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MORE THAN A MARKER: INTERACTION BETWEEN THE CIRCADIAN REGULATION OF TEMPERATURE AND SLEEP, AGE-RELATED CHANGES, AND TREATMENT POSSIBILITIES

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ABSTRACT

The neurobiological mechanisms of both sleep and circadian regulation have been unraveled partly in the last decades. A network of brain structures, rather than a single locus, is involved in arousal state regulation, whereas the suprachiasmatic nucleus (SCN) has been recognized as a key structure for the regulation of circadian rhythms. Although most models of sleep regulation include a circadian component, the actual mechanism by which the circadian timing system promotes—in addition to homeostatic pressure—transitions between sleep and wakefulness remains to be elucidated. Little more can be stated presently than a probable involvement of neuronal projections and neurohumoral factors originating in the SCN. This paper reviews the relation among body temperature, arousal state, and the circadian timing system and proposes that the circadian temperature rhythm provides an additional signaling pathway for the circadian modulation of sleep and wakefulness. A review of the literature shows that increased brain temperature is associated with a type of neuronal activation typical of sleep in some structures (hypothalamus, basal forebrain), but typical of wakefulness in others (midbrain reticular formation, thalamus). Not only local temperature, but also skin temperature are related to the activation type in these structures. Warming of the skin is associated with an activation type typical of sleep in the midbrain reticular formation, hypothalamus, and cerebral cortex (CC). The decreasing part of the circadian rhythm in core temperature is mainly determined by heat loss from the skin of the extremities, which is associated with strongly increased skin temperature. As such, alterations in core and skin

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temperature over the day could modulate the neuronal activation state or "preparedness for sleep" in arousal-related brain structures. Body temperature may thus provide a third signaling pathway, in addition to synaptic and neurohumoral pathways, for the circadian modulation of sleep. A proposed model for the effects of body temperature on sleep appears to fit the available data better than previous hypotheses on the relation between temperature and sleep. Moreover, when the effects of age-related thermoregulatory alterations are introduced into the model, it provides an adequate description of age-related changes in sleep, including shallow sleep and awakening closer to the nocturnal core temperature minimum. Finally, the model indicates that appropriately timed direct (passive heating) or indirect (bright light, melatonin, physical activity) manipulation of the nocturnal profile of skin and core temperature may be beneficial to disturbed sleep in the elderly. Although such procedures could be viewed by researchers as merely masking a marker for the endogenous rhythm, they may in fact be crucial for sleep improvement in elderly subjects. (*Chronobiology International, 17*(*3*), *313–354, 2000*)

Key Words: Aging—Circadian rhythm—Sleep—Temperature—Thermoregulation.

1. INTRODUCTION

As has been reviewed in several articles in the current issue of *Chronobiology International* and elsewhere, there are marked age-related alterations in the circadian patterning of sleep and body temperature. The aim of this article is to investigate whether these changes in sleep and temperature rhythms are merely independent, parallel signs of a changing circadian timing system or, rather, might be connected causally. In the latter case, rational strategies aimed at altering the 24h profile in body temperature may have a therapeutic potential in improving sleep in the elderly. Many findings indicate that changes in the circadian timing system are involved in some of the age-related sleep disturbances, and efforts have already been made to evaluate the sleep-improving effects of a variety of potent modulators of the circadian timing system, such as bright light (Campbell et al. 1993; Murphy and Campbell 1996), melatonin (Garfinkel et al. 1995; Haimov et al. 1995; Wurtman and Zhdanova 1995; Hughes et al. 1998), and physical activity (Van Someren et al. 1994; King et al. 1997; Van Someren et al. 1997). In this article, it is suggested that the alterations in the 24h profile of body temperature caused by these treatments may have contributed to their sleep-improving effects. Furthermore, direct manipulation of the circadian temperature profile (e.g., by means of hot baths) may enhance sleep and induce a ("masked") delay of the core temperature minimum. This delay is thought to be of special therapeutic significance since an early temperature minimum is one of the most important determinants of early awakening in the elderly due to the fact that the ability of the elderly to sustain sleep at the rising portion of the core temperature rhythm is compromised. The following topics are discussed.

The first two sections of this article discuss the relation between body temperature and arousal state as could be mediated by thermosensitive neurons in brain structures involved in arousal regulation. Since the "thermal" input that these neurons receive varies

with the circadian rhythms in core and skin temperature, these rhythms may provide an additional signaling pathway for the circadian modulation of sleep and wakefulness. Thermosensitivity is discussed at the level of behavioral activation and at the level of activity patterns of brain structures involved in sleep regulation. A high brain temperature is associated with an activation type typical of sleep in some structures (hypothalamus, basal forebrain), but with an activation type typical of wakefulness in others (midbrain reticular formation [MRF], thalamus). Not only local temperature, but also skin temperature are related to the activation type in these structures. Warming of the skin is associated with an activation type typical of sleep in the MRF, hypothalamus, and cerebral cortex (CC). The decreasing portion of the circadian rhythm in core temperature is determined mainly by heat loss through the skin of the extremities, which is associated with strongly increased skin temperature. Circadian variation of heat production contributes also, but to a lesser extent (Kräuchi and Wirz-Justice 1994). Thus, the rhythms in core temperature and skin temperature at the extremities could modulate the neuronal and behavioral activation state, resulting in a maximal probability for sleep onset near the peak in skin temperature at the extremities, which is closely related to the maximal rate of change on the decreasing portion of the core temperature rhythm. As such, feedback on the heat distribution over the body may function as a signal indicating whether the behavioral and environmental conditions are met to allow for safe onset of sleep. The feedback may furthermore be of importance in the synchronization of arousal-state transitions in several sleep-related brain structures by simultaneously altering the firing pattern of thermosensitive neurons in these structures. Body temperature may thus provide a third signaling pathway, in addition to tentative synaptic and neurohumoral pathways, for the circadian modulation of sleep. The proposed model for the effect of body temperature on sleep appears to fit the available data better than previous hypotheses that assume only an opposite relationship between temperature and sleep (i.e., that temperature changes result from sleep).

The third section briefly reviews age-related changes in thermoregulation and how they may be involved in disturbed sleep in the elderly.

The article concludes with an overview of therapeutic efforts to improve sleep that either directly or indirectly affect core and skin temperature. Some suggestions for research and application are provided.

2. SLEEP AND THERMOREGULATION

2.1. Changes in Body Temperature and Changes in Sleep: Consequence, Coincidence, or Antecedent?

The relationship between temperature and sleep-wakefulness has been investigated and discussed for centuries (cf. Campbell and Broughton 1994). The Greek philosopher Alcmeaon of Croton—the first to state that the brain, rather than the heart, is the central organ of feeling and thought—assumed “retirement of the blood to the larger blood vessels” with sleep and “rediffusion” with awakening (cf. http://www.magna.com.au/~prfbrown/ancients.html) and thus would have predicted a redistribution of heat to the core of the body. In the seventh century, the opposite was stated by Robert Burton: “A hot brain does not sleep” (cf. Finkbeiner 1998). Recent experiments have favored Burton’s view over the view of Alcmeaon and show that sleep is associated with rediffusion of heat from the core to the periphery of the body (Kräuchi et al. 1999).

Hypotheses and research on the relation between body temperature and sleep have first focused disproportionately on the alterations in temperature and its regulation as a consequence of alterations in arousal state, that is, wakefulness and sleep. More specifically, slow-wave sleep (SWS) has been attributed a homeostatic role in energy conservation or (brain) cooling (cf. McGinty and Szymusiak 1990; Glotzbach and Heller 1994). However, these hypotheses cannot account for a considerable amount of experimental data (cf. Daan et al. 1992). First, species for which energy conservation is not essential also sleep, as do larger mammals such as man, for which the actual savings do not account for more than a few percent of the daily intake of calories (Refinetti and Menaker 1992; Glotzbach and Heller 1994). Second, the parallel drop in core and brain temperatures that coincides with sleep is to a large extent due to a change in body position and occurs also when sleep is not allowed (Beersma and Dijk 1992; Almirall et al. 1993; Van Dongen et al. 1996). Depending on the experimental protocol, the contribution of sleep to the decline in core temperature can be as small as 10% of the amplitude of the core circadian temperature rhythm (cf. Refinetti and Menaker 1992). Furthermore, it has been demonstrated that the decline in core temperature actually precedes, rather than follows, sleep. In the rat, the fall in hypothalamic temperature associated with the transition between wakefulness and sleep occurs 2 minutes before the actual transition to sleep (Gao et al. 1995). In humans, the peak of the rectal temperature rhythm precedes the end of the active period by several hours, and the trough occurs about 2h to 4h before the end of the sleep period (Geschickter et al. 1966; Aschoff 1970; Reinberg and Smolensky 1983). Heat loss by increased peripheral vasodilation starts on average 36 minutes before sleep (Geschickter et al. 1966), and although increases of 84% in peripheral vasodilation take place during sleep as compared to wakefulness, an increase of 30% to 40% occurs already when subjects go to bed (Sindrup et al. 1991, 1992).

Other researchers have paid attention to possible parallels between sleep and body temperature. Starting with poor correlations between the level of core temperature and subsequent sleep onset and depth and followed by somewhat better correlations between the steepness of the drop in core temperature and subsequent sleep (Campbell and Broughton 1994; Murphy and Campbell 1997), it has recently been demonstrated that sleep onset latency correlates best with the amount of heat dissipation preceding sleep (Kräuchi et al. 1999). This result from a well-controlled study confirmed the old idea of Magnussen (1939, 1943) that peripheral vasodilation indicates “Schlafbereitschaft” or “sleep preparedness.” It furthermore illustrates how a fixation on the relationship of sleep with core temperature has postponed progress because the more recent inclusion of the major determinant of the drop in core temperature (i.e., heat loss from the skin) appears to be a more fruitful approach. The parallel between sleep and heat loss is not surprising since the major brain region that drives heat loss (i.e., the preoptic area/anterior hypothalamus [POAH]) is also of crucial importance in sleep regulation. Even at the cellular level, there is an overlap in neurons sensitive to heat (warm-sensitive neurons, WSNs) and neurons changing their firing pattern preceding and during sleep. As such, it might be argued that the association between heat loss and preparedness to sleep is due merely to this overlap in function of some of the neurons within the POAH. However, such parallelism cannot account for all research findings. More specifically, the restoration of sleep impairment in POAH-lesioned animals by placing them in a warm environment (Szymusiak et al. 1991) indicates that there might be more than just parallelism.

This article aims at taking the possible relationship between the heat distribution in the body and sleep preparedness one step further and proposes that sleep might be

affected by this distribution of heat in the body. Such a possible relationship has been suggested by Roberts and Robinson (1969), but received little attention and to our knowledge has not previously been worked out as a model for sleep regulation. Several arguments can be provided for the validity of this "reverse" approach. Evidence for an effect of temperature on arousal states is reviewed in the following paragraphs.

2.2. Brain Structures Involved in Arousal State Regulation

At present, it has become likely that no single brain structure is the master structure that triggers the transition between wakefulness and sleep. Rather, a network of brain structures appears to be involved in the control and phenomenology of arousal states. Sleep is the result of activation of some of these structures and deactivation of others. A detailed discussion of this network is beyond the scope of this paper, but a short summary of the involved structures is given below.

Starting with the work of Moruzzi and Magoun (reviewed in Moruzzi 1969), it has been shown that the most prominent function of the MRF, including the locus coeruleus (LC) and raphé nuclei, is diffuse activation of general levels of activity in the brain, that is, promotion of the waking state. Deactivation of the reticular formation is a sine qua non for the development of sleep (Moruzzi 1969).

Likewise, the posterior hypothalamus (PH) has been called a "waking center," and it appears that the lateral part of the PH is involved in neocortical arousal regulation (Sakai et al. 1990). The arousal-related histaminergic neurons in the tuberomammillary nucleus (TM) located in the ventral PH cease firing prior to sleep onset in both cat and rat (Sherin, Shiromani et al. 1996; Steininger et al. 1996).

Since lesions of the POAH cause long-lasting insomnia, both local chemical and thermostimulation promote sleep (Szymusiak et al. 1991; Alam, McGinty et al. 1996), and a part of the neurons alters the firing rate before sleep onset, the medial preoptic area and the anterior hypothalamus have been suggested to contain "slow wave sleep controlling neurons" (e.g., McGinty and Szymusiak 1990; Koyama and Hayaishi 1994). Recently, the ventrolateral preoptic area has been assigned a key role in sleep initiation and control over the arousal related TM (Sherin, Elmquist et al. 1996; Sherin, Shiromani et al. 1996; Sherin et al. 1998).

The ventromedial diagonal band also contains sleep-related neurons (Hays et al. 1998; Hays et al. 1999; McGinty et al. 1999). More rostrally, the basal forebrain (BF) contains both GABAergic sleep-related neurons and cholinergic arousal-related neurons (Jones and Gebhart 1987; Szymusiak 1995).

The midline, medial, and intralaminar thalamic nuclei (MTN) comprise the nonspecific thalamocortical activation projection involved in the generation of electroencephalographic patterns characteristic for sleep and wakefulness. Hyperpolarization, resulting from a decreased input, changes the firing mode of MTN neurons from a tonic mode during waking to a phasic bursting mode during sleep. Hyperpolarization of GABAergic neurons in the thalamic nucleus reticularis that surrounds the thalamus results in their burst mode firing to the thalamic relay neurons, driving them to bursting in spindle, followed by delta frequency (Steriade et al. 1994; Jones 1998).

Although the CC has not been assigned a regulatory function in sleep-wake regulation, the arousal state is usually classified according to the small amplitude, high-frequency, desynchronized electroencephalogram (EEG) pattern during wakefulness and the

high-amplitude, low-frequency, synchronized EEG pattern during SWS, which results from thalamocortical interaction.

2.3. Effect of Temperature on Arousal States and Brain Structures Involved in Arousal State Regulation

Many studies have demonstrated the presence of thermosensitive neurons throughout the brain. *Thermosensitive neurons* are defined as neurons with an evoked or spontaneous firing rate that depends on local and/or peripheral (cutaneous) temperature. Neurons that increase their firing rate with warming are called warm-sensitive neurons (WSNs), and neurons that increase their firing rate with cooling are called cold-sensitive neurons (CSNs). Generally, warm-sensitive neurons account for about 30% of the neurons in thermosensitive brain structures. Most of them retain their thermosensitivity even when their synaptic input is blocked experimentally (Boulant and Dean 1986; Dean and Boulant 1992; Mackowiak and Boulant 1996). CSNs account for about 10% of the neurons in these structures, and their thermosensitivity usually disappears during synaptic blockade, suggesting that their sensitivity is not intrinsic, but is due to synaptic inhibition from adjacent WSNs (Boulant and Dean 1986; Mackowiak and Boulant 1996).

Although it has been suggested that thermoresponsiveness of neurons is strongest in the POAH (McGinty and Szymusiak 1988), the available data show thermoresponsiveness of similar magnitude in numerous other brain areas, most of which, interestingly, are involved in sleep regulation. In the following paragraphs, the thermosensitivity and the involvement in arousal-state regulation are reviewed for the MRF, hypothalamic areas, basal forebrain, thalamus, and CC. For all these structures, the responses to changes in local as well as skin temperature are briefly discussed insofar as data are available. Although some studies have been criticized because they were performed on anesthetized animals, findings in freely moving animals and acutely immobilized animals are generally identical (cf. Benedek et al. 1982; Wehr 1992). The reported changes were observed with temperature manipulations within the physiological range. Studies in which such things as strong cooling have been applied to knock out a certain brain structure cryogenically (e.g., Cespuglio et al. 1979, 1981) are excluded. It should also be noted that changes in neuronal activity in these structures do not necessarily result from actual thermosensitivity of neurons, but may also result from increased inhibition or excitation from projecting thermosensitive cells.

Thermosensitivity of Neurons in the Midbrain Reticular Formation

Two studies indicate thermosensitivity of otherwise unspecified MRF neurons. In the rabbit MRF, both increased and decreased firing rates were found in a minority of the neurons after local warming, whereas the firing rate of approximately 60% of the neurons was negatively related to skin temperature (Nakayama and Hardy 1969). In the rat, glucose metabolism in the MRF increased with a simultaneous increase in central temperature and decrease in skin temperature (Morimoto and Murakami 1985).

In anesthetized rats, Jahns (1976) demonstrated the presence of predominantly WSNs in the raphé nuclei, the firing rate of which increased with skin temperature. However, Dickenson (1977) demonstrated that most neurons in fact show an inverted V profile, that is, they were warm sensitive with peak firing rates at a skin temperature of, on average, 37.5°C. Slightly higher temperatures, however, induced a very strong de-

crease in firing rate (i.e., the characteristics of CSNs. Since the normal range of core temperature in the rat is approximately 37.0°C to 39.0°C (cf. Refinetti and Menaker 1992), it is most likely that, under physiological circumstances, blood flowing from the core to the skin could indeed induce temperature levels of over 37.5°C at peripheral thermosensors, especially around the maximum of the circadian core temperature rhythm. It should be noted that the thermoreceptive nerve endings in the skin are at the same depth as the cutaneous vascular system (Kenshalo 1970).

Neurons that are sensitive to local temperature are furthermore found in the median and dorsal raphé nuclei in the anesthetized rat, cat, and rabbit (Gordon and Heath 1986). Serotonin release is positively correlated primarily with brain temperature and only secondarily with activity and wakefulness (Weiss and Aghajanian 1971; Imeri et al. 1996). Brain levels of 5-HT after warming or cooling give further support to the thermosensitivity of the serotonergic system. In the rat, an increased brain temperature induced by a high environmental temperature transiently increases the serotonin level in the preoptic area and the anterior hypothalamus (Simmonds 1970) and in various other brain structures, including the SCN (Corrodi et al. 1967).

Thermoregulation has been proposed as one of the many processes in which the locus coeruleus is involved (cf. Morilak et al. 1987). Both unit activity in the locus coeruleus (Morilak et al. 1987) and levels of brain noradrenalin (Corrodi et al. 1967) are positively correlated with body temperature. However, the time course of activation indicates that noradrenergic neurons in the locus coeruleus do not respond to heating itself, but that activation coincides with the onset of thermoregulatory behavior (Morilak et al. 1987). Thus, the locus coeruleus appears to respond to the stress of the stimulus rather than to the thermal input itself.

In summary, although direct thermosensitivity of the locus coeruleus is unlikely, there is considerable evidence that at least the raphé nuclei of the MRF contain a large number of thermosensitive neurons, most of which are warm sensitive (cf. Wehr 1992). Concerning the relation between thermosensitivity and arousal involvement of the MRF, it can be concluded that high brain temperatures enhance MRF neuronal activity, which is associated with wakefulness, whereas high skin temperatures attenuate MRF neuronal activity and may thus favor sleep.

Thermosensitivity of Neurons in the Posterior Hypothalamus

A simultaneous increase in central temperature and decrease in skin temperature enhance glucose metabolism in the PH (Morimoto and Murakami 1985), indicating activation of this arousal structure. However, local heating of this area resulted in spindle and slow-wave EEG activity (Hemingway et al. 1940; Benedek et al. 1982). Thus, the activation of the PH reported by Morimoto and Murakami (1985) is most likely due to the decrease in skin temperature, suggesting that both high brain and high skin temperatures are associated with attenuated neuronal activity in the PH and may thus favor sleep.

Thermosensitivity of Neurons in the Preoptic Area/Anterior Hypothalamus

The POAH is a major thermoregulatory region of the brain, involved in such things as panting, cutaneous vasoconstriction and vasodilation, and shivering (Boulant 1980, 1981). About 30% of its neurons are warm sensitive, that is, their activity is positively correlated with local or peripheral temperature; 10% are cold sensitive, that is, their activity is negatively correlated with local or peripheral temperature; and 60% do not

respond to changes in temperature. Neurons responding to either or both local and skin temperature changes have been demonstrated in numerous studies (e.g., Roberts et al. 1969; Hellon 1970, 1972; Knox et al. 1973; Reaves 1977; Morimoto and Murakami 1985; Travis et al. 1995). In about half of the thermosensitive neurons in the POAH, changes in firing rate in response to both local and peripheral temperature changes occur within the same cell (Boulant and Bignall 1973), mostly in the same direction (e.g., an increase of firing rates after both local and distal warming) (Boulant and Hardy 1974). Whereas some studies indicated that thermosensitive POAH neurons change their firing rate in response to local and skin temperature in an additive way (Wit and Wang 1968; Hellon 1972), the majority of the faster firing neurons especially show an interesting interaction. After warming of the skin in a fairly neutral range, POAH WSNs show a markedly increased firing rate toward a maximum otherwise reached only by extreme local temperatures and moreover decrease their response to changes in local temperature. This interaction is shown in Fig. 1. Thus, when the peripheral temperature is high, the neuron's firing rate is high, relatively independent of changes in local brain temperature, indicating the strong impact of skin temperature on POAH WSNs (Boulant and Hardy 1974).

Concerning the relation between thermosensitivity and arousal involvement of the POAH, it should be noted that a subpopulation of WSNs increases the discharge rate before the onset of and during SWS and decreases the discharge rate before the onset and during wakefulness (Alam et al. 1995a; Alam, McGinty et al. 1996). Such thermosensitive neurons furthermore exhibit increased thermosensitivity during SWS (Alam et al. 1995b; Alam, McGinty et al. 1996). Warm-sensitive sleep-active neurons have also been demonstrated in the ventral lateral preoptic area (Alam, Szymusiak et al. 1996), an

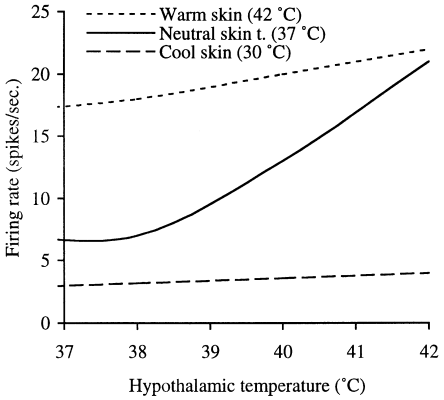


FIGURE 1. Schematic drawing of how skin and brain temperature interact in many preoptic/anterior hypothalamic warm-sensitive neurons (WSNs). Shown is the idealized response of the firing rate (vertical axis) of a single WSN with changes in hypothalamic temperature (horizontal axis) as measured under three different conditions of skin temperature: normal, slightly colder, and slightly warmer. It can be seen that the firing rate stays low, no matter how the brain temperature changes, when the skin is cold. When the skin is only slightly warmed, the firing rate increases toward a maximum, again relatively independent of the local temperature. This firing rate is reached only by extreme local temperature in the case of normal skin temperature. (After Boulant and Bignall 1973.)

area that may play a key role in sleep initiation and consolidation (Sherin, Shiromani et al. 1996). To summarize the thermosensitivity and arousal involvement of the POAH, it can be concluded that both high brain and high skin temperatures are associated with increased neuronal activity of WSNs, with decreased activity of CSNs, and with the induction of sleep.

Thermosensitivity of Neurons in Other Parts of the Basal Forebrain

McGinty and colleagues (Hays et al. 1997; McGinty et al. 1999) demonstrated predominantly WSNs, in a proportion of 30–65%, in the horizontal limb and ventromedial part of the diagonal band of Broca (DBB) in the rat BF. These neurons increase their discharge rate before synchronization occurs in the EEG at sleep onset (McGinty et al. 1999).

Concerning the relation between thermosensitivity and arousal involvement of the DBB, hypnogenic activity has been ascribed to the magnocellular parts of the basal forebrain adjacent to the rostral hypothalamus, including the DBB and the substantia innominata (Szymusiak and McGinty 1986; McGinty and Szymusiak 1989; Szymusiak 1995; Hays et al. 1996). It should be noted here that other parts of the basal forebrain, most notably the nucleus basalis of Meynert, are involved in cortical activation (Szymusiak 1995). Although the effect of skin temperature on sleep-active DBB neurons has not been investigated, it can be concluded that high brain temperatures are associated with increased neuronal activity of WSNs and the induction of sleep.

Thermosensitivity of Neurons in the Thalamus

Local thermosensitive neurons with a prevalence similar to those of the POAH have been demonstrated in rat tissue in vitro in several thalamic nuclei, particularly, but not exclusively, in the arousal-related midline reuniens nucleus (Taylor 1982; Dean et al. 1992; Travis et al. 1995). The majority of local thermosensitive cells are intrinsically warm sensitive (Dean and Boulant 1992; Travis et al. 1995). Neurons sensitive to skin temperature, predominantly of the warm-sensitive type, have been demonstrated in the ventrobasal complex of the rat thalamus. A steep, almost stepwise, increase in ventrobasal thalamic neuron firing is elicited by increasing skin temperature by only 0.5°C in the range of 33°C to 38°C (Hellon and Misra 1973; Jahns 1975). The sensitivity to changes in skin temperature is modulated by the local temperature of the POAH (Morimoto et al. 1988; Sakata et al. 1989). The response is thought to reflect nonspecific arousal rather than thermosensitivity (cf. Kanosue et al. 1985). Whereas these studies on the effect of skin temperature on the thalamus investigated the ventrobasal nucleus, a relay nucleus for thermal signals (Morimoto et al. 1988), the effect of skin temperature on arousal-related thalamic nuclei is of more interest given the model discussed here. We are aware of only a few studies on the effect of peripheral thermostimulation on such a thalamic nucleus. Bullit (1990) reported increased c-fos expression in the MTN of rats after immersion of the hind paw in cold or hot water. However, given the extreme temperatures used in this experiment (4°C and 50°C–60°C), the stimulation should be regarded as noxious. Peschanski et al. (1981) reported increased firing in the posterior intralaminar region with noxious heating of the skin, but no response with innocuous skin heating. WSNs, CSNs, and "inverse WSNs," sensitive to innocuous alteration of skin temperature have been found in an ill-defined region of the thalamus, including posterio-lateral, parafascicularis, and intralaminar nuclei (Schingnitz and Werner 1980a). Although, interest-

ingly, inverse WSNs, which decreased their firing rate with skin warming between 30°C and 40°C, were found almost exclusively in nonspecific thalamic areas, and burst firing was noted in some thermosensitive neurons (Schingnitz and Werner 1980b), the limited details in the reported results do not allow a conclusion on the direction of skin thermosensitivity of thalamic areas involved in arousal regulation. The same holds true for a report of neurons in the reticular thalamus that were excited by skin cooling (Sakata et al. 1989).

Concerning the relation between thermosensitivity and arousal involvement of the thalamus, parts of it are involved in the generation of sleep-associated EEG phenomena. The midline and intralaminar thalamic nuclei relay the activity of the brainstem reticular formation to widespread cortical areas and are thought to play an important role in the neuronal mechanisms of sleep and wakefulness (cf. Groenewegen and Berendse 1994). Low-frequency stimulation of the midline and intralaminar thalamus results in the cortical spindles and slow waves that are associated with sleep. High-frequency stimulation induces cortical desynchronization, which is associated with arousal (Groenewegen and Berendse 1994). The midline and intralaminar thalamic nuclei receive input from tegmental nuclei of the brainstem and are reciprocally connected with the reticular thalamic nucleus, where the sleep spindles originate (Steriade et al. 1994). The intralaminar nuclei project to layer I of the entire neocortex (Llinas and Ribary 1993), where the densest cortical innervation from the serotonergic raphé nuclei also is found (Morin and Meyer-Bernstein 1996). The natural transition of the desynchronized wake EEG via spindles to the slow waves of the sleep EEG are thought to result from diminished input of activating brainstem, hypothalamic, and basal forebrain systems (Steriade et al. 1994). The transition of the thalamocortical neurons from the wake-related single-spike mode to the EEG-synchronizing burst mode is characterized by resting membrane hyperpolarization, in which both low-voltage calcium channel deactivation (Formenti et al. 1996) and K^+ conductance (Steriade et al. 1993) appear to be of importance. Interestingly, it has been demonstrated that WSNs show K^+-dependent prepotential depolarization with heating (Griffin et al. 1996), indicating a relative hyperpolarization with cooling. In rat spinal cord slices, the K^+-evoked glutamate release is strongly dependent on temperature changes in the range 35°C to 40°C; a reduction of approximately 30% per degree centigrade is evoked by lowering the temperature (Dirig and Yaksh 1996). A further interesting observation is that spindle activity shows a marked endogenous circadian rhythm, with a peak coinciding with the habitual sleep onset (Dijk and Czeisler 1995), which is in turn usually time locked to the maximal decrease in core temperature.

To summarize the thermosensitivity of arousal-related nuclei of the thalamus, it can be concluded that a decrease in brain temperature may be associated with increased hyperpolarization of thalamocortical neurons, which is associated with the transition from the relay mode typical for wakefulness, via a spindle mode typical for an arousal state transition, to the slow-wave mode typical for sleep. No conclusion on the effect of innocuous changes of skin temperature can be given at present.

Thermosensitivity of the Cerebral Cortex

It has been shown that the EEG pattern of anesthetized animals can be manipulated by changing skin, body, or brain temperature (Ten Cate et al. 1949; Von Euler and Söderberg 1957; Grahn et al. 1989). In the somatosensory cortex of rats, 40% of the neurons show thermosensitivity in vivo (Hellon et al. 1973). The spontaneous activity of the

majority of these neurons decreased with an increase in skin temperature. Small increases of 0.5°C to 2°C, in the range of normal skin temperatures, induced a 10-fold reduction in firing rate. At stable brain and rectal temperatures, an increase in skin temperature was also found to be associated with EEG synchronization in the rabbit (Nakayama and Hardy 1969). In squirrel monkeys, about a quarter of single cortical neurons tested both precentral and postcentral responded to skin temperature changes, but no indication of the proportions of WSNs and CSNs was reported (Kreisman and Zimmerman 1973). An elevated ambient temperature that did not notably affect hypothalamic temperature but is associated with increased skin temperature significantly increased EEG slow-wave activity in rats (Haskell et al. 1981; Gao et al. 1995). Surprisingly, contrary to these findings, Kanosue et al. (1984) reported EEG desynchronization associated with increased thalamic firing after scrotal warming in rats in which core temperature was kept constant. The effect was not considered intrinsically thermosensitive, but rather a nonspecific reaction to activation of the brainstem reticular formation (Kanosue et al. 1985).

Won et al. (1996) demonstrated that lowering of the body temperature of rats and hamsters reduced the responsiveness of the somatosensory cortex to peripheral afferent stimulation. Local cooling of the hypothalamus induced increased glucose utilization in the sensory cortex of rat (Morimoto and Murakami 1985). In man, late components of somatosensory-evoked potentials disappeared with simultaneous skin and core heating and reappeared after cooling (Dubois et al. 1981).

Concerning the relation between thermosensitivity and arousal involvement of the CC, we are not aware of evidence for a regulatory function of the CC in sleep. However, the classification of an arousal state (e.g., sleep) is usually done by assessing cortical activity from the EEG. As described above, thalamocortical pathways are responsible for the spindles associated with arousal-state transitions between the small-amplitude, high-frequency, desynchronized EEG pattern during wakefulness and the high-amplitude, low-frequency, synchronized EEG pattern during SWS (Lancel et al. 1992).

To summarize the thermosensitivity of arousal-related cortical activity patterns, it can be concluded that high levels of skin temperature are associated with reduced spontaneous and evoked neuronal activity, as well as with the synchronization of cortical activity typical of sleep, whereas the results of altered levels of body and brain temperature are equivocal.

2.4. Summary

Historically, the association of the decline in body temperature and sleep has been addressed unidirectionally: Sleep lowers body temperature. Cooling has even been proposed to be the primary function of sleep. However, in the above sections, it was demonstrated that there is abundant evidence for an opposite view, that is, that changes in core and skin temperature could shift thermosensitive neurons in brain structures involved in arousal regulation toward a firing pattern typical of either sleep or wakefulness. Thermosensitive neurons are found in many structures related to the arousal state. They respond with an increase or decrease of firing to changes in either or both local and skin temperature. A schematic overview is given in Fig. 2.

The next section focuses on how the circadian temperature rhythm could be of importance in the circadian patterning of sleep propensity, and a model is proposed for the involvement of the circadian rhythms in central and skin temperatures in the induction of a synchronized arousal-state transition in the brain structures discussed above.

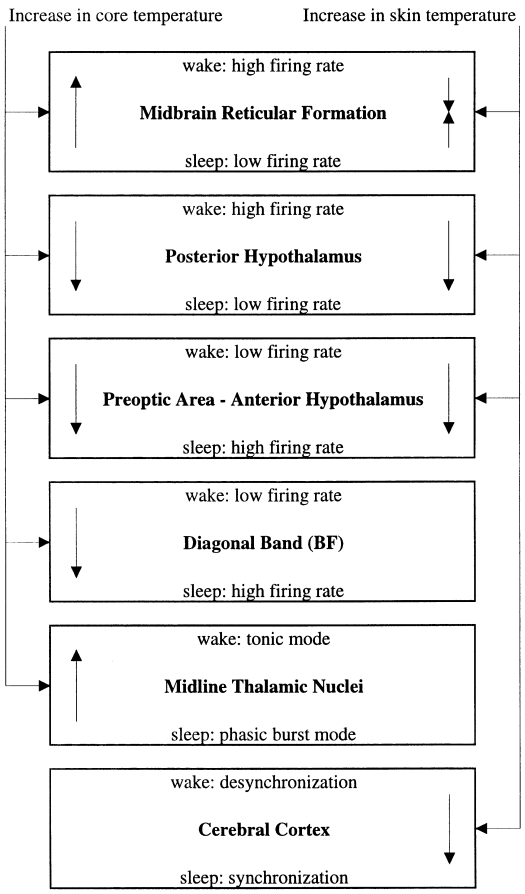


FIGURE 2. Schematic overview of the effect of local and skin temperature on the activity of sleep- and wake-related structures in the brain. Arrows in the rectangles indicate shifts to wake (up) or sleep (down) firing pattern due to increased local (left) or skin (right) temperature.

3. CIRCADIAN RHYTHM IN THERMOREGULATION AND SLEEP: AN INTERACTION MODEL

Based on the interaction between thermosensitivity and sleep-wake regulation as reviewed above, it appears likely that the circadian rhythms of core and skin temperatures might somehow be involved in the circadian rhythm of sleep propensity, sleep depth, and sleep continuation. Before presenting a model in which the effect of these circadian rhythms is described, a basic understanding of the mechanisms underlying the circadian rhythms for core and skin temperature is necessary.

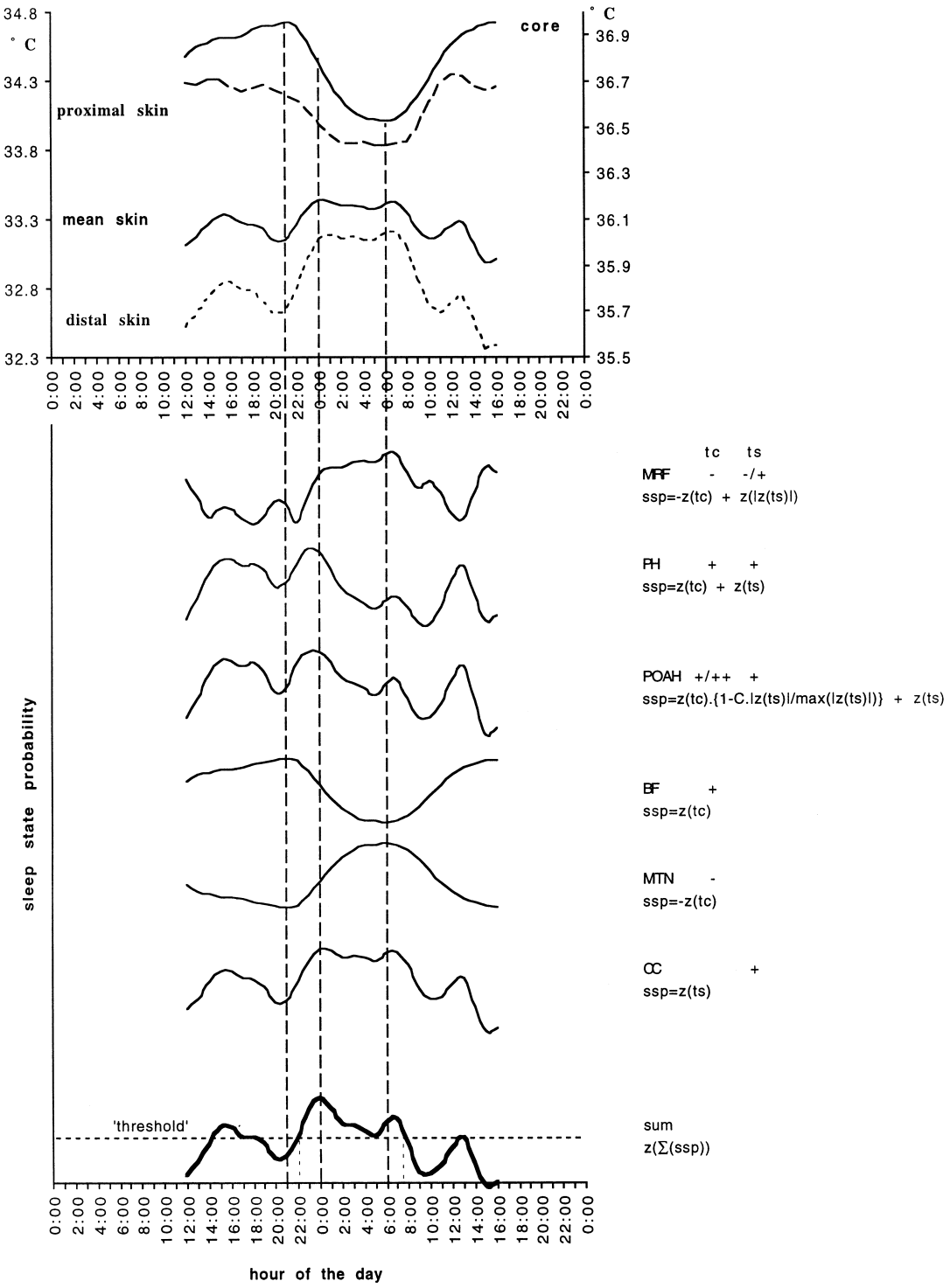
3.1. Regulation of the Endogenous Circadian Rhythm in Body Temperature

Body temperature is determined by the opposing processes of heat production and heat loss. Although changes in heat production contribute to some extent to the circadian

rhythm in temperature, the rhythm, especially the decreasing portion, is primarily determined by variation in heat loss, in rats mainly from the tail and in man from the skin of the extremities (Judy 1976a; Marotte and Timbal 1982; Young and Dawson 1982; Fuller et al. 1985; Gordon 1990; Kräuchi and Wirz-Justice 1994; Refinetti and Menaker 1992). It should be noted here that, under constant routine conditions, the circadian pattern of human proximal skin temperature (trunk and proximal limb parts) has a small amplitude and varies in phase with core temperature, that is, it is low at night, whereas the circadian pattern of distal skin temperature (feet, toes, hand, fingers, ears) shows a stronger amplitude that is out of phase with core temperature, that is, it is high at night (Kräuchi and Wirz-Justice 1994). However, when sleep is allowed, both proximal and distal temperature reach nocturnal values that are significantly higher than daytime values (e.g., Kräuchi et al. 1997).

Heat loss is induced by a reduction in the sympathetic vasoconstrictor outflow. The resulting peripheral vasodilation increases the skin blood flow and temperature, as well as the concomitant dissipation of heat from the blood, through the skin to the cooler environment (Gordon 1990). Thus, with the exception of a small contribution of circadian alterations in heat production, the major changes in core temperature are secondary to increases or decreases of heat loss through the skin. In humans, peripheral vasomotor activity precedes body temperature by 8 minutes to 4h, depending on the protocol (Cranston et al. 1954; Smolander et al. 1993). Minor changes in core body temperature furthermore result from a circadian rhythm in heat production (Kräuchi and Wirz-Justice 1994). Brain temperature is determined by the temperature of the cerebral arterial blood (Hayward and Baker 1969). In humans, the daily decrease in core and brain temperatures mainly results from an increase in distal skin blood flow starting at approximately 20:00 and reaches a maximum plateau of approximately 33.5°C between 23:00 and 7:00. The peak skin temperature at the extremities is timed close to the maximal rate of change in rectal temperature (Aschoff 1947a, 1947b; Marotte and Timbal 1982; Kräuchi and Wirz-Justice 1994). After this nocturnal peak, the skin temperature at the extremities slowly decreases again to a level of approximately 32.2°C at 7:00 (Marotte and Timbal 1982; Kräuchi and Wirz-Justice 1994).

The SCN is seen as the key structure responsible for the circadian rhythm of body temperature. The POAH, which is strongly innervated by the SCN (cf. McGinty and Szymusiak 1990; Watts 1991), is a key structure—but not the only structure (Boulant 1980)—in the control of heat loss mechanisms, including vasodilation (Boulant 1981), and has therefore been proposed to effectuate alterations in body temperature in response to a circadian variation of input from the SCN (cf. Miller 1993). Indeed, circadian variation in the threshold of the level of core temperature necessary for induction of vasodilation has been demonstrated in humans (Stephenson et al. 1984; Tayefeh et al. 1998), resulting in a circadian rhythm with increased nocturnal peripheral vasodilation and heat loss (Wenger et al. 1976; Smolander et al. 1993). However, it is at present unclear how the SCN enforces a circadian rhythm in heat dissipation. POAH lesions do not affect the period and even amplify the amplitude in the circadian body temperature rhythm (Satinoff et al. 1982; Szymusiak et al. 1985). Furthermore, a recent retrograde tracing study of the brain structures responsible for sympathetic outflow to the tail artery failed to find labeling in the SCN, although many of the major hypothalamic SCN-projection sites (paraventricular nucleus, dorsomedial hypothalamus, ventromedial hypothalamus, POAH) were labeled (Smith et al. 1998). Tracing of the SCN may have been missed because these nuclei were not labeled before 7 days after injecting the retrograde tracer,


34.8
° C
34.3
33.8
33.3
32.8
32.3
proximal skin
mean skin
distal skin
core
° C
36.9
36.7
36.5
36.3
36.1
35.9
35.7
35.5
0:00 2:00 4:00 6:00 8:00 10:00 12:00 14:00 16:00 18:00 20:00 22:00 0:00 2:00 4:00 6:00 8:00 10:00 12:00 14:00 16:00 18:00 20:00 22:00 0:00
sleep state probability
'threshold'
hour of the day
tc ts
MRF - -/+
ssp=-z(tc) + z(|z(ts)|)
PH + +
ssp=z(tc) + z(ts)
POAH +/++ +
ssp=z(tc).{1-C.|z(ts)|/max(|z(ts)|)} + z(ts)
BF +
ssp=z(tc)
MTN -
ssp=-z(tc)
CC +
ssp=z(ts)
sum
z(Σ(ssp))

and no observations were made after 7 days. Otherwise, it may also be that the SCN does not make use of this sympathetic neuronal/synaptic pathway to affect heat loss via the tail artery. Another pathway may involve melatonin, which is under control of the SCN, and might alter heat dissipation through both POAH melatonin receptors (Krause and Dubocovitch 1990) and receptors in the vasculature (cf. Cagnacci 1997).

It should be mentioned finally that the SCN can address several pathways to initiate changes in core and peripheral temperatures. First, in diurnal (daytime active) animals, decreased SCN activity during the night appears to favor an inhibition of activity (Edgar and Dement 1994) and the ensuing decrease in metabolic heat production. Furthermore, the physiological effect of a change to a posture associated with inactivity is a strong increase in peripheral blood flow. In nocturnal animals, the majority of the SCN outputs are relayed via neurons located just outside the SCN (Watts 1991; Moore 1996), resulting in an output that is in antiphase with the SCN activity itself (Kubota et al. 1981; Watts 1991; Edgar et al. 1993). Second, the SCN initiates the onset and offset of melatonin release. Melatonin has been shown to increase peripheral blood flow in humans, thus lowering core temperature, while in rat, it has the opposite effect (Carman et al. 1976; Ralph et al. 1979; Strassman et al. 1989; Viswanathan et al. 1990; Badia et al. 1991; Cagnacci et al. 1992; Capsoni et al. 1994; Tzischinsky and Lavie 1994; Geary et al. 1995; Cajochen, Kräuchi, Wirz-Justice et al. 1996; Cagnacci 1997). Such a pathway would be compatible with the finding that peripheral blood flow during the night, when melatonin secretion is maximal, is increased in a diurnal species like humans, but decreases in the nocturnal rats.

3.2. A Model for the Effect of the Circadian Rhythm in Core and Skin Temperature on Thermosensitive Arousal-Related Structures

The thermosensitivity of structures involved in arousal-state regulation opens up the possibility that the biological clock can exert an influence on the arousal state not only via neuronal or neurohormonal pathways, but also by means of its control over the circadian rhythms in skin and core temperature. Here, a crude model for this hypothetical influence is proposed. As has been discussed above, the circadian timing system enforces a 24h rhythm in the central temperature. The fall in body and brain temperatures results primarily from an increased dissipation of heat by means of increased peripheral blood flow. Thus, the declining portion of the core temperature coincides with an increase in distal skin temperature. Proximal skin temperature in constant routine conditions basically reflects core temperature and has a much smaller amplitude than distal skin temperature. The upper panel of Fig. 3 shows smoothed human temperature curves as measured

FIGURE 3. The upper panel shows smoothed average human temperature curves as measured under constant routine conditions (Kräuchi and Wirz-Justice 1994) for both core (upper curve), proximal skin (second curve), mean skin (third curve), and distal skin (lowest curve). The lower panel shows hypothetical sleep-state probability (ssp) curves. High values are associated with increased probability of the sleep state and low values with increased probability of the wake state. Next to the curves the effect of increased core temperature t_c and skin temperature t_s on the sleep probability is indicated by means of minus and plus signs and a formula. See text for explanation.

under constant routine conditions (Kräuchi and Wirz-Justice 1994) for core (upper curve), proximal skin (second curve), mean skin (third curve), and distal skin (lowest curve). The data were gathered from seven healthy males with habitual sleep schedules from 23:48 to 07:30 on average.

The calculation of a mean skin temperature needs some explanation. Whereas several mean skin temperature calculation methods have been published, they have mostly been developed order to estimate heat transfer from the skin to the environment. Since this has been based on body surface, distal ends would have a low weighting factor. However, for the present model, not the heat transfer, but the input the brain receives from different parts of the skin is of importance. Temperature-sensitive nerve endings are widely distributed over the body surface, but are more concentrated in the face, hands, and feet, especially the fingers and toes (Clark and Edholm 1985). In rats, a similar increased density of thermoreceptors and thermosensitivity in the major heat-dissipating skin areas has been reported, especially in the scrotum and most distal part of the tail (Hellon et al. 1975; Schingnitz and Werner 1983; Martinez-Gomez et al. 1994). Regional sensitivity weights for warmth sensation have been proposed by Stevens et al. (1974), but unfortunately cannot be used in the present modeling because the extremities have not been included in their measurements. Hardy and Oppel (1937) noted that the hand and forearm are nearly as sensitive as the whole body surface. The predominance of distal thermoception is reflected in the somatosensory representation of skin areas in the brain, which is extremely dominated by the distal parts (paws/hands and feet/digits) (Jones 1984). Anyone familiar with Penfield and Boldrey's (1937) "homunculus" picture will be familiar with its huge hands, feet, ears, and lips—all main "distal" heat-dissipating structures. The representation of the thermosensitive input from the extremities may even be more extended and diffuse than the familiar "touch"-representation-homunculus (Berman et al. 1998). Despite the limited surface area, the distal skin temperature thus appears more important than the proximal skin temperature. In the model presented here, the distal input has arbitrarily been given twice the weight of the proximal input. Other weighting factors might slightly alter the waveform of the resulting "whole brain sleep-state probability" (see below).

Given the core and skin temperature curves, a hypothetical optimal time window for the transition of wakefulness to sleep, sleep depth, or sleep continuation (depending on the experimental paradigm) can now be derived for all the individual structures related to the arousal state mentioned in the first section of this paper. The model should be regarded as illustrative rather than mathematical since, other than the signs, the relative contributions of skin areas and core temperature to a sleep-associated state in several brain structures are not known. In its present form, the model gives—unless otherwise stated—equal weight to skin and core temperatures and to all brain structures. The lower panel of Fig. 3 represents the sleep-state probability curves for these brain structures.

The upper curve in the lower panel of Fig. 3 represents a hypothetical sleep-state probability curve for the MRF based on normalized skin and core temperature curves. The sleep-state probability *ssp* covaries negatively with (normalized) core temperature since low local temperature is associated with the neuronal activation pattern typical of sleep. It furthermore covaries in a V-curve manner to skin temperature because, as noted above, an increasing skin temperature is associated with the neuronal activation pattern typical of wakefulness up to a certain level, after which further increases are associated with a decrease in the activation. Thus, both the most extreme high and low skin tempera-

tures are associated with sleep-type activity, whereas the average skin temperature is associated with decreased sleep-type activity, which can be expressed as follows:

$$ssp = -z(t_c) + z(|z(t_s)|)$$

where *ssp* is the sleep-state probability, *z* indicates normalized values, t_c is the core temperature, t_s is the skin temperature, and $|\ldots|$ indicates absolute values. High values are associated with increased probability of the sleep state, and low values are associated with increased probability of the wake state.

Similarly, the second curve in the lower panel shows the sum of the normalized core and skin temperatures to represent a sleep probability of the PH in which high local and skin temperatures are associated with the neuronal activation pattern typical of sleep. This is represented simply as:

$$ssp = z(t_c) + z(t_s)$$

with abbreviations as before. The third curve in the lower panel represents the temperature-based sleep probability of the POAH and is the sum of normalized skin temperature and weighted normalized core temperature since high values of both are associated with sleep-type neuronal activation patterns. Because local thermosensitivity is reduced both at low and at high skin temperatures, as shown above, the contribution of changes in core temperature is weighted in such a way that it is reduced to a third (arbitrary) with the most extreme high and low skin temperatures and contributes fully at the average skin temperature as follows:

$$ssp = z(t_c) * \left\{1 - C * \frac{|z(t_s)|}{\max(|z(t_s)|)}\right\} + z(t_s)$$

with abbreviations as above; max(. . .) indicates the maximal value of the time series, and *C* is an arbitrary weighting factor (here, 0.66). The fourth curve in the lower panel shows only the normalized core temperature $z(t_c)$ and represents the sleep probability for other parts of the basal forebrain in which high local temperature is associated with the neuronal activation pattern typical for sleep (BF). The fifth curve in the lower panel shows the inverted normalized core temperature curve $-z(t_c)$ and represents the sleep probability of the MTN, which has a low local temperature that is associated with the neuronal activation pattern typical of sleep. The sixth curve in the lower panel shows the normalized skin temperature curve $z(t_s)$ and represents the sleep probability of the CC, in which high skin temperature is associated with the neuronal activation pattern typical of sleep.

The lowest curve in the lower panel (sum) shows a straightforward (normalized) summation of the sleep probability curves of the seven structures for which thermosensitivity has been demonstrated. Depending on the setting of a threshold level, a temperature window favorable to sleep can thus be determined (indicated with dashed lines). The curve has the rather abstract meaning of sleep-state probability, and its effect may depend on the situation of experimental assessment protocol: When someone is still awake, it can be read as “difficulty staying awake” or “ease of sleep onset”; when someone is asleep, it can be read as “most likely occurrence of slow-wave sleep” and “high-intensity slow-wave activity in the EEG.”

Several things should be noted in the model described here. First, whereas high brain temperatures will favor sleep-related activity in some structures but inhibit it in others, the highest skin temperatures are invariably associated with sleep-related activity in the MRF, CC, PH, and POAH. The possible association of skin temperature with the arousal state in other parts of the basal forebrain and in the midline thalamic nuclei is presently unknown. Second, the sleep probability curves of the basal forebrain and midline thalamic nuclei are in antiphase and thus do not contribute to the summed sleep probability curve. Applying weighting factors would solve this shortcoming. For example, it has been shown in humans that glucose utilization during sleep is lower in the thalamus than in any other part of the brain (Maquet et al. 1992), which is indicative of low levels of neuronal activity and local temperature. This suggests that the contribution of the sleep probability curve for the MTN might be stronger. Application of such a weighting factor would increase the sleep-state probability curve amplitude. Third, the curves for MRF, PH, and POAH are based on an equal contribution of normalized core and skin temperature: Weighting factors may be needed here, also. Fourth, since the temperature curve equations are based on data derived in a constant routine protocol, the naturally occurring influences of changes in environmental light and temperature, activity level, postural change, and the influence of sleep itself on temperature curves are not included. Fifth, the maximum of the curve of the integral brain sleep-state probability not only fits the habitual sleep time, but also its smaller peaks and troughs occur at times associated with the "forbidden zone" and "sleep gates" documented by Lavie (1989, 1997), with the so-called "postlunch dip," and with the timing of increased sleepiness in extended sleep protocols (Gagnon et al. 1985; Dijk, Cajochen, Tobler et al. 1991). A further implication of the model is that, at similar core temperature levels, as occurring at the start of its decay and the end of its rise, the sleep-state probability can still be different because mean skin temperature is not identical at those time points, as has indeed recently been demonstrated by Dijk (1999).

It should be noted here that this model in its present state illustrates only the contribution of circadian alterations in the distribution of heat over the body to the circadian modulation of sleep-state probability. Of course, neuronal and humoral modulations exist, as well as a homeostatic component (Fig. 4). In fact, it is likely that the homeostatic sleep drive may also have a "thermoregulatory" component since it has been noticed already in early deprivation studies that extended sleep deprivation results in decreased core temperature (Bentivoglio and Grassizucconi 1997). A recent series of studies by the group of Rechtschaffen (e.g., 1995) indicates that this heat loss occurs in spite of increasing heat production via food intake, energy expenditure, and nonshivering thermogenesis

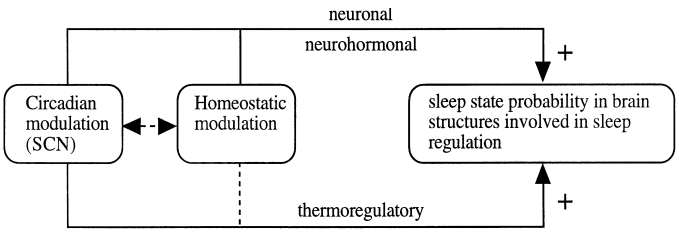


FIGURE 4. Simplified flow chart of the proposed contribution of the circadian rhythm for temperature on sleep-state probability.

and thus is probably due to increased heat transfer to the environment (i.e., increased peripheral vasodilation).

In our model, skin temperature plays an important role. Because the possible involvement of skin temperature in arousal-state regulation has received little attention previously, the following section addresses a few topics that endorse the importance of peripheral input. Previous hypotheses on the relation between sleep and temperature have restricted their scope to the brain itself. Typically, however, the skin plays an extremely important role in both the afferent and efferent thermoregulatory pathways, increasing the a priori likelihood of the involvement of skin temperature in any possible relation between sleep and thermoregulation.

3.3. Importance of Skin Temperature in Thermoregulation and Sleep

As stated above, it appears promising to shift the attention from investigating the relation between sleep and the rhythm in rectal temperature toward the relation between sleep and the rhythm of heat loss and the concomitant changes in both core and skin temperatures. Since the preoptic region is of major importance in the regulation of both temperature and sleep, it might be argued that the relation of the increased vasodilation and temperature of the skin with the ability to fall sleep may just reflect an overlap in the POAH neurons involved in both processes. However, insomnia following a POAH lesion can be restored by placing the animal in a warm environment (Szymusiak et al. 1991), indicating that temperature may indeed feed back on the remaining brain structures involved in arousal regulation.

In fact, input from the skin appears to be of crucial importance, at least for brain structures involved in thermoregulation. First, it is of course of vital importance for any animal confronted with an excessive ambient temperature to initiate avoidance responses before any change in central nervous system temperature can be detected (cf. Crawshaw et al. 1985). Furthermore, in vitro hypothalamic slice studies indicate that, although peripheral input is not a sine qua non prerequisite for local thermosensitivity, the lack of peripheral input in these studies results in very low (<10) firing rates and thermosensitivity that is mainly restricted to extremely high local temperatures (Kelso et al. 1982). Peripheral inputs are necessary to obtain the higher firing rates observed in intact animals (Crawshaw et al. 1985). Indeed, the majority of neurons sensitive to local temperature receive input originating from the skin thermoreceptors (cf. Boulant 1981), perhaps even all of them if all skin areas would be warmed experimentally (Inoue and Murakami 1976).

Also, for brain structures involved in sleep regulation, peripheral input may be of crucial importance. Such input may resolve a discrepancy in the model of McGinty and colleagues (1998), that is, that WSNs in the POAH are involved in sleep initiation. At sleep onset, brain temperature is falling, and sleep-related WSNs would be expected to show a decreased firing rate. However, in fact, sleep onset is associated on the contrary with increased firing of WSNs, (i.e., despite the fall in brain temperature) (McGinty et al. 1998). This discrepancy may be explained by taking into account the effect of peripheral input to these thermosensitive neurons: When core temperature is falling, this is mainly due to increased heat loss (i.e., strongly elevated distal skin temperature). The increase in distal temperature is of a significantly higher magnitude than the local brain temperature changes and may indeed override the changes induced by local temperature

and drive the WSNs to increase their firing rate (see Fig. 1 and Boulant and Bignall 1973).

If, as proposed in this article, thermal input is indeed important in arousal-state transitions, one would expect altered temperature curves in at least some kinds of sleep disorders. Furthermore, since feedback from skin temperature is proposed to be involved in the timing of sleep onset, our hypothesis would predict an attenuated sleep quality when peripheral circulation and/or thermal input from the skin is compromised. Finally, one would predict (pharmacological or physiological) substances that enhance heat loss to be somnogenic and substances that reduce heat loss to disturb sleep. The next paragraphs discuss some of the relevant findings in the literature.

Several studies indicate a reduction in heat dissipation capability in poor sleepers compared to good sleepers. Nocturnal rectal temperature drops less steeply in poor sleepers (Monroe 1967; Mendelson et al. 1984). Lushington and Lack (1995) compared the 24h temperature curves of elderly people who were good and poor sleepers; although this was not tested, their data also indicated that the falling part of the temperature curve in poor sleepers is less steep and of shorter duration. The attenuated drop in rectal temperature suggests a reduced capacity for heat loss by means of peripheral vasodilation and sweating. Indeed, in primary idiopathic sleep-onset insomnia (i.e., the inability to fall asleep in the absence of identifiable physiological or psychological determinants), presleep cutaneous temperature at the extremities is low (Freedman and Sattler 1982). From a wide range of physiological measures, poor sleepers are best discriminated from good sleepers by their increased number of peripheral vasoconstrictions not only during sleep, but also preceding it (cf. Monroe 1967; Nino-Murcia 1992). In addition, poor sleepers have a higher nocturnal basal skin resistance. Furthermore, Pollak et al. (1992) reported that insomniacs show a less steep decline in afternoon activity, which is suggestive of a less steep decline in metabolic rate and consequently body temperature. Indeed, a higher whole body metabolic rate during both the day and the night has been demonstrated in insomniacs as compared to good sleepers (Bonnet and Arand 1995). In elderly insomniacs, a bedtime scheduled closer to the time of the maximum rate of decline in temperature resulted in faster sleep initiation and less-disturbed sleep (Campbell and Broughton 1994).

Another important observation is that disturbed sleep is often associated with stress, in which sympathetic activation attenuates peripheral circulation (Johns et al. 1971; Ancoli-Israel et al. 1986). Adrenaline, the level of which rises dramatically with stress, has a calorigenic effect and attenuates sleep (cf. Minors and Waterhouse 1989). Most sedative and tranquilizing drugs induce vasodilation (cf. Judy 1976a) and can induce hypothermia resulting from increased heat loss (cf. Mendelson and Martin 1992).

Thermal biofeedback, aimed at improving peripheral circulation, has been investigated as a possible treatment for periodic leg movements (PLMs) during sleep. Two studies reported no significant changes in sleep in PLM patients (Ancoli-Israel et al. 1986; Knowles et al. 1996), but these did not measure actual changes in peripheral blood flow or SWS. In two other studies, polysomnographic data were reported. Ware et al. (1988) raised peripheral blood flow by administration of an alpha-adrenergic blocker in two patients with PLM and insomnia and found a slight increase in SWS. Viens et al. (1989) assessed the sleep EEGs of a subject with PLM disorder and sleep-onset insomnia both before and after a 12-week biofeedback treatment in which the subject effectively learned to increase peripheral blood flow. An increase in SWS indeed accompanied this increased peripheral heat loss capacity and could not be attributed to less disturbance of

the sleep by PLMs because the number of PLMs actually increased. It remains to be investigated how increased peripheral vasodilation affects sleep of subjects that are not periodically aroused by PLMs.

In subjects with spinal cord lesions, peripheral thermoception and the ability for peripheral vasodilation are reduced or absent (cf. Freund et al. 1984; Gass et al. 1988; Silver et al. 1991), and vasoconstriction is increased (Wallin and Stjernberg 1984; Schmidt and Chan 1992). Our hypothesis would predict sleep problems in these subjects. A limited number of reports on sleep in subjects with spinal cord lesions indeed suggest that disturbed sleep occurs in a larger proportion of subjects than would be expected only on the basis of their physical restraints. Adey et al. (1968) reported decreased sleep duration and a striking lack of SWS, especially in quadriplegic and, to a lesser extent, paraplegic patients, indicating that a higher spinal lesion level is associated with more prominently disturbed sleep. An epidemiological study of a large number of paraplegics indicated clearly that the willingness to go to bed is lower and the sleep latency longer compared not only to healthy controls, but also to subjects suffering from other chronic illnesses (diabetes mellitus, myocardial infarction, and rheumatism) (Hyyppa and Kronholm 1989). In a recent study, sleep disturbances again were a leading complaint reported by 60% of the patients (De Carvalho et al. 1998).

A similar disturbed feedback from peripheral skin thermoceptors would be expected in burn survivors. Lawrence et al. (1998) reviewed follow-up studies of burn survivors and noted a high frequency of sleep disturbances. They furthermore demonstrated sleep disturbance to be the most common complaint, which moreover was positively correlated with the total body surface area burned, even after statistically eliminating the involvement of stress, anxiety, depression, and pain.

Some lay notions furthermore support the importance of skin and core temperatures in sleep induction—for instance, that it is hard to fall asleep with cold hands or feet (cf. Ohnaka et al. 1995), whereas heating by bathing or sunbathing easily induces drowsiness or even sleep. One of the best remedies against intolerable sleepiness (e.g., during a night shift) is to stand up, which reduces skin blood flow. Furthermore, it has been observed that washing with cold water is one of the few remedies that help hypersomniacs to awaken (Roth et al. 1972).

Another relevant observation is that involuntary sleep bouts in narcoleptic subjects are heralded by an increase in skin temperature (Magnussen 1943) and a decrease in rectal temperature that precedes sleep onset by up to 10 minutes (Pollak and Wagner 1994).

There is some evidence for the predicted association between heat-dissipating and somnogenic properties of physiological or pharmacological substances. Examples of substances that promote heat loss and sleep are melatonin, prostaglandin D2 (Hayaishi 1998), Temazepam (Nicholson et al. 1998), and adenosine (cf. Carley 1998). Examples of substances that promote heat retention and wakefulness are prostaglandin E2 (Hayaishi 1998), methamphetamine (Fukumura et al. 1998), and thyroid hormone (Monane 1992; Moran and Stoudemire 1992; Pierau et al. 1998).

Despite the focus of this section on skin temperature, it should be stressed that both an elevated skin temperature and a fall in core temperature, in combination, are of importance for sleep, as indicated by the model. Indeed, when a lowering of core temperature is prohibited by sleeping in a too hot and/or humid environment, sleep is impaired despite the evoked increase in skin temperature (Bonegio et al. 1988; Ohnaka et al. 1995; Fletcher et al. 1999; Okamoto-Mizuno et al. 1999).

4. AGE-RELATED CHANGES IN THERMOREGULATION

4.1. General Changes

At old age, heat generation is reduced. The human resting metabolic rate shows a curvilinear decline with age, significantly decreasing after the age of about 50 years (Poehlman et al. 1993). This decline is strongly associated with the loss of fat-free weight, which might be preserved with increased physical activity. Furthermore, the sedentary lifestyle of many elderly lowers the heat production from muscular activity (Collins and Exton-Smith 1983).

Moreover, heat retention is also compromised. The decrease in total body water common in the elderly results in a lower thermal buffering capacity and a decreased heat reservoir (Ballester and Harchelroad 1999). When the ambient temperature decreases, there is suboptimal efficiency in diverting blood from the skin to help conserve body heat (cf. Ballester and Harchelroad 1999), which is usually compounded by the loss of insulating subcutaneous tissue (Richey et al. 1988).

On the other hand, the ability to dissipate heat is also compromised in old age. Elderly people show a delayed development of vasodilation with heating (cf. Collins and Exton-Smith 1983) and reduced maximal blood flow capacity of the skin (Martin et al. 1995). Especially over the age of 60, there is a diminished cutaneous vasodilatory response at any given core temperature (Kenney 1988; Kenney et al. 1990; Kenney and Ho 1995; Ho et al. 1997; Minson and Kenney 1997; Minson et al. 1998). The slope of the forearm blood flow (FBF) response to increases in core temperature decreases, whereas the threshold appears unchanged. The decreased vasodilatory capacity results from structural alterations in the skin vasculature (Kenney 1988; Kennaway 1994), alterations in adrenergic control or sensitivity of the skin arterioles (Kenney 1988; Kennaway 1994), reduced vascular supply to skin tissue (cf. Collins and Exton-Smith 1983), and reduced active vasodilator sensitivity (Kenney et al. 1997). Concerning the heat-dissipating properties of melatonin, Cagnacci et al. (1995) demonstrated that, in elderly, not only the nocturnal production of melatonin is compromised, but also the hypothermic effect of melatonin. It is likely that this attenuated vasodilatory response to melatonin in the elderly is due to peripheral, rather than central, changes since, at least in rats, the expression of melatonin receptors in the SCN remains relatively constant with age, whereas on the other hand, a dramatic loss in receptors was found in the arteries (Laitinen et al. 1992). It should be noted finally that, in aged rats, a marked reduction in brain capillaries has been demonstrated that is likely to reduce the net perfusion and thus cooling of the brain, which is normally maximal during SWS (Andreoli et al. 1998).

Thermal perception is also reduced. The increased threshold of cutaneous sensibility might be due to changes in collagen and elastic tissues of the skin (cf. Collins and Exton-Smith 1983; Ballester and Harchelroad 1999).

4.2. Changes in Circadian Temperature Rhythms

Age-related changes in the circadian rhythm in core temperature and its phase relation to sleep are discussed in many articles in this issue of *Chronobiology International* and thus are summarized only very briefly below. Interestingly, all we know at present are the changes in rectal temperature because there is a striking lack of data concerning age-related changes in the circadian variation of the underlying processes generating the circadian rhythm in core temperature: heat generation, retention, and loss.

It was observed more than a century ago that the circadian amplitude of human body temperature declines from childhood to senescence by about 50% (cf. Weinert 2000). This finding—with percentages ranging from 13% to 40%, depending on the protocol—has been replicated in many studies (Weitzman et al. 1982; Vitiello et al. 1986; Czeisler et al. 1992; Duffy et al. 1998; Dijk et al. 2000), but not all (e.g., Monk and Kupfer 2000). A bias of selection of very healthy, nonsedentary elderly may underlie the studies that failed to find significant decreases.

Despite earlier suggestions of a shortening of the intrinsic period of the biological clock with age (Weitzman et al. 1982), a recent, better controlled, forced desynchrony study revealed an average period of 24.18h in both young and older individuals (Czeisler et al. 1999).

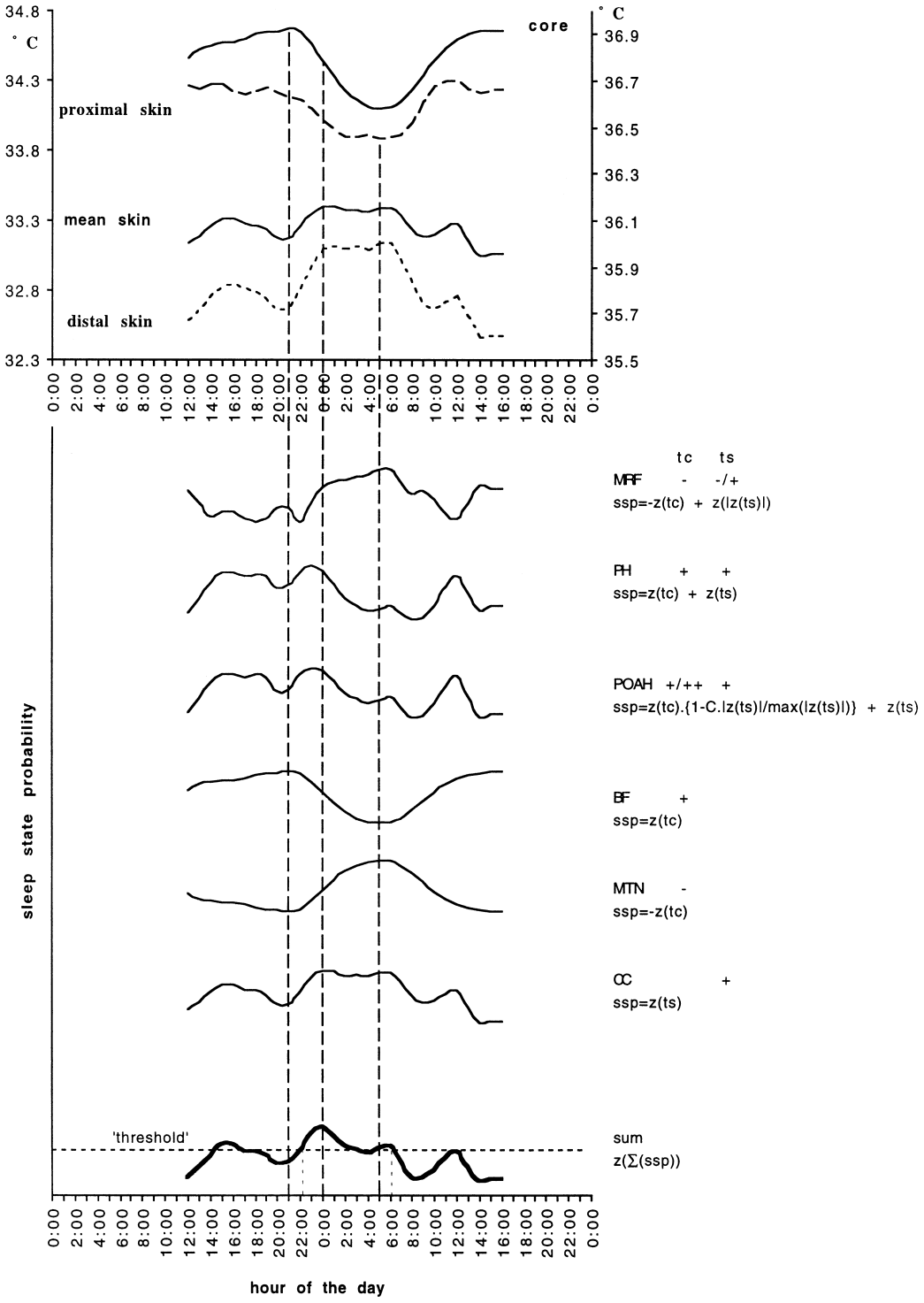
Elderly people show an advanced phase of their temperature rhythm, varying in different studies from about 0.75h to 2h (Czeisler et al. 1992; Duffy et al. 1998). Some studies indicate that it is especially the rising phase of the rectal rhythm that is advanced (Duffy et al. 1998; Monk and Kupfer 2000).

Marked changes occur in the phase relation of the temperature rhythm and the sleep period. Although under constant routine conditions Czeisler et al. (1992) did not find a significant difference in the phase angle between habitual sleep onset between young males and the elderly, the habitual sleep onset in elderly people in a forced desynchrony protocol occurred on average 6.3h before the temperature minimum compared to an average of 5.2h in young adults (Dijk et al. 1999). Also, the habitual wake time is earlier (e.g., Tune 1968; Weitzman et al. 1982; Monk et al. 1991; Czeisler et al. 1992), in fact more than the advance in the temperature minimum would predict (Duffy et al. 1997). This very important finding indicates that elderly people are less able to sustain sleep after the temperature minimum (Duffy et al. 1997), and that the sleep of the elderly is more easily disturbed if the sleep period is misaligned to the temperature phase, that is, when sleep is not scheduled on the falling part of the core temperature rhythm (Dijk et al. 1999). Carrier et al. (1999) could not confirm this age-related difference in phase angle between the temperature minimum and habitual wake time, which may be due to the selection of very healthy elderly people with vigorous life styles and without sleep disturbances.

4.3. Age-Related Sleep Complaints: A Contribution of Changes in Circadian Temperature Rhythms?

It may be clear from the previous sections that the thermoregulatory system functions much less robustly in the elderly compared to young adults. Translating these changes to the model presented above, both decreased amplitude of the core temperature and decreased feedback from the periphery should be included. Given the decreased heat reservoir of the aged body, an advanced discontinuation of nocturnal heat loss and the concomitant high skin temperature would be predicted. We are not aware of any study in which actual distal and proximal skin temperatures have been measured during the sleep-wake cycle of elderly. However, several published core temperature profiles indicate that the rising phase of the rectal rhythm is advanced (e.g., Duffy et al. 1998; Monk and Kupfer 2000), indeed suggesting an advanced decrease in distal temperature.

When “aged” profiles are simulated, again based on the data of Kräuchi and Wirz-Justice (1994), modeling all temperature profiles with an advance of 1h only in the increasing part of the rectal temperature, a 20% decrease in the amplitudes of core and


34.8
° C
34.3
33.8
33.3
32.8
32.3
proximal skin
mean skin
distal skin
core
° C
36.9
36.7
36.5
36.3
36.1
35.9
35.7
35.5
0:00 2:00 4:00 6:00 8:00 10:00 12:00 14:00 16:00 18:00 20:00 22:00 0:00 2:00 4:00 6:00 8:00 10:00 12:00 14:00 16:00 18:00 20:00 22:00 0:00
sleep state probability
tc ts
MRF - -/+
ssp=-z(tc) + z(|z(ts)|)
PH + +
ssp=z(tc) + z(ts)
POAH +/++ +
ssp=z(tc).{1-C.|z(ts)|/max(|z(ts)|)} + z(ts)
BF +
ssp=z(tc)
MTN -
ssp=-z(tc)
CC +
ssp=z(ts)
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0:00 2:00 4:00 6:00 8:00 10:00 12:00 14:00 16:00 18:00 20:00 22:00 0:00 2:00 4:00 6:00 8:00 10:00 12:00 14:00 16:00 18:00 20:00 22:00 0:00
hour of the day

skin temperatures, as well as a 20% decrease in the cutaneous sensitivity, the sleep-state probability depicted in Fig. 5 results. Note the damped amplitude (i.e., the less robust area above the threshold). The closeness to the threshold would predict that a minor reduction of the skin temperature would induce wakefulness in the elderly, but not in young subjects, just as has been reported by Jennings et al. (1993). Furthermore, there is a clearly increased likeliness of early morning awakening. Interestingly and in accordance with the data of Duffy et al. (1998), the elderly would awake closer to their temperature minimum according to the present model. Whereas in the simulation the temperatures were advanced to obtain a 1h shift in the rectal temperature minimum, sleep offset is advanced by approximately 1.5h. Note also that the drive to nap is not reduced.

The model would predict that improvements in sleep would result from altering the curve in such a way that core temperature would be falling for a longer period, and skin temperature would be increased for a longer period. The next section discusses how sleep can be improved by experimental manipulations that affect thermoregulation in accordance with the presented model.

5. EFFECT ON SLEEP OF MANIPULATIONS THAT ALTER CORE AND SKIN TEMPERATURES

5.1. Direct Manipulations of Body Temperature

In young adults, several experiments have been reported in which temperature curves were manipulated by warm baths or warm environments. Horne and colleagues showed that whole body warming in the early afternoon induced sleepiness both during and following the warm baths, decreased sleep latency, and increased SWS power (Horne and Reid 1985; Horne and Shackell 1987). Jordan et al. (1990) applied passive body heating before sleep and reported an increase in SWS. Core temperature data of this study show a steeper fall, starting before sleep onset, that went unnoticed by the authors, however, but appeared to differentiate the experimental and control (no previous heating) curves much better than the marginal difference in temperature at sleep onset to which the effect on sleep was attributed. Other body-heating studies have demonstrated that shorter sleep latencies and more SWS follow body heating in the evening, but not after heating in the morning, and it has been suggested that the drop in temperature following body heating, and its time relation to bedtime, underlies the findings (Bunnell et al. 1988; Di Nisi et al. 1989). Both in rat and humans, body heating is indeed followed by increased heat dissipation and a steeper decline of core body temperature to a lower level than under control conditions (Geschickter et al. 1966; Ogawa et al. 1967; Morairty et al. 1993). Bunnell and Horvath (1985) furthermore warmed subjects after awakening them during the night. The sleep period following this procedure showed an increase in SWS following a decline in core temperature of approximately 1h. Support for the involvement of increased peripheral temperature in the induction of sleep is furthermore

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FIGURE 5. Hypothetical sleep-state probability curve in the elderly, modeled from the data of Fig. 3, with an advance of 1h in the increasing part of the rectal temperature (06:00 and after to 05:00 and after), a 20% decrease in the amplitudes of core and skin temperatures, as well as a 20% decrease in the cutaneous sensitivity. All normalizations are with respect to means and standard deviations of nonattenuated amplitudes. Note the damped amplitude (i.e., a less robust area above threshold) and a clearly increased likeliness of early morning awakening.

provided by the experiments of Morairty and Holm, in which warming of the face promoted sleep, and cooling of the face inhibited sleep (cf. Berger and Phillips 1988). Mere immersion of the feet and lower legs in a hot water bath for half an hour before bedtime affected core temperature only marginally, but did result in a long-lasting elevated skin temperature during the night (Sung et al. 1998). As compared to a hot bath, this manipulation improved SWS and REM sleep even more significantly and sleep onset latency and subjective sleep quality equally.

Relatively few studies have applied passive body heating in the elderly. In a static-charge-sensitive bed (SCSB) study, Kanda and colleagues (1999) reported a decrease of body movements and an increase in subjective sleep quality and ease of falling asleep for both young and elderly subjects after taking a hot bath in the evening. The temperature data indicate a delay in the rectal temperature minimum despite a steeper initial fall of core temperature. In the young subjects, skin temperature was increased by about 1.5°C initially, staying significantly higher during the first 6h of sleep, while slowly returning to normal values. In the aged subjects, skin temperature was not measured validly because of the use of heating blankets. In a series of studies, Dorsey and colleagues (1996, 1998, 1999) showed that enforcing an increase in body temperature in the early evening by taking a hot bath 1.5h to 2h before bedtime resulted in a delay of approximately 1.5h in the nocturnal rectal temperature minimum of elderly female insomniacs. The delay was most pronounced in the subjects who were more phase advanced. The slope of the temperature drop following a hot bath was steeper, indicating increased heat loss and thus increased skin temperature. Skin temperature was not measured, however. The manipulation resulted in a significant increase in SWS and nonsignificant improvements of wakefulness after sleep onset (WASO), total sleep time (TST), and sleep efficiency after sleep onset (SE). There was a strong correlation between the phase shift and the improvements in WASO and SE. Notably, passive body heating was more effective than a new, nonbenzodiazepine hypnotic—with reportedly fewer side effects—in improving subjective and objective sleep quality and—contrary to any hypnotic—increased EEG slow-wave activity.

The timing of the core-temperature-increasing methods is of crucial importance. If a hot bath, bright light, or exercise (see below) is scheduled too close to the sleep period, one may feel too aroused to sleep. Hot baths applied about 1.5h to 2h before bedtime were found beneficial to sleep (Dorsey et al. 1996, 1998, 1999). If the manipulation is timed too long before sleep onset, core temperature may already be back on the baseline level at the onset of sleep, and no increased heat loss during sleep will be attained. In fact, body-heating studies have demonstrated that shorter sleep latencies and more SWS follow body heating in the evening, but not after heating in the morning (Bunnell et al. 1988; Di Nisi et al. 1989).

In summary, sleep improvement after body warming appears to be related to an enhanced and/or prolonged decrease in core temperature during sleep, which again is due to increased heat dissipation with the concomitant increase in skin temperature. As also predicted by the model, a delay in the nocturnal minimum of core temperature would be beneficial to sleep.

5.2. Effects on Sleep of Changes in Thermoregulation and Body and Skin Temperatures Resulting from Other Manipulations

Changes in sleep have also been reported in studies in which the temperature curves were altered concomitantly to other experimental manipulations. Several studies

indicate that exposure to bright light raises body temperature (Badia et al. 1991; Dijk, Cajochen, Borbély et al. 1991; Strassman et al. 1991). Contradictory findings have been reported in bright light studies in which both temperature and sleep were assessed. Bunnell et al. (1992) found a steeper decline in tympanic and rectal temperature following exposure to bright light in the evening; the decline was associated with increased EEG slow-wave activity and a nonsignificant reduction in sleep latency. However, Cajochen et al. (1992) reported increased rectal temperature and sleep latency, as well as attenuated EEG slow-wave activity after late night bright light exposure. Dijk, Cajochen, Borbély et al. (1991) also found an increased level and an attenuated decrease in rectal temperature after late night bright light exposure; the decrease was associated with a significant increase in sleep latency without affecting any other sleep variable. Thus, the effect of bright light exposure on subsequent sleep appears to depend on the effect on body temperature: A stronger decrease is associated with sleep facilitation, whereas an attenuated decrease is associated with a longer sleep latency. It has indeed been shown that bright light exposure during the day causes a stronger release of peripheral vasoconstrictor activity during the subsequent night, resulting in increased skin blood flow and skin temperature and decreased rectal temperature (Aizawa and Tokura 1996). It should be noted that bright light not only temporarily affects temperature, but also can increase the general level of arousal (Badia et al. 1991) as well as shift the circadian rhythm and thereby either improve (Campbell et al. 1993) or disturb (Cajochen et al. 1992) sleep.

In humans, body temperature also can be lowered by administration of melatonin, most likely resulting from an increase in peripheral vasodilation and the concurrent increase in skin temperature and heat loss. Dim light melatonin onset (DLMO) correlates more strongly with the time of the maximum rate of core temperature decline than with the times of all other circadian temperature rhythm variables (peak, minimum, onset of decline, etc.) (Eder et al. 1992) and is also strongly correlated with the nocturnal sleep gate (the timing of the steepest increase in sleepiness) (Tzischinsky et al. 1993). Many studies reported shorter sleep latencies, improved sleep, and increased sleepiness and fatigue-related EEG changes after administration of melatonin (Tzischinsky et al. 1993; Singer, Jackson et al. 1994; Singer, Parrott et al. 1994; Singer, Wild et al. 1994; Tzischinsky and Lavie 1994; Garfinkel et al. 1995; Cajochen, Kräuchi, Von Arx et al. 1996; Zhdanova et al. 1996). It was suggested earlier (Van Den Heuvel and Dawson 1995) that the decline in body temperature following ingestion of melatonin may underlie its somnogenic properties. Van Den Heuvel and Dawson (1995) demonstrated that melatonin suppression attenuated the decrease in core temperature and increased sleep onset latency. Reid et al. (1996) reported decreased core temperature and shorter sleep onset latency after daytime melatonin administration, and their data suggest that the most prominent decrease in sleep onset latency was around the time of the maximal rate of change in core temperature, which coincides with maximal skin temperature of the extremities. The well-established effect of melatonin on both temperature and sleep suggests that melatonin in diurnal animals, such as humans, acts as an effector of the circadian timing system involved in the arousal-state transition from wakefulness to sleep. Since melatonin acts as a peripheral vasoconstrictor in the nocturnal rat, a decrease of melatonin level before light onset could be involved in a similar, but reversed timed redistribution of temperature and sleep onset in rats.

Another manipulation that affects body temperature and thermoregulation is exercise. Skeletal muscle activity causes by far the most marked increase on metabolic rate (Judy 1976b) and thus increases the heat load of the body. In healthy adults, long-term

fitness training affects metabolic rate during the day and the night in an opposing way (Meijer, Janssen et al. 1991; Meijer, Westerterp et al. 1991; Westerterp et al. 1994). Whereas the daytime metabolic rate increases, the nighttime metabolic rate decreases, thus increasing the heat generation circadian amplitude and probably the core temperature amplitude. Indeed, Berger et al. (1988) demonstrated that low oxygen consumption during sleep was associated with a stronger decrease in body temperature.

Many animal and human studies indicate that physical activity affects both circadian rhythms and sleep (for reviews, see Van Someren et al. 1993, 1994, 1997). Generally, a high level of activity practiced regularly over a long period is most efficient for sleep enhancement. The reported improvements in sleep include shorter sleep latencies, more SWS, and longer sleep. Horne and colleagues (Horne and Staff 1983; Horne and Moore 1985) suggested the effect was mediated by alterations in body temperature since cooling of the body during exercise prevented the changes in subsequent sleep (Horne and Moore 1985). Thus, an additional heat load during the day appears to affect sleep during the night. It is likely that a change in skin temperature—which is elevated order to dissipate the heat added to the trunk—may contribute to the sleep-enhancing effect following exercise.

Several factors may be involved in the finding that substantial levels of exercise and long-term training enhance sleep more effectively. First, mild exercise of short duration paradoxically induces a decrease in deep body temperature (Cranston et al. 1954). Second, the reported enhancement of the heat dissipation mechanism during the night (Meijer, Janssen et al. 1991; Meijer, Westerterp et al. 1991; Westerterp et al. 1994) could be related to "training" of the vasodilatory response. Indeed, regular exercise shifts the threshold for vasodilation toward a lower internal temperature, especially after training in a hot environment (Roberts et al. 1977). At low levels of exercise, the peripheral vasculature initially constricts, and dilation occurs only when levels of activity induce a substantial increase in body temperature (Judy 1976a; Gordon 1990). Third, melatonin may be involved in the decline in temperature that follows the body-heating effect of physical activity because increased activity during the day induces an increase in plasma melatonin level (Carr et al. 1981; Theron et al. 1984; L'Hermite-Balériaux et al. 1986; Ronkainen et al. 1986; Strassman et al. 1989; Monteleone et al. 1990). The increase is correlated with the intensity of the exercise (Theron et al. 1984).

Indeed, in the elderly, a low level of physical activity increases the risk of insomnia at 8-year follow-up by an odds rate of ±2 (Morgan and Clarke 1997), whereas regular exercise reduced the prevalence of disturbed sleep in healthy middle-aged to elderly subjects (Sherrill et al. 1998).

6. CONCLUSIONS

Circadian changes in the distribution of heat over the body may contribute to sleep onset and continuation. Both direct and indirect manipulations of this process may have contributed to sleep improvements found after the application of melatonin, bright light, and exercise. Decreased sleep quality in the elderly may be determined in part by age-related changes in thermoregulation. At present, there is a profound lack of sleep studies in which skin temperature has been determined, whereas in fact it may greatly enhance our insight. It is strongly advised to include this assessment in ambulatory studies now that technological developments have made this assessment feasible (e.g., Mini Mitter,

Sunriver, OR; Cambridge Neurotechnology, Cambridge, UK). Preliminary results of temperature manipulation studies suggest that age-related sleep disturbances, in which the altered phase relation between the core temperature minimum and the sleep period appears of crucial importance, are amenable to feasible treatment, such as with hot baths.

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REFERENCES

Adey WR, Bors E, Porter RW. 1968. EEG sleep patterns after high cervical lesions in man. Arch Neurol. 19:377.

Aizawa S, Tokura H. 1996. The effects of different light intensities during the daytime on the forearm blood flow and mean body temperature in the evening. Jpn J Physiol. 46:481–84.

Alam MN, McGinty D, Szymusiak R. 1995a. Neuronal discharge of preoptic/anterior hypothalamic thermosensitive neurons: relation to NREM sleep. Am J Physiol. 269:R1240–49.

Alam MN, McGinty D, Szymusiak R. 1995b. Preoptic/anterior hypothalamic neurons: thermosensitivity in rapid eye movement sleep. Am J Physiol. 269:R1250–57.

Alam MN, McGinty D, Szymusiak R. 1996. Preoptic/anterior hypothalamic neurons—thermosensitivity in wakefulness and non rapid eye movement sleep. Brain Res. 718:76–82.

Alam MN, Szymusiak R, Steininger TL et al. 1996. Sleep-wake activity and thermosensitivity of neurons in the ventral lateral preoptic area of rats. Soc Neurosci Abstr. 22:27.

Almirall H, Aguirre A, Rial RV et al. 1993. Temperature drop and sleep: testing the contribution of SWS in keeping cool. Neuroreport. 5:177–80.

Ancoli-Israel S, Seifert AR, Lemon M. 1986. Thermal biofeedback and periodic movements in sleep: patients' subjective reports and a case study. Biofeedback Self Regul. 11:177–88.

Andreoli E, Zoccoli G, Lucchi ML et al. 1998. Brain capillary perfusion during sleep in the aged rat. J Sleep Res. 7 S2:8.

Aschoff J. 1947a. Einige allgemeine Gesetzmässigkeiten physikalischer Temperaturregulation. Pflugers Arch. 249:125–36.

Aschoff J. 1947b. Zur Regulationsbreite der physikalischen Temperaturregulation. Pflugers Arch. 249:137–47.

Aschoff J. 1970. Circadian rhythm of activity and of body temperature. In: Hardy JD,

Gaffe AP, Stolwijk JAJ, editors. Physiological and behavioral temperature regulation. Springfield, Illinois: Charles C Thomas, pp. 905–19.

Badia P, Myers B, Boecker M et al. 1991. Bright light effects on body temperature, alertness, EEG and behavior. Physiol Behav. 50:583–88.

Ballester JM, Harchelroad FP. 1999. Hypothermia: an easy-to-miss, dangerous disorder in winter weather. Geriatrics. 54:51–52, 55–57.

Beersma D, Dijk DJ. 1992. Selective SWS suppression does not affect the time course of core body temperature in men. J Sleep Res. 1:201–4.

Benedek G, Obal F Jr, Lelkes Z et al. 1982. Thermal and chemical stimulations of the hypothalamic heat detectors: the effects of the EEG. Acta Physiol Acad Sci Hung. 60:27–35.

Bentivoglio M, Grassizucconi G. 1997. The pioneering experimental studies on sleep deprivation. Sleep. 20:570–76.

Berger RJ, Palca JW, Walker JM et al. 1988. Correlations between body temperatures, metabolic rate and slow wave sleep in humans. Neurosci Lett. 86:230–34.

Berger RJ, Phillips NH. 1988. Comparative aspects of energy metabolism, body temperature and sleep. Acta Physiol Scand. (Suppl.) 574:21–27.

Berman HH, Kim KH, Talati A et al. 1998. Representation of nociceptive stimuli in primary sensory cortex. Neuroreport. 9:4179–87.

Bonegio RG, Driver HS, King LM et al. 1988. Circadian temperature rhythm blunting and sleep composition. Acta Physiol Scand. (Suppl.) 574:44–47.

Bonnet MH, Arand DL. 1995. 24-Hour metabolic rate in insomniacs and matched normal sleepers. Sleep. 18:581–88.

Boulant JA. 1980. Hypothalamic control of thermoregulation. In: Morgane PJ, Panksepp J, editors. Handbook of the hypothalamus. New York: Marcel Dekker, pp. 1–82.

Boulant JA. 1981. Hypothalamic mechanisms in thermoregulation. Fed Proc. 40:2843–50.

Boulant JA, Bignall KE. 1973. Hypothalamic neuronal responses to peripheral and deep-body temperatures. Am J Physiol. 225:1371–74.

Boulant JA, Dean JB. 1986. Temperature receptors in the central nervous system. Annu Rev Physiol. 48:639–65.

Boulant JA, Hardy JD. 1974. The effect of spinal and skin temperatures on the firing rate and thermosensitivity of preoptic neurones. J Physiol. 240:639–60.

Bullitt E. 1990. Expression of c-fos-like protein as a marker for neuronal activity following noxious stimulation in the rat. J Comp Neurol. 296:517–30.

Bunnell DE, Agnew JA, Horvath SM et al. 1988. Passive body heating and sleep: influence of proximity to sleep. Sleep. 11:210–19.

Bunnell DE, Horvath SM. 1985. Effects of body heating during sleep interruption. Sleep. 8:274–82.

Bunnell DE, Treiber SP, Phillips NH et al. 1992. Effects of evening bright light exposure on melatonin, body temperature and sleep. J Sleep Res. 1:17–23.

Cagnacci A. 1997. Influences of melatonin on human circadian rhythms. Chronobiol Int. 14:205–20.

Cagnacci A, Elliott JA, Yen SS. 1992. Melatonin: a major regulator of the circadian rhythm of core temperature in humans. J Clin Endocrinol Metab. 75:447–52.

Cagnacci A, Soldani R, Yen SS. 1995. Hypothermic effect of melatonin and nocturnal core body temperature decline are reduced in aged women. J Appl Physiol. 78: 314–17.

Cajochen C, Dijk D-J, Borbely AA. 1992. Dynamics of EEG slow-wave activity and

core body temperature in human sleep after exposure to bright light. Sleep. 15: 337–43.
Cajochen C, Kräuchi K, Von Arx M et al. 1996. Daytime melatonin administration enhances sleepiness and theta/alpha activity in the waking EEG. Neurosci Lett. 207: 209–13.
Cajochen C, Kräuchi K, Wirz-Justice A. 1996. Dynamics of skin and core body temperature and heart rate in human sleep after a single administration of melatonin. J Sleep Res. 5 S1:26.
Campbell SS, Broughton RJ. 1994. Rapid decline in body temperature before sleep: fluffing the physiological pillow? Chronobiol Int. 11:126–31.
Campbell SS, Dawson D, Anderson MW. 1993. Alleviation of sleep maintenance insomnia with timed exposure to bright light. J Am Geriatr Soc. 41:829–36.
Capsoni S, Viswanathan M, De Oliveira AM et al. 1994. Characterization of melatonin receptors and signal transduction system in rat arteries forming the circle of Willis. Endocrinology. 135:373–78.
Carley DW. 1998. Spectral structure of human alpha rhythm in different arousal states. J Sleep Res. 7 S2:38.
Carman JS, Post RM, Buswell R et al. 1976. Negative effects of melatonin on depression. Am J Psychiatry. 133:1181–86.
Carr DB, Reppert SM, Bullen B et al. 1981. Plasma melatonin increases during exercise in women. J Clin Endocrinol Metab. 53:224–25.
Carrier J, Monk TH, Reynolds CF III et al. 1999. Are age differences in sleep due to phase differences in the output of the circadian timing system? Chronobiol Int. 16: 79–91.
Cespuglio R, Faradji H, Gomez ME et al. 1981. Single unit recordings in the nuclei raphe dorsalis and magnus during the sleep-waking cycle of semi-chronic prepared cats. Neurosci Lett. 24:133–38.
Cespuglio R, Gomez ME, Walker E et al. 1979. Effets du refroidissement et de la stimulation des noyaux du systeme du raphe sur les etats de vigilance chez le chat. Electroencephalogr Clin Neurophysiol. 47:289–308.
Clark RP, Edholm OG. 1985. Man and his thermal environment. London: Edward Arnold.
Collins KJ, Exton-Smith AN. 1983. 1983 Henderson Award lecture. Thermal homeostasis in old age. J Am Geriatr Soc. 31:519–24.
Corrodi H, Fuxe K, Hokfelt T. 1967. A possible role played by central monoamine neurones in thermo-regulation. Acta Physiol Scand. 71:224–32.
Cranston WI, Gerbrandy J, Snell ES. 1954. Oral, rectal and oesophageal temperatures and some factors affecting them in man. J Physiol. 126:347–58.
Crawshaw L, Grahn D, Wollmuth L et al. 1985. Central nervous regulation of body temperature in vertebrates: comparative aspects. Pharmacol Ther. 30:19–30.
Czeisler CA, Duffy JF, Shanahan TL et al. 1999. Stability, precision, and near-24-hour period of the human circadian pacemaker. Science. 284:2177–81.
Czeisler CA, Dumont M, Duffy JF et al. 1992. Association of sleep-wake habits in older people with changes in output of circadian pacemaker. Lancet. 340:933–36.
Daan S, Strijkstra A, Barnes BM. 1992. The elusive function of sleep: new insight from hibernators? In: Hiroshige T, Honma K, editors. Circadian clocks from cell to human. Sapporo, Japan: Hokkaido University Press, pp. 165–76.
Dean JB, Boulant JA. 1992. Delayed firing rate responses to temperature in diencephalic slices. Am J Physiol. 263:R679–84.

Dean JB, Kaple ML, Boulant JA. 1992. Regional interactions between thermosensitive neurons in diencephalic slices. Am J Physiol. 263:R670–78.

De Carvalho SA, Andrade MJ, Tavares MA et al. 1998. Spinal cord injury and psychological response. Gen Hosp Psychiatry. 20:353–59.

Dickenson AH. 1977. Specific responses of rat raphe neurones to skin temperature. J Physiol. 273:277–93.

Dijk DJ. 1999. Circadian variation of EEG power spectra in NREM and REM sleep in humans: dissociation from body temperature. J Sleep Res. 8:189–95.

Dijk DJ, Cajochen C, Borbély AA. 1991. Effect of a single 3-hour exposure to bright light on core body temperature and sleep in humans. Neurosci Lett. 121:59–62.

Dijk DJ, Cajochen C, Tobler I et al. 1991. Sleep extension in humans: sleep stages, EEG power spectra and body temperature. Sleep. 14:294–306.

Dijk DJ, Czeisler CA. 1995. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci. 15:3526–38.

Dijk D-J, Duffy JF, Czeisler CA. 2000. Contribution of circadian physiology and sleep homeostasis to age-related changes in human sleep. Chronobiol Int. 17:285–311.

Dijk DJ, Duffy JF, Riel E et al. 1999. Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. J Physiol. 516:611–27.

Di Nisi J, Ehrhart J, Galeou M et al. 1989. Influence of repeated passive body heating on subsequent night sleep in humans. Eur J Appl Physiol. 59:138–45.

Dirig DM, Yaksh TL. 1996. Temperature dependence of evoked glutamate and CGRP release from rat dorsal spinal cord in vitro. Soc Neurosci Abstr. 22:1991.

Dorsey CM, Lukas SE, Cohen-Zion M et al. 1998. Passive body heating versus Zolpidem in older female insomniacs. Sleep. 21 S3:255.

Dorsey CM, Lukas SE, Teicher MH et al. 1996. Effects of passive body heating on sleep of older female insomniacs. J Geriatr Psychiatry Neurol. 9:83–90.

Dorsey CM, Teicher MH, Cohen-Zion M et al. 1999. Core body temperature and sleep of older female insomniacs before and after passive body heating. Sleep. 22:891–98.

Dubois M, Coppola R, Buchsbaum MS et al. 1981. Somatosensory evoked potentials during whole body hyperthermia in humans. Electroencephalogr Clin Neurophysiol. 52:157–62.

Duffy JF, Dijk DJ, Klerman EB et al. 1997. Altered phase relationship between body temperature cycle and habitual awakening in older subjects. Sleep Res. 26:711.

Duffy JF, Dijk DJ, Klerman EB et al. 1998. Later endogenous circadian temperature nadir relative to an earlier wake time in older people. Am J Physiol. 275:R1478–87.

Eder DN, Avery DH, Dahl K. 1992. Estimation of human circadian phase from body temperature using waveform extraction. J Sleep Res. 1 S1:65.

Edgar DM, Dement WC. 1994. Functional role of the suprachiasmatic nuclei in sleep/wake regulation: insights from lesion and transplantation studies. J Sleep Res. 3.

Edgar DM, Dement WC, Fuller CA. 1993. Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. J Neurosci. 13:1065–79.

Finkbeiner AK. 1998. Getting through the sleep gate. The Sciences. September/October: 14–18.

Fletcher A, van den Heuvel C, Dawson D. 1999. Sleeping with an electric blanket: effects on core temperature, sleep, and melatonin in young adults [in process citation]. Sleep. 22:313–18.

Formenti A, Arrigoni E, Mancia M. 1996. Effects on the electroencephalogram induced by the changes in cerebrospinal-fluid CA^{2+}-concentration: cellular mechanisms. Soc Neurosci Abstr. 22:148.

Freedman RR, Sattler HL. 1982. Physiological and psychological factors in sleep-onset insomnia. J Abnorm Psychol. 91:380–89.

Freund PR, Brengelmann GL, Rowell LB et al. 1984. Attenuated skin blood flow response to hyperthermia in paraplegic men. J Appl Physiol. 56:1104–9.

Fukumura M, Cappon GD, Pu C et al. 1998. A single dose model of methamphetamine-induced neurotoxicity in rats: effects on neostriatal monoamines and glial fibrillary acidic protein. Brain Res. 806:1–7.

Fuller CA, Sulzman FM, Moore-Ede MC. 1985. Role of heat loss and heat production in generation of the circadian temperature rhythm of the squirrel monkey. Physiol Behav. 34:543–46.

Gagnon P, De Koninck J, Broughton R. 1985. Reappearance of electroencephalogram slow waves in extended sleep with delayed bedtime. Sleep. 8:118–28.

Gao B, Franken P, Tobler I et al. 1995. Effect of elevated ambient temperature on sleep, EEG spectra, and brain temperature in the rat. Am J Physiol. 268:R1365–73.

Garfinkel D, Laudon M, Nof D et al. 1995. Improvement of sleep quality in elderly people by controlled-release melatonin. Lancet. 346:541–44.

Gass GC, Camp EM, Nadel ER et al. 1988. Rectal and rectal vs. esophageal temperatures in paraplegic men during prolonged exercise. J Appl Physiol. 64:2265–71.

Geary GG, Duckles SP, Krause DN. 1995. Melatonin is a direct vasoconstrictor in cerebral arteries. Soc Neurosci Abstr. 21:157.

Geschickter EH, Andrews PA, Bullard RW. 1966. Nocturnal body temperature regulation in man: a rationale for sweating in sleep. J Appl Physiol. 21:623–30.

Glotzbach SF, Heller HC. 1994. Temperature regulation. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Philadelphia: W. B. Saunders, pp. 260–75.

Gordon CJ. 1990. Thermal biology of the laboratory rat. Physiol Behav. 47:963–91.

Gordon CJ, Heath JE. 1986. Integration and central processing in temperature regulation. Annu Rev Physiol. 48:595–612.

Grahn DA, Radeke CM, Heller HC. 1989. Arousal state versus temperature effects on neuronal activity in subcoeruleus area. Am J Physiol. 256:R840–49.

Griffin JD, Kaple ML, Chow AR et al. 1996. Cellular mechanisms for neuronal thermosensitivity in the rat hypothalamus. J Physiol. 492:231–42.

Groenewegen HJ, Berendse HW. 1994. The specificity of the "nonspecific" midline and intralaminar thalamic nuclei. Trends Neurosci. 17:52–57.

Haimov I, Lavie P, Laudon M et al. 1995. Melatonin replacement therapy of elderly insomniacs. Sleep. 18:598–603.

Hardy JD, Oppel TW, 1937. Studies in temperature sensation. III. The sensitivity of the body to heat and the spatial summation of the end organ responses. J Clin Invest. 16:533–40.

Haskell EH, Palca JW, Walker JM et al. 1981. Metabolism and thermoregulation during stages of sleep in humans exposed to heat and cold. J Appl Physiol. 51:948–54.

Hayaishi O. 1998. Prostaglandins and sleep. In: Meier-Ewert K, Okawa M, editors. Sleep-wake disorders. New York: Plenum, pp. 1–10.

Hays T, Morairty S, Szymusiak R et al. 1996. The effects of temperature and synaptic blockade in vitro on neurons of the horizontal limb of the diagonal band of Broca in the rat basal forebrain. Soc Neurosci Abstr. 22:690.

Hays T, Morairty S, Szymusiak R et al. 1997. The effects of temperature and synaptic blockade in vitro on neurons of the horizontal limb of the diagonal band of Broca in the rat basal forebrain. Brain Res. 746:52–58.

Hays T, Szmymusiak R, McGinty D. 1998. The effects of temperature and muscimol on rat diagonal band neurons. J Sleep Res. 7 S2:114.

Hays TC, Szymusiak R, McGinty D. 1999. GABA(A) receptor modulation of temperature sensitive neurons in the diagonal band of broca in vitro [in process citation]. Brain Res. 845:215–23.

Hayward JN, Baker MA. 1969. A comparative study of the role of the cerebral arterial blood in the regulation of brain temperature in five mammals. Brain Res. 16:417–40.

Hellon RF. 1970. The stimulation of hypothalamic neurones by changes in ambient temperature. Pflugers Arch. 321:56–66.

Hellon RF. 1972. Temperature-sensitive neurons in the brain stem: their responses to brain temperature at different ambient temperatures. Pflugers Arch. 335:323–34.

Hellon RF, Hensel H, Schafer K. 1975. Thermal receptors in the scrotum of the rat. J Physiol. 248:349–57.

Hellon RF, Misra NK. 1973. Neurones in the ventrobasal complex of the rat thalamus responding to scrotal skin temperature changes. J Physiol. 232:389–99.

Hellon RF, Misra NK, Provins KA. 1973. Neurones in the somatosensory cortex of the rat responding to scrotal skin temperature changes. J Physiol. 232:401–11.

Hemingway A, Rasmussen T, Wikoff H et al. 1940. Effects of heating the hypothalamus of dogs by diathermy. J Neurophysiol. 3:329–39.

Ho CW, Beard JL, Farrell PA et al. 1997. Age, fitness, and regional blood flow during exercise in the heat. J Appl Physiol. 82:1126–35.

Horne JA, Moore VJ. 1985. Sleep EEG effects of exercise with and without additional body cooling. Electroencephalogr Clin Neurophysiol. 60:33–38.

Horne JA, Reid AJ. 1985. Night-time sleep EEG changes following body heating in a warm bath. Electroencephalogr Clin Neurophysiol. 60:154–57.

Horne JA, Shackell BS. 1987. Slow wave sleep elevations after body heating: proximity to sleep and effects of aspirin. Sleep. 10:383–92.

Horne JA, Staff LH. 1983. Exercise and sleep: body-heating effects. Sleep. 6:36–46.

Hughes RJ, Sack RL, Lewy AJ. 1998. The role of melatonin and circadian phase in age-related sleep maintenance insomnia: assessment in a clinical trial of melatonin replacement. Sleep. 21:52–68.

Hyyppa MT, Kronholm E. 1989. Quality of sleep and chronic illnesses. J Clin Epidemiol. 42:633–38.

Imeri L, Gemma C, De Simoni MG et al. 1996. Hypothalamic serotonergic activity and brain temperature across the sleep-wake cycle. Soc Neurosci Abstr. 22:605.

Inoue S, Murakami N. 1976. Unit responses in the medulla oblongata of rabbit to changes in local and cutaneous temperature. J Physiol. 259:339–56.

Jahns R. 1975. Types of neuronal responses in the rat thalamus to peripheral temperature changes. Exp Brain Res. 23:157–66.

Jahns R. 1976. Different projections of cutaneous thermal inputs to single units of the midbrain raphe nuclei. Brain Res. 101:355–61.

Jennings JR, Reynolds CFd, Houck PR et al. 1993. Age and sleep modify finger temperature responses to facial cooling. J Gerontol. 48:M108–16.

Johns MW, Gay TJ, Masterton JP et al. 1971. Relationship between sleep habits, adrenocortical activity and personality. Psychosom Med. 33:499–508.

Jones BE. 1998. The neural basis of consciousness across the sleep-waking cycle. Adv Neurol. 77:75–94.

Jones EG. 1984. Organization of the thalamocortical complex and its relation to sensory processes. In: Brookhart JM, Mountcastle VB, editors. Handbook of physiology, section 1: the nervous system. Bethesda, Maryland: American Physiological Society, pp. 149–212.

Jones SL, Gebhart GF. 1987. Spinal pathways mediating tonic, coeruleospinal, and raphe-spinal descending inhibition in the rat. J Neurophysiol. 58:138–59.

Jordan J, Montgomery I, Trinder J. 1990. The effect of afternoon body heating on body temperature and slow wave sleep. Psychophysiology. 27:560–66.

Judy WV. 1976a. Body temperature regulation. In: Selkurt EE, editor. Physiology. Boston: Little, Brown and Company, pp. 677–99.

Judy WV. 1976b. Physiology of exercise. In: Selkurt EE, editor. Physiology. Boston: Little, Brown and Company, pp. 701–26.

Kanda K, Tochihara Y, Ohnaka T. 1999. Bathing before sleep in the young and in the elderly. Eur J Appl Physiol. 80:71–75.

Kanosue K, Nakayama T, Ishikawa Y et al. 1984. Threshold temperatures of diencephalic neurons responding to scrotal warming. Pflugers Arch. 400:418–23.

Kanosue K, Nakayama T, Ishikawa Y et al. 1985. Responses of thalamic and hypothalamic neurons to scrotal warming in rats: non-specific responses? Brain Res. 328: 207–13.

Kelso SR, Perlmutter MN, Boulant JA. 1982. Thermosensitive single-unit activity of in vitro hypothalamic slices. Am J Physiol. 242:R77–R84.

Kennaway DJ. 1994. Effect of a phase advance of the light/dark cycle on pineal function and circadian running activity in individual rats. Brain Res Bull. 33:639–44.

Kenney WL. 1988. Control of heat-induced cutaneous vasodilatation in relation to age. Eur J Appl Physiol. 57:120–25.

Kenney WL, Ho CW. 1995. Age alters regional distribution of blood flow during moderate-intensity exercise. J Appl Physiol. 79:1112–19.

Kenney WL, Morgan AL, Farquhar WB et al. 1997. Decreased active vasodilator sensitivity in aged skin. Am J Physiol. 272:H1609–14.

Kenney WL, Tankersley CG, Newswanger DL et al. 1990. Age and hypohydration independently influence the peripheral vascular response to heat stress. J Appl Physiol. 68:1902–8.

Kenshalo DR. 1970. Cutaneous temperature receptors—some operating characteristics for a model. In: Hardy JD, Gagge AP, Stolwijk JA, editors. Physiological and behavioral temperature regulation. Springfield, Illinois: Charles C Thomas, pp. 802–18.

King AC, Oman RF, Brassington GS et al. 1997. Moderate-intensity exercise and self-rated quality of sleep in older adults. A randomized controlled trial [see comments]. JAMA. 277:32–37.

Knowles J, Ancoli-Israel S, Gevirtz R et al. 1996. The evaluation of thermal biofeedback in the treatment of periodic limb movement disorder. Sleep Res. 25:265.

Knox GV, Campbell C, Lomax P. 1973. Cutaneous temperature and unit activity in the hypothalamic thermoregulatory centers. Exp Neurol. 40:717–30.

Koyama Y, Hayaishi O. 1994. Firing of neurons in the preoptic/anterior hypothalamic areas in rat: its possible involvement in slow wave sleep and paradoxical sleep. Neurosci Res. 19:31–38.

Kräuchi K, Cajochen C, Mori D et al. 1997. Early evening melatonin and S-20098 ad-

vance circadian phase and nocturnal regulation of core body temperature. Am J Physiol. 272:R1178–88.
Kräuchi K, Cajochen C, Werth E et al. 1999. Warm feet promote the rapid onset of sleep. Nature. 401:36–7.
Kräuchi K, Wirz-Justice A. 1994. Circadian rhythm of heat production, heart rate, and skin and core temperature under unmasking conditions in men. Am J Physiol. 267: R819–29.
Krause DN, Dubocovich ML. 1990. Regulatory sites in the melatonin system of mammals. Trends Neurosci. 13:464–70.
Kreisman NR, Zimmerman ID. 1973. Representation of information about skin temperature in the discharge of single cortical neurons. Brain Res. 55:343–53.
Kubota A, Inouye ST, Kawamura H. 1981. Reversal of multiunit activity within and outside the suprachiasmatic nucleus in the rat. Neurosci Lett. 27:303–8.
Laitinen JT, Viswanathan M, Vakkuri O et al. 1992. Differential regulation of the rat melatonin receptors: selective age-associated decline and lack of melatonin-induced changes. Endocrinology. 130:2139–44.
Lancel M, van Riezen H, Glatt A. 1992. The time course of sigma activity and slow-wave activity during NREMS in cortical and thalamic EEG of the cat during baseline and after 12 hours of wakefulness. Brain Res. 596:285–95.
Lavie P. 1989. To nap, perchance to sleep-ultradian aspects of napping. In: Dinges DF, Broughton RJ, editors. Sleep and alertness: chronobiological, behavioral, and medical aspects of napping. New York: Raven Press, pp. 99–120.
Lavie P. 1997. Melatonin: role in gating nocturnal rise in sleep propensity. J Biol Rhythms. 12:657–65.
Lawrence JW, Fauerbach J, Eudell E et al. 1998. The 1998 Clinical Research Award. Sleep disturbance after burn injury: a frequent yet understudied complication. J Burn Care Rehabil. 19:480–86.
L'Hermite-Balériaux M, Casteels S, De Meirleir K et al. 1986. Human melatonin in physiologic and diseased states: neural control of the rhythm. J Neural Transmission. (Suppl.) 21:486.
Llinas R, Ribary U. 1993. Coherent 40-Hz oscillation characterizes dream state in humans. Proc Natl Acad Sci USA. 90:2078–81.
Lushington K, Lack L. 1995. 24-Hour core body temperature in good and poor elderly sleepers. Sleep Res. 24A:523.
Mackowiak PA, Boulant JA. 1996. Fever's glass ceiling. Clin Infect Dis. 22:525–36.
Magnussen G. 1939. Vasomotorische Veränderingen in den Extremitäten im Verhältnis zu Schlaf und Schlafbereitschaft. Acta Psychiatr Neurol. 14:39–54.
Magnussen G. 1943. On narcolepsy II. Studies on diurnal variations in the skin temperatures in narcoleptics. Acta Psychiatr Neurol. 18:457–85.
Maquet P, Dive D, Salmon E et al. 1992. Cerebral glucose utilization during stage 2 sleep in man. Brain Res. 571:149–53.
Marotte H, Timbal J. 1982. Circadian rhythm of thermoregulating responses in man. In: Gautherie M, Albert E, editors. Biomedical thermology. New York: Alan R. Liss, pp. 159–65.
Martin HL, Loomis JL, Kenney WL. 1995. Maximal skin vascular conductance in subjects aged 5–85 yr. J Appl Physiol. 79:297–301.
Martinez-Gomez M, Cruz Y, Salas M et al. 1994. Assessing pain threshold in the rat: changes with estrus and time of day. Physiol Behav. 55:651–57.

McGinty D, Alam N, Hays T et al. 1999. The ventromedial diagonal band and NREM sleep control. Sleep Res Online. 2(S1):700.

McGinty D, Szymusiak R. 1988. Neuronal unit activity patterns in behaving animals: brainstem and limbic system. Annu Rev Psychol. 39:135–68.

McGinty D, Szymusiak R. 1989. The basal forebrain and slow-wave sleep: mechanistic and functional aspects. In: Wauquier A, editor. Slow wave sleep: physiological, pathophysiological and functional aspects. New York: Raven Press, pp. 61–73.

McGinty D, Szymusiak R. 1990. Keeping cool: a hypothesis about the mechanisms and functions of slow-wave sleep. Trends Neurosci. 13:480–87.

McGinty D, Szymusiak R, Alam N et al. 1998. Preoptic/basal forebrain thermoregulatory control of NREM sleep. J Sleep Res. 7 S2:174.

Meijer GA, Janssen GM, Westerterp KR et al. 1991. The effect of a 5-month endurance-training programme on physical activity: evidence for a sex-difference in the metabolic response to exercise. Eur J Appl Physiol. 62:11–17.

Meijer GA, Westerterp KR, Seyts GH et al. 1991. Body composition and sleeping metabolic rate in response to a 5-month endurance-training programme in adults. Eur J Appl Physiol. 62:18–21.

Mendelson WB, Garnett D, Gillin JC et al. 1984. The experience of insomnia and daytime and nighttime functioning. Psychiatry Res. 12:235–50.

Mendelson WB, Martin JV. 1992. Characterization of the hypnotic effects of triazolam microinjections into the medial preoptic area. Life Sci. 50:1117–28.

Miller JD. 1993. On the nature of the circadian clock in mammals. Am J Physiol. 264: R821–32.

Minors D, Waterhouse J. 1989. Masking in humans: the problem and some attempts to solve it. Chronobiol Int. 6:29–53.

Minson CT, Kenney WL. 1997. Age and cardiac output during cycle exercise in thermoneutral and warm environments. Med Sci Sports Exerc. 29:75–81.

Minson CT, Wladkowski SL, Cardell AF et al. 1998. Age alters the cardiovascular response to direct passive heating. J Appl Physiol. 84:1323–32.

Monane M. 1992. Insomnia in the elderly. J Clin Psychiatry. 53(Suppl.):23–28.

Monk TH, Kupfer DJ. 2000. Circadian rhythms in healthy aging—effects downstream from the pacemaker. Chronobiol Int. 17:355–68.

Monk TH, Reynolds CFd, Buysse DJ et al. 1991. Circadian characteristics of healthy 80-year-olds and their relationship to objectively recorded sleep. J Gerontol. 46: M171–75.

Monroe LJ. 1967. Psychological and physiological differences between good and poor sleepers. J Abnorm Psychol. 72:255–64.

Monteleone P, Maj M, Fusco M et al. 1990. Physical exercise at night blunts the nocturnal increase of plasma melatonin levels in healthy humans. Life Sci. 47:1989–95.

Moore RY. 1996. Entrainment pathways and the functional organization of the circadian system. In: Buijs RM, Kalsbeek A, Romijn HJ et al., editors. Progress in brain research. Amsterdam: Elsevier, pp. 103–19.

Morairty SR, Szymusiak R, Thomson D et al. 1993. Selective increases in non-rapid eye movement sleep following whole body heating in rats. Brain Res. 617:10–16.

Moran MG, Stoudemire A. 1992. Sleep disorders in the medically ill patient. J Clin Psychiatry. 53(Suppl.):29–36.

Morgan K, Clarke D. 1997. Risk factors for late-life insomnia in a representative general practice sample. Br J Gen Pract. 47:166–69.

Morilak DA, Fornal CA, Jacobs BL. 1987. Effects of physiological manipulations on locus coeruleus neuronal activity in freely moving cats. I. Thermoregulatory challenge. Brain Res. 422:17–23.

Morimoto A, Murakami N. 1985. [14C]Deoxyglucose incorporation into rat brain regions during hypothalamic or peripheral thermal stimulation. Am J Physiol. 248: R84–R92.

Morimoto A, Murakami N, Sakata Y. 1988. Changes in hypothalamic temperature modulate the neuronal response of the ventral thalamus to skin warming in rats. J Physiol. 398:97–108.

Morin LP, Meyer-Bernstein E. 1996. Distribution of 5-HT terminals and ascending projections of the dorsal and median raphe nuclei in the hamster. Soc Neurosci Abstr. 22:605.

Moruzzi G. 1969. Sleep and instinctive behavior. Arch Ital Biol. 107:175–216.

Murphy PJ, Campbell SS. 1996. Enhanced performance in elderly subjects following bright light treatment of sleep maintenance in insomnia. J Sleep Res. 5:165–72.

Murphy PJ, Campbell SS. 1997. Nighttime drop in body temperature—a physiological trigger for sleep onset. Sleep. 20:505–11.

Nakayama T, Hardy JD. 1969. Unit responses in the rabbit's brain stem to changes in brain and cutaneous temperature. J Appl Physiol. 27:848–57.

Nicholson AN, Stone BM, Turner C et al. 1998. Hypnotic activity of melatonin. J Sleep Res. 7 S2:186.

Nino-Murcia G. 1992. Diagnosis and treatment of insomnia and risks associated with lack of treatment. J Clin Psychiatry. 53(Suppl.):43–47.

Ogawa T, Satoh T, Takagi K. 1967. Sweating during night sleep. Jpn J Physiol. 17: 135–48.

Ohnaka T, Tochihara Y, Kanda K. 1995. Body movements of the elderly during sleep and thermal conditions in bedrooms in summer. Appl Human Sci. 14:89–93.

Okamoto-Mizuno K, Mizuno K, Michie S et al. 1999. Effects of humid heat exposure on human sleep stages and body temperature. Sleep. 22:767–73.

Penfield W, Boldrey E. 1937. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain. 60:389–443.

Peschanski M, Guilbaud G, Gautron M. 1981. Posterior intralaminar region in rat: neuronal responses to noxious and nonnoxious cutaneous stimuli. Exp Neurol. 72: 226–38.

Pierau FK, Sann H, Yakimova KS et al. 1998. Plasticity of hypothalamic temperature-sensitive neurons. In: Sharma HS, Westman J, editors. Brain functioning in hot environment. Progress in brain research. Amsterdam: Elsevier, pp. 63–84.

Poehlman ET, Goran MI, Gardner AW et al. 1993. Determinants of decline in resting metabolic rate in aging females. Am J Physiol. 264:E450–55.

Pollak CP, Perlick D, Linsner JP. 1992. Daily sleep reports and circadian rest-activity cycles of elderly community residents with insomnia. Biol Psychiatry. 32:1019–27.

Pollak CP, Wagner DR. 1994. Core body temperature in narcoleptic and normal subjects living in temporal isolation. Pharmacol Biochem Behav. 47:65–71.

Ralph CL, Firth BT, Gern WA et al. 1979. The pineal complex and thermoregulation. Biol Rev Camb Philos Soc. 54:41–72.

Reaves TA Jr. 1977. Gain of thermosensitive neurons in the preoptic area of the rabbit, oryctolagus cuniculus. J Therm Biol. 2:31–33.
Rechtschaffen A, Bergmann BM. 1995. Sleep deprivation in the rat by the disk-over-water method. Behav Brain Res. 69:55–63.
Refinetti R, Menaker M. 1992. The circadian rhythm of body temperature. Physiol Behav. 51:613–37.
Reid K, Van Den Heuvel C, Dawson D. 1996. Day-time melatonin administration: effects on core temperature and sleep onset latency. J Sleep Res. 5:150–54.
Reinberg A, Smolensky M. 1983. Chronobiology and thermoregulation. Pharmacol Ther. 22:425–64.
Richey ML, Richey HK, Fenske NA. 1988. Aging-related skin changes: development and clinical meaning. Geriatrics. 43:49–52, 57–59, 63–64.
Roberts MF, Wenger CB, Stolwijk JA et al. 1977. Skin blood flow and sweating changes following exercise training and heat acclimation. J Appl Physiol. 43:133–37.
Roberts WW, Bergquist EH, Robinson TCL. 1969. Thermoregulatory grooming and sleep-like relaxation induced by local warming of preoptic area and anterior hypothalamus in opossum. J Comp Physiol Psychol. 67:182–88.
Roberts WW, Robinson TCL. 1969. Relaxation and sleep induced by warming of preoptic region and anterior hypothalamus in cats. Exp Neurol. 25:282–94.
Ronkainen H, Vakkuri O, Kauppila A. 1986. Effects of physical exercise on the serum concentration of melatonin in female runners. Acta Obstet Gynecol Scand. 65:827–29.
Roth B, Nevsimalova S, Rechtschaffen A. 1972. Hypersomnia with “sleep drunkenness.” Arch Gen Psychiatry. 26:456–62.
Sakai K, El Mansari M, Lin JS et al. 1990. The posterior hypothalamus in the regulation of wakefulness and paradoxical sleep. In: Mancia M, Marini G, editors. The diencephalon and sleep. New York: Raven Press, pp. 171–98.
Sakata Y, Morimoto A, Murakami N. 1989. Responses of thalamic neurons in rats to skin cooling and hypothalamic temperature. Am J Physiol. 256:R1293–98.
Satinoff E, Liran J, Clapman R. 1982. Aberrations of circadian body temperature rhythms in rats with medial preoptic lesions. Am J Physiol. 242:R352–57.
Schingnitz G, Werner J. 1980a. Responses of thalamic neurons to thermal stimulation of the limbs, scrotum and tongue in the rat. J Therm Biol. 5:53–61.
Schingnitz G, Werner J. 1980b. Thalamic burst firing—a neuronal code for temperature information. Brain Res. 195:467–70.
Schingnitz G, Werner J. 1983. Thalamic neurons in the rat responding to thermal and noxious stimulation at various sites. J Therm Biol. 8:23–25.
Schmidt KD, Chan CW. 1992. Thermoregulation and fever in normal persons and in those with spinal cord injuries. Mayo Clin Proc. 67:469–75.
Sherin JE, Elmquist JK, Saper CB. 1996. Sleep promotion by the rostral hypothalamus: a potential mechanism. Soc Neurosci Abstr. 22:690.
Sherin JE, Elmquist JK, Torrealba F et al. 1998. Innervation of histaminergic tuberomammillary neurons by GABAergic and galaninergic neurons in the ventrolateral preoptic nucleus of the rat. J Neurosci. 18:4705–21.
Sherin JE, Shiromani PJ, McCarley RW et al. 1996. Activation of ventrolateral preoptic neurons during sleep. Science. 271:216–19.
Sherrill DL, Kotchou K, Quan SF. 1998. Association of physical activity and human sleep disorders. Arch Intern Med. 158:1894–98.

Silver JR, Randall WC, Guttmann L. 1991. Spinal mediation of thermally induced sweating. J Neurol Neurosurg Psychiatry. 54:297–304.

Simmonds MA. 1970. Effect of environmental temperature on the turnover of 5-hydroxytryptamine in various areas of rat brain. J Physiol. 211:93–108.

Sindrup JH, Kastrup J, Christensen H et al. 1991. Nocturnal variations in peripheral blood flow, systemic blood pressure, and heart rate in humans. Am J Physiol. 261: H982–88.

Sindrup JH, Kastrup J, Madsen PL et al. 1992. Nocturnal variations in human lower leg subcutaneous blood flow related to sleep stages. J Appl Physiol. 73:1246–52.

Singer C, Jackson J, Moffit M et al. 1994. Physiologic melatonin administration and sleep-wake cycle in Alzheimer's disease: a pilot study. Sleep Res. 23:84.

Singer C, Parrott K, Sack R et al. 1994. Low dose, sustained-release melatonin treatment in the elderly. Sleep Res. 23:85.

Singer C, Wild K, Sack R et al. 1994. High dose melatonin is well tolerated by the elderly. Sleep Res. 23:86.

Smith JE, Jansen AS, Gilbey MP et al. 1998. CNS cell groups projecting to sympathetic outflow of tail artery: neural circuits involved in heat loss in the rat. Brain Res. 786:153–64.

Smolander J, Harma M, Lindqvist A et al. 1993. Circadian variation in peripheral blood flow in relation to core temperature at rest. Eur J Appl Physiol. 67:192–96.

Steininger TL, Alam MN, Szymusiak R et al. 1996. State dependent discharge of neurons in the rat hypothalamus. Soc Neurosci Abstr. 22:689.

Stephenson LA, Wenger CB, O'Donovan BH et al. 1984. Circadian rhythm in sweating and cutaneous blood flow. Am J Physiol. 246:R321–24.

Steriade M, Contreras D, Amzica F. 1994. Synchronized sleep oscillations and their paroxysmal developments. Trends Neurosci. 17:199–208.

Steriade M, Curro Dossi R, Contreras D. 1993. Electrophysiological properties of intralaminar thalamocortical cells discharging rhythmic (approximately 40 HZ) spike-bursts at approximately 1000 HZ during waking and rapid eye movement sleep. Neuroscience. 56:1–9.

Stevens JC, Marks LE, Simonson DC. 1974. Regional sensitivity and spatial summation in the warmth sense. Physiol Behav. 13:825–36.

Strassman RJ, Appenzeller O, Lewy AJ et al. 1989. Increase in plasma melatonin, beta-endorphin, and cortisol after a 28.5-mile mountain race: relationship to performance and lack of effect of naltrexone. J Clin Endocrinol Metab. 69:540–45.

Strassman RJ, Qualls CR, Lisansky EJ et al. 1991. Elevated rectal temperature produced by all-night bright light is reversed by melatonin infusion in men. J Appl Physiol. 71:2178–82.

Sung E-J, Tochihara Y, Umakoshi Y. 1998. Effects of bathing and feet immersion in a hot water bath on sleep in winter. In: Kawashima Y, editor. Second international conference on human-environment system. Yokohama: Yokohama University, pp. 130–33.

Szymusiak R. 1995. Magnocellular nuclei of the basal forebrain—substrates of sleep and arousal regulation. Sleep. 18:478–500.

Szymusiak R, Danowski J, McGinty D. 1991. Exposure to heat restores sleep in cats with preoptic/anterior hypothalamic cell loss. Brain Res. 541:134–38.

Szymusiak R, DeMory A, Kittrell EM et al. 1985. Diurnal changes in thermoregulatory behavior in rats with medial preoptic lesions. Am J Physiol. 249:R219–27.

Szymusiak R, McGinty D. 1986. Sleep-related neuronal discharge in the basal forebrain of cats. Brain Res. 370:82–92.

Tayefeh F, Plattner O, Sessler DI et al. 1998. Circadian changes in the sweating-to-vasoconstriction interthreshold range. Pflugers Arch. 435:402–6.

Taylor DC. 1982. The effects of nucleus raphe magnus lesions on an ascending thermal pathway in the rat. J Physiol. 326:309–18.

Ten Cate J, Horsten GPM, Koopman LJ. 1949. The influence of the body temperature on the EEG of the rat. Electroencephalogr Clin Neurophysiol. 1:231–35.

Theron JJ, Oosthuizen JM, Rautenbach MM. 1984. Effect of physical exercise on plasma melatonin levels in normal volunteers. S Afr Med J. 66:838–41.

Travis KA, Bockholt HJ, Zardetto-Smith AM et al. 1995. In vitro thermosensitivity of the midline thalamus. Brain Res. 686:17–22.

Tune GS. 1968. Sleep and wakefulness in normal human adults. Br Med J. 2:269–71.

Tzischinsky O, Lavie P. 1994. Melatonin possesses time-dependent hypnotic effects. Sleep. 17:638–45.

Tzischinsky O, Shlitner A, Lavie P. 1993. The association between the nocturnal sleep gate and nocturnal onset of urinary 6-sulfatoxymelatonin. J Biol Rhythms. 8:199–209.

Van Den Heuvel C, Dawson D. 1995. Melatonin: a neuroendocrine mediator of the circadian rhythms of temperature and sleep. Sleep Res. 24A:550.

Van Dongen HPA, Teerlink HPC, Kerkhof GA. 1996. Effects of posture and sleep in the body temperature drop after going to bed. J Sleep Res. 5 S1:235.

Van Someren EJW. 1997. Rest-activity rhythms in aging, Alzheimer's disease and Parkinson's disease. Methodological developments and therapeutic interventions. Ph.D. thesis, Medical Faculty of the University of Amsterdam. Amsterdam: University of Amsterdam

Van Someren EJW. 1999a. Modelling the relation of body temperature and sleep: importance of the circadian rhythm in skin temperature. Sleep Res Online. 2 (S1):634.

Van Someren EJW. 1999b. Modelling the relation of body temperature to sleep: importance of the circadian rhythm in skin temperature. In: Beersma DGM, Arends JBAM, Van Bemmel AL, et al, editors. Sleep-wake research in the Netherlands. Leiden: Dutch Society for Sleep-Wake Research, pp. 153–55.

Van Someren EJW, Lijzenga C, Mirmiran M et al. 1994. Effect of physical activity on the circadian system in the elderly. In: Mallick BN, Singh R, editors. Environment and physiology. New Delhi: Narosa, pp. 153–63.

Van Someren EJW, Lijzenga C, Mirmiran M et al. 1997. Long-term fitness training improves the circadian rest-activity rhythm in healthy elderly males. J Biol Rhythms. 12:146–56.

Van Someren EJW, Mirmiran M, Swaab DF. 1993. Non-pharmacological treatment of sleep and wake disturbances in aging and Alzheimer's disease: chronobiological perspectives. Behav Brain Res. 57:235–53.

Viens M, Swingle P, De Koninck J. 1989. The treatment of periodic leg movements in sleep using thermal biofeedback: a failure to replicate. Sleep Res. 18:318.

Viswanathan M, Laitinen JT, Saavedra JM. 1990. Expression of melatonin receptors in arteries involved in thermoregulation. Proc Natl Acad Sci USA. 87:6200–3.

Vitiello MV, Smallwood RG, Avery DH et al. 1986. Circadian temperature rhythms in young adult and aged men. Neurobiol Aging. 7:97–100.

Von Euler C, Söderberg U. 1957. The influence of hypothalamic thermoceptive structures

on the electroencephalogram and gamma motor activity. Electroencephalogr Clin Neurophysiol. 9:391–408.

Wallin BG, Stjernberg L. 1984. Sympathetic activity in man after spinal cord injury. Outflow to skin below the lesion. Brain. 107:183–98.

Ware JC, Blumoff R, Pittard JT. 1988. Peripheral vasoconstriction in patients with sleep related periodic leg movements. Sleep. 11:182–86.

Watts AG. 1991. The efferent projections of the suprachiasmatic nucleus: anatomical insights into the control of circadian rhythms. In: Klein DC, Moore RY, Reppert SM, editors. Suprachiasmatic nucleus. The mind's clock. New York: Oxford University Press, pp. 77–106.

Wehr TA. 1992. A brain-warming function for REM sleep. Neurosci Biobehav Rev. 16: 379–97.

Weinert D. 2000. Age-dependent changes of the circadian system. Chronobiol Int. 17: 261–83.

Weiss BL, Aghajanian GK. 1971. Activation of brain serotonin metabolism by heat: role of midbrain raphe neurons. Brain Res. 26:37–48.

Weitzman, ED, Moline ML, Czeisler CA et al. 1982. Chronobiology of aging: temperature, sleep-wake rhythms and entrainment. Neurobiol Aging. 3:299–309.

Wenger CB, Roberts MF, Stolwijk JA et al. 1976. Nocturnal lowering of thresholds for sweating and vasodilation. J Appl Physiol. 41:15–19.

Westerterp KR, Meijer GA, Schoffelen P et al. 1994. Body mass, body composition and sleeping metabolic rate before, during and after endurance training. Eur J Appl Physiol. 69:203–8.

Wit A, Wang SC. 1968. Temperature-sensitive neurons in preoptic-anterior hypothalamic region: effects of increasing ambient temperature. Am J Physiol. 215:1151–59.

Won CK, Kim BK, Jung NP et al. 1996. Differential changes of afferent sensory transmission to the SI cortex during transient lowering of body temperature between rat and hamster. Soc Neurosci Abstr. 22:105.

Wurtman RJ, Zhdanova I. 1995. Improvement of sleep quality by melatonin. Lancet. 346:1491.

Young AA, Dawson NJ. 1982. Evidence for on-off control of heat dissipation from the tail of the rat. Can J Physiol Pharmacol. 60:392–98.

Zhdanova IV, Wurtman RJ, Morabito C et al. 1996. Effects of low oral doses of melatonin, given 2–4 hours before habitual bedtime, on sleep in normal young humans. Sleep. 19:423–31.