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The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects

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SUMMARY The aim of this study was to compare the effects of total sleep deprivation (TSD), rapid eye movement (REM) sleep and slow wave sleep (SWS) interruption and sleep recovery on mechanical and thermal pain sensitivity in healthy adults. Nine healthy male volunteers (age 26–43 years) were randomly assigned in this double blind and crossover study to undergo either REM sleep or SWS interruption. Periods of 6 consecutive laboratory nights separated by at least 2 weeks were designed as follows: N1 Adaptation night; N2 Baseline night; N3 Total sleep deprivation (40 h); N4 and N5 SWS or REM sleep interruption; N6 Recovery. Sleep was recorded and scored using standard methods. Tolerance thresholds to mechanical and thermal pain were assessed using an electronic pressure dolorimeter and a thermode operating on a Peltier principle. Relative to baseline levels, TSD decreased significantly mechanical pain thresholds (−8%). Both REM sleep and SWS interruption tended to decrease mechanical pain thresholds. Recovery sleep, after SWS interruption produced a significant increase in mechanical pain thresholds (+ 15%). Recovery sleep after REM sleep interruption did not significantly increase mechanical pain thresholds. No significant differences in thermal pain thresholds were detected between and within periods. In conclusion this experimental study in healthy adult volunteers has demonstrated an hyperalgesic effect related to 40 h TSD and an analgesic effect related to SWS recovery. The analgesic effect of SWS recovery is apparently greater than the analgesia induced by level I (World Health Organization) analgesic compounds in mechanical pain experiments in healthy volunteers.

KEYWORDS pain, selective sleep interruption, total sleep deprivation

INTRODUCTION

Sleep and pain are two interrelated phenomena. Pain may interrupt or disturb sleep, but changes in sleep pattern could also influence pain perception (Onen 1998). There are several clinical studies showing sleep disturbances related to painful organic disorders. However clinical investigations concerning the influence of sleep disturbances on pain sensitivity are scarce and controversial. These are mainly total and selective sleep deprivations using physical methods (electrical, auditory or tactile stimuli).

After a total sleep deprivation (TSD) of approximately 60 h duration in 6 healthy male volunteers, Cooperman *et al.* (1934) observed that the threshold for pain sensitivity was greatly reduced in each of the 6 subjects. The threshold of cutaneous sensibility to touch and pain was measured by means of the sets of hairs of von Frey applied to the skin of the face, ear, wrist and fingers. The lowering of pain threshold appeared to be correlated to the duration of sleep deprivation.

Selective sleep stage deprivations have been performed in investigations concerning fibromyalgia. Six healthy subjects were deprived of stage 4 sleep (Moldofsky *et al.* 1975) and then seven other subjects were deprived of REM sleep (Moldofsky

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and Scarisbrick 1976). Musculoskeletal tenderness, measured by dolorimetry in the evening prior to sleep and immediately on arising the next morning, was increased only after the nights of stage 4 deprivation. Remission of musculoskeletal tenderness accompanied the return of undisturbed slow wave sleep (SWS). More recently, in a non-controlled, open study, 12 healthy middle aged women were deprived of SWS for 3 consecutive nights (Lentz *et al*. 1999). In a subgroup of seven subjects, authors reported a 24% decrease in musculoskeletal pain threshold, and an increase in discomfort, after the third SWS deprivation night (Lentz *et al*. 1999). Older *et al*. (1998) also assessed the effects of SWS interruption on pain thresholds and fibromyalgia-like symptoms. Thirteen healthy volunteers were subjected to 3 consecutive nights of SWS interruption and six subjects not undergoing any sleep deprivation served as controls. No statistically significant differences in musculoskeletal pain thresholds as a function of condition (baseline, SWS interruption, recovery) were detected between or within groups. Morning average normalized dolorimetry scores were lower than evening scores in both groups during all three conditions.

It seems reasonably certain that these sleep manipulations produce disturbances of metabolism and alter some central nervous system functions. The relative importance of SWS and REM sleep in nociception may be demonstrated by observing pain thresholds following total and selective sleep deficiencies. Only a few studies however, have been reported, and controlled experiments with more accurate pain measurements are needed.

The aim of the present experiment was to compare the effects of total sleep deprivation, selective sleep interruption (REM and SWS) and sleep recovery on mechanical and thermal pain sensitivity in healthy adults.

MATERIALS AND METHODS

The studies described below were approved by the local Human Ethics Committee (CCPPRB d'Auvergne). Written informed consent was obtained from all subjects and all were provided with a standard honorarium for their participation.

Subjects

Nine healthy male volunteers between the ages of 26 and 43 years were studied. Average age was 31 years. Before entering the study, a medical history was taken and subjects underwent a medical examination. Volunteers with known psychiatric or medical disorders including chronic pain or repetitive acute pain disorders, documented/probable parasomnias, sleep apnea, other hypersomnias or insomnias, any medical condition requiring monitoring or medication, or a history of drug and alcohol abuse were excluded. All subjects had a Pittsburgh Sleep Quality Index and a body weight (Body Mass Index) in the normal range. They were required to maintain regular and adequate nocturnal sleep unless one week prior to the enrollment in the study.

They were instructed to refrain from taking any drugs or alcohol, to avoid drinking caffeinated beverages and to refrain from napping for one week prior to and during each experimental period.

Experimental design

Nine subjects underwent two sequences of testing with a counterbalancing order of SWS and REM sleep interruption. In this crossover study, repeated measures were performed in each sequence composed by 6 consecutive laboratory nights 'ABSTR'. These nights (N) comprised: N1 Adaptation (undisturbed sleep, electrodes in place but recording not performed); N2 Baseline (undisturbed sleep, polysomnography); N3 Total sleep deprivation (with two observers); N4 SWS or REM sleep interruption-1 (on-line polysomnography); N5 SWS or REM sleep interruption-2 (on-line polysomnography); N6 Recovery (undisturbed sleep, polysomnography). The two study periods were separated by at least 2 weeks, and scheduling constraints sometimes necessitated a longer between-period interval, in one case of 5 weeks. During each experiment, lights-off time was 23.00 h ($\pm$ 30 min) and lights-on time was 07.00 h ($\pm$ 30 min).

Following baseline polysomnography, each morning (between 08.30 h and 09.30 h) and afternoon (between 16.30 h and 17.30 h) dolorimetry, thermotest and vigilance tests were performed. All subjects were trained in all test measures prior to the start of experiment.

After Adaptation (N1), Baseline (N2) and Recovery Nights (N6), the subjects were absent from the laboratory between 10.00 h and 16.00 h. During this period they were instructed to refrain from taking any drugs or alcohol, and to avoid drinking caffeinated beverages. They were also told not to sleep outside the laboratory but otherwise to maintain their usual regimen of physical and mental activity.

Sleep stage interruption

Polysomnography

Standard polysomnographic recordings were carried out using an Embla Digital Polysomnograph with Somnologica software (Flaga hf., Reykjavik, Iceland), which consists of an integrated system of amplifiers and computerized data collection. Eight channels of electroencephalogram (EEG) (Fp1-A2, Fp2-A1, Fz-A1, Cz-A2, C3-A2, C4-A1, O1-A2, O2-A1), two channels of electrooculogram (EOG), one channel of submental electromyogram (EMG), and one channel of precordial electrocardiogram (ECG) were applied. Only during the first baseline night a thoracic belt, and a thermistor placed at the nose and mouth were used to screen for sleep disturbed breathing. The data were displayed on a color monitor at 30 s epoch lengths and monitored on-line by the same certified sleep specialist (SHO) throughout the experiment.

Sleep scoring and definition of parameters

Sleep was scored visually in 30 s epochs (recording speed: 10 mm s^{-1}) according to the Rechtschaffen and Kales criteria

(1968). SWS (stage 3 and 4) was identified as delta EEG waves with amplitudes ≥ 75 μV and frequencies of 0.5–2 Hz. Stage 3 sleep was defined as 20–50% delta waves in a 30 s epoch; stage 4 was defined as 51–100% delta waves in a 30 s epoch. Criterion for REM sleep was the simultaneous occurrence of rapid eye movements, low amplitude submental EMG, and low amplitude desynchronized EEG with an absence of both K-complexes and sleep spindles. Total sleep time was defined as time spent in sleep stages S1, S2, S3, S4, REM and movement time (MT). Sleep latency was calculated as the time from the lights-off until the sleep onset. The sleep onset was considered as the first 2 min of consecutive sleep epochs (any stage). REM sleep latency was defined as the time from sleep onset to the first REM period.

Total sleep deprivation

This procedure was used to maintain sufficient 'sleep pressure' during the selective sleep interruption period and to avoid the induction of prolonged waking episodes by the arousing stimuli. During the nocturnal period, two different observers (from 19.00 h to 02.00 h and from 02.00 h to 08.00 h) accompanied each subject to ensure that he stayed awake. Additionally, subjects were required to enter a keystroke on a computer every 10 min between 23.00 h and 08.00 h. If this failed to occur, an 80 dB alarm sounded. To ensure that the subject stayed awake during the following diurnal period (between 08.00 h and 23.00 h), he was accompanied at all times by medical staff. Except for the total sleep deprivation and recovery nights, all subjects were blinded to the type of selective sleep stage deprivation performed.

SWS interruption

During nights 4 and 5, subjects were aroused from SWS by an auditory stimulus (calling their name), or by physical stimulation (shaking) as required. In general, SWS was interrupted when roughly one-third of the viewing screen contained delta waves. SWS interruption was continued until at least 2 epochs of an earlier sleep stage (stage 1 or 2) were observed or until the subject awoke.

REM sleep interruption

During nights 4 and 5, subjects were awakened from REM sleep by an auditory stimulus (calling their name), or by physical stimulation (shaking) as required. In general, sleep was interrupted when roughly one-third of the viewing screen contained REM sleep.

Dolorimetry

Thermal pain

Thermal stimuli were delivered through a microprocessor-controlled thermode (Somedic Thermotest, Somedic AB, Hörby, Sweden) using a rectangular 2.5×5 cm contact thermode operating on a Peltier principle, which was applied to the thenar eminence. The cut-off limit for warm stimulation was 52°C. The heat pain tolerance threshold (HPTT) was determined using the method of limits. The temperature of the probe, starting from a baseline temperature of 30°C, was gradually increased (1.0°C sec^{-1} rate of change) until the subject signaled that the threshold had been reached by pressing a button (Hilz *et al*. 1995). This value was recorded and the stimulator returned to baseline. If cut-off limits were reached before the relevant threshold, the thermode automatically returned to baseline. The HPTT was calculated as the average of 5 determinations performed with intervals of 10–15 s between each stimulation.

Pressure pain

Pressure pain tolerance threshold (PPTT) was evaluated using an electronic pressure dolorimeter (Somedic AB). A 28 mm^2 circular probe was applied at a pressure of 1.1 N sec^{-1} with a cut-off limit of 1750 kPa. The subject indicated when the pain tolerance threshold was reached by pressing a button. This threshold was calculated as the average of four determinations performed on the 2nd phalanx (mid phalanx) of the 2nd, 3rd, 4th and 5th fingers of the non-dominant hand (Brenum *et al*. 1989).

The subjects were told to define the PPTT and the HPTT when they experienced 'the most intense pain sensation tolerable'.

Pain tests were carried out by an investigator (AA) blind to the type of sleep manipulation performed and each subject was blinded to his previous pain score.

Data presentation and statistical analysis

Results are presented as mean ± standard error of the mean (SEM). In order to improve discrimination between different sleep manipulations, values from morning and afternoon measurements were averaged to give a daily mean pain tolerance score. The mean score obtained at day 2 become the baseline score for each subject. Subsequent mean pain tolerance scores were divided by the baseline score to give a normalized score expressed as percentage variation.

In this crossover study the main hypothesis we tested was that there is no difference in mean pain scores by condition (baseline, total sleep deprivation, selective sleep interruption, recovery) according to the type of sleep manipulation. Paired parametric tests were used after checking that the data were normally distributed. Concerning sleep study data and pain tolerance, an analysis of variance (ANOVA) for repeated measurements was followed, when appropriate post hoc analysis was performed by Fisher's PLSD test. Relationships between sleep amounts (SWS, REM sleep) and normalized pain tolerance scores were analysed using a correlation test. Significance level for all tests was set up at $P < 0.05$.

RESULTS

In this two-way crossover study, at the beginning (N2 and D2) and at the end (N6 and D6) the interperiod comparisons of

sleep parameters and mechanical as well as thermal pain threshold values (Tables 1 and 2) were not statistically different ($P > 0.05$).

Concerning pain threshold values, no significant differences were found between the morning and the afternoon assessments.

Sleep data

The analysis of sleep in the SWS and REM sleep interruption periods included measurements of total sleep time, sleep latency, REM sleep latency, number of provoked arousals, and sleep stage amounts and percentages (Tables 3 and 4).

Table 1 Means of absolute baseline (am/pm) mechanical pain tolerance values (kPa)

Subject	*SWS interruption period Day2 Mean (± SEM)*	*REM sleep interruption period Day2 Mean (± SEM)*
1	925 (24)	827 (26)
2	500 (27)	817 (65)
3	1173 (57)	994 (65)
4	970 (97)	1124 (58)
5	1611 (179)	973 (27)
6	813 (12)	754 (21)
7	1169 (39)	1006 (2)
8	988 (39)	1370 (229)
9	799 (36)	743 (14)

Table 2 Means of absolute baseline (am/pm) thermal pain tolerance values (°C)

Subject	*SWS interruption period Day2 Mean (± SEM)*	*REM sleep interruption period Day2 Mean (± SEM)*
1	48.5 (0.05)	49.1 (0.1)
2	46.2 (0.2)	45.4 (0.8)
3	49.3 (0.1)	49.2 (0.1)
4	49.0 (0.3)	46.9 (0.7)
5	51.0 (0.2)	51.8 (0)
6	49.0 (0.6)	49.9 (0.4)
7	49.6 (0.01)	49.8 (0.6)
8	51.9 (0.01)	50.7 (0.1)
9	47.6 (05)	49.1 (1.1)

Relative to the baseline night (N2), SWS interruption had a number of consequences:

1 A pronounced decrease in the amount of stage 3 + 4 sleep during the interruption nights (N4, $P < 0.0001$; N5, $P < 0.0001$);

2 A significant increase in the amount of stage 3 + 4 sleep during the recovery night (N6, $P = 0.001$);

3 No significant modification in the amount of stage 1 + 2 sleep;

4 A significant decrease in the amount of stage REM sleep during interruption nights (N4, $P = 0.01$; N5, $P = 0.004$). On the recovery night (N6) the amount of REM sleep reached baseline levels.

Compared with the baseline night (N2) REM sleep interruption produced:

1 A dramatic decrease in REM sleep amount during interruption nights (N4, $P = 0.0001$; N5, $P = 0.0001$).

2 A strong rebound of REM sleep amount relative to the baseline level during the recovery night (N6, $P < 0.0001$).

3 A significant decrease in the amount of stage 1 + 2 sleep during interruption nights (N4, $P = 0.01$; N5, $P = 0.004$) but not during recovery night (N6).

4 A 'rebound' in the amount of stage 3 + 4 sleep, on the 'first recovery night' following the TSD (N4, $P = 0.009$). Other nights (N5, N6), the amount of stage 3 + 4 sleep is stabilized at baseline levels.

After the TSD, SWS interruption was more difficult than REM sleep interruption and required significantly more provoked arousals on the first and second interruption nights (N4, $P < 0.0001$; N5, $P < 0.0001$).

Dolorimetry

Mechanical pain (pressure pain) tolerance

Total sleep deprivation (Fig. 1). After pooling normalized pain scores prior to any selective sleep interruption (two comparable experimental conditions where nine subjects were assessed twice), normalized mechanical pain scores decreased significantly on TSD days, relative to baseline (D2 vs. D3, $P = 0.003$). However, when baseline and TSD days were compared separately in the SWS interruption and REM sleep

Table 3 Sleep EEG data for the slow wave sleep (SWS) interruption period

Sleep variable	*Night 2 Baseline Mean (± SEM)*	*Night 3 Total Sleep Deprivation*	*Night 4 SWS Interruption Mean (± SEM)*	*Night 5 SWS Interruption Mean (± SEM)*	*Night 6 Recovery Mean (± SEM)*
Total sleep time (min)	426.3 (11.7)	–	322.5* (12.8)	301.5* (14.0)	497.6* (15.9)
Sleep latency (min)	21.5 (6.6)	–	5.33* (1.3)	4.2* (1.4)	5.0* (1.3)
REM latency (min)	144.2 (29.7)	–	170.3 (30.0)	179.8 (24.8)	102.7 (16.1)
Number of provoked arousals	0.0 (0.0)	–	101* (7.8)	89.8* (8.2)	0.0 (0.0)
Movement Time (min)	2.1 (0.8)	–	0.2 (0.1)	0.6 (0.2)	4.2 (1.5)
Sleep Stage (1 + 2) (min)	212. 7 (15.1)	–	197.0 (14.6)	167.8 (17.8)	217.0 (20.7)
Sleep Stage (3 + 4) (min)	124.5 (6.8)	–	56.3* (4.4)	57.5* (9.1)	163.7* (10.6)
Sleep Stage REM (min)	86.9 (5.6)	–	68.8* (6.2)	75.5* (5.9)	112.5 (10.7)

* Values significantly different from those of the baseline night, $P < 0.05$.

Table 4 Sleep EEG data for the rapid eye movement (REM) sleep interruption period

Sleep variable	*Night 2 Baseline Mean (± SEM)*	*Night 3 Total Sleep Deprivation*	*Night 4 REM Interruption Mean (± SEM)*	*Night 5 REM Interruption Mean (± SEM)*	*Night 6 Recovery Mean (± SEM)*
Total sleep time (min)	440.0 (8.8)	–	368.5* (10.7)	310.5* (11.7)	482.1* (14.7)
Sleep latency (min)	11.5 (3.3)	–	2.8* (0.4)	5.0* (0.9)	7.8 (0.9)
REM latency (min)	109.6 (17.9)	–	110.1 (25.2)	74.9 (18.2)	70.1 (16.3)
Number of provoked arousals	0.0 (0.0)	–	13.8* (1.8)	17.3* (1.4)	0.0 (0.0)
Movement Time (min)	1.5 (0.6)	–	1.5 (0.6)	5.7 (4.9)	3.9 (1.0)
Sleep Stage (1 + 2) (min)	222.5 (10.7)	–	178.2* (13.9)	171.3* (6.3)	193.3 (14.8)
Sleep Stage (3 + 4) (min)	125.9 (10.8)	–	169.9* (12.7)	119.8 (9.8)	154.1 (11.5)
Sleep Stage, REM (min)	90.0 (3.1)	–	18.7* (3.6)	13.6* (2.1)	130.8* (9.1)

* Values significantly different from those of the baseline night, $P < 0.05$.

Table 5 The analgesic effects of level I (WHO) pain relief drugs relative to placebo in healthy volunteers

Drug	*Dose (oral)*	*Time of assessment after drug intake*	*Mean analgesic efficiency compared to placebo*	*Reference*
Aspirin	1500 mg	90 min	12% ≈	Forster *et al.* 1988
Acetaminophen	1000 mg	Mean of scores between 30 and 140 min	1.6%	Forster *et al.* 1992
Ibuprofen	800 mg	Mean of scores between 30 and 140 min	3.9%	Forster *et al.* 1992
	600 mg	Mean of scores between 90 and 240 min	12% ≈	Petersen *et al.* 1997
	600 mg	100 min (experiment on UVB-irradiated skin).	12% ≈	Bickel *et al.* 1998
Dipyrone	1000 mg	Mean of scores between 30 and 140 min	6.7%	Forster *et al.* 1992

Experimental pain was induced by pinching the interdigital webs. Scores approximated from histograms and curves (≈).

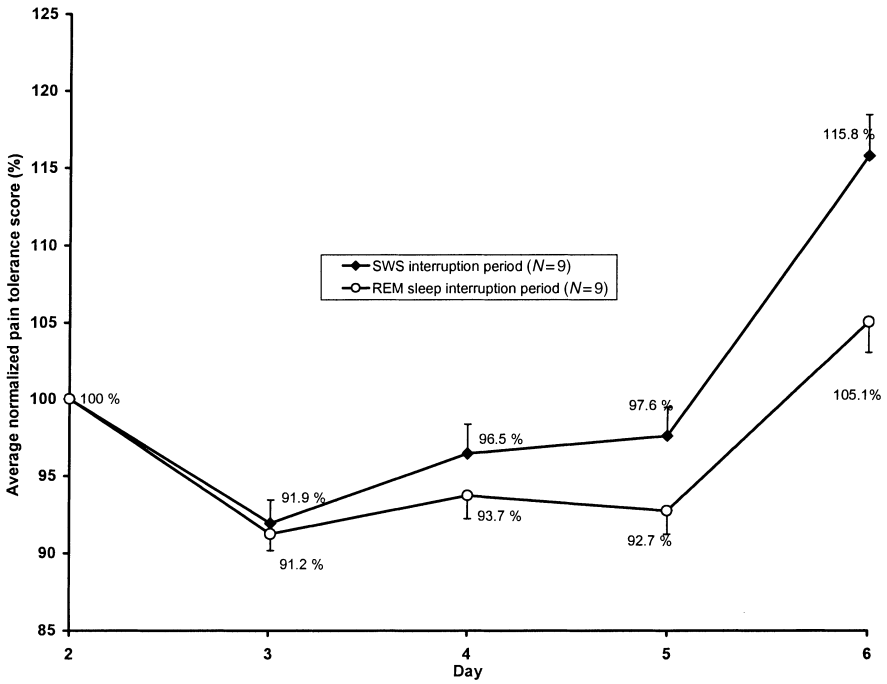

Figure 1. Average normalized mechanical pain tolerance score under conditions of slow wave sleep (SWS) and rapid eye movement (REM) sleep interruption. Pain tolerance was assessed at baseline day (D2), after total sleep deprivation (D3), selective sleep interruption (D4, D5) and sleep recovery (D6). All values are ratios in which the mean pain tolerance score at the indicated measurement is the numerator and the mean pain tolerance score at D2 (baseline) is the denominator. SWS recovery produced a significant enhancement of pain tolerance (D2 versus D6, $P = 0.04$). The differences between periods were not statistically significant.

interruption periods no significant change was observed because of the small number of subjects in each group ($n = 9$).

SWS interruption period (Fig. 1). Relative to baseline, SWS interruption did not significantly decrease normalized pain scores. However, on the recovery day, mechanical pain scores were significantly higher than on the baseline day (D2 vs. D6, $P = 0.04$). Relative to the TSD day, normalized pain scores were substantially increased on the recovery day (D3 vs. D6, $P = 0.003$). On the recovery day, pain scores were significantly higher than on the first and second SWS interruption days (D4 vs. D6, $P = 0.01$; D5 vs. D6, $P = 0.02$). This phenomenon could reflect a 'rebound' effect following SWS deprivation.

REM sleep interruption period (Fig. 1). Relative to baseline, normalized pain scores were not affected significantly on the REM sleep interruption and the recovery days. Relative to the TSD day, normalized mechanical pain scores were significantly higher only on the recovery day (D3 vs. D6, $P = 0.02$).

SWS vs. REM sleep interruption periods. Normalized pain thresholds on corresponding days (*D3*, *D4*, *D5*, *D6*) of the two sleep manipulation periods were not significantly different.

Thermal pain tolerance

Total sleep deprivation. After pooling normalized pain scores prior to any selective sleep interruption, thermal pain scores did not decrease on TSD days with respect to baseline.

SWS interruption period. Relative to baseline, normalized pain scores were not changed significantly on the SWS interruption and on the recovery days. Relative to the TSD day, normalized pain scores were not significantly different on the SWS interruption and on the recovery days.

REM sleep interruption period. Relative to baseline, normalized thermal pain scores were not affected significantly on the REM sleep interruption and on the recovery days. Relative to the TSD day, normalized thermal pain scores were unchanged on the interruption and on the recovery days.

SWS vs. REM sleep interruption periods. Normalized thermal pain thresholds on corresponding days of the two treatment periods were not significantly different.

Sleep amount and pain tolerance correlation

The increase in normalized mechanical pain tolerance scores was significantly correlated to the increase in SWS amount ($r = 0.53$; $P = 0.003$) (Fig. 2). The amount of REM sleep and normalized mechanical pain tolerance scores were not significantly correlated.

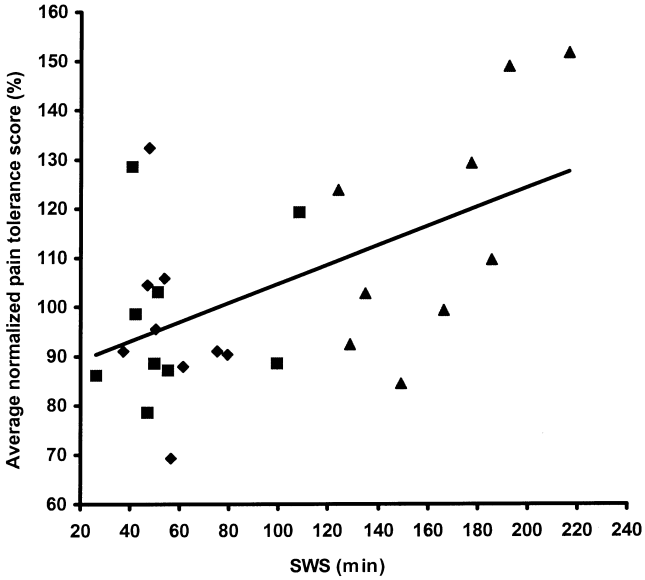

Figure 2. Correlation between slow wave sleep (SWS) amount and average normalized mechanical pain tolerance score after SWS interruption (■ D4, ◆ D5) and recovery (▲ D6) days. Sleep amount and pain were compared in healthy subjects ($n = 9$) by using a correlation test ($r = 0.53$; $P = 0.003$).

DISCUSSION

This paper describes a new experimental protocol, 'ABTSR' (Adaptation, Baseline sleep, Total sleep deprivation, two Selective sleep interruption nights, Recovery sleep), which we have developed to study the effects of sleep deprivation in healthy volunteers. The 40 h TSD induces a sleep pressure, partly filling the place of selectively interrupted sleep on two subsequent nights. The selectively interrupted sleep selectively rebounds on recovery night (Tables 3 and 4). The ABTSR produces significant neurophysiological contrasts between different experimental days. We have shown for the first time that sleep recovery with massive SWS rebound is associated with an increase in pain tolerance thresholds (Fig. 1).

Methods for sleep deprivation and pain assessment

The few studies concerning sleep manipulation and pain sensitivity in healthy subjects published previously have given conflicting results (Moldofsky *et al.* 1975; Older *et al.* 1998; Lentz *et al.* 1999). Indeed, the effects of SWS deprivation have not been compared to REM sleep deprivation or TSD in the same experiment. Inversely to our design 'ABTSR', the effects of recovery sleep have not been investigated (Lentz *et al.* 1999) or pain assessments during the day following a recovery sleep have been incomplete (Older *et al.* 1998). However, we can strongly argue that recovery sleep is a different state compared to baseline sleep. In particular, TSD and SWS interruption induce a decrease in sleep onset latency, an increase in SWS amount and delta power and an increase in total sleep time on the recovery night (Brunner *et al.* 1993; Dijk *et al.* 1993). REM sleep deficit gives rise to an immediate rebound when 'SWS pressure' is low as well as a decrease in REM sleep latency (Brunner *et al.* 1990; Endo *et al.* 1998).

Sleep parameters

The most potent physiological stimulus for REM sleep, and especially also for SWS, is previous sleep deprivation. A TSD

of 40 h induces a significant increase in SWS propensity on the subsequent night (N4) and a reduction in SWS latency. However during night 4, the propensity for REM sleep is less important.

During the SWS interruption nights, the mean SWS amount was 56 min, vs. 125 min at baseline (−55%). From prior investigations we have calculated SWS amounts of 62 min vs. 84 min (−26%) (Moldofsky and Scarisbrick 1976) and 24 min vs. 70 min (−66%) (Older *et al.* 1998). Therefore we have produced a SWS reduction, which is within the range of the two previous studies.

A reduction of total sleep time on nights 4 and 5 in both SWS and REM sleep interruption sequences was observed. This phenomenon may be related to two different conditions. Firstly, repetitive provoked arousals shortening the total sleep time. Secondly, homeostatic and chronobiological requirements in which the deprivation of a specific sleep stage is not replaced totally by other sleep stages (in spite of prolonged time in bed) to give the same total sleep time every night.

On REM sleep interruption nights our mean REM sleep amount is 16 min, vs. 90 min at baseline. A previous study (Moldofsky and Scarisbrick 1976) produced 28 min vs. 97 min. Our REM sleep interruption efficiency (−82%) was similar to that reported by others (−71%; Moldofsky and Scarisbrick 1976).

When TSD is followed by nights of SWS interruption, the onset of REM sleep is delayed and its amount is diminished (Table 3). REM sleep therefore seems to start after a 'sufficient' amount of SWS. This is in accordance with the homeostatic hypothesis, each bout of REM sleep is triggered by the occurrence of the bout of non-REM sleep that precedes it (Benington and Heller 1994). As the SWS pressure declines, the onset of REM sleep is shortened and its amount is increased (Table 4).

Dolorimetry

Thermal pain tolerance thresholds were not significantly disturbed by TSD or selective sleep stage interruption. Two factors could explain this lack of significant difference. Firstly, the fairly low capacity of thermal tests to discriminate small changes in pain threshold (Yarnitsky *et al.* 1996). Secondly the possible interference of skin temperature on thermal pain tolerance thresholds. We did not measure skin temperature in this study. However, no significant change in oral temperature was observed in 9 young adult male volunteers subjected to TSD for 40 h (Corsi-Cabrera *et al.* 1996).

Relative to baseline, all sleep restrictions (TSD, SWS, REM sleep) in this study tended to decrease mechanical pain tolerance thresholds. However we only observed a statistical significance for the TSD period when all results at the beginning of each period (D3) were pooled (Fig. 1). In healthy adults the 'hypersensitivity' to mechanical stimulation is greater after TSD (−8.1% to −8.8%) than after other selective sleep stage interruptions (SWS interruption D4 = −3.5%, D5 = −2.4%; REM sleep interruption D4 = −6.3%; D5 = −7.3%) (Fig. 1). In addition, it has been argued that SWS deprivation induces a fibromyalgia like syndrome at specific tender points (Moldofsky and Scarisbrick 1976; Lentz *et al.* 1999). Our results suggest that sleep deprivation, and particularly TSD, may cause nonspecific hyperalgesia to mechanical stimuli, which is not confined to specific tender points.

No significant difference in mechanical pain thresholds following the selective sleep manipulations can be found. However, this lack of difference could be the result of an insufficient statistical power due to the fairly low number of subjects unrolled in our study.

The present data show for the first time a rebound effect for mechanical pain tolerance after SWS recovery. Average normalized mechanical pain scores observed during the recovery day following SWS restitution are statistically higher than on all other experimental days. This antinociceptive effect against mechanical pain is 15.8% above the baseline score. SWS amount and mechanical pain tolerance are statistically correlated (Fig. 2). REM sleep restoration enables pain ratings to be increased slightly over baseline scores. However, after SWS rebound, the increase in mechanical pain score is significant. The magnitude of this phenomenon is larger than or equivalent to the changes in pain threshold resulting from the administration of level I (World Health Organisation) analgesic compounds. As a matter of fact, the increase of mechanical pain threshold following the administration of aspirin, acetaminophen, dipyrone or ibuprofen is approximately between 2 and 12% compared to placebo (Table 5) (Forster *et al.* 1988, Forster *et al.* 1992; Petersen *et al.* 1997).

We could speculate about the role of prostaglandin D_2, interleukine-1 beta and tumor necrosing factor, which on the one hand are influenced by sleep manipulations and on the other hand are known to interfere with pain modulation process. However the mechanism underlying the relationship between disturbed sleep and pain remains a mystery and merits further study.

CONCLUSION

This experimental study in healthy adult volunteers has demonstrated an hyperalgesic effect related to 40 h TSD and an analgesic effect related to SWS recovery. The analgesic effect of SWS recovery is apparently greater than the analgesia induced by level I (WHO) analgesic drugs in mechanical pain experiments in healthy volunteers.

After TSD, mechanical pain tolerance is lower than after selective sleep stage deprivation. Both SWS and REM sleep may produce an additional analgesic effect. However SWS seems to be implicated to a greater extent in pain mechanisms. After recovery nights from REM sleep and SWS, mechanical pain tolerance increases. Recovery from SWS produces a greater analgesic effect than that observed after recovery from REM sleep.

Determining the physiological basis of the pain ratings used in pharmacological studies of analgesic compounds as well as other sensory responses is a challenge for future research. For

example, it would be of interest to determine whether pharmacologically-induced changes in sleep architecture are correlated with responses to various nociceptive stimuli. The neurophysiological or other mechanisms that underline pain sensitivity relative to different states of vigilance must be established for the optimal prescribing of analgesic and hypnotic drugs.

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