7

The effects of sodium oxybate on core body and skin temperature regulation in narcolepsy

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ABSTRACT

Study objectives: Patients suffering from narcolepsy with cataplexy show altered skin temperatures, resembling the profile that is conductive to sleep onset in healthy controls. Temperature manipulation counteracting the altered temperature profile improves both daytime and nocturnal narcoleptic sleep-wake disturbances. The aim of the present study is to investigate the effects of Sodium Oxybate, a widely used drug to treat narcolepsy, on the 24-hour profiles of temperature and sleep-wakefulness in narcolepsy patients and controls.

Design: Prospective case-control study.

Setting: Tertiary narcolepsy referral center in a university hospital.

Patients or participants: Eight hypocretin-deficient, male narcolepsy with cataplexy patients and eight healthy matched controls.

Interventions: Temperatures of the core body and proximal and distal skin areas, as well as the sleep-wake state were measured twice for 24 hours while participants maintained a supine posture. After the baseline assessment, 2 x 3 grams of Sodium Oxybate was administered for five nights, immediately followed by the second assessment.

Measurements and results: At baseline, daytime core body temperature and proximal skin temperature were significantly lower in narcolepsy patients compared to controls (core: 36.78 ± 0.05°C vs. 36.97 ± 0.05°C, F = 8.31, $P = 0.01$; proximal: 33.4 ± 0.26°C vs. 34.32 ± 0.26°C, F = 5.66, $P = 0.03$). In patients, Sodium Oxybate administration increased proximal skin temperature during the day (F = 6.46, $P = 0.04$) to a level similar as measured in controls, but did not affect core body temperature, distal temperature or distal-proximal temperature gradient (DPG). Sodium Oxybate administration normalized the predictive value of DPG for the onset of daytime naps ($P < 0.01$).

Conclusions: Sodium Oxybate improved the symptoms of narcolepsy in concert with a partial normalization of the skin temperature profile, by increasing daytime proximal skin temperature and by restoring the known relationship between skin temperature and daytime sleep propensity.

INTRODUCTION

Narcolepsy with cataplexy is a sleep disorder characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis and impaired maintenance of nocturnal sleep.[131] A decreased level of hypocretin-1 (orexin-A) in the CSF is the hallmark of the disease and is considered to explain all narcolepsy symptoms.[46]

Skin and core body temperature play an important role in sleep and wake regulation.[97;219;220] Wake is associated with a relatively low skin temperature and a relatively high core body temperature, while sleep is associated with a higher skin temperature and a lower core body temperature. Sleep onset is preceded by a decline in core body temperature and an increase in skin temperature. The decrease in core body temperature is mediated through increased skin perfusion, which consequently leads to the increase in skin temperature, and facilitates cooling of the body.[221;222] These changes are facilitated in part by the postural change from an upright to a supine position that commonly occurs during sleep.[223]

Previous studies demonstrated an altered diurnal profile of skin temperature in narcolepsy. Compared with controls, patients with narcolepsy show an increased distal skin temperature and a decreased proximal skin temperature in the waking state.[23;25;224] This pattern may be considered as characteristic of lowered vigilance[225;226] or even 'sleep promoting', since it is also seen in controls immediately before sleep onset.[97;219] Indeed, temperature manipulation studies in narcoleptic patients counteracting these changes have shown to improve nocturnal sleep and excessive daytime sleepiness.[24;25] All together, these findings suggest a relationship between hypocretin function, temperature and sleep regulation.

Gammahydroxybutyrate (GHB) is a hypnotic used to improve nocturnal sleep and EDS in narcolepsy.[227] GHB has a wide range of effects, but the exact mechanisms are still unclear. Altered thermoregulation is one of the effects described in animal studies and human case reports. Rodent studies demonstrate a slight increase in core body temperature after administration of a low dose of GHB (5-10 mg/kg) and a clear decrease in core body temperature in higher doses (< 500 mg/kg).[99] Several studies describe hypothermia in humans with GHB intoxication.[100;101]

Sodium Oxybate (SXB) is the sodium salt of GHB and is registered for the treatment of narcolepsy. Its effects are comparable to the effects of GHB. Given the impact of GHB on temperature regulation, the altered pattern of skin temperature in narcolepsy and the positive effects of SXB on sleep in narcolepsy patients, it may be hypothesized that

the treatment effect of SXB may in part be mediated by its possible restorative effect on temperature regulation. The aim of the present study is to investigate the effect of SXB on core body and skin temperature in relation to its effects on sleep. Therefore, we continuously measured sleep, core body temperature and skin temperature for 24 hours in narcolepsy patients and controls, before and after five days of treatment with SXB during a constant routine protocol.

METHODS

Subjects

8 male narcolepsy patients (18-65 years of age) were included after informed consent. They all fulfilled the criteria for narcolepsy with cataplexy according to the International Classification of Sleep Disorders-2 (ICDS-2),[118] suffered clear-cut cataplexy and were hypocretin-1 deficient. Two patients were drug naive, one patient was tapered from antidepressants ≥ 2 weeks prior to the study, and 2 patients had prior history with SXB; however, no subject took SXB within 20 days of study initiation. The other patients did not take any medication for at least several months prior to beginning the study. Eight healthy male controls, free of any neurologic, endocrine or psychiatric disease, were individually matched for age and body mass index (BMI).

Study design (Figure 7.1)

The results of this study originate from an extensive protocol that was described previously.[133;173;228] All subjects stayed overnight in the hospital and underwent a baseline 24h temperature measurement and polysomnography. During this measurement subjects remained (semi)supine except for bathroom visits. Lights were switched off at 23:00h and switched on at 7:30h, and daytime naps were allowed. At 8:30h, 13:00h and 18:00h a standardized cold meal was served and during the whole day water and tea (caffeine free) were available. Following the baseline study, subjects were treated with SXB for five consecutive days, the first and the 5th day in the hospital. A second 24h temperature measurement and polysomnography was performed on the 5th day of SXB use.

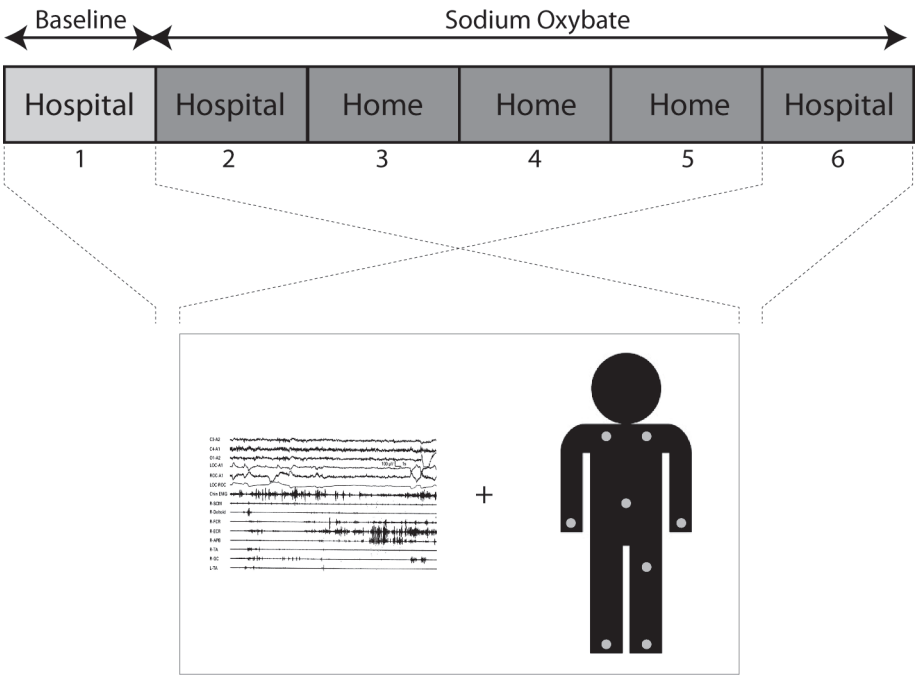

Figure 7.1 At day 1 subjects underwent a 24h temperature measurement and polysomnography without any treatment. Following this baseline study, subjects were treated with SXB for five consecutive days, the first and the 5th day in the hospital. A second 24h temperature measurement was performed on the 5th day of SXB use. The dots on the man indicate the location of the iButtons for skin temperature measurement.

Medication protocol

To monitor possible side effects, the first SXB administration was done in the hospital. Since food reduces the bioavailability of the drug, patients were not allowed to eat for at least 2.5 hours prior to drug administration. Subjects received 3 grams SXB at 23:00h and 3:00h. When no adverse-effects were experienced, subjects were allowed to continue the study and used this dosage of SXB for the next 4 nights. The 5th night the subjects spent in the hospital again for the second measurement.

Temperature measurement

During the baseline measurement and 5th night of SXB use, subjects stayed overnight in the hospital and a 24h temperature measurement was performed.

Core body temperature was measured with a wireless monitoring system: an ingestible and biocompatible capsule with Vitalsense monitor (Mini Mitter Company Inc., A Respironics, Inc. Company Bend, Oregon, USA).[229]

Skin temperature was measured with wireless monitoring systems: Thermochron iButtons (type DS1921H-F50; Maxim Integrated products, Inc., Sunnyvale, CA, USA)[230] Skin temperature was measured at 7 locations: left infraclavicular area, both hands, abdomen (1cm above the umbilicus), left midthigh (musculus rectus femoris) and both feet. Distal skin temperature was obtained from the temperatures at the thenar area at the palmar side of both hands and medial metatarsal area at the plantar sides of both feet.[231] Proximal skin temperature contained the infraclavicular, the thigh and abdominal temperature. Additionally, the distal-proximal temperature gradient (distal minus proximal skin temperature, DPG) was calculated.

Both core body temperature and skin temperature were sampled once per minute with a temperature resolution of 0.125°C.

Sleep analysis

Polysomnographic sleep recordings were performed with a portable, Embletta X100 recorder (Embla Broomfield, CO, USA) and scored by an experienced sleep technician according to the American Academy of Sleep Medicine criteria.[119]

Daytime naps were defined as naps if they fulfilled the following criteria: (1) a period of any sleep stage (I, II, III or REM) during the 'lights on' period (between 7:30h and 23:00h), (2) for at least two consecutive minutes, (3) no sleep was registered at least 10 minutes prior to the nap.

Data analysis and statistics

To compare sleep characteristics between patients and controls unpaired t-tests were used. Paired t-tests were used to analyze sleep characteristics before and during SXb administration. Analysis of differences for the number of daytime naps between patients and controls was performed with the Mann Whitney *U* test and the Related-Samples Wilcoxon Signed Rank test because of small group size and skewed distribution.

To evaluate group differences, group by time of day differences and treatment by time of day effects on temperature, the mean temperature of each episode of 30 minutes was

calculated. With these data Generalized Linear Model for repeated measures with Huynh-Feldt corrections were run using IBM SPSS 20 (Illinois) with between factor narcolepsy and within factors SXB and time of day. This analysis was performed on the 24 hours data, and separately for daytime (7:30h-23:00h) and night time (23:00h-7:00h). Posthoc t-tests were used to evaluate the times of day where narcolepsy or SXB related differences reached significance.

To evaluate the effect of temperature on nap probability in patients at baseline and during SXB administration, mixed effect logistic regression analysis (MlwiN, Center for Multilevel Modeling, Institute of Education, London, UK) was applied to account for the 2-level hierarchical dependency of the data structure: temperatures measured each minute (time of day), nested within subjects. For all analysis the outcome variable was sleep onset, which was binomially coded for every 1 minute epoch (since temperature was measured once per minute) as wake = 0 and sleep onset = 1. The predictive value of temperature for the odds of sleep onset was evaluated using logistic regression. The equation evaluated was as follows: $\text{logit}(P_{ij}) = \beta 0ij + \beta 1 \times Xij$ (subscripts indicate time of day i for subject j), with P representing the sleep onset probability and X representing either proximal skin temperature, distal skin temperature, distal-proximal temperature gradient (DPG) or core body temperature. For each of these temperatures, this analysis was performed with three different regressors. The first regressor evaluated was the temperature during the minute prior to the 1-minute epoch. The second and third regressor rather evaluated the predictive value of monotonic changes in temperature prior to sleep onset. To this end, the second regressor was the difference between the temperature immediately prior to the 1-minute epoch and the temperature 5 minutes before. The third regressor was the difference between the temperature immediately prior to the 1-minute epoch and the temperature 15 minutes before.

RESULTS

Subjects

Eight patients (mean age 38.0 ± 4.7 years) and eight controls (mean age 37.9 ± 4.1 years) were included after informed consent. Mean BMI was 28.1 ± 1.6 kg/m^2 for patients and 27.4 ± 1.4k g/m^2 for controls.

Sleep

Sleep characteristics are given in Table 7.1. During the day, patients were significantly less awake compared to controls ($P = 0.004$). SXB administration, results in significantly less stage I/II sleep during the day ($P = 0.049$), and a trend towards more wake ($P = 0.052$) was seen. SXB intake demonstrated a significantly higher percentage slow wave sleep during the night in patients ($P = 0.014$) and in controls ($P = 0.045$).

Daytime napping occurred in all patients at baseline and during SXB administration, varying from 3 to 16 naps per patient at baseline and from 3 to11 naps per patient during treatment. At baseline three controls took 2 or 3 daytime naps per person, while during SXB administration five controls took one nap. Both at baseline and during SXB administration, patients had significantly more daytime naps then controls (baseline number of naps for patients and controls, respectively: N = 57 and N = 8, $P < 0.01$; treatment number of naps for patients and controls, respectively: N = 46 and N = 5, $P < 0.01$). No significant improvement in the number of daytime naps was seen in controls ($P = 0.334$) or in patients ($P = 0.248$) during SXB administration.

Temperature in narcolepsy patients vs. controls at baseline

Temperature profiles are demonstrated in Figure 7.2 and the results of statistical analysis in Table 7.2. Patients had a significantly lower core body temperature. Proximal skin temperature showed a trend to be lower in patients (F = 4.13, df = 1, $P = 0.06$), while in distal skin temperature and in distal-proximal temperature gradient (DPG) no significant differences were found. Analysis of the effect of group by time of day showed a nearly significant effect of narcolepsy by time of day for proximal skin temperature (F = 2.24, df = 5.49, $P = 0.05$).

Separate analysis of daytime and night time temperatures demonstrated a significantly lower proximal skin temperature (F = 5.66, df = 1, $P = 0.03$) and core body temperature (F = 8.31, df = 1, $P = 0.01$) in patients during daytime. Furthermore, a significant effect of group by time of day was seen for core body temperature during daytime (F = 2.82, df = 7.11, $P = 0.01$) and for distal skin temperature during nighttime (F = 4.34, df = 2, $P = 0.02$).

Post-hoc tests indicated a significantly ($P < 0.05$) lower core body temperature in narcolepsy between 16:30 and midnight (00:00) and between 10:00 and 12:00 the next morning. The same was found in proximal skin temperature between 15:30 and 23:00 and between 11:00 and 12:00 the next morning.

Table 7.1 Sleep variables before and after SXB administration

	Patients (N = 8)			Controls (N = 8)			Patients vs. controls (baseline)
	Baseline	SXB	*P*	Baseline	SXB	*P*	*P*
Wake total (%)	61.0 ± 2.9	61.6 ± 2.2	0.787	68.9 ± 2.1	70.4 ± 2.4	0.284	0.045*
Wake day (%)	80.4 ± 4.1	84.9 ± 3.3	0.052	96 .5 ± 2.2	98.4 ± 1.0	0.333	0.004**
Wake night (%)	25.8 ± 5.7	19.2 ± 4.3	0.064	18.5 ± 4.0	19.2 ± 5.8	0.484	0.316
Stage I/II total (%)	29.0 ± 1.4	26.2 ± 1.4	0.070	24.9 ± 2.4	21.0 ± 2.2	0.092	0.156
Stage I/II day (%)	14.7 ± 2.9	11.2 ± 2.6	0.049*	2.6 ± 1.7	1.6 ± 1.0	0.463	0.003**
Stage I/II night (%)	55.1 ± 2.5	53.4 ± 3.7	0.497	65.5 ± 5.7	56.4 ± 5.2	0.078	0.117
SWS total (%)	3.7 ± 0.7	7.6 ± 1.2	0.018*	2.6 ± 0.7	6.6 ± 0.9	0.045*	0.263
SWS day (%)	2.1 ± 0.6	2.7 ± 1.1	0.526	0.05 ± 0.05	0.05 ± 0.05	0.356	0.013*
SWS night (%)	6.5 ± 1.9	16.5 ± 3.0	0.014*	7.2 ± 2.0	18.5 ± 2.4	0.045*	0.818
REM total (%)	6.3 ± 1.8	4.6 ± 1.0	0.112	3.7 ± 0.8	2.1 ± 0.8	0.055	0191
REM day (%)	4.3 ± 1.7	1.2 ± 0.5	0.050	0.8 ± 0.5	0.0 ± 0.0	0.175	0.077
REM night (%)	12.6 ± 3.0	10.8 ± 2.1	0.309	8.8 ± 1.8	5.8 ± 2.3	0.133	0.305
Sleep time total (min.)	561.1 ± 41.9	552.8 ± 31.9	0.787	447.9 ± 29.9	426.9 ± 34.0	0.284	0.045*
Sleep time day (min.)	254.1 ± 64.4	140.9 ± 30.8	0.117	32.4 ± 20.7	15.0 ± 9.3	0.326	0.010*
Sleep time night (min.)	378.4 ± 29.2	411.9 ± 22.0	0.064	415.6 ± 19.7	411.9 ± 29.5	0.484	0.316

Percentages of sleep stages during the 24 hours of study, before and during SXB administration. Data are shown as mean ± SEM.

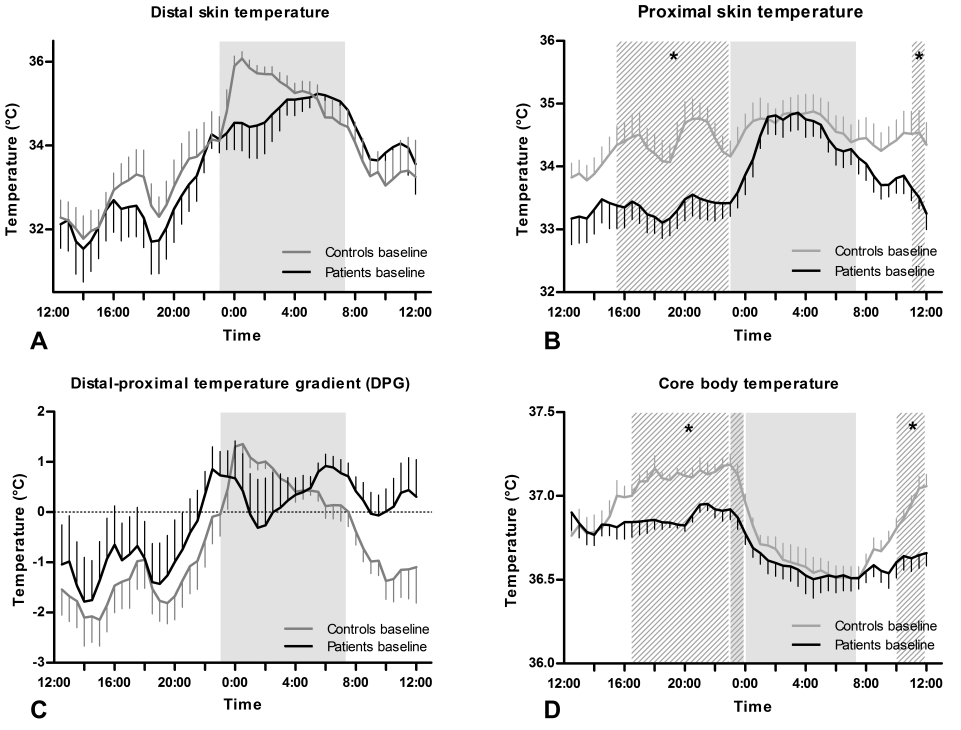

Figure 7.2 Temperature profiles of narcolepsy patients vs. controls.

Table 7.2 Temperatures of controls vs. patients at baseline

	df	F	*P*-value
Group effect			
Proximal skin temperature	1	4.13	0.06
Distal skin temperature	1	0.17	0.69
DPG	1	0.52	0.48
Core body temperature	1	6.46	0.02*
Group by time of day effect			
Proximal skin temperature	5.49	2.24	0.05
Distal skin temperature	7.46	1.25	0.28
DPG	8.91	1.75	0.09
Core body temperature	4.83	1.96	0.10

* $P < 0.05$.

Temperature in narcolepsy patients: baseline vs. SXB (Table 7.3, Figure 7.3)

In patients, a significant main effect of SXB on proximal skin temperature (F = 6.41, df = 1, *P* = 0.04) as well as a nearly significant SXB by time of day effect (F = 2.22, df = 4.80, *P* = 0.08)

Table 7.3 Temperatures at baseline vs. during SXB administration

	Controls			Patients		
	df	F	*P*-value	df	F	*P*-value
Treatment effect						
Proximal skin temperature	1	0.03	0.88	1	6.41	0.04*
Distal skin temperature	1	0.48	0.51	1	2.11	0.19
DPG	1	1.41	0.27	1	0.46	0.52
Core body temperature	1	0.01	0.91	1	2.07	0.19
Treatment by time of day effect						
Proximal skin temperature	5.06	0.61	0.70	4.80	2.22	0.08
Distal skin temperature	6.48	0.37	0.91	11.05	1.36	0.21
DPG	6.74	0.33	0.93	9.44	1.56	0.14
Core body temperature	5.74	1.65	0.16	7.58	1.56	0.16

* $P < 0.05$.

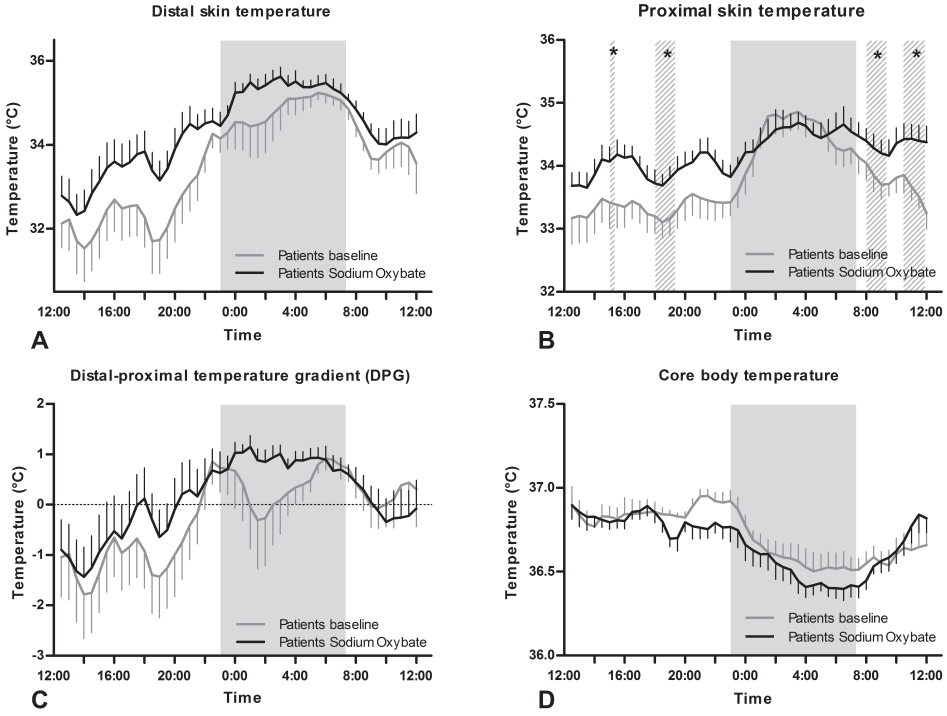

Figure 7.3 Temperature profiles of narcolepsy patients at baseline and during SXB administration. **(A)** distal skin temperature in patients at baseline and during treatment with SXB, **(B)** proximal skin temperature in patients at baseline and during treatment with SXB, **(C)** distal-proximal temperature gradient (DPG) in patients at baseline and during treatment with SXB **(D)** core body temperature in narcolepsy patients at baseline and during treatment with SXB. The gray area indicates the lights off period and the striped area the period during which the temperature significantly differed according the post-hoc tests (* $P < 0.05$). Data are expressed as mean ± SEM.

was seen. Additional separate daytime and night time analysis demonstrated that proximal skin temperature was higher during the day in the SXB condition (F = 6.46, df = 1, *P* = 0.04), but no difference was found during night time (F = 0.08, df = 1, *P* = 0.79). In post-hoc tests significance (*P* < 0.05) was reached from 15:00 to 16:00, from 18:00 to 19:30, and from 8:00 to 9:30 and 10:30 to 12:00 the next morning.

For core body temperature, distal skin temperature and DPG, no main significant effect was found for SXB administration.

Summarizing, SXB administration in patients increased proximal skin temperature at several time points during daytime. There was no effect on core body temperature, distal skin temperature and DPG.

Temperature in controls: SXB vs. baseline (Table 7.3)

In controls, no significant effect of SXB or SXB by time of day was found on core body temperature, skin temperatures and DPG.

The predictive value of temperature changes in the onset of daytime naps (Table 7.4).

Since daytime napping was rare in controls, only daytime naps in patients were analyzed. Mixed effect logistic regression analysis of sleep onset in patients at baseline revealed no predictive value of the four temperature variables for daytime sleep onset. However, during SXB administration changes in DPG significantly predicted sleep onset. Change in DPG 15 minutes prior to sleep onset, 5 minutes prior to sleep onset and DPG one minute prior falling asleep significantly predicted daytime napping (respectively O.R. 1.99 (*P* = 0.009), O.R. 2.23 (*P* = 0.042) and O.R. 1.33 (*P* = 0.029) per degree Celsius change in temperature).

DISCUSSION

The aim of this study was to investigate the effects of SXB on core body and skin temperature in relation to its effects on sleep in patients suffering from narcolepsy with cataplexy. This is the first study in which both core body and skin temperature were measured in combination with continuous sleep registration in narcolepsy. At baseline, patients had significantly lower daytime core body and proximal skin temperatures compared to controls. In patients, SXB increased nocturnal slow wave sleep (SWS), normalized proximal skin temperature, and strengthened the relationship between changes in skin temperature and subsequent daytime sleep onset.

Table 7.4 Effect of temperature on daytime lapse probability

	Baseline				Treatment SXB			
	O.R.	95% CI	Z	*P*	O.R.	95% CI	Z	*P*
Proximal skin temperature								
1 minute prior to sleep onset	1.32	0.79-2.29	0.97	0.331	0.81	0.44-1.48	-0.69	0.489
5 minutes prior to sleep onset	1.27	0.22-7.20	0.27	0.784	0.31	0.05-2.02	-1.22	0.221
15 minutes prior to sleep onset	0.96	0.36-2.54	-0.08	0.934	0.39	0.12-1.23	-1.60	0.110
Distal skin temperature								
1 minute prior to sleep onset	0.96	0.79-1.16	-0.46	0.642	1.24	0.98-1.57	1.77	0.077
5 minutes prior to sleep onset	1.51	0.89-2.58	1.52	0.129	2.48	0.77-8.01	1.51	0.130
15 minutes prior to sleep onset	1.35	0.90-2.02	1.41	0.159	1.90	0.95-3.78	1.82	0.069
DPG								
1 minute prior to sleep onset	0.91	0.73-1.13	-0.85	0.393	1.33	1.03-1.71	2.18	0.029*
5 minutes prior to sleep onset	1.45	0.83-2.53	1.32	0.186	2.23	1.03-4.82	2.03	0.042*
15 minutes prior to sleep onset	1.33	0.89-1.97	1.41	0.159	1.99	1.18-3.36	2.59	0.009**
Core body temperature								
1 minute prior to sleep onset	0.59	0.16-2.21	-0.78	0.437	1.23	0.37-4.05	0.34	0.732
5 minutes prior to sleep onset	1.51	0.01-160.25	0.17	0.863	4,29	0.01-1798.59	0.47	0.637
15 minutes prior to sleep onset	0.20	0.01-4.40	-1.01	0.311	16.68	1.01-276.09	1.97	0.049

Results of mixed effect logistic regression analysis for patients without SXB and patients during SXB administration (nights were excluded), indicating effects of temperature fluctuations as regressor for fluctuations in lapse probability (odds ratio per degree Celcius change in temperature). The logistic regression model was as follows: $\text{logit}(P_{ij}) = 0_{ij} + \beta 1 \times X_{ij}$ (subscripts indicate time of day i for subject j), with P representing the lapse probability and X representing either proximal skin temperature, distal skin temperature, distal-proximal temperature gradient (DPG) or core body temperature at the moments: difference between the temperature during the 1-minute epoch prior to sleep onset and 15 minutes prior to sleep onset, difference between the temperature during the 1-minute epoch prior to sleep onset and 5 minutes prior to sleep onset or the temperature during the 1-minute epoch prior to sleep onset. * $P < 0.05$; ** $P < 0.01$.

An altered thermoregulatory profile in narcolepsy

In the present study, core body temperature and proximal skin temperature were lower in narcolepsy, mainly caused by significant differences during daytime. No significant differences in distal skin temperature were found, although the nocturnal time course of distal skin temperature significantly differed between patients and controls.

The finding of a decreased daytime proximal skin temperature in narcolepsy patients compared to controls was previously demonstrated as well.[23] In contrast to our current findings, this previous work also reported a higher distal skin temperature. The combination of the increased distal skin temperature and the decreased proximal skin temperature in that study resulted a higher distal-proximal temperature gradient (DPG). Comparison of the present study with the previous one indicates that the absence of a higher distal skin temperature in patients, and subsequently the absence of a higher DPG, is mainly due to a higher distal skin temperature in controls in the current study. Since a higher distal skin temperature can be a direct consequence of a supine position,[232] maintaining this position throughout our study can be the explanation of the higher distal skin temperature found in controls. Concertedly, these results indicate that narcolepsy patients are likely to attain, even in an upright or sitting position, the high distal skin temperature that healthy controls reach only when remaining in a supine position.

We found a lower core body temperature during the day in patients. In the past, core body temperature has been more extensively studied than skin temperature. Unfortunately, previous studies in narcolepsy are not conclusive at this point; results vary from an elevated core body temperature to a lowered core body temperature.[25;233-236] Manipulation studies demonstrate a minimal effect of manipulation of core body temperature on sleep propensity,[25;221;231] however, a high core body temperature is associated with higher vigilance.[25;222]

SXB normalizes temperature profiles in narcolepsy

In patients, SXB administration significantly increased daytime proximal skin temperature, reaching levels comparable with healthy controls. Paradoxically, based on previous temperature manipulation studies proximal skin warming would result in increased sleepiness.[24;231;237] This finding is in contradiction with the knowledge that SXB reduces the amount of daytime sleep attacks.[238] However, warming up the skin by direct manipulation as performed in this previous study, may represent a different physiological mechanism compared with the intrinsic skin warming resulting from SXB administration.

In healthy subjects, sleep onset is preceded by a decline in core body temperature and an increase in distal skin temperature.[222] In healthy controls, an increased DPG is associated with a lower vigilance[225;226] and an accelerated sleep onset.[97;219] In narcolepsy, a shorter sleep onset latency was found to be associated with an increase of proximal and distal skin temperatures and, to a lesser extent, an increase of the DPG.[23] However, none of these studies concerned spontaneous daytime napping in narcolepsy patients. Analysis of spontaneous naps in (semi) supine position in the present study revealed an absence of predictive value for any of the temperature measurements in narcolepsy patients at baseline. Surprisingly, during SXB administration an increase in DPG did become predictive for subsequent daytime sleep onset. The relationship between skin temperature and sleep onset that is known to exist in controls thus seemed to be restored by the administration of SXB.

Does altered thermoregulation play a role in SXB's effects on sleep?

An increase in nocturnal SWS, previously reported to be one of the principal effects of SXB on sleep,[238-241] was confirmed in this study. If this is mediated by an altered temperature regulation is questionable, since there were no nocturnal temperature effects seen during SXB intake in this study. The relatively high percentage of wake during the night in controls is probably due to the laboratory settings.

Study limitations

Since body position directly affects skin temperature, the major limitation of this study is the setting during which patients were in (semi) supine position for 24 hours. This body position differs from the situation in normal daily life, and the setting in previous studies. Moreover, the clinical effects of SXB on nocturnal sleep can already be experienced with the dose we have used in the first night of its use, but it usually takes several weeks and a higher dose to obtain significant improvement of EDS. Subsequently, it is presumable that there are some long-term effects, particularly during daytime that may have been missed in this study. Furthermore, the present study only included male subjects, while men and women are equally affected with narcolepsy.

Conclusion

In conclusion, during a constant routine protocol a decreased daytime core body and proximal skin temperature were observed in narcolepsy patients compared to controls. Administration of SXB normalized the sleep wake pattern as well as the temperature profiles in narcolepsy patients. Furthermore, SXB restored the relationship between skin temperature and subsequent sleep onset – that is known to exist in controls – in patients. To further explore the role of SXB in temperature regulation and sleep in narcolepsy, studies with patients and controls of both sexes have to be performed in normal daily life.

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