Hypocretin deficiency : neuronal loss and functional consequences

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Manipulation of Skin Temperature improves Nocturnal Sleep in Narcolepsy

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CHAPTER 11

Manipulation of Skin Temperature improves Nocturnal Sleep in Narcolepsy

Objective **Besides excessive daytime sleepiness, disturbed nocturnal sleep is a major complaint of patients with narcolepsy. Previously, we showed alterations in skin temperature regulation in narcoleptic patients that were related to increased sleepiness. Furthermore, temperature manipulations improved daytime vigilance and maintenance of wakefulness. In this study, we investigated the effect of skin temperature manipulations on nocturnal sleep in narcolepsy.**

Methods **Polysomnography was obtained during two nights in eight patients (5 males) diagnosed with narcolepsy with cataplexy according to the ICSD-2 criteria (mean age 28.6 ± 6.4, range 18-35 years). Proximal and distal skin temperature was manipulated using a comfortable thermosuit and slowly cycled within a range normally observed during sleep (34.9 - 35.4 °C). The distribution of different sleep stages and nocturnal wakefulness was compared between different skin temperature conditions.**

Results **Proximal skin warming significantly suppressed wakefulness and enhanced slow wave sleep (SWS). In contrast, distal skin warming enhanced wakefulness and stage 1 sleep at the cost of SWS and REM sleep. The optimal combination of proximal skin warming and distal skin cooling led to a 160% increase in SWS, a 50% increase in REM-sleep and a 68% decrease in wakefulness, compared to the least beneficial combination of proximal skin cooling and distal skin warming.**

Conclusion **Subtle skin temperature manipulations under controlled conditions significantly improved the typical nocturnal sleep problems in narcolepsy. These results indicate that skin temperature control could have therapeutic relevance.**

Introduction

The four classical symptoms of narcolepsy are excessive daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis.[1] During the last years, disturbed nocturnal sleep has gained increasing attention as a fifth core symptom that severely affects quality of life.[2] Nocturnal polysomnography in patients with narcolepsy shows a fragmentation of the normal sleep pattern with frequent arousals and a decrease in slow wave sleep.[3-5] Several hypnotics, including sodium oxybate (gammahydroxybutyrate), are currently used to improve sleep in narcolepsy.[6]

Narcolepsy is caused by a loss of the neuropeptide hypocretin (orexin), a neurotransmitter that is produced by neurons in the lateral hypothalamus.[7] Hypocretin neurons are normally active during wakefulness and hypocretin is thought to stabilize sleep/wake patterns by activating wake-promoting brain areas.[8] However, the exact role of hypocretin in stabilizing nocturnal sleep is unknown.

There is a relation between sleep and both core body and skin temperature.[9,10] In a comfortable environmental temperature, core body temperature is lower and skin temperature is higher during the night than during the day.[10,11] Conversely, sleep initiation is facilitated when the temperature of the distal skin (hands and feet) is relatively high.[12] There seems to be a causal relation as mild warming of the skin promotes daytime sleep onset.[13] Moreover, active manipulation of skin temperature does affect night time sleep in healthy controls.[14] It is thought that sensory afferents conveying information about skin temperature modulate the firing rate of thermosensitive neurons in the sleep regulating systems including the preoptic area/anterior hypothalamus, which is the major thermoregulatory center of the mammalian brain and a key structure in arousal state control.[15]

In a previous study, we reported disturbances in skin-temperature regulation in narcolepsy.[16] Narcoleptic subjects showed a combination of a higher distal skin temperature and a lower proximal skin temperature, which in healthy subjects is associated with the process of falling asleep.[17] In a follow-up study, we were able to affect both daytime vigilance and maintenance of wakefulness by manipulating skin and core body temperature.[18] To explore whether manipulation of skin temperature can also be beneficial as a tool to improve nocturnal sleep in narcolepsy, we performed subtle manipulations of proximal and distal skin temperature during two nocturnal sleep episodes in eight narcoleptic patients.

Materials and Methods

Subjects

Eight narcoleptic patients (5 males, 18-35 years of age; mean ± SD: 28.6 ± 6.4 years) participated with informed consent. All suffered from excessive daytime sleepiness and typical cataplexy according to the ICSD-2 criteria for narcolepsy with cataplexy.[19] All subjects were free of medication, except for one female subject using oral contraceptives. All females participated between day 4 and day 12 of the menstrual cycle (mid-follicular phase or pseudo-follicular phase). The protocol was approved by the local Medical Ethics Committee.

Design

A previously described design was used to differentially manipulate proximal and distal skin temperature and to determine the effects of these manipulations on sleep depth.[14] Subjects refrained from caffeine, alcohol and tobacco for 8 hours before reporting at the sleep laboratory at 22:00 hr. There they were prepared for polysomnography and fitted with a thermosuit. At midnight, lights were turned off and subjects were allowed

Table 1

Stage	OR	$T_{suit-prox}$ 95% CI	P	OR	$T_{suit-dist}$ 95% CI	P
Wake	0.81	(0.77-0.84)	***	1.11	(1.06-1.16)	***
S1		ns		1.22	(1.16-1.28)	***
S2		ns			ns	
SWS	1.23	(1.17-1.29)	***	0.85	(0.81-0.89)	***
REM		ns		0.87	(0.83-0.92)	***

The odds ratio (OR), confidence interval (CI) and significance (P) for the occurrence of each sleep state as modulated by the temperature of the thermosuit warming the distal and proximal skin (per 1˚C). S1, stage 1 sleep; S2, stage 2 sleep; SWS, slow wave sleep; REM, rapid-eye-movement sleep; Tsuit-prox, proximal suit temperature; Tsuit-dist, distal suit temperature; ns, not significant.

to sleep until 06:00 hr. From 00:30 hr till 06:00 hr, their proximal and distal skin temperatures were manipulated. After this, subjects slept one night at home after which they returned for a second hospital night, during which the temperature manipulation sequence was inverted to that of the first night.

Temperature manipulations and measurement

Starting at 0:30 hr, the temperature of the proximal skin ($T_{skin-prox}$) and the temperature of the distal skin ($T_{skin-dist}$) were differentially manipulated by slowly cycling the temperature of thermosuit water perfusion (figure 1). The thermosuit (Coretech Cool tube suit, Med-Eng Systems Inc., Ottawa, Canada) was connected to two sequence programmed computer-controlled bath/circulation thermostats (K6KP, Lauda, Lauda-Königshofen, Germany). The suit temperature (T_{suit}) stayed at constant plateaus of either 15 or 30 minutes with slow (15 min) transitions in-between. The order of skin temperature manipulations was different for each subject using a balanced design. Tsuit cycled between 31.9 ± 0.1 ºC (mean ± SE) in the 'cool' and 34.8 ± 0.1 ºC in the 'warm' condition, as measured once per minute on the isolated inflow tubes at their proximal and distal connections with thermosuit (PT100 thermistors, RTD-3-3105, Omega, Stanford, USA). This range was specifically chosen to match the previously reported range of temperatures normally present in the bed microclimate.[20] The temperature of the environmental air was kept at 21˚C.

Core body temperature was measured rectally. Proximal skin temperature was measured at three places: right on the middle of the frontal aspect of the thigh, abdomen (1 cm above the navel), and the right infraclavicular area. Distal skin temperature was measured at four points: thenar eminence of the left and right hand and medial plantar aspect of the left and right foot. Temperature was measured using thermistors (PT100 thermistors, RTD-3-3105, Omega, Stanford, USA) and digitally recorded at 1 Hz using a Embla A10 recorder (Flaga, Reykjavik, Iceland). Data was analysed using Somnologica software (Flaga). An automated procedure was applied to remove occasional artefacts and to calculate average distal and proximal skin temperature by a weighted average as described before.[21] Temperature data were averaged over 30 second intervals synchronized to the sleep stage epochs.

Sleep recordings

Polysomnographic sleep recordings were performed according to standard procedures and consisted of electroencephalography (EEG), electromyography, and electrooculography.[22] Polysomnography signals were also recorded with the A10 recorder. Sleep was scored by one person blinded to the temperature conditions in 30 sec. epochs according to the Rechtschaffen and Kales criteria using Somnologica software.[22] Sleep stages 3 and 4 were combined into the single class 'slow wave sleep'.

Statistical Analysis

The main outcome measures of this study were the effects of proximal and distal skin warming or cooling (per 1° Celsius) on the odds ratios for the occurrence of each sleep stage (stage 1, stage 2, slow wave sleep, REM-sleep and wakefulness). Multilevel regression modelling was applied to account for the interdependency of the data points inherent to the hierarchical structure of the dataset: sleep epochs within nights within subjects (MLwiN software, Centre for Multilevel Modelling, Institute of Education, London, UK).[23] The regression models included parameters to account for nonlinear changes over time that could lead to correlated residual error. The analyses included all epochs during the skin temperature cycles (from 00:30 hr. until 6:00 hr.). To determine the effects of skin temperature manipulation on the probability of occurrence of sleep stages, longitudinal multilevel logistic regressions were applied for each sleep stage classification, with the current presence or absence of that stage as dummy coded dichotomous dependent variable and $T_{suit\text{-}prox}$ and $T_{suit\text{-}dist}$ as predictor variables. Optimal regression models were selected using the likelihood ratio chi-square test.[23] Odds ratios were translated into sleep stage probabilities at every time point during the night for the maximal and minimal thermosuit temperature levels using the transformation ex/(1+ex), where x represents the regressor part of the best fitting model. A separate plot was generated to visualize the regression prediction for the cumulative sleep stage probability during the mean upper (34.8 ± 0.1 °C) and lower (31.9 ± 0.1 °C) T_{suit} levels. Two-tailed significance levels were set at 0.05.

Results

Induced temperatures

The thermosuit was able to differentially manipulate proximal and distal skin temperature in narcoleptic patients (see example of one night in one patient in Figure 11.1). The temperature manipulations of the proximal part of the thermosuit accounted for 53.8% of the variance in mean $T_{skin\text{-}prox}$. For the warm and cool periods, $T_{skin\text{-}prox}$ averaged 35.1 ± 0.1 °C versus 34.7 ± 0.1 °C respectively. Likewise, the independently manipulated temperature of the distal part of the thermosuit accounted for 44.0% of the variance in mean $T_{skin\text{-}dist}$. $T_{skin\text{-}dist}$ averaged 35.5 ± 0.05 °C versus 35.1 ± 0.05 °C for the warm and cool levels respectively. Thus, the manipulations forced the skin temperature to slowly cycle within a very subtle 0.4 °C range (see temperature graph in Figure 11.1). The manipulations left core body temperature virtually unchanged (skin temperature manipulations accounted for only 2.5% of the variance in core body temperature).

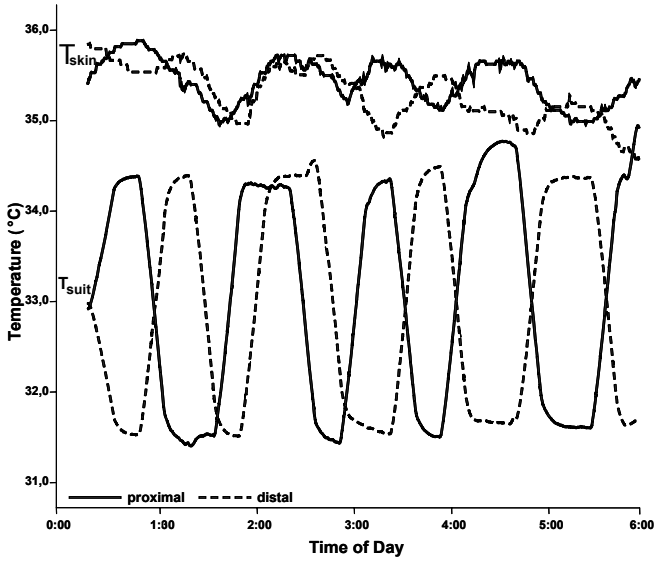

Figure 11.1
Sample night of one patient
Example of a temperature profile induced in one patient during a single night. The lower traces show the temperature of the proximal (straight line) and distal (dotted line) parts of the thermosuit. The upper traces show the actually induced proximal and distal skin temperatures.

Effect of temperature manipulation on sleep stage distribution
Thermosuit manipulation of the temperature of the proximal and distal skin significantly affected sleep depth and the occurrence of wakefulness. Table 1 shows that proximal warming (per 1°C increase in $T_{suit\text{-}prox}$) suppressed wakefulness (OR 0.81 [0.77-0.84], p<0.001) and enhanced slow wave sleep (OR 1.23 [1.17-1.29], p<0.001). In contrast, distal warming (per 1°C increase $T_{suit\text{-}dist}$) enhanced wakefulness (OR 1.11 [1.06-1.16], p<0.001) and stage 1 sleep (OR 1.22 [1.16-1.28], p<0.001) sleep at the cost of slow wave sleep (OR 0.85 [0.81-0.89], p<0.001) and REM sleep (OR 0.87 [0.83-0.92], p<0.001). There were no significant effects on the occurrence of stage 2 sleep.

A graphical representation of the sleep stage distribution is given in Figure 11.2, showing the optimal thermal condition of proximal skin warming and distal skin cooling (right bar) and least beneficial combination of proximal skin cooling and distal skin warming (left bar). The optimal skin temperature combination led to a 160% increase in slow wave sleep, a 50% increase in REM-sleep and a 68% decrease in wakefulness.

Discussion

This study shows that subtle manipulation of proximal and distal skin temperatures has beneficial effects on nocturnal sleep in narcolepsy. When the proximal skin was warmed, slow wave sleep increased and wakefulness was suppressed. In contrast, warming of the distal skin suppressed slow wave and REM-sleep, while enhancing wakefulness and stage-1 sleep.

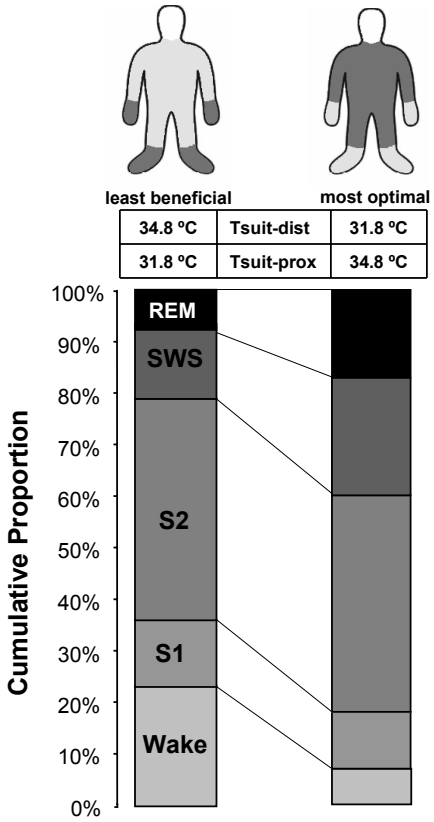

Figure 11.2

Sleep stage distribution

A graphical representation of the proportion of the sleep stages during the optimal (distal cooling and proximal warming) and least beneficial (distal warming and proximal cooling) manipulation scheme. The proportions were derived in separate logistic regressions for each sleep stage. For graphical purposes only, the figure was rescaled to 100%.

Fragmented nocturnal sleep is a major and difficult to treat problem for many patients with narcolepsy. Currently, treatment of this invalidating symptom is based on hypnotics, most notably sodium oxybate,[24] which increases SWS and REM-sleep, while suppressing wakefulness.[25,26] Of note, effects of these hypnotics are at best similar in quality as to the effects found in this study using manipulation of skin temperature. Moreover, this method is non-invasive and did not produce any adverse effects.

This study was designed in such a way that different manipulation schemes were equally and randomly distributed over the test subjects in a balanced way. As such, the effects cannot have been caused by time of night or circadian effects, but can be solely attributed to the manipulation of skin temperature. Skin temperature manipulations were applied while keeping a constant temperature of the ambient air, which was breathed and to which the face was exposed. We do not expect that elevating ambient temperature would lead to any comparable sleep profit, because it is essential to differentially manipulate proximal and distal temperatures. Worse sleep has indeed been reported with an air temperature of 30˚C, as compared to 18˚C and 23˚C.[27]

The fact that subtle changes in skin temperature affect sleep in both narcoleptic patients and healthy controls,[14] shows that the basic hypothalamic circuitry involved in temperature and sleep regulation is intact in narcolepsy and is uninfluenced by

the hypocretin deficiency. Temperature manipulations can have beneficial effects in narcolepsy, both during the night as well as during the day. Previously, we showed that distal cooling improve maintenance of wakefulness during the day while distal warming increased sleep propensity. Here we show that, although warm hands and feet promote the onset of sleep, having a higher distal skin temperature or actively warming the distal skin during the whole night does not improve sleep quality.

In this study, no subject experienced the optimal or least beneficial combination of proximal and distal manipulations continuously during a full night. It would be of interest to confirm the positive effects found in this study using a controlled trial in which the optimal and least beneficial temperature conditions are compared to one another and with the baseline situation.

In conclusion, selective manipulation of skin temperature can be applied to ameliorate one of the core symptoms of narcolepsy, disturbed nocturnal sleep. Effects of temperature manipulation were of such a magnitude, that this new approach could potentially supplement other established methods to improve nocturnal sleep in narcolepsy.

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