Altered Skin-Temperature Regulation in Narcolepsy relates to Sleep Propensity

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Context | In healthy subjects, sleep propensity increases when the distal skin temperature increases relative to the proximal skin temperature. This increase results from increased blood flow in the skin of the extremities and is, among other factors, controlled by the hypothalamic circadian clock, as is sleep. Because narcolepsy is characterized by hypothalamic alterations, we studied skin temperature in narcoleptic patients in relation to their characteristically increased sleep propensity during the day.

Methods | Distal and proximal skin temperature and their gradient (DPG) were measured during a Multiple Sleep Latency Test. This allowed temperature to be studied during wakefulness, at sleep onset and during sleep.

Patients | Fifteen unmedicated narcolepsy patients with cataplexy and 15 controls.

Results | In subjects in the waking state, DPG was higher in narcoleptics than in controls throughout the day (time by group interaction, p < .0001), due to increased distal skin temperature and decreased proximal skin temperature. The increase in DPG was related to a shorter subsequent sleep-onset latency (p = .02). Once asleep, narcoleptics maintained their elevated distal skin temperature and DPG (p < .0001), whereas proximal skin temperature increased to reach normal levels.

Conclusion | This is the first demonstration of a dramatic alteration of daytime skin temperature control in narcolepsy. Even awake narcoleptic patients showed a DPG higher than that which healthy controls achieve when asleep. This observation suggests that hypocretin deficiency in narcolepsy affects skin-temperature regulation and invites further examination. Skin-temperature control might ultimately even have therapeutic implications for the alleviation of narcoleptic symptoms.

Introduction

The circadian regulation of sleep and body temperature are intimately related: the core temperature is lowest during the major sleep period at night. This temperature decline at night is mainly due to an increase in skin blood flow causing skin warming and dissipation of body heat. Skin temperature in people is therefore higher during the night than the day, a rhythm that is the inverse of the core temperature curve. During daytime quiet wakefulness, distal skin areas are usually cooler than proximal
ones, which is expressed as a negative distal-to-proximal gradient (DPG). The distal skin warms up when hypothalamically regulated sympathetic cutaneous vasoconstrictor tone is released, opening a dense network of arteriovenous anastomoses in the skin of the extremities. Many factors, such as light, may induce a relative cooling of the distal skin. Fewer conditions induce distal skin warming; the most notable are activation of heat-loss mechanisms due to body heating, changing of body posture from upright to supine, or, at night, conditions that are under the control of the hypothalamic circadian timing system. Interestingly, and recognized by Magnussen as early as the 1930s, an increase in distal skin temperature may herald sleep onset. More-recent studies in healthy subjects have shown that sleep latency could in fact be predicted from skin-temperature distribution prior to the attempt to sleep. Krauchi et al showed that, the more the distal temperature increased toward the proximal temperature, the less time it took to fall asleep. They hypothesized that skin temperature modulates neuronal activity in sleep-regulating brain areas and might thus promote falling asleep. Indeed, animal studies have shown that afferents conveying skin-temperature information modulate the firing rate of thermosensitive neurons in the preoptic anterior hypothalamus, a region known to be crucial in promoting sleep. The first direct support for a sleep-modulating role of skin temperature was recently provided in a controlled experiment in healthy young subjects, whose sleep onset could be accelerated by means of very subtle skin warming, even though this was slightly uncomfortable.

Narcolepsy is clinically characterized by excessive daytime sleepiness and cataplexy. The hypothalamus is crucially involved in narcolepsy, with a selective loss of hypocretin (orexin)-producing neurons in the perifornical region. It should be noted that the hypocretin system not only regulates the sleep-wake cycle, but also plays a role in metabolic and autonomic functions: hypocretin administration in rodents not only increases heart rate, but also elevates body temperature. Whereas the diurnal core body temperature rhythm is preserved in narcolepsy—possibly with minor changes as compared with healthy subjects—no prior study has systematically examined a major determinant of this rhythm, ie, skin-temperature regulation. We investigated skin-temperature regulation in narcolepsy during the day on which a standardized Multiple Sleep Latency Test (MSLT) was conducted. The protocol allowed for an investigation of skin-temperature regulation during both upright and supine wakefulness and sleep and of the relationship between skin-temperature regulation and sleep propensity in narcoleptic patients and healthy controls.

Materials and Methods

Subjects
After obtaining informed consent, we included 15 unmedicated patients with narcolepsy (6 men). All suffered from excessive daytime sleepiness and unequivocal cataplexy and thereby fulfilled the criteria of narcolepsy with cataplexy (International Classification of Sleep Disorders). Twelve patients who had never received any treatment were tested shortly after diagnosis. The remaining 3 patients discontinued their medication at least
1 week prior to the study. Fifteen age- and sex-matched unmedicated control subjects, free of any neurologic or psychiatric disease, were recruited through an advertisement in a local newspaper. All subjects were instructed to follow their normal sleep routine the night before the testing day. In all subjects, subjective sleepiness was assessed using the Epworth Sleepiness Scale. Results from 1 man with narcolepsy had to be excluded because of temperature-data loss.

**Study Design**

Continuous skin-temperature measurements were performed during a standard MSLT\(^5\) comprising five 20-minute periods during which subjects were asked to lie down on a bed in a quiet room and instructed to try to fall asleep after lights out. Periods started around 9:30 am, 11:00 am, 12:30 pm, 2:00 pm, and 3:30 pm. Sleep was measured using the standard polysomnographic montage, with sleep stages scored in 30-second epochs according to Rechtschaffen and Kales.\(^6\) Sleep latency was defined as the time from lights out to the first epoch of any sleep stage, including stage 1.\(^7\)

**Skin-Temperature Measurement**

Skin temperature was measured using a wireless monitoring system consisting of 9 Thermochron iButtons (type DS1921H; Maxim/Dallas Semiconductor Corp, Sunnyvale, CA, USA). The iButton is a small (16 x 6 mm) coin-like device that measures and stores temperature data between +15°C and +46°C, with an accuracy of 1°C and a 0.125°C resolution.\(^8\) Temperature was sampled once per minute; data were transferred to a computer for analysis after completion of the recordings. iButtons were fixed to the skin with Fixomull tape (Beiersdorf, Hamburg, Germany). A weighted average proximal skin temperature (\(T_{\text{prox}}\)) was obtained bilaterally on the middle of the frontal aspect of the thigh and the infraclavicular areas, and on the abdomen.\(^9\) Average distal skin temperature (\(T_{\text{dist}}\)) was obtained from the thenar eminence of both hands and the medial plantar aspect of both feet.\(^9\) In addition to the distal and proximal

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**Figure 9.1** Study Design

This scheme shows the different conditions that were used for analysis. Temperature data (see Figure 2) were averaged for conditions A, B, and C of each of the 5 Multiple Sleep Latency Test (MSLT) tests. Condition A represents the skin temperature during the unrestrained active wakefulness state prior to the sleep-latency tests. Condition B represents skin temperature during quiet wakefulness at rest in bed, as measured from lights out until sleep onset. Condition C represents the skin temperature during the last 5 minutes of each MSLT test, where healthy subjects were also asleep during almost all their nap opportunities (88%).

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skin temperatures, their gradient (distal minus proximal skin temperature, DPG) was calculated, providing an optimal estimate of distal skin blood flow.²

Data Analysis and Statistics
Given the skewed distribution of sleep latency, all analyses were performed on logarithmically transformed values, which effectively normalized the distribution (Kolmogorov–Smirnov test: p = .001 before, p = .40 after log-transformation). The mean Tprox, Tdist, and DPG were calculated for each of 3 different conditions (Figure 9.1): before sleep out of bed (A), before sleep in bed (B), and sleep (C). The 20 minutes running from 30 to 10 minutes prior to the start of each of the 5 MSLT periods were labeled condition A and concern the skin-temperature state during wakefulness prior to the sleep-latency tests, which may contain both upright and sitting postures. The 10 minutes directly preceding the lightsoff moment were not analyzed to preclude systemic changes associated with the preparations for bedtime. The mean Tprox, Tdist, and DPG were also obtained for the period beginning with the last measurement before lights off and ending with the first temperature sample after sleep onset (Figure 9.1). This interval, labeled condition B, represents the thermoregulatory state when lying awake in bed. Inclusion of 1 temperature sample before lights off and 1 temperature sample following sleep onset was necessary to be able to estimate the skin temperature for occasional test periods with a sleep latency of 0. When subjects did not fall asleep during a test period, sleep latency was noted as 20 minutes. Data from the last 5 minutes of the 20-minute MSLT periods, when subjects slept, were also averaged and resulted in “condition C,” which therefore concerned sleep. Temperature data of conditions B and C include the onset of long-lasting changes induced by the postural change to a supine position. Differences in sleep-latency and skin-temperature variables between narcoleptic patients and control subjects were tested for the conditions A, B, and C using linear regression, including group (narcolepsy or control), time of day (1 to 5 for the 5 MSLT periods), and a group-by-time interaction, followed by posthoc analyses on individual time points in case of significant group-by-time interactions. Regression analyses were performed using the MLwiN software (Center for Multilevel Modeling, Institute of Education, London, UK), which allows the inclusion of incomplete cases. Due to technical problems, the temperature measurements prior to the first test period were incomplete in 3 cases. The within-subject influence of skin-temperature variables on sleep-onset latency was tested using linear regression analyses for the healthy control and narcolepsy groups separately. In order to prevent the detection of spurious relations due to covariance of the diurnal modulation of both sleep-latency and temperature profiles, models included time up to the second order as needed. Optimal regression models were selected using the likelihood ratio χ² test. Data and effect estimates are given as mean ± SEM. All reported p values are 2-sided, with .05 as the significance threshold.

Results

Subjects and Basic Sleep Parameters
The mean age of the included subjects was 35.9 ± 2.4 years for patients and 35.9 ± 2.5
years for controls. Epworth Sleepiness Scale results were $17.9 \pm 0.7$ for patients and $4.7 \pm 0.8$ for controls. All patients scored in the pathologic range of the Epworth Sleepiness Scale ($>12$). As expected, the mean sleep latency was significantly shorter ($p < .0001$ for log-transformed values) in narcoleptic subjects ($2.9 \pm 0.6$ minutes) than in controls ($10.6 \pm 0.8$ minutes, Figure 9.2D).

**Group Differences in Skin Temperature**

Figure 9.2 shows the distal (a), proximal (b), and DPG (c) temperatures preceding and during the 5 MSLT test periods and the sleep latency (d). Group differences between narcoleptic and control subjects on skin-temperature values took the form of interaction effects with time of day; no differences were observed around the first MSLT, but differences grew over the day. Regression analyses confirmed strong group-by-time interactions for Tdist and DPG during wakefulness both prior to and following lights off (conditions A and B, Figure 9.1, all $p < .0001$) and during sleep (condition C, Figure 9.1, both $p < .0001$). Significant group-by-time interactions for Tdist were limited to the wakefulness condition prior to lights off (condition A, $p < .02$). Posthoc tests of individual time points indicated significantly elevated DPG in narcolepsy during wakefulness both prior to and following lights off (conditions A and B) at the third ($p = .04$ and $p = .05$, respectively), the fourth ($p = .03$ and $p = .02$, respectively), and the fifth ($p = .001$ and $p = .002$, respectively) test period. During condition C (when healthy subjects were also asleep in 88% of their nap opportunities), DPG differed at all but the first MSLT (all $p < .03$). Posthoc tests indicated that the elevated Tdist during condition B (wakefulness in bed) in narcolepsy reached significance only for the fifth MSLT period ($p = .01$). During condition C, the Tdist differed at all but the first MSLT (all $p < .03$). Posthoc tests indicated that the lowered Tprox during condition A in narcolepsy reached significance only for the fourth test period ($p = .04$) and completely normalized during condition C (all $p > .73$).

**Within-Subject Relation of Skin Temperature With Sleep Latency**

In the patient group, DPG prior to lights off (condition A, Figure 9.1) showed no relation to subsequent sleep-onset latency. However, under the more-controlled conditions (a supine posture and no physical activity) between lights off and sleep onset (condition B, Figure 9.1), significance was reached, indicating a $12\% \pm 6\%$ shorter (log-transformed) sleep-onset latency per degree increase in DPG. The association between skin temperature and sleep latency was even stronger for proximal and distal skin temperature per se than for their difference. Every degree higher proximal skin temperature prior to lights off was associated with a $22\% \pm 10\%$ ($p = .01$) shorter (log-transformed) sleep-onset latency. Similarly, every degree higher distal skin temperature prior to lights off was associated with an $11\% \pm 5\%$ ($p = .007$) shorter (log-transformed) sleep-onset latency. The association between distal skin temperature and sleep-onset latency remained when measured between lights off and sleep onset: a $13\% \pm 5\%$ ($p = .003$) shorter log-transformed sleep-onset latency per degree higher distal skin temperature. Within control subjects, an association between sleep-onset latency and skin temperature could only be derived from the proximal skin temperature before lights off: sleep-onset latency (log-transformed) was $11\% \pm 4\%$ shorter per degree higher proximal skin temperature ($p = .0008$).
Figure 2

Results

Mean ± SEM profiles of (a) distal and (b) proximal skin temperature, (c) distal-to-proximal skin temperature gradient (DPG), and (d) sleep latency over the day in narcoleptic patients (black) and controls (grey). The 5 vertical bars indicate the successive 20-minute, lights-out, in-bed periods. Due to technical problems, the temperature measurements prior to the first test period were incomplete in 3 cases. The data for these cases were extrapolated in the figure but not in the data analysis. Each point represents 1 minute of temperature data. For readability, error bars are shown only at 5-minute intervals.
DISCUSSION

The most important and novel finding of the present study is that, throughout the day, distal skin temperature was elevated in narcoleptics. In healthy subjects, the occurrence of such prolonged high distal temperatures is normally restricted to 3 circumstances: the first concerns the night, in association with the circadian phase of lowered core body temperature. The second concerns prolonged heat stress during the day, and the third concerns a continuous supine posture. Distal skin temperature increased over the day in narcoleptic patients, resulting in a higher DPG during both wakefulness and sleep. Even during wakefulness, narcoleptic patients maintained a DPG that control subjects did not even reach asleep in a supine posture. Once asleep, the distal skin temperature and DPG of narcoleptic patients remained higher than that of controls, whereas their lowered proximal skin temperature found before bedtime normalized. The second major finding of the present study was that the higher DPG during wakefulness was associated with increased sleep propensity in narcolepsy, the same as was demonstrated in healthy controls under strictly controlled laboratory conditions. This relationship is therefore preserved in narcolepsy and may even be enhanced, since the relationship was stronger in the narcolepsy than in the control group. The elevated gradient between distal and proximal skin temperature that narcoleptic patients maintain might be interpreted as a “sleep-promoting” pattern of skin temperature. In our control group, DPG did not predict sleep latency, in contrast to published studies. We explain this through less-strictly controlled experimental conditions. However, this makes it even more remarkable that such an effect was found in the narcolepsy group even under conditions of considerable variance. A third important observation is that, even though DPG was associated with sleep propensity in narcoleptic subjects, distal and especially proximal skin temperature per se were even more strongly related to sleep latency. In controls, proximal skin temperature was even the only significant predictor of sleep-onset latency. This robust influence of proximal skin temperature on sleep propensity is in line with the recent demonstration that sleep latency is dramatically reduced when proximal skin temperature is subtly increased using a “thermosuit.”

Skin Versus Core Temperature

In contrast with our skin-temperature measurements, previous studies in narcoleptics focused on core body temperature. Some researchers have found no significant differences in the mean or circadian pattern of core body temperature in narcolepsy. Pollak and Wagner reported that naps in narcoleptic patients were heralded by a small decrease in core temperature, which is compatible with the present demonstration of increased distal skin blood flow, which can accommodate heat loss. Other researchers found core body temperature in narcoleptics to be elevated at nighttime. Also, narcoleptics were reported to show an attenuated circadian amplitude and slower morning rise of the core body temperature, as well as an earlier temperature minimum, which both fit the present finding of a continuation into sleep of the increased distal skin blood flow and consequently heat loss. Core body temperature was not measured within this study so as not to affect MSLT procedures and interpretation. However, this study focused on the difference between distal and proximal skin temperatures that are largely irrespective of the actual core body temperature.
**Temperature and the Nature of Sleepiness**

The excessive daytime sleepiness in narcolepsy may take different forms: patients may complain of a continuous feeling of sleepiness, or sleepiness may manifest itself as a sudden falling asleep. This clinical heterogeneity is reflected in 2 theoretical frameworks that have been devised to describe the pathophysiologic mechanisms for excessive daytime sleepiness in narcolepsy. The frequent sleep attacks are nicely described by a so-called loss of “state-boundary-control”: the shifts between the waking and sleeping states occur too easily. This theory is supported by the fact that, over the 24 hours of a day, narcoleptics do not have an increased total amount of sleep. Furthermore, newly developed models of sleep-wake control propose the existence of a “sleep switch” that needs to be stabilized by the hypocretin system. Hypocretin deficiency therefore destabilizes this switch, resulting in frequent state shifts in narcolepsy. In addition to this switching problem, however, narcoleptics may also have a continuously depressed level of wakefulness. Earlier authors have emphasized this continuously increased sleep propensity, or sleep “pressure.” If skin temperature may be taken as an indirect indicator of sleep propensity, then the fact that narcoleptics have an elevated DPG throughout the day suggests that their sleep drive is continuously increased or their waking drive decreased. This would explain why hypocretin deficiency leads not only to a loss of state-boundary-control but also to a constant state of sleepiness as well.

Within our study, no polysomnography was performed during the night prior to the MSLT. We have thus not been able to establish possible group differences in homeostatic sleep pressure, which may be presumed but are unlikely to fully account for our results. However, a number of previous findings do not favor the simple explanation of the altered skin-temperature distribution merely reflecting an increased homeostatic sleep pressure. Such an interpretation would not account for our observation that the DPG of narcoleptic subjects also stayed significantly higher than the DPG of healthy subjects when both groups were asleep. Furthermore, in healthy subjects at rest in a thermoneutral condition, sleep deprivation does not affect distal skin blood flow. Recent controlled experiments have demonstrated that skin temperature shows a circadian modulation over the day but is unaffected by the homeostatic buildup of sleep pressure associated with sleep deprivation. Thus, whereas sleep propensity is known to be regulated by both a circadian and a homeostatic component, the thermal state of the skin is normally linked to the circadian component, and a link to the homeostatic component appears less likely. Distal temperature does not change if prolonged wakefulness generates a homeostatic buildup of sleep pressure but is regulated to be low during the day and high at night. This circadian modulation most likely underlies the high distal skin temperature seen around the first MSLT in healthy controls, possibly combined with a need to reduce any heat load induced by traveling to the hospital, since the early-morning threshold for cutaneous vasodilation is already reached with a mild heat load. The relatively high distal skin temperature decreased after the first MSLT session in healthy controls, whereas it continued to increase throughout the day in narcoleptic patients.
**Relation to Hypocretin Deficiency**

The altered DPG in narcolepsy is indicative of chronically decreased sympathetic distal vasoconstrictor tone in narcolepsy, which may ultimately be attributed to a hypocretin deficiency. In rats, hypocretin-labeled fibers have been demonstrated in the primary areas involved in the regulation of tail vasoconstriction, including the preoptic and lateral hypothalamic areas and the periaqueductal gray,\textsuperscript{33-35} which show moderate to high levels of hypocretin-immunoreactive axons.\textsuperscript{36} Hypocretin deficiency may result in lower sympathetic tone and reduced vasoconstriction, as has been shown in hypocretin-knockout mice.\textsuperscript{37} However, the possible mechanisms involved need further study, especially since intracerebroventricular injection of hypocretin in rats did not significantly affect tail skin temperature in one study\textsuperscript{38} and even increased distal skin (tail) temperature in another.\textsuperscript{39} Regardless of the cause of the altered skin-temperature distribution in narcolepsy, the possible consequences of the altered distribution warrant further research. Firstly, thermoregulatory processes may be investigated in narcolepsy, such as the vasoconstrictor responses to cold stress or to standing. Secondly, further studies, now underway, may address whether manipulation of skin temperature affects sleep propensity in narcoleptic patients, as in healthy subjects.\textsuperscript{19} If so, skin-temperature manipulation may ultimately be applied therapeutically for alleviation of narcoleptic symptoms.

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**References**


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