Chronobiology International, 23(1&2): 475–484, (2006)

ISSN 0742-0528 print/1525-6073 online
DOI: 10.1080/07420520500545854

Taylor & Francis
Taylor & Francis Group

THERMOREGULATORY EFFECTS OF MELATONIN IN RELATION TO SLEEPINESS

Kurt Kräuchi,[1] Christian Cajochen,[1] Mona Pache,[2] Josef Flammer,[2] and Anna Wirz-Justice[1]

[1]*Centre for Chronobiology, University Psychiatric Clinics, Basel, Switzerland*
[2]*University Eye Clinic, Basel, Switzerland*

Thermoregulatory processes have long been implicated in the initiation of human sleep. In this paper, we review our own studies conducted over the last decade showing a crucial role for melatonin as a mediator between the thermoregulatory and arousal system in humans. Distal heat loss, via increased skin temperature, seems to be intimately coupled with increased sleepiness and sleep induction. Exogenous melatonin administration during the day when melatonin is essentially absent mimics the endogenous thermophysiological processes occurring in the evening and induces sleepiness. Using a cold thermic challenge test, it was shown that melatonin-induced sleepiness occurs in parallel with reduction in the thermoregulatory set-point (threshold); thus, melatonin may act as a circadian modulator of the thermoregulatory set-point. In addition, an orthostatic challenge can partially block the melatonin-induced effects, suggesting an important role of the sympathetic nervous system as a link between the thermoregulatory and arousal systems. A topographical analysis of finger skin temperature with infrared thermometry revealed that the most distal parts of the fingers, *i.e.*, fingertips, represent the important skin regions for heat loss regulation, most probably via opening the arteriovenous anastomoses, and this is clearly potentiated by melatonin. Taken together, melatonin is involved in the fine-tuning of vascular tone in selective vascular beds, as circulating melatonin levels rise and fall throughout the night. Besides the role of melatonin as "nature's soporific", it can also serve as nature's nocturnal vascular modulator.

Keywords Melatonin, Circadian rhythm, Thermoregulation, Sleepiness, Body temperature

INTRODUCTION

The idea that body temperature and sleep are interrelated is based on evolutionary history. Mammalian sleep evolved in association with endothermy (Zepelin, 2000), and all species, regardless of level of development,

Address correspondence to Kurt Kräuchi, Centre for Chronobiology, University Psychiatric Clinics, Wilhelm Klein Strasse 27, CH-4025 Basel, Switzerland. E-mail: kurt.kraeuchi@upkbs.ch

and independent of temporal niche, usually rest or sleep during the circadian trough of their core body temperature (CBT) rhythm (Glotzbach and Heller, 2000). Early studies in humans revealed a close temporal relationship between sleep onset and the CBT rhythm (Czeisler et al., 1980; Zulley et al., 1981). Sleep is typically initiated on the declining portion of the CBT curve when its rate of change and body heat loss are maximal (Zulley et al., 1981; Campbell and Broughton, 1994). A variety of sleep-promoting manipulations, and agents like benzodiazepines or alcohol, have soporific effects (Dawson and Reid, 1997; Gilbert et al., 1999), at least partially through enhancing heat loss mechanisms, *i.e.*, increase of distal skin temperature (DIST, the mean skin temperatures of hands and feet; Kräuchi et al., 1997c). Thus, the concept it is the increased DIST (and hence body heat loss) that is crucial for sleepiness and sleep initiation is supported by a number of studies (Baker et al., 1976; Brown, 1979; Kräuchi et al., 1999a). In this paper, we review our own studies done during the last decade showing a crucial role for melatonin in the relationship between the thermoregulatory and arousal systems in humans. In order to understand how melatonin influences thermophysiology and sleepiness, it is necessary to first elucidate how the circadian rhythm of CBT is regulated.

THE CIRCADIAN REGULATION OF CBT AND SKIN TEMPERATURES IN RELATION TO MELATONIN AND SLEEPINESS

CBT, which reflects about 70% of body heat content, is determined by the balance between heat production and heat loss, which changes over time as revealed by the circadian rhythm of CBT (Aschoff et al., 1974). Heat production undergoes a circadian rhythm, which is phase advanced by $\sim$1 h compared to the circadian rhythm in heat loss, and this phase angle difference determines the circadian amplitude of $\sim$0.25°C in CBT (Aschoff et al., 1974). However, the circadian pattern of heat loss and heat production is not represented by uniform sine waves; heat loss in the evening is more dominant than reduction in heat production, and *vice versa* in the morning (Kräuchi and Wirz-Justice, 1994).

Under resting conditions, the thermoregulatory system in humans consists of two compartments, the heat-producing core and the heat-loss-regulating shell (Aschoff, 1971). To regulate the endogenous circadian CBT rhythm, changes in shell size take place. DIST rises in the evening; whereas, proximal skin temperature (PROX; weighted mean skin temperatures of the thigh, stomach, infraclavicular region, and forehead; Kräuchi et al., 1997c), heat production, and CBT decline, and this pattern switches in the morning (Aschoff and Heise, 1972; Kräuchi and Wirz-Justice, 1994). Convective blood transport is the main route of heat redistribution from

the core to the distal extremities (Aschoff, 1971). These distal parts of the body (*e.g.*, fingers) have ideal (round) surface shapes for good heat transfer to the environment. They are the main heat loss effectors of the body (Aschoff, 1971). The core is homeostatically regulated within a narrow range. In contrast, the shell is rather poikilothermic and therefore largely dependent on environmental conditions. The shell represents the thermo-effector-site of a feed-forward regulation for the core and serves as a kind of thermic protector for it (Aschoff, 1971), *i.e.*, the shell is regulated before CBT is influenced. In a cold environment, the shell is large, in a warm environment the shell is small (Aschoff, 1971). Shell size is regulated via constriction or dilatation of peripheral blood vessels, mainly the smooth muscles of the arterioles, and additionally, in distal skin regions, the smooth muscles in arteriovenous anastomoses (AVAs) (Aschoff, 1971; Hales, 1985).

Furthermore, it has been established the homeostatic control of CBT is mediated by a hierarchically organized set of neuronal mechanisms, with the preoptic area of the hypothalamus at the top of the hierarchy (Satinoff, 1978). In addition to the homeostatic principle, a rostral projection from the circadian pacemaker (in the suprachiasmatic nuclei [SCN]) to the preoptic area serves the circadian modulation of CBT (Moore and Danchenko, 2002). Nocturnal secretion of the pineal hormone melatonin, which is also under the control of the SCN, plays a crucial role in the endogenous regulation of CBT in the evening (Cagnacci et al., 1997). There is now emerging evidence to indicate that changes in body temperatures may trigger somnogenic brain areas, *e.g.*, medial preoptic area (Szymusiak et al., 2001) and ventrolateral preoptic area (Saper, 2002), to initiate sleep, either indirectly through nerve afferents activated by cold and warm receptors located in the dermis and core, or directly through changes in core blood temperature leading to changed spinal cord and brain temperatures (Van Someren, 2000). However, the interrelationship between thermoregulatory and sleepiness/sleep regulatory mechanisms is rather complex. Recent studies indicate that the medial preoptic area controls sleep and temperature through independent, but overlapping, neuronal circuits (for reviews see Van Someren, 2000; Saper, 2002; Kumar, 2004), whereby the role of melatonin in the sequence of events remains to be clarified.

In summary, the endogenous down-regulation of CBT in the evening is a result of well orchestrated thermophysiological processes, with body heat loss being an important determining component. So the next question is how is the thermophysiological orchestra that occurs in the evening related to melatonin secretion and increased sleepiness?

In humans, the circadian CBT rhythm is 12 h out of phase from the circadian melatonin rhythm, and it is, at least partially, involved in the regulation of its circadian amplitude (Cagnacci et al., 1992). The circadian

rhythm of melatonin is in phase with DIST; whereas, the temporal patterns in CBT and PROX are phase locked to the inverse pattern of subjective ratings of sleepiness, *i.e.*, alertness (Lack and Gradisar, 2002; Gradisar and Lack, 2004). The inverse regulation of DIST and PROX can be explained by the different vascular regulation of blood flow in these skin regions. Proximal skin regions contain exclusively capillaries having mainly nutritive functions. Skin blood flow through capillaries is a slow process. Therefore, the circadian time course of blood flow through capillaries in the proximal skin regions follows the time course of core body temperature, and CBT and PROX show similar circadian amplitudes of about 0.25°C. Distal skin regions (*e.g.*, fingertips and toes) contain not only capillaries but are enriched with AVAs having mainly thermoregulatory function (Hales, 1985). Moreover, with respect to CBT, the circadian time courses of melatonin and DIST are about 2 h phase advanced. This circadian phase relationship provides correlative hints about the causality between melatonin secretion, DIST, PROX, CBT, and sleepiness. DIST and melatonin seem to be better predictors of sleepiness than PROX and CBT (Kräuchi et al., 1999a, 2000). Results of the following study are more than correlative, since it showed that melatonin administered in the afternoon at 13:00 h, when its endogenous secretion is low, increases heat loss via distal skin regions. Subsequently PROX and CBT decline, together with induction of sleepiness. Therefore, exogenous melatonin mimics the effects occurring naturally in the evening (Kräuchi et al., 1997a); however, the dose of melatonin administration seems to be of importance (for discussion see, *e.g.*, Cagnacci et al., 1997; Reiter and Tan, 2003; Van den Heuvel et al., 2005).

HOW DOES MELATONIN AFFECT THE THERMOSTAT?

In order to test how melatonin affects the thermostat of the thermoregulatory system, a cold challenge test was done 2 h after daytime melatonin (5 mg per os) or placebo administration. The cold stimulus was given in the form of eating 200 g crushed ice, which induces peripheral vasoconstriction by a central reflex. The aims of the study were to clarify whether: i) the melatonin-induced effects can be blocked by core body cooling, ii) melatonin changes the set-point (threshold) or sensitivity (gain) of the thermoregulator, and iii) sleepiness is related to increased heat loss or decreased CBT (Kräuchi et al., 1999b).

Within the first 2 h after melatonin administration, DIST (mean skin temperature of the hands and feet) and sleepiness increased significantly; whereas, CBT (rectal temperature) and PROX—the weighted mean skin temperature of the forehead, stomach, thigh, and infraclavicular skin region (for details see Kräuchi et al., 2000)—decreased (Figure 1a). After placebo administration, core body cooling decreased both the CBT and

skin temperatures, especially DIST, together with a decrease in sleepiness. Core body cooling after melatonin administration induced the same responses as in the placebo condition, indicating that CBT was defended at a lower level. In other words, melatonin decreased the thermoregulatory threshold (or set-point) for distal vasoconstriction. This conclusion

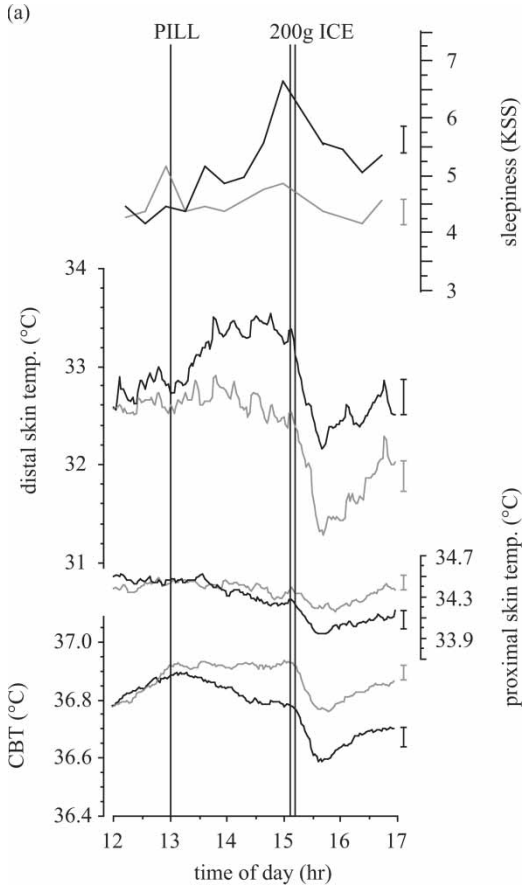

FIGURE 1 ***A.*** Mean ± SEM. (vertical lines on the right) of core body temperature (CBT), proximal and distal skin temperatures (continuously measured at 2 min intervals) and subjective ratings of sleepiness (KSS, Karolinska Sleepiness Scale: 1 = very alert, 9 = very tired) assessed at 20 40 min intervals of 10 healthy men (mean ± SD: 25 ± 4 yrs). Subjects received either melatonin (5 mg per os; black lines) or placebo (gray lines) at 13:00 h in a balanced order. The subjects remained supine in bed under unmasking conditions of a constant routine protocol from 09:45 h until the end of the study. 200 gm of crushed ice was ingested in 5 to 10 min. The results were analyzed by two-way ANOVAs for repeated measures (Kräuchi et al., 1999b). ***B.*** Core body temperature *vs.* distal skin temperature plot of mean melatonin (dots) and mean placebo (crosses) data from 12:30 to 17:00 h. The black lines indicate mean slopes of ice cooling data between 15:05 to 17:00 h (individual slopes were not significantly different after placebo and melatonin administration; Wilcoxon signed rank test, $p > 0.1$). Studies were conducted in accordance with the international and Journal standards for research on human subjects (Touitou et al., 2004).

(*continued*)

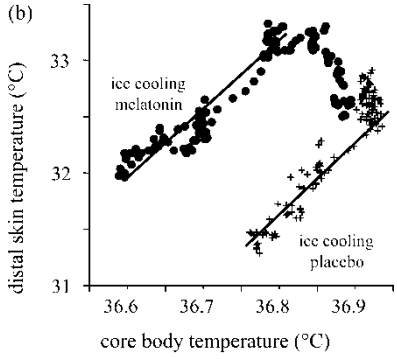

FIGURE 1 Continued.

has been confirmed by a CBT *vs.* DIST plot analysis (Figure 1b); melatonin did not change the gain (or sensitivity) of the thermoregulatory system after ice intake (similar slopes), but clearly reduced the threshold (set-point) to a lower CBT level. This finding makes sense from a thermophysiological point of view; that is, if there would be no influence of melatonin on the central thermostat, the latter would immediately induce counter-reactions to achieve a constant CBT level, *i.e.*, via distal vasoconstriction. Clearly this was not the case. Isolated peripheral effects of melatonin, *e.g.*, on AVAs, therefore do not occur. The results further show a parallel time course of sleepiness and DIST after melatonin administration and ice ingestion (Figure 1), which is in contrast to the changes of CBT. This finding indicates that sleepiness is intimately connected with DIST and not primarily with reduction of CBT.

In a recent placebo-controlled study the influence of exogenous melatonin (3 mg per os at 11:00 h) on cutaneous vasodilatation and local sweat rate of the forearm was tested during local body warming, *i.e.*, placement of lower limbs in a hot water bath at 42°C (Aizawa et al., 2002). Melatonin administration lowered the thermoregulatory set-point for the autonomic thermoregulation of vasodilatation and sweat secretion. Therefore, it can be postulated that the well-described circadian rhythm in the set-point (threshold) of the thermoregulator (*e.g.*, Johnson, 1986) can also be mediated by melatonin.

In summary, this study demonstrates that i) the soporific and thermoregulatory action of melatonin cannot be blocked by core body cooling, ii) melatonin induces a change in the threshold and not in the gain of the thermoregulatory system, and iii) a decrease in CBT *per se* does not always induce sleepiness, *i.e.*, sleepiness is associated with heat loss and not primarily with a decrease in CBT.

In a subsequent study, we investigated whether an orthostatic challenge counteracts the melatonin-induced thermoregulatory and

soporific effects (Cajochen et al., 1997; Kräuchi et al., 1997b). A shift from a supine to standing position is a severe challenge to the human cardiovascular system, evoking a central and local reflex via the rise in sympathetic nervous activity. Specific melatonin receptors are located in rat peripheral arteries, suggesting a role for melatonin in vascular regulation. Indeed, in rat-tail arteries (the tail is the main thermoeffector site in this animal), melatonin interacts with noradrenaline in vasoconstrictor activity (Viswanathan et al., 1990; Dubocovich et al., 2000; Masana et al., 2002). MT1 receptors potentiate the vasoconstrictory effect of noradrenaline at low doses of melatonin (nM-range); whereas, MT2 receptors reduce the vasoconstrictory effect of noradrenaline in micromolar concentrations (Dubocovich et al., 2000; Masana et al., 2002). This suggests that in humans as well, melatonin could produce its effects on the thermoregulatory system via modulation of sympathetic nerve activity. We therefore administered melatonin (5 mg per os) or placebo at 13:00 h at the same time as when the subjects had to stand up from a supine position and remain standing for 2 h (Kräuchi et al., 1997b). Standing up decreased skin temperatures and sleepiness and increased CBT. The decreases in skin temperatures after orthostatic challenge were most pronounced in lower body sites. These changes were totally reversed at the end of the subsequent supine period (except for distal skin regions). The hand, a skin region that undergoes minor changes with orthostasis, showed a significant increase in temperature after melatonin administration and remained unaffected by the postural changes. However, the orthostatic challenge almost completely blocked all other melatonin-induced changes. In the subsequent supine period, CBT reduction as well as augmented sleepiness was more pronounced after melatonin than after placebo ingestion. This finding indicates that the thermoregulatory and soporific effects of melatonin can be partially blocked by orthostatic changes, probably via modulation of sympathetic nerve activity (Ray, 2003).

THROUGH WHICH DISTAL SKIN REGION DOES MELATONIN INDUCE HEAT LOSS?

For some decades it has been known that the hand and fingertip, especially the nail bed, contains the greatest number of AVAs, the dorsal proximal parts the fewest, and the planar sites of the phalanxes an intermediate number (Grant and Bland, 1931). Based on these findings, we focused in the next study on the fingers, which are a good model to study the specificity of melatonin's action on blood flow elevation and, hence, increases in skin temperature and heat loss. In a topographical analysis of finger skin temperature using infrared thermometry, melatonin (5 mg per os) or placebo was administered in a double-blind balanced order at 14:00 h (Kräuchi et al., 2002). Melatonin once more exhibited

significant thermolytic and soporific effects (ΔCBT: -0.07 ± 0.03°C; mmVAS sleepiness: $+15.4 \pm 6.8$ mm; ANOVA for repeated measures, $p < 0.05$). Baseline skin temperatures were highest on the fingernail (third phalanx, dorsal) and lowest on the most proximal first phalanx. The skin temperature on the palmar site of the third phalanx was 1.1°C lower than it was on the fingernail. Melatonin induced a uniform increase in skin temperature of 0.81°C, which was independent of skin regions. A typical result is shown in Figure 2. It is known that, in order to achieve a skin temperature-increase of similar magnitude on proximal and distal regions, a much larger increase of blood flow is required in the distal than proximal parts, *i.e.*, skin regions with similar skin temperature loose more heat from distal than proximal sites. Therefore, our results indicate a higher skin blood flow elevation by melatonin in the fingertip than in the proximal finger, most probably by opening of the AVAs.

An important question is whether melatonin in human beings acts directly on melatonin receptors (MT1 and MT2) in blood vessel muscles of diverse skin regions at proximal and distal sites. To our knowledge, no such studies exist. The observation that endogenous or exogenous melatonin decreases PROX and increases DIST, fit nicely with the idea that melatonin MT1- and MT2-receptors are differently located in diverse

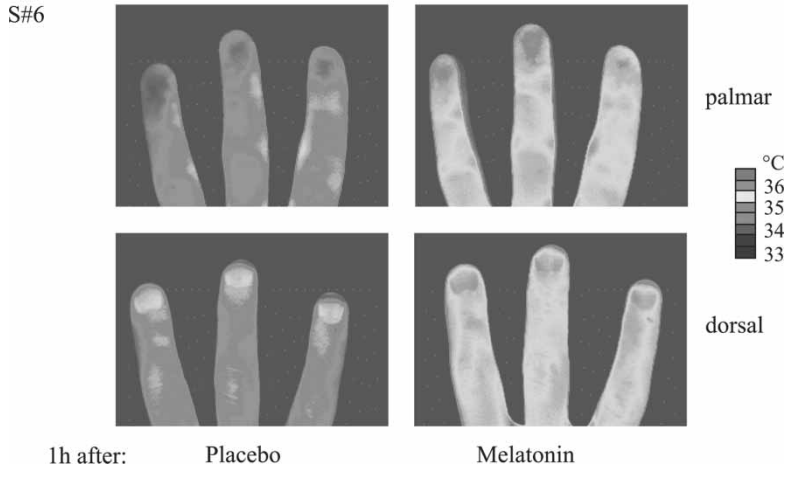

FIGURE 2 11 healthy men (mean ± SD: age = 26 yr ± 2; BMI 22.2 ± 1.7) received melatonin (5 mg per os) or placebo at 14:00 h in a balanced order. Skin temperatures of the fingers were measured by an infrared cam (TH3100mr Thermo Tracer; NEC San-ei Instruments Ltd., Tokyo, Japan; room temperature: 26 ± 1°C) 30 min before and 60 min after ingestion of melatonin or placebo. CBT (sublingual) and subjective ratings of sleepiness (mm VAS; 0 mm = extremely alert, 100 mm = extremely tired) were measured in parallel (for results see text). The subjects remained in a sitting position 30 min before and during assessments. Mean skin temperatures of dorsal and palmar skin regions of the first, second, and third phalanx of the middle finger were analyzed (Kräuchi et al., 2002). Studies were conducted in accordance with the international and Journal standards for research on human subjects (Touitou et al., 2004).

vascular beds. MT1-receptors with their vasoconstrictory properties might be preferentially located in the precapillary smooth muscles in both proximal and distal skin regions; whereas, MT2-receptors with their vasodilatatory properties might be preferentially located in AVAs in distal skin regions. Our initial pilot studies in this direction found no MT1- or MT2-immunoreactivity in post-mortem finger tip preparations (K. Beier, E. Savaskan, F. Meier; unpublished data). However, for a final conclusion further studies are needed. It also remains to be established whether melatonin acts solely as a peripheral hormone on vascular smooth muscles, or as a central agent, *e.g.*, modulating sympathetic nerve activity, or both.

In conclusion, there is growing evidence that melatonin is involved in the fine-tuning of vascular tone in selective vascular beds as circulating melatonin levels rise and fall throughout the night. Melatonin not only seems to be "nature's soporific," but also nature's nocturnal vascular modulator.

REFERENCES

Aizawa, S., Tokura, H., Morita, T. (2002). The administration of exogenous melatonin during the daytime lowers the thermoregulatory setpoint in humans. *J. Therm. Biol.* 27:115–119.

Aschoff, J. (1971). Temperaturregulation. In: Gauer, O.H., Kramer, K., Jung, R., eds. *Energiehaushalt und Temperaturregulation. Physiologie des Menschen*. Munich: Urban & Schwarzenberg, pp. 43–112.

Aschoff, J., Heise, A. (1972). Thermal conductance in man: Its dependence on time of day and of ambient temperature. In: Itoh, S., Ogata, K., Yoshimura, H., eds. *Advances in Climatic Physiology*. Tokyo: Igako Shoin, pp. 334–348.

Aschoff, J., Biebach, H., Heise, A., Schmidt, T. (1974). Day night variation in heat balance. In: Monteith, J.L., M.L.F., ed. *Heat Loss from Animals and Man*. London: Butterworths, pp. 147–172.

Baker, M.A., Cronin, M.J., Mountjoy, D.G. (1976). Variability of skin temperature in the waking monkey. *Am. J. Physiol.* 230:449–455.

Brown, C.C. (1979). Toe temperature change: A measure of sleep onset? *Waking Sleeping* 3:353–359.

Cagnacci, A., Elliot, J.A., Yen, S.S.C. (1992). Melatonin: A major regulator of the circadian rhythm of core body temperature in humans. *J. Clin. Endocrinol. Metab.* 75:447–452.

Cagnacci, A., Kräuchi, K., Wirz-Justice, A., Volpe, A. (1997). Homeostatic versus circadian effects of melatonin on core body temperature in humans. *J. Biol. Rhythms* 12:509–517.

Cajochen, C., Kräuchi, K., Wirz-Justice, A. (1997). The acute soporific action of daytime melatonin administration: effects on the EEG during wakefulness and subjective alertness. *J. Biol. Rhythms* 12:636–643.

Campbell, S.S., Broughton, R.J. (1994). Rapid decline in body temperature before sleep: fluffing the physiological pillow? *Chronobiol. Int.* 11:126–131.

Czeisler, C.A., Weitzman, E.D., Moore-Ede, M.C., Zimmerman, J.C., Knauer, R.S. (1980). Human sleep: its duration and organization depend on its circadian phase. *Science* 210:1264–1267.

Dawson, D., Reid, K. (1997). Fatigue, alcohol and performance impairment. *Nature* 388:235.

Dubocovich, M., Masana, M., Benloucif, S. (2000). Molecular pharmacology and function of melatonin receptor subtypes. In: Olcese, J., ed. *Melatonin After Four Decades*. Kluwer Academic Edition, New York: Plenum Publishers, pp. 181–190.

Gilbert, S., Van den Heuvel, C., Dawson, D. (1999). Daytime melatonin and temazepam in young adult humans: equivalent effects on sleep latency and body temperatures. *J. Physiol.* 514.3:905–914.

Glotzbach, S.F., Heller, H.C. (2000). Temperature regulation. In: Kryger, M.H., Roth, T., Dement, W.C., eds. *Principles and Practice of Sleep Medicine*. 3rd Ed. Philadelphia: W.B. Saunders Company, pp. 289–304.

Gradisar, M., Lack, L. (2004). Relationships between the circadian rhythms of finger temperature, core temperature, sleep latency, and subjective sleepiness. *J. Biol. Rhythms* 19:157–163.

Grant, R.T., Bland, E.F. (1931). Observations on arteriovenous anastomoses in human skin and in the bird's foot with special reference to the reaction to cold. *Heart* 15:385–411.

Hales, J.R.S. (1985). Skin arteriovenous anastomoses, their control and role in thermoregulation. In: Johansen, K., Burggren, W.W., eds. *Cardiovascular Shunts. Alfred Benzon Symposium 21*. Copenhagen: Munksgaard, pp. 433–451.

Johnson, J.M. (1986). Nonthermoregulatory control of human skin blood flow. *J. Appl. Physiol.* 61: 1613–1622.

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–R826.

Kräuchi, K., Cajochen, C., Wirz-Justice, A. (1997a). A relationship between heat loss and sleepiness: effects of postural change and melatonin administration. *J. Appl. Physiol.* 83:134–139.

Kräuchi, K., Cajochen, C., Hofmann, M., Wirz-Justice, A. (1997b). Melatonin and orthostasis: Interactions of posture with subjective sleepiness, heart rate, and skin and core temperature. *Sleep Res.* 26:79.

Kräuchi, K., Cajochen, C., Möri, D., Graw, P., Wirz-Justice, A. (1997c). Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. *Am. J. Physiol.* 272:1178–1188.

Kräuchi, K., Cajochen, C., Werth, E., Wirz-Justice, A. (1999a). Warm feet promote the rapid onset of sleep. *Nature* 401:36–37.

Kräuchi, K., Werth, E., Wüst, D., Renz, C., Wirz-Justice, A. (1999b). Interaction of melatonin with core body cooling: sleepiness is primarily associated with heat loss and not with a decrease in core temperature. *Sleep* 22(Suppl1):285–286.

Kräuchi, K., Cajochen, C., Werth, E., Wirz-Justice, A. (2000). Functional link between distal vasodilation and sleep-onset latency? *Am. J. Physiol.* 278:R741–R748.

Kräuchi, K., Pache, M., von Arb, M., Flammer, J., Wirz-Justice, A. (2002). Infrared thermometry of finger and face skin temperatures after melatonin administration. *Chronobiol. Int.* 19:993–994.

Kumar, V.M. (2004). Body temperature and sleep: are they controlled by the same mechanism? *Sleep Biol. Rhythms* 2:103–124.

Lack, L., Gradisar, M. (2002). Acute finger temperature changes preceding sleep onsets over a 45-h period. *J. Sleep Res.* 11:275–282.

Masana, M.I., Doolen, S., Ersahin, C., AL-Ghoul, W.M., Duckles, S.P., Dubocovich, M.L., Krause, D.N. (2002). MT2 melatonin receptors are present and functional in rat caudal artery. *J Pharmacol. Exp. Ther.* 302:1295–1302.

Moore, R.Y., Danchenko, R.L. (2002). Paraventricular-subparaventricular hypothalamic lesions selectively affect circadian function. *Chronobiol. Int.* 19:345–360.

Ray, C.A. (2003). Melatonin attenuates sympathetic nerve response to orthostatic stress in humans. *J. Physiol* 551:1043–1048.

Reiter, R.J., Tan, D.-X. (2003). What constitutes a physiological concentration of melatonin. *J. Pineal Res.* 34:79–80.

Saper, C.B. (2002). The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu. Rev. Neurosci.* 25:433–469.

Satinoff, E. (1978). Neural organization and evolution of thermal regulation in mammals. *Science* 201: 16–22.

Szymusiak, R., Steininger, T., Alam, N., McGinty, D. (2001). Preoptic area sleep-regulating mechanisms. *Arch. Ital. Biol.* 139:77–92.

Touitou, Y., Portaluppi, F., Smolensky, M.H., Resning, L. (2004). Ethical principles and standards for the conduct of human and animal biological rhythm research. *Chronobiol. Int.* 21:161–170.

Van den Heuvel, C., Ferguson, S.A., Macchi, M.M., Dawson, D. (2005). Melatonin as a hypnotic: *Con Sleep. Med. Rev.* 9:71–80.

Van Someren, E.J.W. (2000). More than a marker: interaction between circadian regulation of temperature and sleep, age-related changes, and treatment possibilities. *Chronobiol. Int.* 17:313–354.

Viswanathan, M., Laitinen, J.T., Saavedra, J.M. (1990). Expression of melatonin receptors in arteries involved in thermoregulation. *Proc. Natl. Acad. Sci. USA.* 87:6200–6203.

Zepelin, H. (2000). Mammalian sleep. In: Kryger, M.H., Roth, T., Dement, W.C., eds. *Principles and Practice of Sleep Medicine*. Philadelphia: W.B. Saunders Company, pp. 82–92.

Zulley, J., Wever, R., Aschoff, J. (1981). The dependence of onset and duration of sleep on the circadian rhythm of rectal temperature. *Pflügers Arch.* 391:314–318.