Unravelling narcolepsy : from pathophysiology to measuring treatment effects

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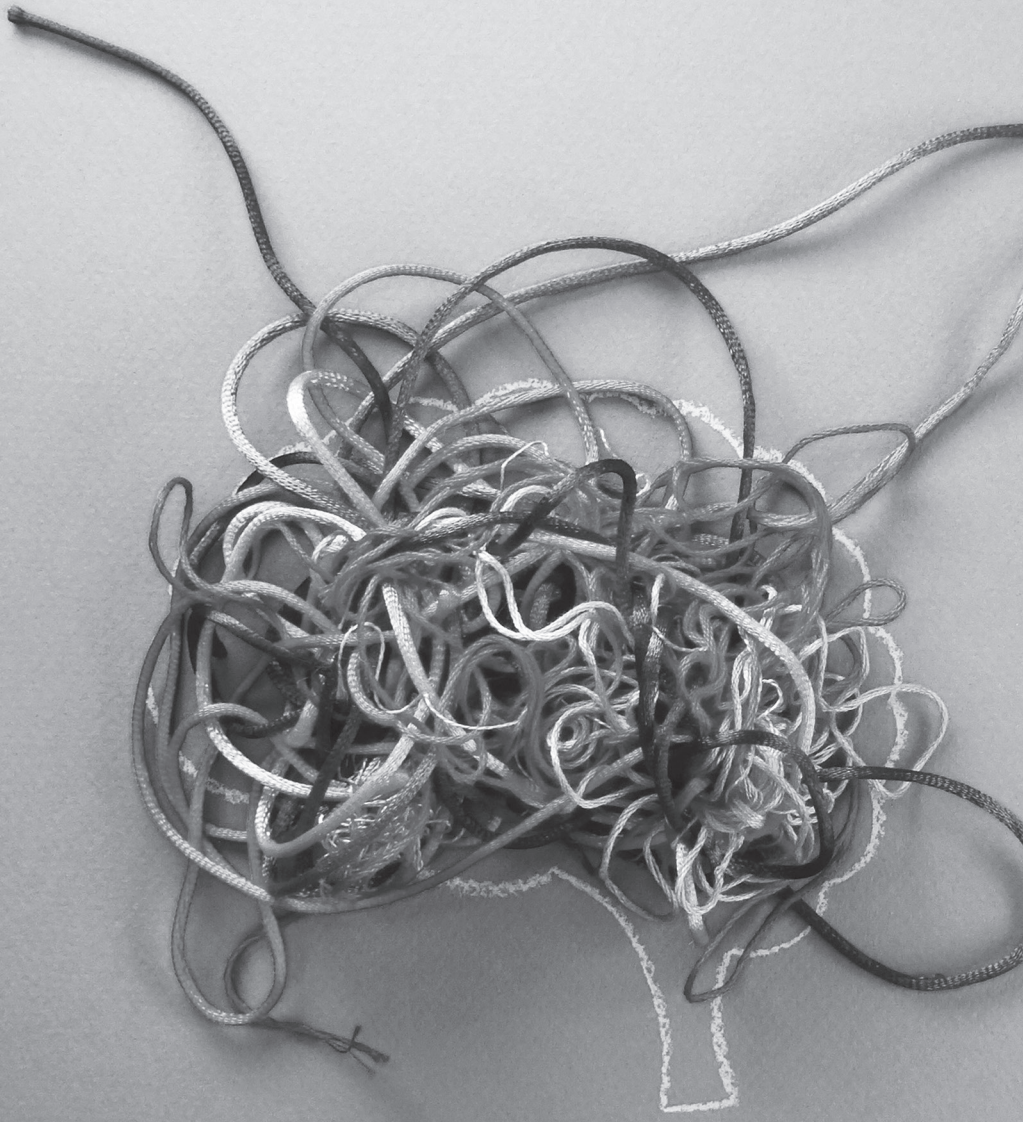

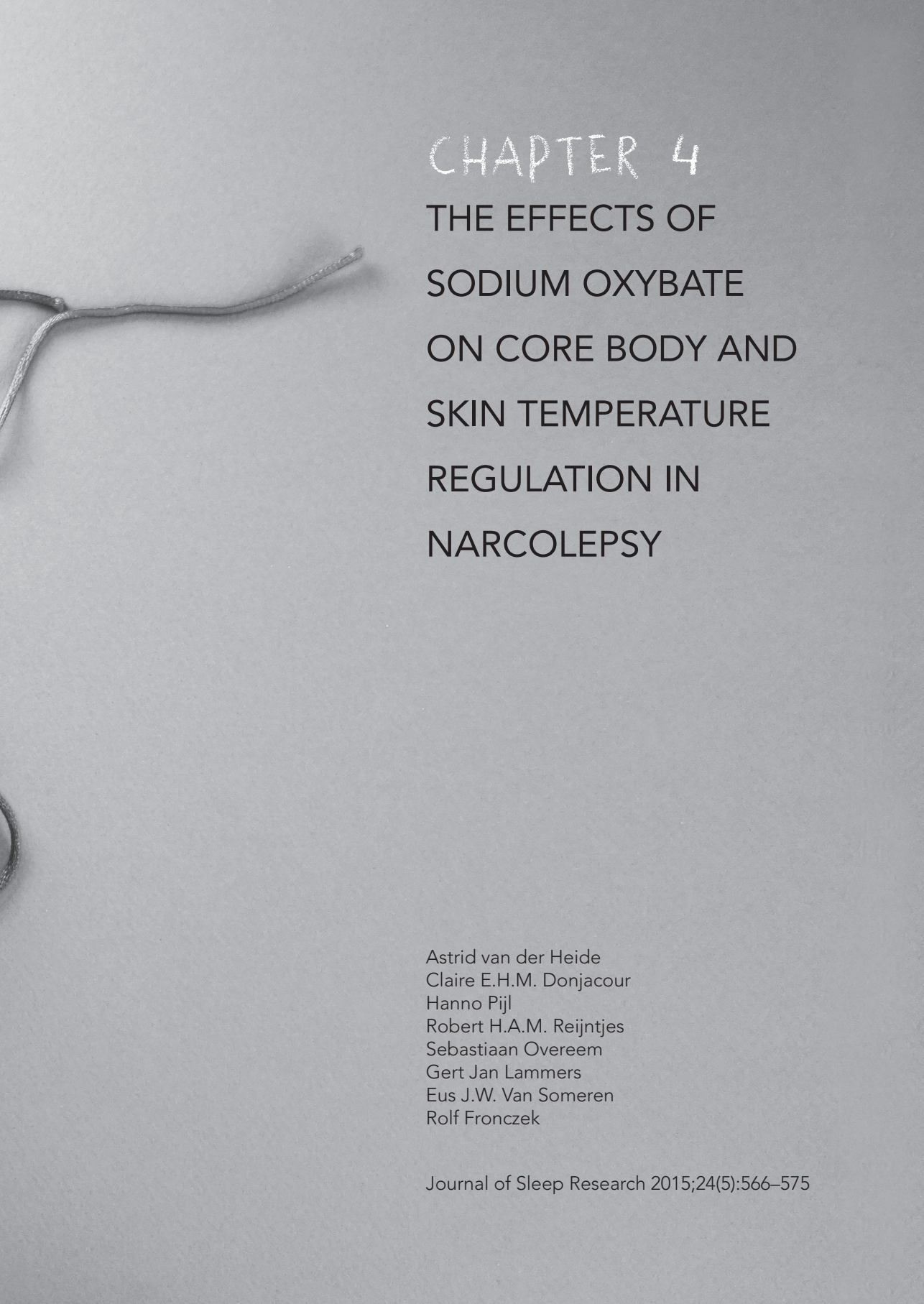

CHAPTER 4

THE EFFECTS OF SODIUM OXYBATE ON CORE BODY AND SKIN TEMPERATURE REGULATION IN NARCOLEPSY

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Journal of Sleep Research 2015;24(5):566–575

SUMMARY

Patients suffering from narcolepsy type 1 show altered skin temperatures, resembling the profile that is related to sleep onset in healthy controls. 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. Eight hypocretin-deficient male narcolepsy type 1 patients and eight healthy matched controls underwent twice temperature measurement of core body and proximal and distal skin, and the sleep-wake state for 24 hours. After the baseline assessment, 2 x 3 grams of sodium oxybate was administered for five nights, immediately followed by the second assessment. At baseline, daytime core body temperature and proximal skin temperature were significantly lower in narcolepsy patients (core: 36. 8±0.05°C vs. 37.0±0.05°C, $F=8.31$, $p=0.01$; proximal: 33.4±0.26°C vs. 34.3±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 in controls, but did not affect core body temperature, distal temperature or distal-proximal temperature gradient (DPG). Sodium oxybate administration normalised the predictive value of distal skin temperature and DPG for the onset of daytime naps ($p<0.01$). In conclusion, sodium oxybate administration resulted in a partial normalisation of the skin temperature profile, by increasing daytime proximal skin temperature and by strengthening the known relationship between skin temperature and daytime sleep propensity. These changes seem to be related to the clinical improvement induced by SXB treatment. A causal relation is not proven.

INTRODUCTION

Narcolepsy with cataplexy (narcolepsy type 1) is a sleep disorder characterised by excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis and impaired maintenance of nocturnal sleep.[1] 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.[2]

Skin and core body temperature play an important role in sleep and wake regulation.[3-5] 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.[6,7] These changes are facilitated in part by the postural change from an upright to a supine position that commonly occurs during sleep.[8]

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.[9-11] This pattern may be considered as characteristic of lowered vigilance[12,13] or even 'sleep promoting', since it is also seen in controls immediately before sleep onset. Indeed, temperature manipulation studies in narcoleptic patients counteracting these changes have shown to improve nocturnal sleep and excessive daytime sleepiness.[10,14] 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.[15] 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).[16] Several studies describe hypothermia in humans with GHB intoxication.[17,18]

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 SXB administration during a constant routine protocol.

METHODS

Subjects

Eight male narcolepsy patients (18–65 years of age) were included after informed consent. They all fulfilled the criteria for narcolepsy type 1 according to the International Classification of Sleep Disorders-3 (ICDS-3),[1,19] 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). Written informed consent was obtained from all subjects. The study was approved by the ethics committee of the Leiden University Medical Centre.

Study design (Figure 4.1)

The results of this study originate from an extensive, constant routine protocol that was described previously.[2,20-22]

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. Subjects were allowed to take daytime naps whenever they wanted. At 8:30h, 13:00h and 18:00h a standardised cold meal was served and during the whole day water and tea (caffeine free) were available. Following the baseline study, subjects ingested 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.

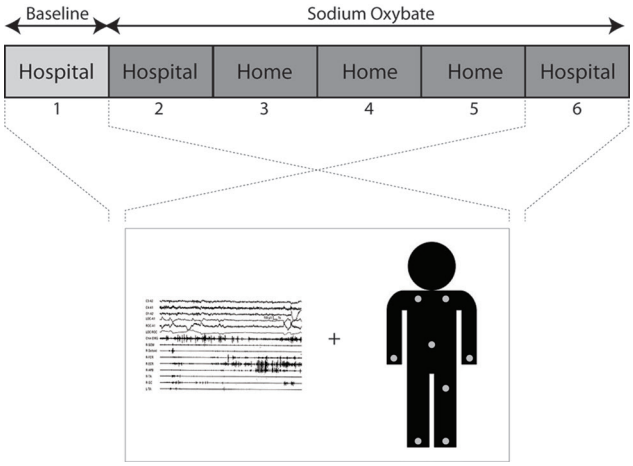

Figure 4.1 Study design.
At day 1 subjects underwent a 24h temperature measurement and polysomnography without any treatment. Following this baseline study, subjects were treated with SXB for five consecutive days, the first and the 5th day in the hospital. A second 24h temperature measurement was performed 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. Whether subjects were responders or not was not explicitly determined.

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).[3-5,23]

Skin temperature was measured wirelessly using Thermochron iButtons (type DS1921H-F50; Maxim Integrated products, Inc., Sunnyvale, CA, USA).[6,7,24] Skin temperature was measured at 8 locations: bilateral infraclavicular area, both hands, abdomen (1 cm 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.[8,25] 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.[9-11,26]

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) all subjects were awake at least 10 min 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 analyse 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 administration 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 effects analysis (R version 3.1.1) was performed. For all analysis, the outcome variable was sleep onset, which was binomially coded for every 30 seconds epoch as wake = 0 and sleep onset = 1 (further sleep-epochs were excluded from analysis). As fixed effects, the different temperatures (proximal, distal, core body and DPG), intervention and time (without interaction term) were entered into the model. As random effects, we had intercepts for subjects. For each of the temperatures, this analysis was performed with three different regressors. The first regressor evaluated was the temperature during the 30 seconds prior to the first sleep 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 30-seconds epoch and the temperature 5 minutes before. The third regressor was the difference between the temperature immediately prior to the 30-seconds epoch and the temperature 15 minutes before. P-values were obtained by likelihood ratio tests of the full model with the effect in question against the model without the effect in question.

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±1.4 kg/m^2 for controls.

Sleep characteristics are given in Table 4.1. During the day, patients were significantly less awake compared to controls (p=0.004). SXB administration resulted 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). SXB administration did not result in change in the prevalence of sleep onset REM periods neither during daytime, nor during night time sleep onset.

Table 4.1 Sleep variables before and after SXB administration

	Patients (N=8)			Controls (N=8)			Patients vs. controls (baseline)
	Baseline	SXB	p-value	Baseline	SXB	p-value	p-value
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 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 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 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 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.

Daytime napping occurred in all patients at baseline and during SXB administration, and varied from 3 to16 naps per patient at baseline and from 3 to11 naps per patient during administration. 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 than controls (baseline number of naps for patients and controls, respectively: N=57 and N=8, $p<0.01$; number of naps during SXB administration 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 shown in Figure 4.2 and the results of statistical analysis in Table 4.2. 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 ($F=2.24$, $df=5.49$, $p=0.05$).

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 4.2 Results of analysis of 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

* $p<0.05$.

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 night time (F=4.34, df=2, p=0.02).

Temperature in narcolepsy patients: baseline vs. SXB (Table 4.3, Figure 4.3)

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) 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.

Summarising, 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.

Table 4.3 Results of analysis of temperatures at baseline vs during SXB administration

	Controls			Patients		
	df	F	p-value	df	F	p-value
Administration 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
Administration 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.

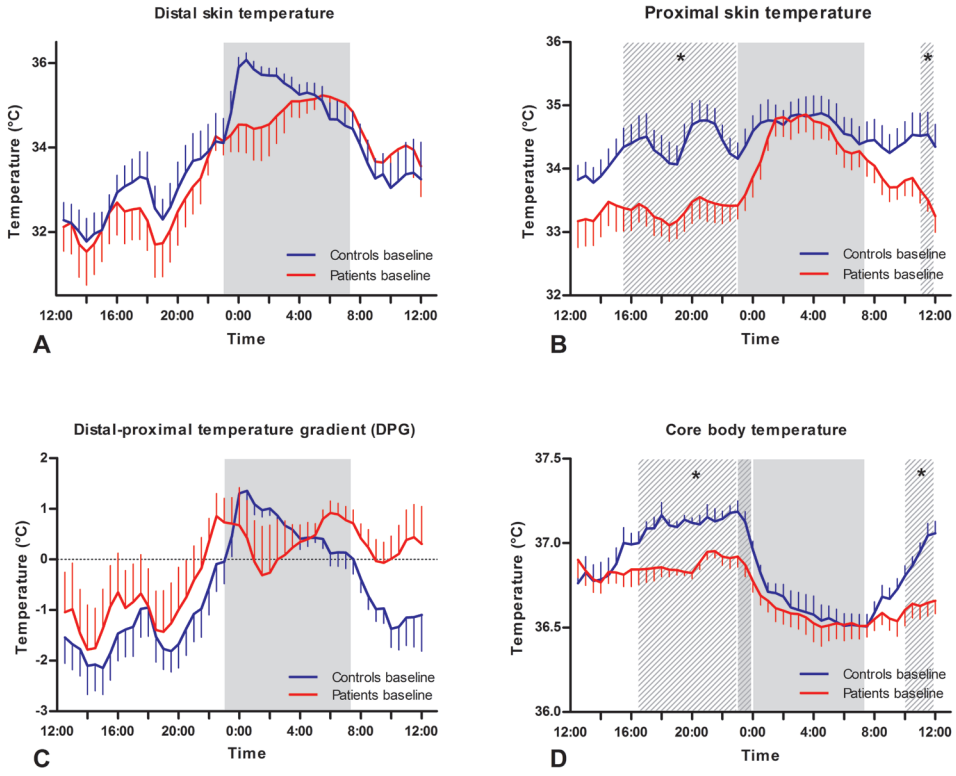

Figure 4.2 Mean ± SEM temperature profiles patients vs. controls.
(A) distal skin temperature in patients and controls at baseline, (B) proximal skin temperature in patients and controls at baseline, (C) distal-proximal temperature gradient (DPG) in patients and controls at baseline (D) core body temperature in narcolepsy patients and controls at baseline. The grey area indicates the lights off period and the striped area the period during which the temperature significantly differed according the post-hoc tests (* $p<0.05$).

Temperature in controls: baseline vs. SXB (Table 4.3)

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 on the onset of daytime naps (Table 4.4)

Since daytime napping was rare in controls, only daytime naps in patients were analysed. Mixed effects analysis of sleep onset in patients at baseline revealed predictive effects of change in proximal skin temperature during the 5 minutes prior to sleep onset, distal skin

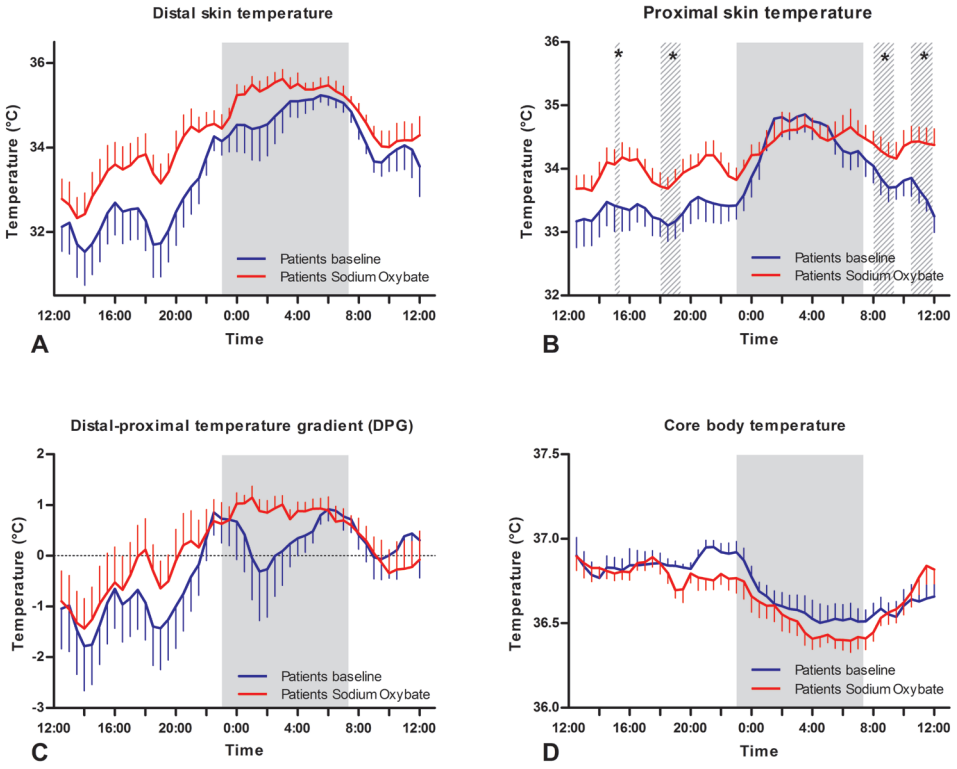

Figure 4.3 Mean ± SEM temperature profiles patients at baseline and during SXB administration. (A) distal skin temperature in patients at baseline and during SXB administration, (B) proximal skin temperature in patients at baseline and during SXB administration, (C) distal-proximal temperature gradient (DPG) in patients at baseline and during SXB administration (D) core body temperature in narcolepsy patients at baseline and during SXB administration. The grey area indicates the lights off period and the striped area the period during which the temperature significantly differed according the post-hoc tests (* $p<0.05$).

temperature and DPG during the 15 minutes prior to sleep onset. During SXB administration the same effects were seen for distal skin temperature and DPG, supplemented with a predictive value of proximal skin temperature, distal skin temperature and DPG during the epoch prior to falling asleep. No predictive value of core temperature was seen for daytime sleep onset, nor at baseline, neither during SXB administration.

Table 4.4 Effect of temperature on daytime nap probability

	Baseline			SXB administration		
	Estimate	SE	p-value	Estimate	SE	p-value
Proximal skin temperature						
At 30 seconds prior to sleep onset	0.0	0.1	0.588	0.1	0.1	0.013*
Change 5 minutes prior to sleep onset	3.7	1.4	0.006**	0.9	1.4	0.518
Change 15 minutes prior to sleep onset	-1.5	0.8	0.064	0.1	0.8	0.948
Distal skin temperature						
At 30 seconds prior to sleep onset	0.1	0.1	0.479	0.4	0.1	0.002**
Change 5 minutes prior to sleep onset	-0.3	0.6	0.571	1.2	0.7	0.110
Change 15 minutes prior to sleep onset	0.8	0.4	0.029*	1.4	0.4	0.002**
DPG						
At 30 seconds prior to sleep onset	0.1	0.1	0.578	0.3	0.1	0.020*
Change 5 minutes prior to sleep onset	-0.2	0.6	0.744	1.0	0.7	0.143
Change 15 minutes prior to sleep onset	0.8	0.4	0.027*	1.2	0.4	0.005**
Core body temperature						
At 30 seconds prior to sleep onset	0.0	0.0	0.405	0.0	0.0	0.925
Change 5 minutes prior to sleep onset	-0.1	2.2	0.957	-0.7	2.6	0.787
Change 15 minutes prior to sleep onset	0.6	1.3	0.666	-1.6	1.6	0.326

Results of linear mixed effects analysis for patients at baseline and patients during SXB administration (nights were excluded), indicating effects of temperature fluctuations as regressor for fluctuations in lapse probability. Analysis was performed for proximal skin temperature, distal skin temperature, distal-proximal temperature gradient (DPG) or core body temperature at the moments: difference between the temperature during the 30-seconds epoch prior to sleep onset and 15 minutes prior to sleep onset, difference between the temperature during the 30-seconds epoch prior to sleep onset and 5 minutes prior to sleep onset or the absolute temperature during the 30-seconds epoch prior to sleep onset. * $p<0.05$; ** $p<0.01$.

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 type 1. 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), normalised proximal skin temperature, and strengthened the relationship between changes in skin temperature and subsequent daytime sleep onset.

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.[9,12,13] 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,[10,14,27] maintaining this position throughout our study can be the explanation of the higher distal skin temperature found in controls. Consecutively, 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 healthy controls, a lower core body temperature is associated with sleep, and would theoretically result in a lower ability to maintain wakefulness. 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.[10,15,28-31] Manipulation studies demonstrate a minimal effect of manipulation of core body temperature on sleep propensity,[6,10,16-18,25] however, a high core body temperature is associated with higher vigilance.[7,10]

SXB normalises temperature profiles in narcolepsy

In patients, SXB administration significantly increased daytime proximal skin temperature, reaching levels comparable with healthy controls. In controls, proximal skin warming resulted in decreased sleep onset latency.[25,32] In narcolepsy, however, despite the previously described lowered daytime proximal skin temperature, no beneficial effect of daytime proximal skin

warming was found.[10] These findings do not point to changes in temperature as the primary mechanism through which SXB reduces the amount of daytime sleep attacks.[33] Warming up the skin by direct manipulation may represent a different physiological mechanism compared with the intrinsic skin warming resulting from SXB administration.

However, two other mechanisms might explain the positive effects of these temperature changes as a consequence of SXB administration. First, SXB induces more consolidation of sleep, i.e. probably lowers the known increased sleep stage shift index.[34] Second, although for a short time, in high dosages SXB is reported to increase the sympathetic response,[35,36] while a chronically decreased sympathetic distal vasoconstrictor tone was hypothesised to be causal to the previously found increased DPG and the subsequently increased sleep propensity.[9]

In healthy subjects, sleep onset is preceded by a decline in core body temperature and an increase in distal skin temperature.[7] In healthy controls, an increased DPG is associated with a lower vigilance[12,13] and an accelerated sleep onset.[3,4] 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.[9] 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 a predictive value for proximal skin temperature, distal skin temperature and DPG in narcolepsy patients at baseline and during SXB administration. This relationship between an increase of skin temperature and subsequent sleep onset is known to exist in controls, exists in narcolepsy patients as well, and is even more clear after SXB administration.

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,[33,37-39] 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 in 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 optimal clinical improvement, and significant improvement of cataplexy and EDS. Subsequently, it is presumable that there are some important long-term effects, particularly during daytime that may have been missed in this study. Furthermore, the present study included a relatively small number of patients (of whom two were drug naive and the others discontinued treatment), and only male subjects, while men and women are equally affected with narcolepsy. This might have led to an underestimation of the actual effects of SXB and limits the generalisation of the results.

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 improved the sleep wake pattern, and partially normalised the temperature profiles in narcolepsy patients. Furthermore, SXB strengthened 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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