The effect of sleep deprivation on pain

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Chronic pain syndromes are associated with alterations in sleep continuity and sleep architecture. One perspective of this relationship, which has not received much attention to date, is that disturbances of sleep affect pain. To fathom this direction of cause, experimental human and animal studies on the effects of sleep deprivation on pain processing were reviewed. According to the majority of the studies, sleep deprivation produces hyperalgesic changes. Furthermore, sleep deprivation can counteract analgesic effects of pharmacological treatments involving opioidergic and serotonergic mechanisms of action. The heterogeneity of the human data and the exclusive interest in rapid eye movement sleep deprivation in animals so far do not allow us to draw firm conclusions as to whether the hyperalgesic effects are due to the deprivation of specific sleep stages or whether they result from a generalized disruption of sleep continuity. The significance of opioidergic and serotonergic processes as mediating mechanisms of the hyperalgesic changes produced by sleep deprivation are discussed.

Key Words: *Opioids; Pain; Serotonin; Sleep deprivation*

Patients with chronic pain syndromes often suffer from sleep disturbances (1). However, it is difficult to determine the direction of cause between pain and sleep disturbance. The usual perspective favours an arousal-augmenting function of pain, which prevents the initiation or the continuation of sleep. Alternatively, it is believed that the modulation of pain and sleep-wake regulation share common neurobiological systems, in particular the central serotonergic one (2). Consequently, the association of pain and disturbed sleep might be a secondary phenomenon due to a common neurobiological dysfunction. Finally, a rather unusual perspective is that poor sleep can interfere with pain processing. With this latter direction of relation in mind, we have addressed the following issues by reviewing the literature with a clear focus on experimental studies. The following perspectives may help to integrate the reviewed findings.

1. *The relationship between sleep disturbances and pain as suggested by correlational data.* The majority of studies on the relationship between sleep and pain were not based on an experimental design, but relied on correlations only. In this section, a brief summary of the clinical investigations

L'effet du manque de sommeil sur la douleur

Les syndromes de douleur chronique s'associent à des altérations de la continuité et de l'architecture du sommeil. L'une des perspectives de ce lien, qui n'a pas reçu beaucoup d'attention jusqu'à présent, c'est que les troubles du sommeil influent sur la douleur. Pour sonder cette orientation de la cause, on a analysé des études expérimentales menées sur des humains et sur des animaux afin d'établir les effets du manque de sommeil sur le mécanisme de la douleur. D'après la plupart des études, le manque de sommeil produit des modifications hyperalgésiques. De plus, il peut contrer les effets analgésiques des traitements pharmacologiques mettant en cause des modes d'action opioïdénériques et sérotoninergiques. L'hétérogénéité des données humaines et l'intérêt exclusif pour le manque de sommeil paradoxal chez les animaux jusqu'à présent nous empêchent d'établir avec certitude si les effets hyperalgésiques sont imputables au manque de phases précises du sommeil ou à un dérèglement généralisé de la continuité du sommeil. On se penche sur l'importance des processus opioïdénériques et sérotoninergiques à titre de mécanismes médiateurs des modifications hyperalgésiques produites par le manque de sommeil.

is given, including their first clues concerning the influence of disturbed sleep on pain, and their limitation in deriving causal relations.

2. *Sleep deprivation as a methodological approach to mimic disturbed sleep and derive experimental evidence for algesic effects.* A comprehensive review of animal and human studies, which used sleep deprivation as an independent variable and examined its influence on pain processing, is provided.
3. *Assumptions on the algesic mechanisms of sleep deprivation.* Results from animal studies suggest various neurochemical changes during and after sleep deprivation, which seemed to be involved in the modulation of pain. With a focus on the serotonergic system, sleep deprivation affects 5-hydroxytryptamine (5-HT) turnover (3), the firing rate of serotonergic neurons in the dorsal nucleus raphe (4) and 5-HT receptor functions (5). Given the well-known pain inhibitory effects of 5-HT, these changes may be tentatively integrated into a serotonergic model of hyperalgesic action of sleep deprivation.

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THE RELATIONSHIP BETWEEN SLEEP AND PAIN AS SUGGESTED BY CORRELATIONAL DATA

The overnight augmentation of muscular pain in fibromyalgia patients led to the assumption of a pathogenic role of disturbed sleep in pain conditions. Moldofsky et al (6) were among the first to investigate both sleep physiology and pain in fibromyalgia patients. They observed an increased ratio of alpha waves during nonrapid eye movement (NREM) sleep, the so-called "alpha-delta sleep". The authors suggested that an increased arousal during slow wave sleep interferes with the restorative function of sleep. Interestingly, the pressure pain thresholds markedly decreased from evening to morning in parallel.

Subsequent polysomnographic studies, in which nocturnal sleep of healthy subjects was assessed for comparison, failed to confirm a fibromyalgia specificity of the alpha-delta sleep. Horne and Shackell (7) found no significant differences in the ratio of alpha activity in NREM sleep between fibromyalgia patients and healthy control subjects. Furthermore, an increased ratio of alpha waves during NREM sleep was observed in other conditions of chronic pain (eg, in rheumatoid arthritis [8], and in conditions with primary insomnia [9]). However, these findings showing a lack of specificity of alpha-delta sleep for fibromyalgia do not rule out the assumed contribution of disturbed sleep to the development of chronic pain. This assumption was strengthened by a recent study by Argargün et al (10) of fibromyalgia patients. The subjective quality of sleep as assessed by the Pittsburgh Sleep Quality Index was inversely related to pressure pain sensitivity in these patients.

Given that disturbed sleep may contribute to chronic pain, the question arises whether the effect is direct or mediated by other factors. Jennum et al (11) showed that in comparison to healthy control subjects, fibromyalgia patients exhibit more arousal episodes during night sleep. However, this group difference in sleep architecture was strongly related to the occurrence of respiratory disorders in patients with fibromyalgia. Thus, the apparent causation may reflect third-party factors. Depression also needs to be considered as a mediating factor because of its association with sleep disorders and chronic pain (12).

Finally, there is also evidence that disturbed sleep augments acute pain. Raymond et al (13) investigated inpatients with burn injuries. The subjective quality of night sleep was a significant predictor for pain intensity on the following day. In contrast, the pain intensity of the day before did not predict the sleep quality of the following night.

The correlational data reported here suggest that sleep disturbances caused by pain facilitate subsequent pain. However, it is not clear whether a change in sleep architecture or a deprivation of certain sleep stages is the relevant etiological factor. The next section provides a systematic review of experimental data on the effects of sleep deprivation on pain to address this question.

EXPERIMENTAL ANALYSIS OF THE EFFECT OF SLEEP DEPRIVATION ON PAIN

This review of the literature is based on MEDLINE research for the years 1962 to October 2003 using the keywords "sleep", "sleep deprivation" and "sleep interruption", combined with "pain", for human and animal studies. An article was included

if sleep deprivation in its total, selective or partial form was used as an independent variable, and any subjective or behavioural measure of pain was used as a dependent variable. Furthermore, only studies that met minimal methodological requests (with respect to sample size and description, control of sleep deprivation, quality of pain measurement and suitability of statistics) were reviewed.

HUMAN DATA

A total of seven studies met the inclusion criteria (Table 1). The guiding study in this field is the one by Moldofsky et al (6); clinical aspects of this study were already considered in the preceding section. The authors proposed that an NREM sleep disturbance is involved in the pathogenesis of fibromyalgia, and that NREM sleep interruption causes myalgic pain. Six healthy men underwent a selective (stage 4) sleep deprivation period for three nights. Sleep deprivation was preceded by an adaptation night and followed by a recovery night. During each experimental phase, pressure pain sensitivity was measured at the respective tender points for the diagnosis of fibromyalgia. Muscular pain was assessed using a rating scale. During the stage 4 sleep deprivation period, both pressure pain sensitivity and muscular pain increased. The changes were accompanied by an increased arousal seen on the sleep electroencephalogram (EEG) but not by prolonged periods of being awake. The validity of this study was hampered by the fact that a control group was missing. Thus, the changes observed might have been due to unfamiliar sleeping conditions in a laboratory, or might have resulted from any kind of sleep disruption, not necessarily from deprivation of sleep stage 4.

Some of these objections were addressed in a second study by Moldofsky and Scarisbrick (14) by adding the results of a second group to the data of Moldofsky et al (6). Seven healthy individuals were deprived selectively from rapid eye movement (REM) sleep in the same experimental setting. REM sleep deprivation did not lower the pressure pain thresholds, and muscular pain increased only to a small degree. Thus, the marked changes observed after stage 4 sleep deprivation were not replicated by REM sleep deprivation.

In contrast to those studies, Drewes et al (15) analyzed the effects of total sleep deprivation on pain detection (for pressure and heat) and tolerance thresholds (for pressure) in 10 healthy individuals. The repeated measurements at short intervals of 2 h (starting at 23:00 and ending at 07:00), with an additional assessment the next day (at 23:00), indicated no changes in pain detection and tolerance thresholds. The study by Older et al (16) was one of the few controlled ones comparing three days of noise-induced disruption of slow wave sleep in 13 subjects with three days of normal night sleep in six subjects. Furthermore, the potential role of hormones as a mediating factor between sleep and pain was tested by assessing insulin-like growth factor (IGF-1). The idea of an involvement of IGF-1 in the relation between disturbed sleep and pain was derived from observations on fibromyalgia patients, who tend to have low IGF-1 levels. The EEG showed more arousal during slow wave sleep deprivation and an increased portion of REM sleep. However, pressure pain thresholds and IGF-1 serum levels did not change. In contrast, somatic complaints increased after the third night of sleep deprivation.

TABLE 1
Human experiments on the effects of sleep deprivation on pain

Author (reference)	Subjects	Treatment	Design	Pain-related measurements	Main results
Moldofsky et al, 1975 (6)	Healthy males, n=6	SW-SD for 3 consecutive nights	Repeated measures over 7 days with the conditions: – baseline – treatment – recovery	Pain thresholds: – mechanical (26 sites in the musculoskeletal system, which are vulnerable in fibromyalgia patients) Subjective ratings of body complaints	Decreased mechanical pain thresholds after SW-SD More musculoskeletal symptoms after SW-SD
Moldofsky and Scarisbrick, 1976 (14)	Healthy subjects, n=13 (12 males, 1 female)	SW-SD vs REM-SD for 3 consecutive nights	Comparison of two independent groups (SW- vs REM-SD) including repeated measures over 7 days with the conditions: – baseline – treatment – recovery	Pain thresholds: – mechanical (26 sites in the musculoskeletal system, which are vulnerable in fibromyalgia patients) Subjective ratings of body complaints	Decreased mechanical pain thresholds after SW-SD, but no changes in mechanical pain thresholds after REM-SD SW-SD-group reported after the SD-nights more musculoskeletal symptoms compared with REM-SD group
Drewes et al, 1997 (15)	Healthy subjects, n=10	Total SD for 1 night	Repeated measures during the night and following day	Pain thresholds: – mechanical (pain detection and pain tolerance thresholds) – thermal (pain detection thresholds)	No changes in pain detection and tolerance thresholds over the time
Older et al, 1998 (16)	Healthy subjects, n=19	SW-SD for 3 consecutive nights	Controlled comparison of two independent groups (SW-SD vs. untreated controls) including repeated measures over 7 days with the conditions: – baseline – treatment – recovery	Pain thresholds: – mechanical Subjective rating of body complaints (VAS) Neuroendocrine assessment: – IGF-1	No differences in pain thresholds within or between groups More body complaints after third SW-SD Night (compared with controls) No changes of IGF-1 after SD
Lentz et al, 1999 (17)	Healthy females, n=12	SW-SD for 3 consecutive nights	Repeated measures over 5 days with the conditions: – baseline – treatment	Pain thresholds: – mechanical: thresholds were assessed on 16 specific sites, which are vulnerable in fibromyalgia, and on additional two control sites Skinfold tenderness Skin reactive hyperemia Subjective ratings of body complaints	Decreased tender point pain thresholds after the second and third SW-SD night, compared with baseline Pain thresholds on control sites were decreased after third SW-SD night Higher skinfold tenderness after the third SW-SD night Increased vasodilatation to mechanical stimulation (inflammatory flare response) after the third SW-SD night More musculoskeletal discomfort after the third SW-SD night
Arima et al, 2001 (18)	Healthy males, n=10	SW-SD for 3 consecutive nights	Repeated measures over 6 days with the conditions: – baseline – treatment – recovery	Pain thresholds: – mechanical (masseter muscle) EMG (masseter muscle) Maximum voluntary occlusal force Subjective rating of body complaints (VAS)	No effects of SW-SD on pain thresholds No effects of SW-SD on EMG activity, maximum voluntary occlusal force and VAS ratings
Onen et al, 2001 (19)	Healthy males, n=9	Total SD for 1 night, the following 2 nights – REM-SD or – SW-SD	Controlled crossover study with a counter-balanced order of REM- and SW-SD (two sequences). Repeated measures over 6 days with the conditions: – baseline – treatment – recovery	Pain thresholds: – thermal (pain tolerance thresholds) – mechanical (pain tolerance thresholds)	Mechanical pain tolerance thresholds were decreased after total SD Recovery sleep after SW-SD produced increase in mechanical pain tolerance thresholds

EMG Electromyography; IGF-1 Insulin-like growth factor 1; REM-SD Rapid eye movement sleep deprivation; VAS Visual analogue scale; SD Sleep deprivation; SW-SD Slow wave sleep deprivation

The findings of Older et al (16) were in contrast to the results of Lentz et al (17), who also investigated the effects of "slow wave sleep disruption" over three nights. Although the study was uncontrolled, the comprehensive assessment of pain highlights this study in comparison with others. At the tender points designated for the diagnosis of fibromyalgia, the pressure pain thresholds decreased after two or three nights of slow wave sleep disruption. The same response also occurred at the control points after the third night. At this time, muscle complaints also became more frequent. Interestingly, the flare response gained strength during the course of slow wave sleep disruption, suggesting an activation of mechanisms involved in neurogenic inflammation.

The studies reported so far were partly designed to look for a relationship between sleep deprivation or disruption and the incidence of fibromyalgia-like pain, which is pain at various sites of the body. In contrast, an interest in the regional pain of temporomandibular disorder (TMD) inspired the study of Arima et al (18), conducted in 10 healthy men. The question was whether the pattern of sleep disruption observed in TMD patients, which is characterized by an increased amount of EEG desynchronization during night sleep, can be experimentally modelled in healthy individuals with the consequence of occurrence of TMD-like symptoms. A variety of tests for TMD-like symptomatology (eg, pressure pain threshold above the temporomandibular joint, occlusal force, electromyography of the masseter muscle, and visual analog scale ratings for pain and other somatic complaints) revealed no changes due to slow wave sleep disruption (disruption of NREM sleep stages 3 and 4 by use of a computer controlled sound stimulation). However, the validity of the findings is uncertain because no substantial reduction of the portion of slow wave sleep could be obtained during the second and third night of sleep deprivation. Furthermore, for the first nights, no compensatory increase of NREM sleep stages 1 and 2 was reported. It is unclear whether these findings indicate problems in the experimental procedures or in the statistics applied.

The best study, using current standards of methodology in this field, is the one by Onen et al (19). Sleep deprivation was accomplished in its total form, as "slow wave" and as REM sleep deprivation. The authors made use of a crossover design, in which nine healthy men ran through a night of total sleep deprivation for 40 h, and then through two consecutive nights with either slow wave sleep or REM sleep interruption, ending with a recovery night in any case. Pain tolerance thresholds were assessed in the evening and in the morning. Total sleep deprivation decreased pressure pain tolerance thresholds compared with a baseline period, a finding that was not obtained for the heat pain tolerance thresholds. Both REM and slow wave sleep interruption tended to decrease pressure pain tolerance thresholds. Only recovery sleep after slow wave sleep interruption produced an increase in pressure pain tolerance thresholds, but not after REM sleep interruption. A compensatory larger portion of slow wave sleep stages 3 and 4 during the recovery night paralleled the increase in pressure pain tolerance thresholds.

SUMMARY OF EXPERIMENTAL INVESTIGATIONS OF HUMANS

There are only a few human studies available on the effects of sleep deprivation on pain, and the findings are not always

consistent (Table 1). Nevertheless, the results tend to indicate that sleep deprivation does produce hyperalgesic changes in healthy subjects. Thereby, the term "hyperalgesic change" is not used to describe a pathophysiological state, but the direction of change in pain sensitivity. The deprivation or the disruption of slow wave sleep especially has appeared to exert this effect, whereas results on the effects of selective REM sleep deprivation remain unclear. The findings of Onen et al (19) suggest that slow wave sleep deprivation makes individuals more sensitive to noxious stimuli, and that recovery from this type of deprivation has the opposite effect. Interestingly, the hyperalgesic action of slow wave sleep deprivation was mainly observed when tested by pressure pain stimulation. Pressure pain stimulation targets both superficial and deep tissue nociception, whereas heat pain stimulation targets primarily superficial tissue nociception. Accordingly, pressure pain stimulation appears to reflect muscle and skin nociception, whereas heat pain stimulation allows only the assessment of skin nociception (20). Muscle nociception is likely to be influenced to a much stronger degree by the descending pain inhibitory control system than skin nociception (21). It is possible that slow wave sleep disruption affects this descending pain inhibitory control system and, thereby preferentially, pressure pain sensitivity. Such an effect is very likely a systemic, not a regional, one. The findings of Lentz et al (17) and Onen et al (19) corroborate the idea of a systemic change in pain sensitivity because similar results were obtained when testing multiple sites.

It should be critically noted that individual factors (eg, age or sex of study subjects), which have not yet been controlled sufficiently, may interact with the effects of sleep deprivation on pain. Furthermore, sleep deprivation is known to produce additional effects like sleepiness, increased fatigue, negative mood or cognitive dysfunctions, which might cause or mimic a modulation of pain processing. Other somatosensory functions (ie, responses to innocuous stimuli) might be of special relevance in this context and have been neglected so far. Therefore, it is still questionable whether the observed effects are due to specific alteration of pain processing. Finally, because all human studies were designed for ethical reasons to examine short term (up to three nights) effects of sleep deprivation only, these findings permit only a limited generalization to chronic pain conditions with weeks, months or even years of disturbed sleep.

ANIMAL DATA

Hicks et al (22) conducted the first experiment on animals investigating the effects of sleep deprivation on nociception (Table 2). In a controlled study in Sprague-Dawley rats, the authors assessed the effects of REM sleep deprivation on nociceptive sensitivity (tail flick to electrical stimuli). REM sleep deprivation rendered the rats more sensitive to the electrical stimuli for a long period of time, up to 24 h. The duration of the deprivation (1, 2 or 3 days) was of no influence. Subsequently, Hicks et al (23) showed that REM sleep deprivation for four days decreased nociceptive thresholds for as long as 96 h after termination of the sleep deprivation procedure.

Ukponmwan et al (24) examined the relationship between REM sleep and opioidergic activity. To test this, Wistar rats were selectively deprived from REM sleep and compared with "stressed" animals and untreated (control) animals. After a

TABLE 2
Animal experiments on the effects of sleep deprivation on pain

Author (reference)	Animals	Treatment	Design	Pain-related measurements	Main results
Hicks et al, 1978 (22)	Sprague-Dawley rat, n=36	REM-SD of different length: 1, 2 and 3 consecutive days	5 groups with repeated measures. After preliminary analysis: Comparison of two independent groups (REM-SD vs. untreated controls)	Nociceptive thresholds: – electrical (tail electric shock test)	Decreased nociceptive thresholds immediately, 3 h and 24 h after REM-SD Effect of decreased nociceptive thresholds was independent to the length of REM-SD
Hicks et al, 1979 (23)	Sprague-Dawley rat, n=30	REM-SD for 4 consecutive days	3 groups with repeated measures. After preliminary analysis: Comparison of two independent groups (REM-SD vs untreated controls)	Nociceptive thresholds: – electrical (tail electric shock test)	Decreased nociceptive thresholds immediately, 24 h and 96 h after REM-SD
Ukponmwan et al, 1984 (24)	Wistar rat, n=210	REM-SD for 4 consecutive days	3 groups (REM-SD vs stress vs controls) under the following conditions: (a) cold water-swim analgesia or (b) phosphoramidon or (c) morphine	Nociceptive thresholds: – mechanical (paw pressure test)	Conditions a, b and c produced antinociceptive effects in stressed and untreated (control-) rats No antinociceptive effect of conditions a, b and c in sleep-deprived animals
Ukponmwan et al, 1986 (25)	Wistar rat, n≥171	REM-SD for 4 consecutive days	2 groups (REM-SD vs controls) under different pharmacological conditions: (a) deprenyl (b) beta-phenylethylamine (c) phosphoramidon (d) deprenyl + phosphoramidon (e) beta-phenylethylamine + phosphoramidon (f) deprenyl + beta-phenylethylamine + phosphoramidon	Nociceptive thresholds: – mechanical (paw pressure test)	REM-SD decreased basal nociceptive thresholds (without pharmacological intervention) compared with untreated (control) rats Conditions c, d, e and f produced increased nociceptive thresholds in the control group compared with the sleep deprived group No differences in nociceptive thresholds between REM-SD and control group under conditions a and b
Asakura et al, 1992 (26)	ddY mouse, n=20	REM-SD for 2 consecutive days	Comparison of two independent groups: REM-SD vs untreated controls	Nociceptive thresholds: – thermal (hot plate test)	No difference in the hot plate test between the groups
Onen et al, 2000 (27)	Wistar rat, n=16	REM-SD for 3 consecutive days	Comparison of two independent groups (REM-SD vs controls) including repeated measures with the conditions: - baseline - treatment - recovery	Nociceptive thresholds: – mechanical (paw pressure test)	Decreased nociceptive thresholds after 48 h and 72 h REM-SD Recovery sleep after REM-SD produced increased nociceptive thresholds
Onen et al, 2001 (28)	Wistar rat, n=64	REM-SD for 3 consecutive days	Comparison of two independent groups (REM-SD vs controls) including repeated measures with the conditions: - baseline - treatment	Nociceptive thresholds: – thermal (hot water tail-immersion test) – mechanical (paw pressure test) Quantification of nociceptive behavior: – vocalizations to noxious electrical stimuli – behavioral response to noxious chemical stimuli (formalin test)	REM-SD induced decreased nociceptive thresholds to thermal and mechanical stimuli REM-SD increased number and intensity of vocal responses to electrical stimuli No differences in the formalin test between or within groups
Dametto et al, 2002 (29)	Wistar rat, n not stated	REM-SD for 4 consecutive days (in groups of 6 rats)	3×2 factorial design: - REM-SD vs two different control groups with no REM-SD - Social stable vs social unstable conditions	Nociceptive thresholds: – electrical foot shocks with assessment of flinch response and/or vocalization	No difference between the groups in flinch response REM-SD deprived animals showed higher vocalization-thresholds No interaction of REM-SD with social stress during SD

SD Sleep deprivation; REM-SD Rapid eye movement sleep deprivation

treatment period of 96 h, antinociceptive opioidergic mechanisms were activated either by stress produced by swimming for five minutes in ice cold water or by the intracerebroventricular (icv) application of the enkephalinase-inhibitor phosphoramidon or morphine. All three opioidergic treatments increased the thresholds for paw-pinch in both the control and the "stress" animals. However, in the rats deprived from REM sleep, these effects were not present.

In a subsequent study, Ukponmwan et al (25) considered the dependency of opioidergic antinociception on the availability of monoamines. Consequently, they did not only induce antinociception by application of phosphoramidon (icv) 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 (MAO)-B inhibitor deprenyl (intraperitoneally) and the MAO-B substrate beta-phenylethylamine (icv). Deprenyl and beta-phenylethylamine potentiated the antinociceptive effects of phosphoramidon. This effect was abolished by an REM sleep deprivation of 96 h. 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 et al (26) investigated the consequences of REM sleep deprivation over 48 h in mice using a variety of behavioural and neurochemical tests. They found no impact of REM sleep deprivation on nociceptive sensitivity as assessed by the hot-plate test.

Onen et al (27) assessed the vocalization threshold to noxious mechanical stimuli during three days of REM sleep deprivation and a subsequent recovery period of four 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 h with a tendency to "overshoot" toward increased nociceptive thresholds. This observation of a normalization contrasts with the findings of Hicks et al (22,23), who continued to observe enhanced nociception even after a period of 48 h of recovery sleep. In a subsequent study, Onen et al (28) examined the effect of REM sleep deprivation over three days using a variety of tests of nociception (paw pressure test, hot water immersion test, tail electric shock test, formalin test) in Wistar rats. REM sleep deprivation increased the nociceptive sensitivity to mechanical, thermal and electrical stimuli, but not to chemical stimuli (formalin test). In a recent study, Dametto et al (29) investigated the effects of REM sleep deprivation in Wistar rats over 96 h with a focus on performance in different conditioning tasks. They also assessed the nociceptive thresholds (vocalization or flinch behaviour to electrical foot shocks) as a covariate to examine their influence on learning performance. The authors used a novel sleep deprivation procedure ("modified multiple platform technique"), in which the rats are placed with mates onto platforms. By use of this method, they observed an increased vocalization threshold but no change in flinch behaviour. The indication of an antinociceptive effect of REM sleep deprivation, which contrasts with all other animal studies described so far, might be due to the differences in methods used (eg, social contact was allowed only in the modified multiple platform technique).

SUMMARY OF THE EXPERIMENTAL INVESTIGATIONS OF ANIMALS

The experimental animal data are much more consistent than those obtained from studies in humans (Table 2). REM sleep deprivation was observed to increase nociceptive behaviour in almost all studies. This suggests a hyperalgesic action of REM sleep deprivation. 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 depriving NREM sleep stages. Thus, it might be possible that the observed effects are not due to a specific REM sleep deprivation but due to a general and unspecific disruption of sleep.

MECHANISMS OF ACTION

The majority of the studies on the relationship between sleep deprivation or sleep disruption and pain are able to describe this issue, but their results are not able to allow for conclusions about the mechanisms of action. First hints on the mechanisms of action responsible for the hyperalgesic effect of sleep deprivation were provided by the study of Ukponmwan et al (24). According to their results, the analgesic action of endogenous and exogenous opioids is dependent on undisturbed sleep architecture/continuity because selective REM sleep deprivation prevents opioid analgesia. This points to an effect of REM sleep deprivation or disruption of sleep continuity in general on the activity of the opioid system. Sleep deprivation may cause an inhibition of opioid protein synthesis (30) and/or a reduced affinity of mu- and delta-opioid receptors (31). The potentiation of the opioidergic analgesic effects, produced by the application of enkephalinase-inhibitors and an MAO-B inhibitor or by MAO-B substrates, can be nullified by REM sleep deprivation (25).

This suggests the involvement of further neurotransmitter systems. The MAO-B inhibitor deprenyl stimulates dopaminergic but also serotonergic activity (32), the latter of which is of special interest in the context of sleep and pain regulation. For example, tryptophan depletion leads to a loss of potency of morphine in producing analgesia (33). This effect is due to the neurochemistry of the descending pain inhibitory control system, which contains opioidergic and monoaminergic (serotonergic, noradrenergic) links (34). Furthermore, decreased levels of 5-HT and 5-hydroxyindole acetic acid in different brain areas were found in rats after REM sleep deprivation for 96 h (35,36). One can speculate that REM sleep deprivation, or a disruption of sleep continuity in general, renders the serotonin system functionally unable to support pain inhibition produced by opioidergic activation. These speculations are limited by the fact that only long periods of sleep deprivation or sleep disruption (greater than 72 h) were investigated. In contrast, shorter periods of sleep deprivation (less than or equal to 24 h) have appeared to enhance 5-HT activity in animals in various cerebral structures (3). However, a recent study of Bjorvatn et al (37) using *in vivo* microdialysis showed a gradual decline of extracellular serotonin levels during an 8 h sleep deprivation period in two different brain structures

(frontal cortex, 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 (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 the pain system at a given time. Furthermore, there is evidence that other neurotransmitter systems (especially noradrenergic and cholinergic) and neuroimmunological factors (particularly the interleukins [38]) 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 is congruent with the changes in pain experience observed in humans. Sleep deprivation appears to enhance pressure pain sensitivity and to induce muscle pain, as shown in this review. Muscle nociception is much more subject than skin nociception to the descending pain inhibitory system (27).

To further examine these ideas, experiments that are designed to examine specific mediating factors (such as opioidergic and serotonergic neurotransmission), and are capable of delineating the active part of sleep deprivation and the affected part of the pain system, are necessary. A variety of methodological approaches seems to be useful for that purpose,

such as the use of agonist/antagonist strategies, the assessment of neuroendocrinological and neuroimmunological factors and of neurotransmitters and their metabolites, the comparison of selective and total sleep deprivation, the use of experimental pain measures reflecting various levels of the pain system, and the use of human and animal studies. In addition, the relationship between abnormalities in sleep physiology and pain in clinical conditions with specified evidence of altered neurochemical systems needs further investigation.

CONCLUSIONS

In this review, evidence that the deprivation or the disturbance of sleep enhances pain sensitivity and causes pain was examined. Pain disturbs sleep by inducing arousal and triggering all other neurobiological sequels of stress that are incompatible with an undisturbed sleep. Hence, an ongoing cycle might arise starting either with disturbed sleep or with pain in which the two components stabilize or even augment each other. Accordingly, sufficient management of disturbed sleep might alleviate pain. On the other hand, better pain relief may promote more restorative sleep, which then further assists in long-term pain relief.

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