Sleep Loss and REM Sleep Loss are Hyperalgesic

Timothy Roehrs, PhD; Maren Hyde, BS; Brandi Blaisdell, MS; Mark Greenwald, PhD; Thomas Roth, PhD

1Henry Ford Health System, Sleep Disorders and Research Center, Detroit, MI; 2Department of Psychiatry and Behavioral Neurosciences, School of Medicine, Wayne State University, Detroit, MI

INTRODUCTION

DISTURBED SLEEP IS A FREQUENT COMPLAINT OF PEOPLE EXPERIENCING ACUTE AND CHRONIC PAIN. OBJECTIVE ELECTROPHYSIOLOGIC STUDIES OF SLEEP in surgery patients with acute pain have documented reductions in sleep and rapid eye movement (REM) sleep time, frequent brief arousals, and also longer awakenings during 1 to 6 days of postsurgical recovery.1-7 Any number of confounding factors, including the sleep environment and the hormonal-biochemical response to the surgical insult, limit the ability to attribute the observed sleep disturbance to the pain in postsurgical recovery. Similarly, disturbed sleep has been reported in electrophysiologic studies of patients with various chronic pain disorders.8-12 Again, much of this literature is limited due to inadequate diagnostic rigor, including the comorbidity of depression and anxiety disorders, and of primary sleep disorders.

An important observation arising from these studies, even with their limitations, is the bidirectionality in the pain-sleep relation (i.e., pain disturbs sleep and disturbed or shortened sleep enhances pain). One approach to avoiding the various confounds inherent in clinical studies is assessing pain sensitivity in healthy, pain-free adults after sleep manipulations. An early total sleep deprivation study conducted by Nathaniel Kleitman and his students reported “cutaneous sensitivity to touch remained unchanged,” whereas “that to pain showed a progressive increase during the period of deprivation.”13 The pain-threshold reduction began to emerge after an initial 8 hours of sleep loss. While reported anecdotally in sleep-deprivation studies, over all these years, only a few studies have directly assessed pain during sleep deprivation. The few modern studies indicate that total sleep deprivation has a hyperalgesic effect.14 However, in clinical conditions with acute or chronic pain, sleep is never totally absent. Sleep time is merely reduced or its staging disrupted. Thus, we first tested the hypothesis that reduced sleep time would have a hyperalgesic effect. While there are no systematic studies of sleep-time reductions, as opposed to total deprivation, several studies have assessed the hyperalgesic effects of selective sleep-stage deprivation. Due to the description of the alpha-delta sleep anomaly (i.e., an admixture of electroencephalogram [EEG] alpha and delta frequencies) in fibromyalgia patients and patients with chronic pain, the sleep-stage deprivation studies have focused on slow-wave sleep. The results have been inconsistent, although they do suggest that when stage 3-4 sleep deprivation has hyperalgesic effects, it occurs with concomitant reductions of sleep time.15-17

We have therefore used a novel radiant heat stimulation methodology to assess pain sensitivity following modest sleep loss and sleep-stage specific loss of REM sleep. We chose to focus on REM sleep because of some intriguing conflicting information. On the one hand, opioid analgesics have been shown to suppress acetylcholine release and REM sleep when administered to brain...
regions that generate REM sleep in animals. On the other hand, acetylcholine is known to promote both analgesia and REM sleep. The central role of acetylcholine in the control of REM sleep is well established. As to its role in analgesia, animal studies have shown that cholinomimetics have an analgesic effect and clinical studies have shown that cholinergic agonists can be used for pain control. Several studies have now shown that REM sleep deprivation in rats produces a lowered response threshold to electrical or mechanical stimulation (i.e., hyperalgesia) that endures for at least 24 hours following the deprivation. Finally, a very recent human study reported an inverse relationship between the amount of REM sleep time and the pain response to a noxious stimulus in pain-free normal subjects. Thus, we tested the hypothesis that REM sleep deprivation would have a hyperalgesic effect.

The methodology we used to assess pain threshold measured finger withdrawal latency (seconds) to radiant thermal stimuli of 5 different intensities. Observation of differential withdrawal latency to the 5 stimulus intensities provides a means of assessing the internal validity of the pain-threshold measurements in a given protocol. In addition, this methodology has been used to demonstrate the dose-dependent analgesic effects of smoked marijuana, and we showed an analgesic effect of codeine in our preliminary studies.

**METHODS**

**Participants**

The participants were men and women between the ages of 18 and 35 years without psychiatric or medical disease, primary sleep disorders, current use of central nervous system-acting drugs, or a history of drug or alcohol abuse. All affirmed they were currently without psychiatric or medical disease, primary sleep disorders, current use of central nervous system-acting drugs, or a history of drug or alcohol abuse. All affirmed they were currently drug-free. All had sleep efficiencies of > 80% (total sleep time / time in bed) and an average sleep latency of > 8 minutes on the Multiple Sleep Latency Test (MSLT). The demographic characteristics of the participants in both the sleep loss and the REM sleep loss protocols are outlined in Table 1. Both protocols were approved by the Institutional Review Board, and all participants made an informed consent and were paid for their participation.

**Experimental Design**

**Sleep-Loss Protocol**

The sleep-loss protocol was conducted in a repeated-measures design with each participant undergoing 4 conditions of 2 days’ duration each. The conditions were: 8 hours TIB (11:00 PM to 7:00 AM), 2 hours TIB (5:00-7:00 AM), 9.5 hours TIB (11:00 PM to 8:30 AM) with REM interruption, and 9.5 hours TIB (11:00 PM to 8:30 AM) with a non-REM (NREM) yoked-control interruption. Presentation of the 8- and 2-hour TIB conditions was counterbalanced to occur before and after the REM- and NREM-interruption conditions. The REM condition had to precede the NREM condition, as the REM-condition results created each participant’s schedule for awakenings for the NREM condition. Thus, for example, condition order for participant 1 was 8 hours TIB, REM, NREM, and 2 hours TIB; for participant 2, it was 2 hours TIB, REM, NREM, and 8 hours TIB; and, for participant 3, it was 8 hours TIB, REM, NREM, 2 hours TIB, etc. Between each condition, 3 to 7 days of recovery were provided.

**Experimental Procedures**

**Sleep Recordings**

The standard methods for the electrophysiologic recording of sleep were used. The recordings obtained from each participant included standard central (C3-A2) and occipital (Oz-A2) EEGs, bilateral horizontal electrooculograms, submental electromyogram, and electrocardiogram recorded with a V5 lead. In addition, on the screening night, airflow was monitored with oral and nasal thermistors and leg movements with electrodes placed over the left tibialis muscles, and tabulated as to frequency of events.

**REM Sleep Loss and NREM Yoked Control**

The REM sleep-deprivation procedures of Nykamp et al were used. On the REM-deprivation nights, participants were awakened following the first 30-second epoch of unequivocal stage REM sleep, as reflected by reduced muscle tone, a low-voltage mixed-frequency EEG, and the first eye movement. They got out of bed and were kept awake for 15 minutes before being allowed to return to bed and to sleep. During the 15-minute awakening, participants completed a short reaction-time task. The epoch number of each awakening was recorded, and, on the NREM night, participants were awakened on the same epoch if they were in NREM sleep. If in REM sleep, the awakening was delayed until after the first 1 minute of NREM sleep. The TIB on REM and

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**Table 1—Demographic and Sleep Characteristics of Study Participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sleep Loss</td>
</tr>
<tr>
<td>Women/Men, No.</td>
<td>6 / 1</td>
</tr>
<tr>
<td>Age, y</td>
<td>25.9 ± 4.2</td>
</tr>
<tr>
<td>Screening sleep efficiency, %</td>
<td>82.0 ± 10.9</td>
</tr>
<tr>
<td>MSLT mean sleep latency, min</td>
<td>11.7 ± 4.9</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM unless otherwise indicated. REM refers to rapid eye movement; MSLT, Multiple Sleep Latency Test.
NREM nights was extended to 9.5 hours (11:00 PM-8:30 AM) as compensation for the loss in total sleep time due to the experimental awakenings. The sleep recordings were scored by an independent rater to verify the accuracy of REM and NREM awakenings. A 90% accuracy rate was required, and deviations invalidated the following day’s data. No sessions had to be redone. However, data from 1 participant were removed from analysis because the subject stayed awake throughout both REM-deprivation nights.

**Pain Threshold Assessments**

The participant was seated in a comfortable chair at a desk across from a research assistant who administered the pain-threshold testing. The test device, housed in a small metal box, was placed on the desk in front of the participant, and the control device operated by the research assistant was hidden from the participant’s view. The participant’s hand was placed on top of the metal box, and the pad of the index finger (fingerprint whorl) was centered over a 3-mm hole through which the heat source, a 100-watt projection bulb located at a fixed distance from the subject’s finger, radiated. A photocell detected the finger withdrawal from the heat source and stopped the timer. Radiant heat intensity was adjusted with a potentiometer on each trial, and 5 intensities (87.6°F-104.9°F) were presented in random order. Both fingers were tested, and the 2 withdrawal latencies were averaged to produce a stable estimate of responding to each of the 5 heat intensities. Throughout the procedure, finger temperature was monitored with a thermistor attached to the middle finger of 1 hand. Test trials were initiated only when finger temperature was between 88°F and 92°F. Fingers were heated or cooled as necessary to bring finger temperature to criteria. Participants were tested at 10:30 AM and 2:30 PM during the day following the nighttime sleep manipulation. The primary dependent measure for this test was mean finger-withdrawal latency (in seconds) for each of the 5 thermal intensities.

**Multiple Sleep Latency Test**

The MSLT was performed according to the standard protocol on the day following the 2 nocturnal recordings and was given at 2-hour intervals starting at least 1.5 hours after arising, typically at 10:00 AM, noon, 2:00 PM, and 4:00 PM. For each latency test, participants lay down in a bed in quiet and dark rooms with the instruction to try to go to sleep. They remained in bed for 20 minutes after 3 consecutive epochs of stage 1 sleep or an epoch of another sleep stage or after 20 minutes of continuous wake had occurred. Sleep latency was scored as the time, in minutes, to the first epoch of sleep, and the mean latency of the 4 tests was the primary dependent measure.

**Data Analyses**

The primary dependent measure was mean finger-withdrawal latency in seconds. These data were analyzed with general linear model analyses for repeated measures factors (SYSTAT, Software Inc, Richmond, CA) using Greenhouse-Geisser corrected degrees of freedom. In the first set of analyses, 2 factors were assessed, time of test (AM-PM) and stimulus intensity (low–high temperatures). These analyses were conducted on the 8-hour TIB finger withdrawal latency data to test for stimulus intensity and time-of-day effects. We hypothesized that latencies would be shortened as a function of increasing stimulus intensity and that afternoon test latencies would be shorter than morning latencies. In subsequent analyses, mean finger withdrawal latency averaged over the intensities was the variable analyzed, and 1-factor analyses were conducted with the factor being sleep condition (3 conditions in the sleep-loss protocol and 4 conditions in the REM-loss protocol). Significant main effects of condition were followed by posthoc comparisons. In the sleep-loss protocol, the 8-, 4-, and 0-hour conditions were compared, and we hypothesized that the 0-hour TIB latencies would be shorter than the 8-hour TIB latencies and that the 4-hour TIB latencies would be intermediate. In the REM sleep loss protocol, the 8-h TIB, 2-h TIB, REM, and NREM yoked conditions were compared. We hypothesized that the 2-hour TIB latencies would be shorter that the 8-hour TIB latencies and that the REM latencies would be shorter than the 8-hour TIB and NREM latencies. Observation of shorter latencies in the REM versus NREM condition comparison was critical to our hypothesis that REM sleep loss per se is hyperalgesic.

**RESULTS**

We first assessed the internal validity of our pain-threshold assessment in these protocols by comparing finger-withdrawal latency (seconds) to the 5 different stimulus intensities on tests conducted at 10:30 AM and 2:30 PM after 8 hours of TIB the previous night (see Figure 1). Finger-withdrawal latency was significantly shortened as stimulus intensity increased ($F_{4,24} = 17.3, p < .001$). We also found significant time-of-test differences, with the 2:30 PM finger-withdrawal latencies being shorter than those of the 10:30 AM testing ($F_{1,5} = 12.5, p < .01$) and an interaction of intensity by time of test ($F_{4,24} = 3.59, p < .05$). Therefore, we focused subsequent assessments of the effect of sleep manipulations on the 10:30 AM pain-threshold testing.

We then compared finger-withdrawal latency on the morning after 8 hours of TIB to that of 4 hours and 0 hours of TIB (see Figure 2). Reduced TIB produced a significant reduction in finger-
The amount of time spent in REM sleep was reduced by approximately 60% relative to that of the 8-hour TIB condition (18.4%) (F[2,12] =9.9, p < .005). On posthoc tests, the 4-h TIB condition differed from the 8-h TIB condition (p < .05), and the 0-h TIB condition differed from the 4-h and 8-h TIB condition (p < .05).

Finger withdrawal latency (F[3,12] =11.33, p < .005). A significant reduction of finger-withdrawal latency as a function of increasing stimulus intensity (F[3,12] =25.4, p < .001) and a significant TIB by intensity interaction (F[3,12] =3.39, p<.04) were also found. The lowest intensities were less sensitive to the TIB reduction, and, therefore, we assessed the effect of the TIB reduction on the highest stimulus intensities. The mean finger-withdrawal latency to the 3 highest intensities was reduced as a function of condition (F[2,10] =9.9, p < .001) and was shorter after the 4 hours of TIB than the 8 hours of TIB (p < .05). The total sleep deprivation (0 hours TIB) further reduced finger-withdrawal latency relative to that of the 4 hours of TIB (p < .05) on posthoc tests.

In the 4 hours of TIB scheduled from 3:00 AM to 7:00 AM, the amount of time spent in REM sleep was reduced by approximately 60% relative to that of the 8 hours of TIB (35.9 vs 87.2 minutes). We therefore compared finger-withdrawal latency after REM sleep deprivation relative to a yoked control condition during which sleep was interrupted from NREM sleep in the same pattern and frequency as the REM-deprivation night. We included the 8-hour and 2-hour TIB conditions as controls. Total sleep time for the REM deprivation (5.3 hours) and the NREM yoked-control (5.2 hours) nights did not differ, but they both differed significantly from the total sleep time of the 8 hours of TIB (6.7 hours) (F[2,10] =16.9, p < .001). The percentage of REM sleep on the REM-deprivation night (3.68%) was significantly reduced relative to that of the NREM night (14.33%), and both differed significantly from the 8-hour TIB condition (18.4%) (F[2,10] =36.1, p < .001). The same result was found for minutes of REM sleep, and a small elevation of NREM stage 1 sleep was seen in the REM and NREM sleep-interruption conditions. (See Table 2 for all the sleep-stage data.)

In the REM sleep loss protocol, as we found in the sleep-loss protocol, reduced TIB was hyperalgesic (main effect of condition: F[3,12] =10.7, p < .001). Mean finger-withdrawal latency for the 3 highest intensities was significantly reduced after 2 hours of TIB relative to 8 hours of TIB (p < .02). We further found that REM sleep loss is hyperalgesic. Finger-withdrawal latency after the REM-deprivation night was significantly shorter relative to that of the NREM yoked (p < .05) and 8-hour TIB (p < .02) control nights and did not differ from that of the 2-hour TIB night (see Figure 3). We conducted the same sleep manipulations for a second night and continued to observe significantly reduced finger-withdrawal latency in the REM deprivation, NREM yoked, and 2-hour TIB conditions relative to that of the 8-hour TIB condition.

### Table 2—Sleep Stages for Each Experimental Condition

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sleep time, min</th>
<th>Sleep stage, %</th>
<th>REM sleep deprivation</th>
<th>NREM sleep yoked</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>7.0 ± 1.4</td>
<td>11.9 ± 1.9</td>
<td>12.8 ± 2.6</td>
<td>5.4 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>56.7 ± 1.9</td>
<td>64.4 ± 2.8</td>
<td>53.1 ± 3.1</td>
<td>37.7 ± 4.3</td>
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</tr>
<tr>
<td>3-4</td>
<td>15.6 ± 3.0</td>
<td>20.0 ± 2.8</td>
<td>19.8 ± 5.1</td>
<td>34.8 ± 4.3</td>
<td></td>
</tr>
<tr>
<td>REM</td>
<td>18.4 ± 1.6</td>
<td>3.7 ± 1.6</td>
<td>14.3 ± 3.6</td>
<td>22.1 ± 4.1</td>
<td></td>
</tr>
<tr>
<td>Stage REM, min</td>
<td>88.3 ± 9.3</td>
<td>12.2 ± 3.5</td>
<td>49.0 ± 13.3**</td>
<td>24.0 ± 4.7</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM unless otherwise indicated. REM refers to rapid eye movement; *p < .05
**p < .01 vs 8-h time-in-bed condition
***p <.05 vs non-rapid eye movement sleep in posthoc comparisons
aMain effect of condition F[2,10] =16.9, p < .001; *Main effect of condition F[2,10] =8.8, p < .01; *Main effect of condition F[2,10] =36.1, p < .001; **Main effect of condition F[2,10] =43.4, p < .001 on generalized linear model 1-factor analyses for repeated measures.

Figure 2—Mean finger-withdrawal latency (mean of 3 highest intensities) as a function of 8, 4, and 0 hours of time in bed (TIB) on the 10:30 AM test. A generalized linear model 1-factor analysis for repeated measures yielded main effects of condition (F[3,12] =9.9, p < .01). On posthoc tests, the 4-h TIB condition differed from the 8-h TIB condition (p < .05), and the 0-h TIB condition differed from the 4-h and 8-h TIB condition (p < .05).

Figure 3—Mean finger-withdrawal latency (mean of 3 highest intensities) as a function of 8 and 2 hours of time in bed (TIB) and rapid eye movement (REM) deprivation and yoked non-REM (NREM) awaking conditions on the 10:30 AM test. (Cdn refers to sleep conditions) A generalized linear model 1-factor analysis for repeated measures yielded main effects of condition (F[3,12] =10.7, p < .001). On posthoc tests, the REM-deprivation condition differed from the NREM yoked-control condition (ctl) (p < .05) and the 8-h TIB condition (p < .02) and was similar to the 2-h TIB condition, which differed from the 8-h TIB and NREM conditions (p < .02).
DISCUSSION

These are the first human data to show that modest sleep-time reductions, as opposed to total sleep deprivation, and specific REM sleep deprivation have a hyperalgesic effect. While sleep time was reduced in the REM-deprivation condition relative to the 8-hour control condition, it was similarly reduced in the NREM yoked-control condition. Our REM-deprivation procedure was successful, as REM time was reduced to about 12 minutes for the night, which differed from the amount of REM time in the NREM yoked control. Finger-withdrawal latency was shortened in the REM-deprivation condition relative to the NREM yoked control and shortened to the level found in the 2-hour TIB condition. In the NREM yoked-control condition, sleep time was shortened by 90 minutes and REM time by 40 minutes, compared with the 8-hour TIB control condition. This modest night 1 sleep time and REM-time reduction was not sufficient to alter the pain threshold the following morning relative to the 8-hour TIB control.

These study results further indicate that the sleep-loss effects accumulate over nights and the accumulated sleep loss is associated with hyperalgesia. After the 2 nights of sleep interruption, the REM versus NREM differential hyperalgesia was lost. This suggests that the loss of approximately 40 minutes of REM and 90 minutes of sleep on each of the 2 nights in the NREM yoked-control condition accumulated to reduce NREM finger-withdrawal latency to the level for that of the 2-hour TIB and REM conditions. In contrast, no significant accumulation from night 1 to 2 in next-day hyperalgesic effects for the 2-hour TIB condition was observed. This suggests either that an adaptation to this more extreme sleep loss occurs or that our pain assessment was insensitive to the accumulated sleep loss. That is, there may be a baseeffect to our pain assessment. Thus, while accumulation of these sleep-loss effects did occur, it was limited in this study.

Several limitations of the present results need to be discussed. The sleep loss and specific REM sleep loss effects may be unique to the class of nociceptors being stimulated in this study, the thermal receptors. Mechanical and polymodal nociceptors are also present in skin and deep tissues, and, furthermore, among the thermal receptors, there are receptors specific for heat and cold. Secondly, the heightened sensitivity observed in this study may not be specific to pain. Other somatosenses such as touch or pressure were not assessed in this study. It also must be emphasized that the effects observed in the present study are acute effects, and how these effects change over time needs further study. Finally, it should be noted that the REM-specific hyperalgesia was lost during the second day of assessment.

The neurobiology and mechanisms underlying REM deprivation associated hyperalgesia are not clear, but very complex. Several lines of evidence, each quite incomplete, reflect this complexity. We indicated that there is evidence that the cholinergic system is involved in both REM sleep and analgesia. REM sleep deprivation in rats decreases cholinergic activity, which may then in turn reduce cholinergic analgesic function. Also, REM sleep deprivation depletes extracellular brainstem levels of serotonin and its metabolite (5-HIAA). Descending brainstem modulation of nociception has received much research attention, and some data implicated serotoninergic cells in brainstem inhibition of nociception. Sleep deprivation and specific REM sleep deprivation have also been shown to enhance whole-brain excitatory amino-acid concentrations, including glutamate, which may, through the descending pain-control pathway, facilitate nociceptive transmission. Finally, REM sleep deprivation may impact the endogenous opioid system. Total sleep deprivation has been shown to reduce mu and delta opioid binding in the rat limbic system.

The REM deprivation associated hyperalgesia shown in this study has potential clinical significance. In the studies of the sleep of postoperative patients, one of the consistently reported findings has been an absence of REM sleep for 1 to 2 nights after surgery. As mentioned, the cause for the REM deprivation is difficult to determine in these clinical studies. One important factor is administration of opiate medications, which are REM-suppressing drugs. Early animal studies have shown REM sleep suppression with morphine and methadone. The majority of human data have been collected in abstinent opiate addicts, and they show dose-dependent decreases in REM sleep with morphine. In addition, a recent study in healthy, nonaddict, pain-free adults showed that a low clinical dose of morphine decreased REM sleep to 15%, compared with 20% on placebo. Whether this level of REM sleep loss, a 30% reduction in minutes of REM, is sufficient to produce hyperalgesia the following day is not clear. But the point is that various clinical conditions and pharmacologic treatments that reduce REM sleep time may produce hyperalgesia. Further research will be required to address these potential clinical implications.

How the acute REM deprivation and hyperalgesia effects observed in this study change over time is unclear, as well as how these data relate to chronic pain conditions. One class of REM-suppressing agents, the antidepressants, is administered effectively as treatment for various chronic pain conditions. That is, in chronic pain conditions, REM suppression apparently is not hyperalgesic but, rather, is associated with therapeutic effects. Several points need to be emphasized in discussing this conflict. First, antidepressants differ from opioids in their REM-suppressing characteristics. Tolerance develops rapidly to opioid suppression of REM, while antidepressant-associated REM suppression does not show tolerance. Further, the degree of REM suppression with opioids is generally not as great as that for antidepressants. Second, in chronic pain, the clinical characteristics and underlying pathophysiology are likely quite different from those of acute pain experienced by an otherwise healthy normal. Such a difference is reflected in a recent study from this laboratory, in which the recovery response to a 4-hour sleep restriction was compared among patients with fibromyalgia, rheumatoid arthritis, and age-matched controls. The patients with fibromyalgia, compared with the patients with rheumatoid arthritis and controls, showed a REM rebound on the recovery night. That is, the 4 hours of sleep restriction uncovered an underlying REM pressure in the patients with fibromyalgia that was not present in the patients with rheumatoid arthritis and healthy controls.

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