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7

Effects of Impaired Sleep Quality and Sleep Deprivation on Diurnal Pain Perception

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An important percentage of patients with chronic pain report poor sleep (Morin et al. 1998; Lavigne et al. 2005; Ohayon 2005). Furthermore, patients suffering from postoperative acute pain undergo profound changes in sleep time and sleep architecture (Onen et al. 2005; Roehrs and Roth 2005). The intuitive perspective is that pain produces an increase in arousal, which prevents the initiation or continuation of sleep during the night and leads to sleepiness and napping during the day (Smith and Haythornthwaite 2004). However, this perspective is too simplistic to determine the direction of the interaction between pain and sleep disturbance. The modulation of pain and the regulation of sleep-wake cycles may share common neurobiological systems, in particular central serotoninergic neurotransmission (Foo and Mason 2003). Consequently, it is conceivable that pain and disturbed sleep might be secondary phenomena due to a common neurobiological dysfunction.

The current perspective is that poor sleep can interfere with pain processing. For example, a longitudinal study in fibromyalgia patients reported that the pain intensity of the previous day influences the quality of sleep of the following night, which in turn determines the intensity of pain the next day (Affleck et al. 1996). Such a relationship has been described as circular (Lavigne et al. 2005). The influence of the quality of the previous night's sleep on pain during the day is supported by recent studies by Raymond et al. (2001, 2004), who investigated acute pain in patients with burn injuries. The subjective quality of the previous night's sleep was a significant predictor of pain intensity the next day. In contrast, the pain intensity of the previous day did not reliably predict the sleep quality of the following night.

This chapter focuses on the effects of sleep quality, and especially of sleep deprivation (restriction of total sleep time or of a given sleep stage), on experimental pain in both healthy individuals and pain patients. Experimental pain studies, in contrast to clinical studies in patients with painful conditions, allow for better control of the influences on the pain system of loss of sleep time and perturbation of sleep architecture. Experimental pain allows the use of standard noxious stimuli at a standard magnitude and duration. Such stimuli may be chemically, thermally, or electrically induced, as described by Bentley in this volume. It is important to emphasize that the deterioration of sleep quality is frequently associated with a longer delay in sleep onset, more frequent awakenings, and difficulties in maintaining the continuity of sleep. These variables all result in a loss of sleep time, subjective reports of poorer sleep quality, and lower sleep efficiency (time asleep divided by time in bed). Therefore, understanding the effects of sleep deprivation on pain perception is crucial to understanding the relationship between sleep quality and pain (for reviews see Kundermann et al. 2004a; Lautenbacher et al. 2006).

EFFECTS OF SLEEP QUALITY ON PAIN PERCEPTION

The quality of sleep can be assessed by objective measures (polysomnography or actigraphy) and by subjective parameters (self-report questionnaires), which do not always match or correlate perfectly (Onen et al. 2005). More information on such methods is found in the chapters by Smith and Buenaver and by Lavigne et al. in this volume.

OBJECTIVE SLEEP QUALITY

Interest in using objective parameters to assess sleep quality in pain research arose from the assumption of a pathogenic role of disturbed sleep in fibromyalgia in relation to reports of muscular pain. A pioneering study by Moldofsky et al. (1975) investigated the cause of poor sleep, both in experimental subjects and in fibromyalgia patients. Moldofsky's group observed an increased ratio of alpha electroencephalographic (EEG) waves during non-rapid eye movement (non-REM) sleep in fibromyalgia patients. They assumed that this "alpha-delta sleep" was a sign of an increased arousal pressure during slow-wave sleep (SWS, which is the deep sleep that dominates sleep stages 3 and 4,) and of interference with the restorative function of non-REM sleep.

Subsequent polysomnographic studies, in which the nocturnal sleep of healthy subjects was assessed for comparison, failed to confirm the specificity of alpha-delta sleep to fibromyalgia. Horne and Shackell (1991) found no significant difference in the ratio of EEG alpha activity in non-REM sleep between

fibromyalgia patients and healthy control subjects. Furthermore, an increased ratio of alpha waves during non-REM sleep was observed in patients with other chronic pain conditions, such as rheumatoid arthritis (Drewes et al. 1998), and in patients diagnosed with primary insomnia (Schneider et al. 2001). Most of the data accumulated in recent years suggests that this sleeping pattern is not specific to fibromyalgia and that it does not necessarily lead to pain (Mahowald and Mahowald 2000).

Another feature of poor non-REM sleep in fibromyalgia patients has recently gained interest in relation to pain perception. Landis et al. (2004) observed a reduced incidence and frequency of sleep spindles during stage 2 of non-REM sleep in women with fibromyalgia. These two parameters not only differentiated patients from pain-free women who served as a control group but also demonstrated substantial correlations with pressure pain thresholds in these two groups (even after statistical control for depression and age). The authors concluded that the deficits in spindle generation suggest an impairment of thalamocortical sensory gating, which in turn compromises sleep integrity in fibromyalgia patients. An increase in spindle incidence in the sleep of fibromyalgia patients suggest that sleep-promoting influences are activated to "fight" against arousal pressure (see Parrino et al., this volume).

Whereas the authors of the studies described above focused on the relationship of non-REM sleep features with pain perception, Smith et al. (2005) investigated the association of REM characteristics (latency and duration) with pain perception in pain-free women (see also Smith and Buenaver, this volume). Interestingly, measures of heat pain threshold appeared to be unrelated to the REM features, whereas indicators of temporal pain summation elicited by suprathreshold repetitive heat stimulation, which are experimental markers of the escalating pain processes in chronic pain (Staud et al. 2001), were significantly related to the percentage of REM sleep (positive correlation) and REM latency (negative correlation). Accordingly, conditions with an unbalanced preponderance of REM sleep are probably associated with pain-augmenting central nervous system factors such as increased temporal summation.

SUBJECTIVE ASSESSMENT OF SLEEP QUALITY

Only a few studies have used subjective measures to examine the influence of sleep quality on pain perception. In a population-based study with a large sample (n = 425), Chiu et al. (2005) observed a strong negative relationship between subjective sleep quality as rated on the "Sleep Problem Scale" and pressure pain threshold. Correspondingly, Argargun et al. (1999) found that the subjective quality of sleep, as assessed by the Pittsburgh Sleep Quality Index, was inversely related to pressure pain sensitivity in fibromyalgia patients. Both

findings suggest that poor sleep quality may be associated with hyperalgesic changes.

The conclusions of most of the studies reported above are based on correlation analysis. They do suggest that subjective and objective changes in sleep quality are apt to alter pain perception. However, due to the diversity of potential qualitative alterations of sleep and the lack of systematic investigations of their effects on pain perception, it is not clear whether changes in pain perception depend on changes in sleep architecture, a complete interruption of sleep, or a deprivation of certain sleep stages. In the next section we will review the experimental data on the effects of sleep deprivation on pain perception.

EXPERIMENTAL ANALYSIS OF THE EFFECT OF SLEEP DEPRIVATION ON PAIN PERCEPTION

HUMAN DATA

As mentioned above, the pioneering study in this field was conducted by Moldofsky et al. (1975). These authors proposed that the interruption of non-REM sleep causes a myalgia similar to the pain experienced by patients with fibromyalgia. Sleep deprivation was restricted to a selective non-REM sleep stage—stage 4—for three consecutive nights. Interestingly, both pressure pain sensitivity and the frequency of occurrence of musculoskeletal pain increased following stage 4 sleep deprivation. The study sample consisted of six healthy men, and the fact that no control group was used casts some doubt on the study's validity. Thus, it remains possible that the observed changes might be due to unfamiliar sleeping conditions in a laboratory or to the potential effects of any kind of sleep disruption on the next morning's mood or fatigue state. Both factors may have influenced reports of pain perception. Because this study did not compare the role of stage 4 sleep deprivation against deprivation of any other sleep stage, Moldofsky and Scarisbrick (1976) enrolled seven healthy individuals in a study that tested selective deprivation of REM sleep. Interestingly, the authors found that REM sleep deprivation did not lower pressure pain thresholds or modify reports of muscular pain.

A series of studies conducted 20 years later challenged these original findings. In contrast to Moldofsky's methods, Drewes et al. (1997) analyzed the effects of total sleep deprivation on pain detection (for pressure and heat pain) and tolerance thresholds (for pressure) in 10 healthy individuals. Again, due to the absence of a control condition, the data must be interpreted with caution. No changes in pain detection or tolerance thresholds were observed using repeated measurements at intervals of 2 hours (starting at 11 p.m. and ending at 7 a.m.),

with an additional assessment the next day (at 11 p.m.). Accordingly, the finding of generalized hyperalgesia following selective deprivation of stage 4 sleep was seemingly not replicated in this uncontrolled study.

The first study, to our knowledge, that used a control condition was that of Older and colleagues (1998). These authors compared the effect of three nights of sleep under noise-induced disruption of SWS in 13 healthy subjects to the effect of three normal nights of sleep (with no disruption) in 6 matched subjects. Previous observations that fibromyalgia patients tend to have low levels of insulin-like growth factor (Bennett et al. 1997) prompted Older et al. to assess the potential role of this hormone as a mediating factor for sleep and pain. Whereas pressure pain thresholds and serum levels of insulin-like growth factor did not change, various somatic complaints, including pain assessed on visual analogue scales, increased after the third night of SWS deprivation. Although this study did not support generalized hyperalgesia in relation to sleep deprivation, an heightened likelihood of the occurrence of pain appeared to result from prolonged periods of disrupted sleep, and this finding is supported by the studies described in the following sections.

Lentz and colleagues (1999) also investigated the effects of SWS disruption over three nights in 12 healthy middle-aged women. Although the study did not include a control group, pain was assessed more comprehensively than in earlier reports. Pain threshold was estimated at the tender points designated for the clinical diagnosis of fibromyalgia. Interestingly, pressure pain thresholds decreased after two and three nights of SWS disruption. The same response also occurred at the non-tender "control" points after the third night. At this time, muscle complaints also became more frequent. Interestingly, the flare response assessed by means of the cotton swab test gained strength during the course of SWS disruption, suggesting an activation of mechanisms involved in neurogenic inflammation and hyperalgesia with more widespread distribution of pain.

The studies reported so far were conducted in normal and healthy subjects and were designed to examine the relationship between sleep deprivation or disruption and the incidence of fibromyalgia-like tenderness and pain, which represent anatomically generalized changes in pain sensitivity. Another study design was used to test changes in regional pain perception in relation to sleep deprivation (Arima et al. 2001). This study, conducted in 10 healthy men, tested pain in the face and temporomandibular area by measuring pressure pain threshold above the temporomandibular joint, by testing occlusal force, by using electromyography of the masseter muscle, and by taking visual analogue scale ratings of pain and other somatic complaints. The study did not reveal any difference in pain variables following disruption of sleep stages 3 and 4 by noise emitted by an EEG-controlled system. The meaning of these findings is not definite because no substantial reduction of SWS could be achieved in the

second and third nights of sleep deprivation, and in the first night no compensatory increase in non-REM sleep stages 1 and 2 occurred.

One of the most remarkable studies in the field of sleep deprivation on pain perception compared the effect of total sleep deprivation to selective deprivation of SWS or REM sleep in healthy subjects (Onen et al. 2001a). The authors used a cross-over design, in which nine healthy men spent six consecutive nights in the sleep laboratory—the first to allow adaption to the sleep laboratory, and the second to serve as a baseline night without sleep interruption. A third night of total sleep deprivation was followed by two consecutive nights of either SWS deprivation or REM sleep interruption. The study ended with a recovery night in both cases. Pressure and heat pain tolerance thresholds were assessed in the evening and in the morning. Total sleep deprivation significantly decreased pressure pain tolerance thresholds (compared to baseline) but had no effect on heat pain tolerance. Both REM and slow-wave sleep interruption tended to decrease, in a nonsignificant fashion, pressure pain tolerance thresholds. A novel finding also emerged from the very strong study design, in that a rebound effect was found after the recovery sleep night following SWS deprivation only; a significant increase in pressure pain tolerance thresholds was observed. No such effect was noted for the REM deprivation arm of the study. In other words, a larger portion of compensatory SWS (sleep stages 3 and 4) during the recovery night paralleled the increase in pressure pain tolerance thresholds. Later in this chapter, we will propose a model to tentatively explain why only mechanical pain was altered and not thermal pain threshold.

In our own laboratory, we investigated the effects of two nights of total sleep deprivation (separated by two nights of undisturbed sleep) in comparison to two nights of undisrupted sleep (Kundermann et al. 2004b). Twenty healthy subjects were assigned either to the sleep deprivation or to the undisrupted nocturnal sleep arm of the study. Heat pain thresholds decreased significantly after sleep deprivation, with a rebound back to baseline after the recovery nights. Findings were similar for cold pain thresholds, although this method of pain induction tended to produce less reliable and statistically nonsignificant results. The pain specificity of our results was established by assessing thermal sensitivity to nonpainful stimuli (warmth and cold thresholds), which showed no changes after sleep deprivation.

Finally, a recent observation merits attention. Roehrs et al. (2006) reported that total (8-hour) or partial (4-hour) sleep deprivation reduced finger-withdrawal latency after heat radiation, which does not compare well with other experimental pain parameters. The study was conducted in seven healthy individuals. The investigators also observed that REM sleep deprivation induced hyperalgesic changes. This finding is opposite to that of Moldofsky and Scarisbrick (1976). It is important to note that the REM sleep deprivation

procedure reduced not only REM sleep duration but also total sleep time. The hypothesized hyperalgesic effect occurred the next morning and was greater than after a non-REM control condition. However, this differential effect could not be replicated after a second night of deprivation.

Only a few human studies are available on the effects of sleep deprivation on pain perception, and some of their findings are inconsistent. Nevertheless, they tend to show that total sleep deprivation may produce hyperalgesic changes in healthy subjects. The selective disruption of SWS has shown this effect more consistently, while results on the effects of selective REM sleep deprivation remain unclear. The findings of Onen et al. (2001a) further suggest that while deprivation of either SWS or REM sleep can make individuals more sensitive to noxious stimuli, a rebound analgesic effect is found only on recovery from SWS deprivation.

The studies described above must be interpreted with caution because the hyperalgesic action of sleep deprivation was observed in relatively small samples. When we replicated the methods of Onen et al. (2001a) in our laboratory in a larger sample, we found that experimental heat pain stimulation yielded similar hyperalgesic effects following total sleep deprivation (Kundermann et al. 2004b). This finding suggests that the effect of sleep deprivation on pain perception is greater when tested by experimental use of pressure pain than by use of heat pain and that experiments using heat pain tests will require more subjects to reach statistical power. Another explanation may be the possibility that pressure pain stimulation targets nociceptors in both superficial and deep tissues, whereas heat pain stimulation targets primarily nociceptors in superficial tissue. Accordingly, pressure pain stimulation appears to reflect muscle and cutaneous nociceptive processes, whereas heat pain stimulation allows only for the assessment of cutaneous nociceptive processes (Graven-Nielsen and Mense 2001). The processing of muscle pain is likely to be influenced to a much stronger degree than cutaneous nociceptive processing by the descending pain inhibitory control system (Mense 2000). It is possible that SWS disruption affects the descending pain inhibitory control system and thereby preferentially affects pressure pain sensitivity. Such an effect may be more generalized, or systemic, rather than regional. The findings of Lentz et al. (1999) and Onen et al. (2001a) support the concept of a generalized/widespread pain mechanism or a systemic change in pain sensitivity because the results were similar when they tested pain threshold at multiple sites.

Individual factors, such as the age, gender, and subclinical pathophysiology of study subjects, that have not been controlled sufficiently might interact with the effects of sleep deprivation on pain in humans. Furthermore, sleep deprivation is known to produce additional effects such as sleepiness, increased fatigue, negative mood, and cognitive dysfunctions, which might cause or mimic a

modulation of pain processing, perhaps by increasing general irritability. Our study (Kundermann et al. 2004b) excluded general somatosensitive changes underlying a probable change in hyperalgesia after sleep deprivation because a similar pattern of changes was not observed for sensitivity to nonpainful stimuli. Given that the above experimental human studies were designed with ethical values in mind and used only short-term sleep deprivation (up to three nights), the findings only allow a cautious generalization to chronic pain conditions that may persist for weeks, months, or even years. A recent study by Haack and Mullington (2005) demonstrated that as few as 4 days of partial sleep deprivation can be sufficient to trigger a diversity of pain symptoms (increased visual analogue scale ratings of muscular, joint, and back pain) and mood alteration in healthy individuals. This finding stresses that changes in pain perception and in mood need a certain time to appear and that the cumulative effect of both pain and sleep perturbation needs to be further identified.

ANIMAL DATA

Hicks et al. (1978) were among the first investigators to conduct experiments in animals on the effects of sleep deprivation on nociceptive processes. In a controlled study in Sprague-Dawley rats, these authors assessed the effects of REM sleep deprivation on nociceptive sensitivity by measuring the tail-flick response to electrical stimuli. REM sleep deprivation rendered the rats more sensitive to the electrical stimuli for a long period of up to 24 hours. The duration of REM sleep deprivation (1, 2, or 3 days) was of no influence. Subsequently, Hicks et al. (1979) showed that REM sleep deprivation for 4 days decreased nociceptive thresholds for as long as 96 hours after termination of the sleep deprivation procedure.

Ukponmwan et al. (1984) examined the relationship between REM sleep and opioidergic activity. They treated rats with phosphoramidon (an enkephalinase-inhibitor, 250 μg, administered intracerebroventricularly [i.c.v.]) or morphine (20 μg i.c.v.) or subjected them to cold-water swim (at 5°C for 5 minutes). All three treatments led to consistent analgesia (increased thresholds for paw-pinch.) The antinociceptive effect of phosphoramidon, morphine, and cold-water swim was abolished by 96 hours of REM sleep deprivation.

In a subsequent study, Ukponmwan et al. (1986) tested whether the potentiation of opioidergic antinociception by monoamines can be prevented by REM sleep deprivation. Consequently, they not only induced opioidergic antinociception by i.c.v. application of phosphoramidon as in the preceding study, but also tried in some of the experimental conditions to augment the effect by concurrent application of both the monoamine oxidase B (MAO-B) inhibitor deprenyl (intraperitoneally) and the MAO-B substrate beta-phenylethylamine

(i.c.v.). Deprenyl and beta-phenylethylamine potentiated the antinociceptive effects of phosphoramidon. This effect was abolished by REM sleep deprivation for 96 hours. Taken together, the two studies of Ukponmwan et al. suggest that REM sleep deprivation interferes with pain-inhibitory effects mediated by opioidergic and monoaminergic mechanisms.

Asakura and colleagues (1992) used a variety of behavioral and neurochemical tests to investigate the consequences of REM sleep deprivation over 48 hours in mice. Accordingly, the investigation of nociception was not the primary goal of the study. The authors found no impact of REM sleep deprivation on nociceptive sensitivity as assessed by the hotplate test, a finding that contrasts with almost all the other animal data available. This difference may be due to the type of nociceptive test used. May et al. (2005) observed a similar pattern of results when using the hotplate test to assess the effects of REM sleep deprivation in old Sprague-Dawley rats. In young animals, a significant increase in nociceptive sensitivity was only induced by REM sleep deprivation with the lower of two temperatures (44°C vs. 52°C). The authors concluded that different nociceptive pathways (C vs. Aδ fibers) are activated by the two temperatures and that only the C-fiber pathway is modulated by REM sleep deprivation.

Onen et al. (2000) assessed the vocalization threshold of Wistar rats to noxious mechanical stimuli (paw-pressure test) during 3 days of REM sleep deprivation and a succeeding recovery period of 4 days. REM sleep deprivation did not augment nociception from the very beginning but only after the second day. During recovery, the thresholds normalized with a delay of 48 hours, with a nonsignificant tendency to "overshoot" toward increased nociceptive thresholds. This observation of an "early" normalization contrasts with the animal findings of Hicks et al. (1978, 1979), who continued to observe enhanced nociception even after a period of 48 hours of recovery sleep. In a subsequent study, Onen et al. (2001b) examined the effect of REM sleep deprivation over 3 days using a variety of tests of nociception (the paw pressure test, hot water immersion test, tail electric shock test, and formalin test) in Wistar rats. REM sleep deprivation increased nociceptive sensitivity to mechanical, thermal, and electrical stimuli but not to chemical stimuli (formalin test).

In a recent study, Dametto et al. (2002) investigated the effects of REM sleep deprivation in Wistar rats over 96 hours with a focus on performance in different conditioning tasks. They also assessed nociceptive threshold (vocalization or flinch behavior to electrical foot shocks) as a covariate to examine its influence on learning performance. The authors used a novel sleep deprivation procedure, the "modified multiple platform technique" (MMPT), in which the rats are placed with mates onto platforms. The REM-deprived rats were compared to non-deprived rats from different housing conditions. By use of this method, the authors observed an increased vocalization threshold in the

REM-deprived rats but no change in flinch behavior. The indication of an antinociceptive effect of REM sleep deprivation disagrees with the rest of the animal data described so far. The method of sleep deprivation may account in part for the differences (e.g., social contact was allowed only in the MMPT). Interestingly, only the studies from Asakura et al. (1992) and Dametto et al. (2002) reported opposite findings, which may be due to differences in methods of testing, animal housing, and so on. Obviously, more clarity is needed on the effect of animal REM sleep deprivation in relation to pronociceptive effects.

In summary, the experimental animal data are much more consistent than those obtained from studies in humans. REM sleep deprivation was observed to promote pronociception (i.e., increased sensitivity to noxious stimuli) in almost all studies. In addition, REM sleep deprivation appeared to prevent the analgesic action of endogenous and exogenous opioids. Furthermore, the potentiation of the analgesic action of opioids by monoamines was abolished by REM sleep deprivation. Although many of the animal studies were controlled and had a sufficient sample size, the exclusive focus on REM sleep deprivation does not resolve issues regarding the effects of non-REM sleep deprivation; the exclusive interest in REM sleep deprivation so far has very likely had a methodological basis because REM sleep deprivation is easier to accomplish in rodents. Thus, it might be the case that the observed effects are specific to REM sleep deprivation and are not due to a general and unspecific disruption of sleep.

SPECULATIONS ON THE MECHANISMS OF ACTION

The data regarding the effects of sleep quality and sleep deprivation on pain perception in humans and in animals appear conflicting and do not support an assumption of straightforward identical mechanisms of action across species.

In humans, non-REM sleep appears to produce or restore pain-suppressive capacities. As a consequence, interruption or deprivation of non-REM sleep enhances pain perception, leading to hyperalgesia the day after. Furthermore, the findings of Smith et al. (2005) suggest that an increased drive of REM sleep strengthens the mechanisms of central sensitization or, in other words, promotes pain perception. However, the recent findings of Roehrs et al. (2006), suggesting that REM sleep deprivation renders subjects specifically hyperalgesic, cast doubt on the latter assumption. Moreover, the REM deprivation procedure applied to human sleep also results in considerable alterations in sleep architecture and total sleep loss that reduce the generalization of this finding to the chronic pain condition. The effect of any sleep disturbance may alter sleep continuity and modify ultradian sleep structure and macro- and micro-architecture and reduce our ability to control for such interrelated variables (Lautenbacher et al. 2006; see also Parrino et al. and Smith and Buenaver chapters in this volume).

In contrast, in many animal studies, deprivation of REM sleep produced hyperalgesia, rendering REM a physiological state or period that seems also to produce or restore antinociception. We need evidence to prove whether this phenomenon is linked to the return of intense brain and autonomic activities that characterize REM sleep (see Peever and McGinty chapter in this volume). Given that sleep states are not perfectly comparable between humans and animals and that the animal studies have focused exclusively on the effects of REM sleep on nociception (leaving non-REM sleep largely uninvestigated), speculation on the mechanisms of action of sleep deprivation on pain perception in humans requires caution.

Given that non-REM and REM sleep states are controlled by a reciprocal monoaminergic-cholinergic interaction in the brainstem (Pace-Schott and Hobson 2002; see Peever and McGinty, this volume), a weak monoaminergic tone unbalances this interaction and leads to a relative increase in REM compared to non-REM sleep and to non-REM sleep disorders; for example, fibromyalgia and depression appear to be conditions with such a pathophysiology and are linked with the resulting sleep disorders (O'Mally et al. 2000; Wilson and Argyropoulos 2005). The two conditions are also associated with a diversity of pain symptoms, a fact that is still necessary to mention in the case of depression (Lautenbacher et al. 1999). We postulate that it is predominantly in conditions with systemic, nonregional, and functional pain complaints that sleep disorders involving reduced and compromised non-REM sleep and a relative increase in REM sleep contribute to the development of pain. The majority of the data on the effects of changes in sleep quality and of sleep deprivation on pain perception in humans fit with these assumptions. Whether this effect is direct or due to the mediating factor of an unbalanced interaction between monoaminergic and cholinergic systems remains to be determined.

The findings of Ukponmwan et al. (1984, 1986) reported in the preceding section suggest that the effects of sleep deprivation are mediated by opioidergic and monoaminergic mechanisms. Although this study specifically addressed REM sleep deprivation, the consequences on general sleep architecture remained undetermined and might have been far-ranging. The MAO-B inhibitor deprenyl, which is antagonized by sleep deprivation, stimulates dopaminergic but also serotoninergic activity (Celada and Artigas 1993), and the latter is of special interest in the context of sleep and pain regulation. For example, tryptophan depletion leads to a loss of the potency of morphine in producing analgesia (Abbott et al. 1992). This effect is due to the descending pain inhibitory control system, which contains opioidergic and monoaminergic (serotoninergic and noradrenergic) links (Basbaum and Fields 1984). One can speculate that non-REM sleep deprivation or a disruption of sleep continuity in general renders the serotoninergic system functionally unable to act concomitantly with the inhibitory system activated by opioids.

The effect of sleep deprivation on serotonin is controversial; both increases and decreases in 5-HT activity have been reported (presumably dependent on the time frame of investigation) (Farooqui et al. 1996; Blanco-Centurion et al. 2001). A recent study by Bjorvatn et al. (2001) using in vivo microdialysis showed a gradual decline of extracellular serotonin levels during an 8-hour sleep deprivation period in two different brain structures, the frontal cortex and hippocampus, which are projection areas of the dorsal and median raphe nuclei. The time course of the overall change in activity of the 5-HT system induced by sleep deprivation is difficult to determine because presynaptic changes (release, turnover) or postsynaptic changes (receptor density, receptor sensitivity) may be produced. Moreover, adaptive regulatory processes counterbalancing these changes can be assumed. Consequently, it is difficult to predict the direction of the 5-HT-modulated change in nociceptive processing at a given time. Furthermore, there is evidence that other neurotransmitter systems (especially noradrenergic) and neuroimmunological factors (specifically the interleukins; Rogers et al. 2001) are affected by sleep deprivation and are involved in the modulation of pain.

The idea of a transient disturbance of the descending pain inhibitory control system by sleep deprivation and especially by non-REM sleep deprivation is congruent with the changes in pain experience observed in humans. Sleep deprivation appears to enhance predominantly pressure pain sensitivity originating in part from muscle nociceptors and to increase the vulnerability to muscle pain, as shown in this chapter. Muscle nociception is much more subject to the descending pain inhibitory system than skin nociception (Mense 2000; Graven-Nielsen and Mense 2001), as outlined earlier in this chapter.

SUMMARY

In this chapter we have reviewed evidence from human and animal studies that used total or partial sleep deprivation as tools of investigation. It must be kept in mind that even selective deprivation of certain sleep stages (REM vs. non-REM 3 and 4) does not allow for very specific conclusions because any alteration in sleep architecture has repercussions on other variables that prevent solid control of all parameters regulating sleep and arousal.

Evidence from the literature supports the hypothesis that deterioration of sleep quality according to subjective and objective criteria as well as sleep deprivation in almost every form enhance pain perception. The latter can eventually lead to pain. The factors that have been shown to be of relevance are summarized in Table I. In humans disturbance or deprivation of non-REM sleep appears to be able to induce hyperalgesia, and the protection of non-REM sleep

Table I
Sleep-related influences on pain perception in humans and on behavioral signs of nociception in animals the following day

Variables	Changes in Pain Perception	Reference
In Humans		
Alpha-delta sleep during non-REM sleep stages	◆	Moldofsky et al. 1975
Disturbed spindle activity during stage 2 non-REM sleep	◆	Landis et al. 2004
REM sleep frequency (relative duration)	◆	Smith et al. 2005
REM sleep latency	❖	Smith et al. 2005
Subjective sleep quality	❖	Agargun et al. 1999; Chiu et al. 2005
Total sleep deprivation	◆◆	Onen et al. 2001a; Kundermann et al. 2004b; Roehrs et al. 2006
Non-REM sleep deprivation	◆	Moldofsky et al. 1975; Lentz et al. 1999
REM sleep deprivation	◆	Roehrs et al. 2006
In Animals		
REM sleep deprivation	◆◆◆ (except hotplate test)	Hicks et al. 1978, 1979; Ukponmwan et al. 1984, 1986; Onen et al. 2000, 2001b

◆◆◆ Strong evidence for increase; ◆◆ moderate evidence for increase; ◆ weak evidence for increase; ❖ weak evidence for decrease.

may act as a pain-suppressive factor, but evidence-based data are awaited before firm conclusions can be confirmed. In contrast, preliminary evidence suggests that excessive REM sleep may act as a pain-promoting factor, although the data obtained are not definitive.

Pain, in turn, disturbs sleep by inducing arousal and triggering all other neurobiological sequels of stress, which are incompatible with sleep's alleostatic processes, such as recovery from fatigue. Hence, an ongoing cycle might arise, starting either with disturbed sleep or with pain, in which the two components maintain or even augment each other (Lavigne et al. 2005). Accordingly, adequate management of disturbed sleep might alleviate pain (Smith and Haythornthwaite 2004). On the other hand, better pain relief with medication or cognitive and behavioral management may promote more restorative sleep, which in turn would assist in long-term pain relief (see chapters by Beaulieu and Walczak and by Smith and Haythornthwaite in this volume).

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