhythms, many physiological processes and behavioural functions, including sleep, are circadian in nature. In order to determine which aspects of sleep are influenced by the circadian system, experimental protocols have been developed in which an individual's sleep/wake cycle becomes disassociated from circadian control.[12,13] Of these experimental protocols, one of the most common designs is called a forced desynchrony protocol. Subjects adhere to a specified sleep/wake schedule with a period longer than normal (such as 28 h) and remain isolated from environmental cues. Being removed from environmental cues, other physiological rhythms (such as T_C, melatonin, cortisol) free-run with the period of the circadian pacemaker.[14] As a result, sleep is initiated at different periods of circadian time over a number of days, with the changing influence of circadian system typically being measured indirectly through changes in T_C. These experiments have demonstrated that sleep onset latency (SOL) decreases rapidly as T_C declines and is shortest around the T_C minimum. In contrast, sleep is consistently terminated on the ascending portion of the T_C curve. From these results, it has been concluded that sleep initiation (sleep propensity) and sleep duration are influenced by circadian phase.

A schematic representation of the generation of circadian rhythmicity is illustrated in Fig. 1. In addition to a circadian component, the sleep/wake cycle is influenced by a homeostatic component. The interaction between these two components of sleep is schematically illustrated in Fig. 1 and is referred to as the two-process model of human sleep regulation.[20] Briefly, the homeostatic process (S) increases as the time spent awake increases. It is this built up drive (or 'sleep pressure') that determines the amount of deep sleep (or slow wave sleep; SWS) that occurs in the first part of the sleep period. Immediately following sleep onset, sleep pressure declines rapidly. Process C, refers to the influence of the internal body clock that, unlike process S, interacts with the sleep/wake cycle through the promotion of both sleep and wakefulness. Process C increases across the day and reaches its peak shortly before habitual sleep onset time. In contrast, process C decreases across the night and reaches its minimum shortly before habitual wake up time. In this way, process C serves to consolidate wakefulness at the end of the day when process S is high and also to consolidate

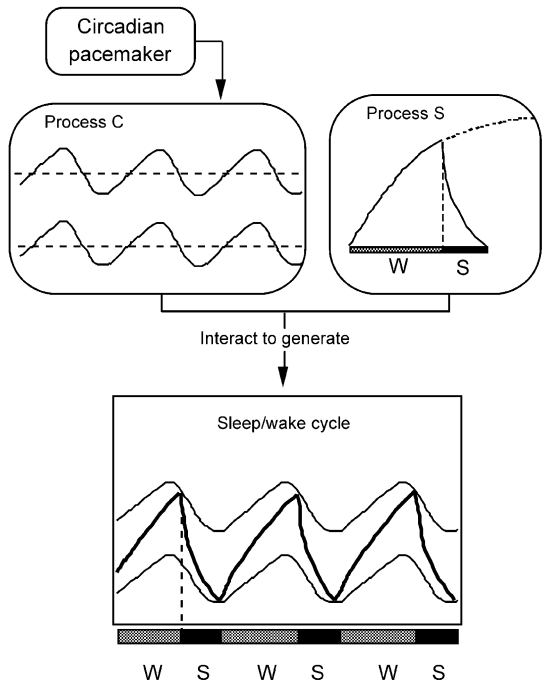

Figure 1 Two-process model of sleep regulation (adapted from Ref. [21]) illustrating the oscillations of Process S between the upper and lower thresholds of sleep regulated by Process C.

sleep at the end of the night when process S is low. As a result of the positioning of both these processes a consolidated 7–9 h bout of sleep can occur at night and a consolidated 15–17 h bout of wakefulness can occur during the day.

Practice points

- sleep is influenced by at least two processes, a homeostatic and a circadian process
- while changes in T_C can reflect changes in circadian function, it also reflects changes in thermoregulatory control

Relationship between sleep and temperature

Historically, changes in T_C accompanying changes in sleep propensity have typically been attributed to the influence of the circadian system on sleep. This belief was a consequence of the association between the timing of sleep onset and changes in T_C consistently observed under temporal isolation and in forced desynchrony protocols. However, as will be discussed in following sections, a clear relationship between these variables also exists under a wide range of experimental conditions where both sleep and temperature have been manipulated. As such, it is possible that the actual thermoregulatory changes themselves may play a role in sleep regulation. That is, in addition to circadian and homeostatic processes, sleep propensity may be affected by a thermoregulatory process.

Changes in temperature following sleep onset

Despite the current interest in the relationship between sleep propensity and temperature, the association between sleep, in general, and temperature has been recognised for many years. For example, in the early 20th century there was some debate as to whether the nocturnal reduction in T_C was a result of sleep itself or simply due to a change in posture. From initial studies, it was concluded that, provided subjects remained still and quiet in bed, neither sleep nor waking affected temperature.[24] However in 1933, Kleitman and Doktorsky[25] demonstrated that, while lying down did reduce T_C (by a mean value of 0.11 °C), a further reduction in T_C was observed at sleep onset with a mean temperature decline of 0.15 °C. This so-called sleep-evoked effect of sleep onset on T_C has been replicated in several laboratory studies (e.g. Ref[26]) and confirmed under the strictly controlled conditions of a constant routine protocol. Under these conditions, a mean sleep-evoked T_C reduction of 0.31 °C was documented.[27]

The effects of physical manipulations of temperature on sleep

Thermoregulatory changes following sleep onset

As interest in the relationship between thermoregulation and sleep developed, experiments were conducted to determine the effects of ambient temperature on sleep quality (which includes factors such as SOL, total sleep time, nocturnal arousals, amount of SWS and the amount of rapid eye movement sleep).[28–34] Not only did these experiments provide insight into the role of temperature in the progression between sleep

states (e.g. NREM-REM; see Ref. [29] for review), but as will be discussed below, resulted in a significantly more active role of temperature in the process of sleep regulation being postulated.

Experiencing difficulty falling asleep in a very hot or cold environment is a ubiquitous phenomenon. As such, early researchers investigating the effect of ambient temperature on sleep expected that both increasing and decreasing ambient temperature would result in reduced sleep quality. Initially, results conformed to these expectations; however, ambient temperatures were typically manipulated by more than 2.5 °C.[30] In contrast, when T_C changes were induced within the normal circadian range (under 0.5 °C) opposing effects were observed. In one study, a significant SWS increase was observed in young women following exposure to a mildly cold environment (after sleep onset), sufficient to reduce T_C by 0.2 °C.[31] In another study, increasing T_C by 0.3 °C (relative to the control night) via the use of an electric blanket increased nocturnal awakenings and the number of changes between sleep stages in 16 healthy young adults.[32] Yet, it could be argued that these changes in sleep parameters simply resulted from a reduction in thermal comfort (due to the heat of the electric blanket). However, such a hypothesis could not account for the findings of a novel sleep experiment by Edwards where T_C was altered by the use of a spicy evening meal of Tabasco sauce and mustard.[35] While the spicy meal increased T_C (compared with the baseline night) for the first two hours of sleep only, this short period of elevated temperature was sufficient to significantly decrease the total amount of SWS achieved.

As a consequence of the above findings, it became clear that changes in T_C were not simply a consequence of sleep onset and resulted in the suggestion that T_C changes may, in fact, be involved in the regulation of sleep itself (e.g. Ref. [22]). While this theory was initially greeted with a degree of scepticism, further insight into the role of temperature in sleep initiation came from a series of studies where temperature was manipulated several hours prior to the initiation of sleep.

Changes in thermoregulation prior to sleep onset

A number of studies demonstrated that increasing T_C by passive heating or exercise prior to sleep could increase sleep propensity (as measured by SOL) and also increase SWS.[33,34] Although the authors of these papers suggested that it was body heating that facilitated sleep, other researchers later suggested that a reduction in body temperature may be one of the mechanisms involved in sleep regulation. Notably, if the heating occurred in the evening, SOL was significantly reduced, however, heating in the morning or afternoon did not affect subsequent SOL at habitual bedtime.[33] In light of these results, it is possible that increasing T_C by passive heating or exercise may also influence sleep via a similar mechanism. That is, passive or exercise-induced heating causes a rebound phenomena where, following a large increase in T_C (e.g. 2 °C) several hours prior to sleep onset, the homeostatic thermostat drives heat loss mechanisms in order to regain thermal balance. This results in a rapid decline in T_C together with an increase in peripheral heat loss. Interestingly, as peripheral heat loss is the predominant mechanism for the nocturnal T_C decline,[10] the above findings are consistent with the much earlier, and largely forgotten, work of Magnussen[36] who stated that peripheral vasodilation was an indicator of sleep preparedness.

Indeed, Magnussen's hypothesis has been further supported by several studies where SOL has been reduced by increasing peripheral heat loss. For example, a reduction in the normal night time latency to sleep onset was observed in both older and younger subjects following a warm evening bath.[37] Importantly, the bath significantly increased peripheral heat loss (inferred from an increased peripheral skin temperature) at the time of sleep onset compared with when no bath was taken. Similarly, a more recent study by Sung and Tochihara[38] demonstrated that SOL could be reduced simply by warming the feet in the evening (by the use of a foot bath).

From these results, it is clear that while manipulation of temperature prior to sleep can affect SWS, the most commonly manipulated sleep parameter has been SOL. More specifically, for sleep onset to be facilitated, it seems that there must be an increase in peripheral heat loss and/or a reduction in T_C around the time of sleep onset. Importantly, additional research performed by van den Heuvel and colleagues have demonstrated that the changes in temperature around sleep onset are not simply epiphenomena.[39] Specifically, these researchers observed that the changes in peripheral temperature that occur prior to sleep onset were of similar magnitude and occurred at the same time relative to sleep onset regardless of whether sleep was initiated at 2300 h or at 0100 h. That is, although the actual time of sleep onset was delayed by 2 h, the increase in peripheral temperature remained the same. Therefore, it is likely that pre-sleep changes in temperature are not simply a result of circadian regulation but are intrinsically linked with sleep onset. The changes in core and skin

temperatures before and after sleep onset are schematically illustrated in Fig. 2 (adapted from Ref. [40]). As well as the changes in absolute core temperature, the changes in distal skin (feet) and proximal skin (trunk) temperatures are shown. In addition, the rate-of-change in core body temperature as well as the distal-proximal skin temperature gradient (DPG), a measure of blood flow in distal skin regions, are illustrated.

The effects of pharmacological manipulations of sleep on temperature: A causal relationship between temperature and sleep propensity?

Not only are there clear examples of temperature affecting sleep onset itself, but also changes in temperature are highly correlated with

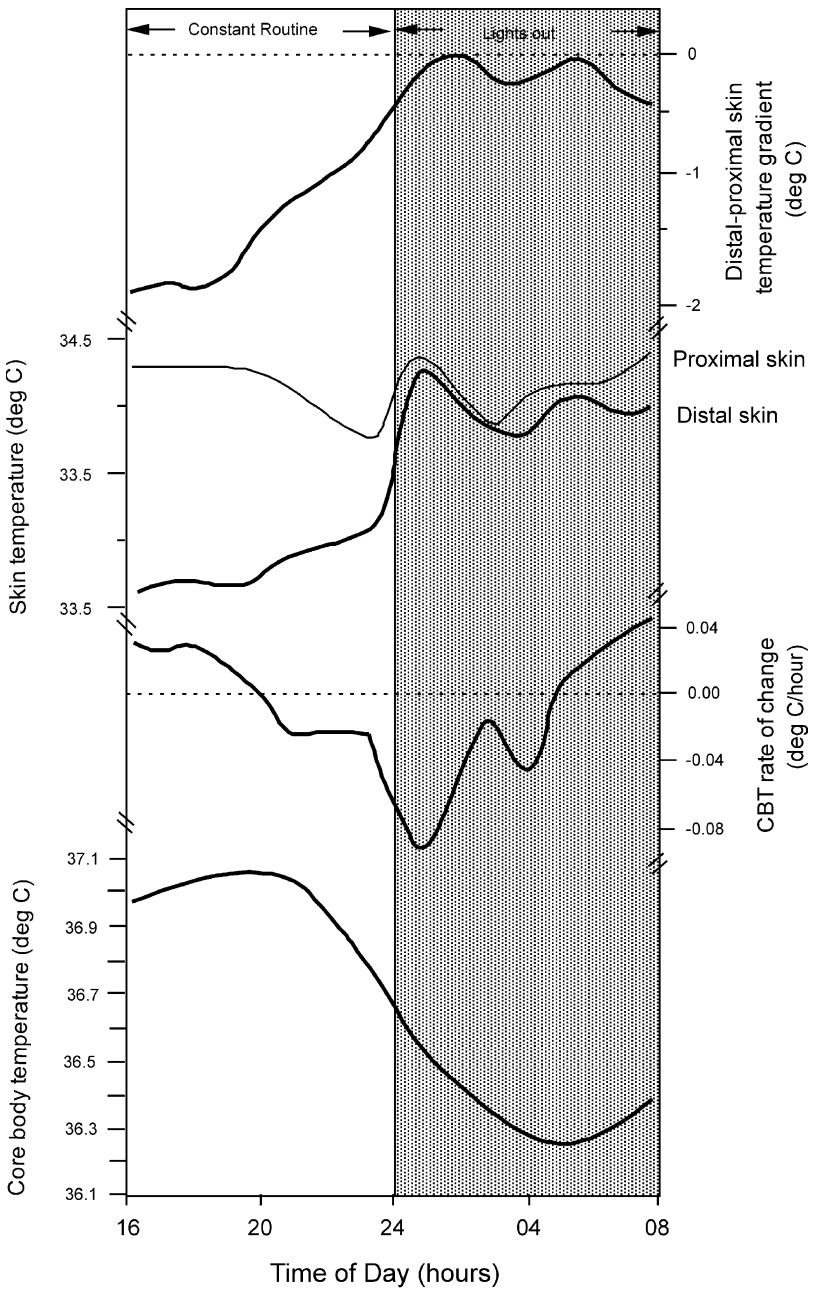

Figure 2 Schematic representation of the changes in core body and skin temperatures before and after normal bedtime. In addition to raw temperatures, the rate of change in core body temperature (CBT) and the distal-proximal skin temperature gradient (a measure of blood flow in distal skin regions) are illustrated. Figure is adapted from Ref. [40].

the likelihood of falling asleep. In recent times, thermoregulatory effects have been documented following the administration of sedative-hypnotic and also alerting agents. For example, somnogenic agents such as melatonin[41-45] and benzodiazepines[46-48] increase sleep propensity while decreasing T_C. In contrast, agents such as caffeine, amphetamines, nicotine and cocaine decrease sleep propensity and increase body temperature.[49]

The capacity of melatonin to affect both sleep propensity and body temperatures has been utilised by several research groups to examine the relationships between temperatures and sleep propensity in more detail. Not only did melatonin reduce T_C and increase peripheral heat loss, but also, the time taken to reach sleep onset was directly related to the degree of peripheral heat loss.[23,40] Using a multiple regression model, the minimum T_C following melatonin administration was a significant predictor of SOL ($r = 0.27$; $p < 0.05$). However, the best predictor of SOL was the distal-proximal skin gradient (DPG), an index of peripheral heat loss ($r = -0.47$; $p < 0.05$). As such, these findings reinforced the idea that warm feet may promote the rapid onset of sleep.[23]

However, not all researchers agree with this functional relationship between sleep propensity and thermoregulatory variables. The most common criticism raised is that the data supporting this hypothesis are only correlational and, therefore, cannot prove whether it is changes in sleepiness that are changing temperature or whether it is the change in temperature that is influencing sleep. Other researchers even debate whether the relationship even exists at all. For example, one group demonstrated that, although daytime melatonin administration (at 1100 h) did reduce T_C and SOL (in a 2-h nap from 1200-1400 h), T_C was not reduced until 1.5 to 3 h after the end of the nap. From these results, the authors concluded that the 'data suggest a dissociation of the hypothermic and hypnotic effects of melatonin'.[50] However, a problem with this conclusion is that only a single SOL was measured. Therefore, it is possible that, had multiple SOL tests (MSLTs) been used instead of a single nap, sleep propensity may have continued to increase until the time frame coinciding with the decline in T_C. It is also possible that, although T_C was not yet reducing at the time of sleep onset (due to thermal inertia), peripheral heat loss may have been increasing at this time, however, heat loss was not measured in this study.

Like melatonin, a significant temporal relationship between sleep propensity and body temperatures has been documented following the daytime administration of another soporific agent, temazepam.[47,51] Sleep propensity has been correlated significantly with both the timing of heat loss as well as the decline in T_C. In other words, sleep propensity was greatest when peripheral heat loss was maximal and when T_C was declining most rapidly.[47,51] The robustness of this relationship (see Fig. 3) was investigated experimentally by reducing the soporific efficacy of temazepam by inducing a mild temazepam tolerance (by administering temazepam for seven consecutive days) and measuring the effects on T_C and peripheral heat loss.[47] Accompanying a significant attenuation of the soporific effects of temazepam was a significant attenuation of both the decrease in T_C, as well as the increase in peripheral heat loss. Further, when sleep propensity was low, both the rate of decline in T_C and the degree of heat loss were also low but as sleep propensity increased, so did both the rate of decline in T_C and the degree of heat loss.[47] Importantly, temperature changes were associated with increased or decreased sleep propensity rather than simply sleep onset itself. Therefore these findings reinforce the idea that changes in temperature prior to sleep onset act as a trigger to feel sleepy and therefore increase the chance of falling asleep.

Perhaps the most compelling evidence to support a role of thermoregulation in sleep regulation has come from the results obtained by Kräuchi and colleagues[23] following an examination of the thermoregulatory and soporific effects of both evening melatonin administration and a carbohydrate-rich meal. Despite the fact that these treatments had different thermoregulatory effects (the carbohydrate meal increased T_C), for both manipulations, SOL was always shorter when heat loss was greater. A regression analysis revealed that in both manipulations, while the change in T_C was a significant predictor for sleep onset, the better predictor was again the degree of heat loss.[23]

Practice points

- irrespective of circadian phase, sleep onset results in a characteristic reduction in T_C and increase in peripheral heat loss
- an increase in sleep propensity is consistently associated with a reduction in T_C and an increase in peripheral heat loss
- when this reduction in T_C and increase in peripheral heat loss is attenuated, sleep propensity is also attenuated

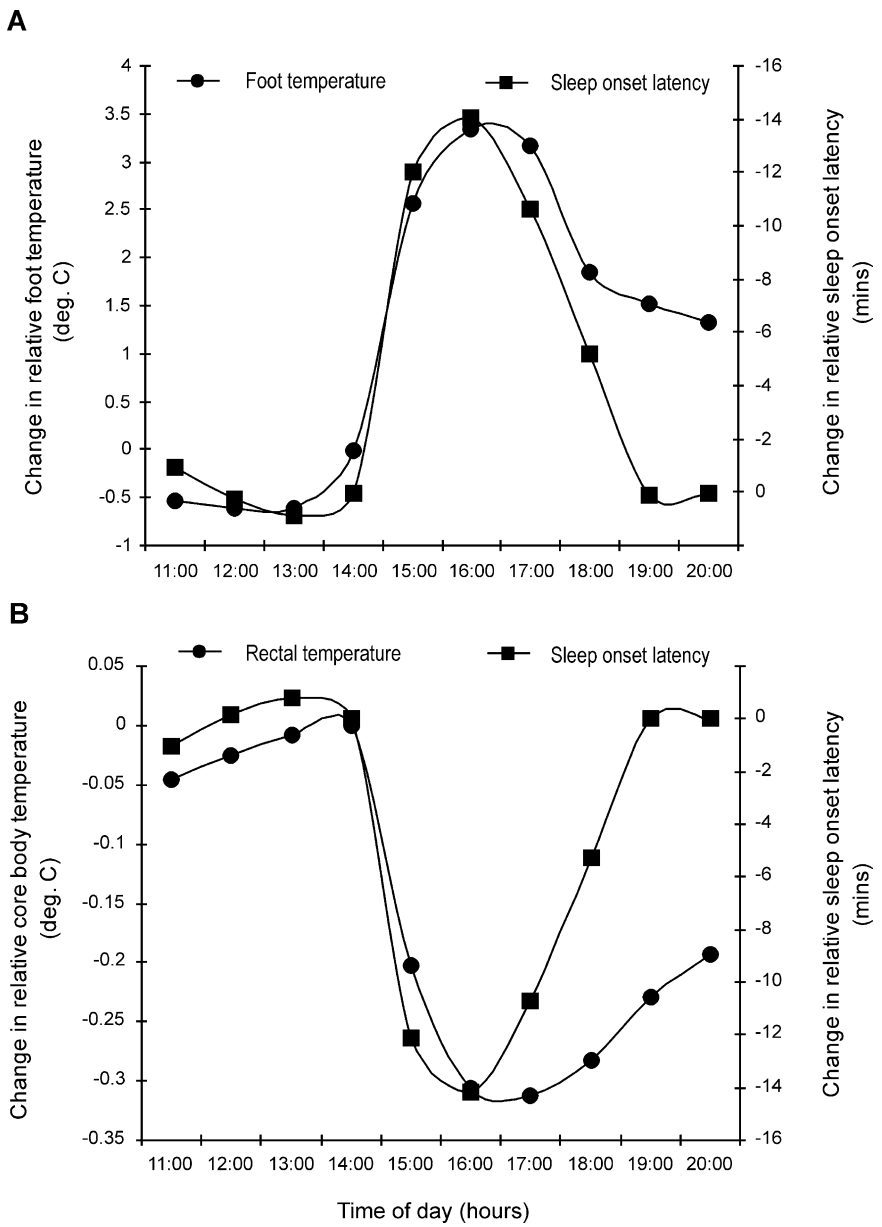

Fig. 3 Illustrates the temporal relationship between relative (treatment-placebo) sleep onset latency and both relative (treatment-placebo) core body (B) and foot (A) temperatures before and after a 30 mg dose of temazepam administered orally at 1400 h. While sleep onset latency values are identical in 3A and 3B, the scale is reversed in Fig. 3A to facilitate visualising the relationship between sleep and temperature. Figure is taken from data used in Ref. [47].

Integrating the effects of sleep-on-temperature with the effects of temperature-on-sleep

It is clear that temperature and sleep are closely interlinked under a wide range of situations. This has resulted in considerable debate as to the possible mechanisms driving these changes in temperature and sleep. One of the central themes in this debate has been the question of whether the relationship between sleep propensity and T_C reflects circadian control or reflects a causal relationship between the two variables. There is no doubt that, under normal conditions, the primary factor driving this relationship is circadian control. However, given the fact the relationship remains following manipulation of sleep and/or temperature, it could be argued that the changes in temperature that are normally under circadian control, act to

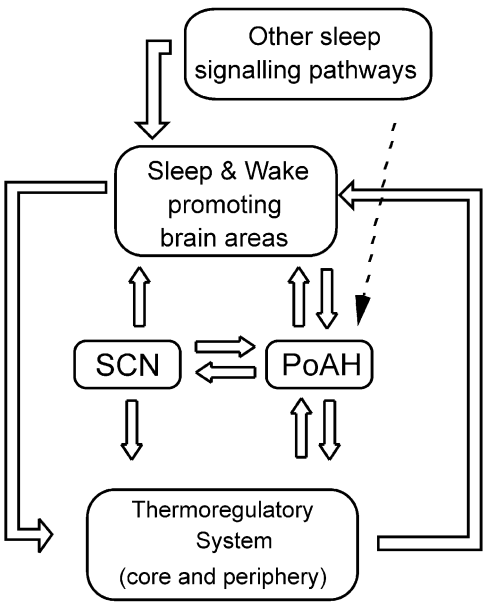

Fig. 4 Schematic illustration of how changes in thermoregulation such as an increase in peripheral temperature (T_{periph}) or decrease in core temperature (T_C) is able to trigger directly, and via the PoAH, sleep and wake promoting areas of the brain to initiate sleep. It also illustrates circadian (via SCN) control of sleep and temperature.

reinforce the direct effect of the circadian system on sleep initiation (see Fig. 4).

The second of the central themes in this debate has been the question of whether sleep onset affects core body and skin temperature or whether these temperatures affect sleep propensity. As is clearly illustrated in the previous sections of this review, there is evidence to support each point of view. However, rather than simply examining each point of view in isolation, we believe a more complete picture can be obtained when this research is united under a common functional process. Specifically, we contend that the temperature changes before and after sleep onset form a positive feedback loop where sleep is facilitated and subsequently reinforced. That is, the reduction in T_C and increase in heat loss prior to sleep increases sleep propensity thereby facilitating sleep onset. In turn, sleep onset results in a further decrease in T_C (the sleep-evoked T_C decline) and increase in heat loss, which reinforces this drive to sleep. Thus, the sleep bout is consolidated. The fact that reduced nocturnal arousals and increased SWS have also occurred following the experimental reduction of T_C following sleep onset provides support for the idea that the sleep-evoked reduction in T_C is not simply a by-product of posture and metabolic changes but that it is intrinsically linked with sleep regulation. Similarly, the fact that SOL is reduced by a rapid decline in T_C and increase in peripheral temperature occurring prior to sleep onset supports the idea that these thermoregulatory changes may act as a physiological trigger for sleep initiation. Not only is this theory consistent with the experimental data described in previous sections but is further supported by the neuroanatomical animal research described below.

The role of the PoAH and thermosensitive neurones in sleep regulation

Neuroanatomical research revealed that sleep could be initiated following physical warming of the PoAH[52,53] and also following chemical stimulation of the same area.[54] Such a finding implicated activation of the PoAH in the normal initiation of sleep. Consistent with such a hypothesis, groups of warm-sensitive neurons in the PoAH were found to increase their firing rate at sleep onset and decrease their firing just before arousal in animals,[55] an observation confirmed by immunocytochemistry.[56] This finding was important as the activation of these PoAH thermosensitive neurons also affected the discharge rate of neurons in other brain areas known to regulate sleep and wakefulness.[57,58] Such areas include the posterior hypothalamus, basal forebrain, and the dorsal raphe nuclei. When taken together, these findings provided evidence to support a role of temperature in sleep regulation.

However, the most compelling evidence for such a role came from the finding that heating of peripheral skin resulted in an increase in the firing of warm-sensitive neurons in the PoAH and other brain areas known to be involved in sleep regulation.[55,56] Not only did this indicate that a neural pathway existed between peripheral skin and somnogenic brain areas, but it provided a specific neurophysiological mechanism through which an increase in peripheral skin temperature may be able to affect sleep propensity.[40,59]

A model of sleep regulation

Integrating the available neuroanatomical and physiological research, a model is proposed below to explain how an increase in peripheral

heat loss, whether by pharmacological manipulation, exercise, or hot baths, is able to increase sleepiness. In addition, the role of temperature changes following sleep onset in the regulation of sleep will be explained. This model is schematically illustrated in Fig. 4. While previous authors such as van Someren[60] have proposed a mechanism through which the thermoregulatory system may act as a signalling pathway to the circadian system, this paper is the first to propose a mechanism by which pre and post sleep temperature changes facilitate both the initiation and consolidation of sleep.

When an individual attempts to sleep, blood supply to the peripheral vasculature is increased.[61] Heat loss is achieved due to the shunting of blood from the arterioles to the venules through arteriovenous anastomoses. This increased blood flow increases the heat transfer per unit of time while the increase in skin temperature creates a positive thermal gradient with the environment allowing the conduction, convection and radiation of heat to occur. This rapid increase in heat loss stimulates thermosensitive neurones in peripheral skin that innervate the PoAH. This activity stimulates thermosensitive neurones in the PoAH that are responsible for sleep initiation. In turn, efferent warm-sensitive neurones in the PoAH are stimulated which innervate other somnogenic brain structures while thermosensitive neurones innervating wake promoting brain areas are inhibited. The overall result, therefore, is the activation of sleep promoting areas and the inhibition of wake promoting areas resulting in an increase in sleepiness, which leads to sleep onset. Sleep onset is associated with a reduction in the set point of the PoAH resulting in further peripheral heat loss and a sustained reduction in T_C. As before, the increase in heat loss continues to activate the thermosensitive neurones innervating sleep promoting brain areas. In this way, a positive feedback loop is formed between the thermoregulatory system and the sleep/wake promoting areas of the brain and, as a consequence, the promotion of sleep is reinforced resulting in sleep consolidation.

Clearly, the thermoregulatory sleep signalling system is not the only mechanism or pathway through which sleep is regulated. Nevertheless, as is illustrated in Fig. 4, regardless of the mechanism initiating sleep, such a mechanism would interact with other sleep signalling systems as the sleep-evoked temperature effect would always reinforce the sleep process.

Practice points

- neuroanatomical research in animals indicates that a thermosensitive neural pathway exists from peripheral skin sites to the PoAH and from the PoAH to sleep and wake promoting brain areas
- it is possible that this neural pathway may account for why an increase in peripheral heat loss is associated with an increase in sleep propensity

Thermoregulatory changes in sleep disorders

The above sections have summarised the effects that manipulations of T_C have on sleep and have highlighted a potential role of a rapid decline in T_C and an increase in heat loss in sleep initiation. Interestingly, investigation of the thermoregulatory changes associated with several sleep disorders also provides indirect support for a role of thermoregulatory changes in sleep propensity. For example, sleep onset insomniacs have been found to have a delay in their T_C rhythm of approximately 2.5 h indicating they are normally attempting to initiate sleep before the nocturnal decline in T_C.[62] Similarly, other clinical research has found that impaired heat loss capacity is associated with a prolonged latency to sleep onset in patients with vasospastic syndrome.[63] Changes in thermoregulatory function are also thought to play an important role in the sleep disturbance that occurs due to ageing, with an advance in the T_C rhythms of certain older individuals between 0.75 and 2 h indicating these individuals are attempting to sleep after the decline in T_C.[64,65] In addition, the normal decline in T_C experienced by the elderly is typically 0.3–0.4 °C less than young adults,[66] which indicates that the degree of heat loss may be significantly impaired in these individuals. Similar findings have been obtained by Lushington and colleagues[67] who reported that the circadian T_C decline in older poor sleepers was significantly attenuated compared with older good sleepers, indicating that heat loss was also attenuated in the group of poor sleepers. It could be argued, therefore, that certain sleep disorders may be the result of an individual attempting to initiate sleep at a time when heat loss and/or their decline in T_C is not optimal.

Conclusion

It is apparent that thermoregulatory variables such as T_C and peripheral heat loss are associated with sleep propensity under a wide range of experimental situations. It also appears that the thermoregulatory control centre, the PoAH, is not only directly involved in the regulation of sleep and wakefulness, but also innervates other somnogenic brain regions. Taken together, it is possible that, in addition to other systems such as the circadian system, the thermoregulatory system may act as a signalling pathway in the regulation of sleep and wakefulness. If this is the case, then the sleep-evoked temperature changes are also likely to reinforce the promotion of sleep through this thermoregulatory pathway resulting in a sustained drive for sleep. The fact that warming of the periphery may induce sleep provides the basis for the development of a range of new and novel techniques to facilitate sleep. Indeed, the apparent success of simple methods such as warm foot baths in facilitating the sleep of healthy adults highlights the potential of such endeavours. Importantly, however, this thermoregulatory model of sleep regulation needs to be empirically tested. For example, sleep propensity could be measured while temperature is manipulated at different circadian phases.

Research agenda

Future research should:

- conduct empirical research to test the model proposed in this paper
- determine whether treatments utilising this thermoregulatory sleep signalling pathway such as warm foot baths are able to benefit clinical groups such as sleep onset insomniacs
- employ recent advances in thermal imaging technology to examine the dynamic, whole body changes in temperature around sleep onset. In this way, a more complete picture of the relationship between heat loss and sleep may be achieved

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