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CLINICAL REVIEW

Sleep deprivation and pain perception

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Summary Chronically painful conditions are frequently associated with sleep disturbances, i.e. changes in sleep continuity and sleep architecture as well as increased sleepiness during daytime. A new hypothesis, which has attracted more and more attention, is that disturbances of sleep cause or modulate acute and chronic pain. Since it is well-known that pain disturbs sleep the relationship between the two has since recently been seen as reciprocal. To fathom the causal direction from sleep to pain we have reviewed experimental human and animal studies on the effects of sleep deprivation on pain processing. According to the majority of the studies, sleep deprivation produces hyperalgesic changes. Furthermore, sleep deprivation can interfere with analgesic treatments involving opioidergic and serotonergic mechanisms of action. The still existing inconsistency of the human data and the exclusive focus on REM 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.

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Introduction

Patients with chronic pain syndromes often suffer from insomnia.^{1,2} However, it is a chicken and egg problem to determine the direction of causation between pain and sleep disturbance. The usual perspective favors an arousal enhancing function of pain, which prevents the initiation or the continua-

tion of sleep and leads in addition to sleepiness and napping during daytime.³ Alternatively, it is believed that the modulation of pain and sleep-wake regulation share common neurobiological systems, in particular the central serotonergic neurotransmission.⁴ Consequently, pain and disturbed sleep might be secondary phenomena due to a common neurobiological dysfunction. Finally, a rather recent perspective is that poor sleep can interfere with pain processing. We adopted this latter perspective when reviewing the literature with a clear focus on experimental studies (for an earlier review see⁵).

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The majority of studies on the relationship between sleep and pain was not based on an experimental design, but relied on correlational data. In the first section, we give a brief summary of these clinical studies, which are nevertheless descriptively helpful although being limited in determining causal relations. In the second section we provide a comprehensive review of animal and human experiments, in which sleep deprivation was used as independent variable and pain processing as dependent one. In the third section we are concerned with the potential algescic mechanisms of sleep deprivation. Various neurochemical changes during and after sleep deprivation have been observed, which are likely involved in processing of pain. As an example, sleep deprivation affects 5-hydroxytryptamine (5-HT) turnover,⁶ the firing rate of serotonergic neurons in the dorsal nucleus raphé⁷ and 5-HT receptor functions.⁸ There is a well-known central pain inhibitory effect of serotonin, which allows putting forward the hypothesis of a serotonergic mechanism bridging hyperalgesia and sleeping deprivation.

Correlational analysis of the relationship between sleep and pain

The overnight increase in muscular pain of fibromyalgia patients led to the assumption of a pathogenic role of disturbed sleep in this pain condition. As a consequence, Moldofsky et al.⁹ investigated in parallel sleep physiology and pain in fibromyalgia patients. They observed an increased ratio of alpha waves during non-rapid eye movement (NREM) sleep, the so-called 'alpha-delta sleep', which is indicative for an increased arousal during slow wave sleep. This change was assumed to interfere with the restorative function of NREM sleep. Interestingly, the pressure pain thresholds decreased substantially overnight in parallel.

Subsequent polysomnographic studies, in which the nocturnal sleep of healthy subjects was assessed for comparison, failed to confirm a specificity of the alpha-delta sleep for fibromyalgia. Horne and Shackell¹⁰ found no significant differences in the ratio of alpha activity in NREM sleep between fibromyalgia patients and healthy controls. Furthermore, an increased ratio of alpha waves during NREM sleep was observed in other conditions of chronic pain e.g., in rheumatoid arthritis,¹¹ and in conditions with primary insomnia.¹² However, this lack of specificity of alpha-delta sleep for fibromyalgia does not rule out a contribution of disturbed sleep to the development

of chronic pain, as suggested recently by a study of Argargun et al.¹³ on fibromyalgia patients. The authors found that 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 pave the way to chronic pain, the question arises whether the effect is direct or mediated by other factors. Jennum et al.¹⁴ demonstrated again that fibromyalgia patients exhibit more arousal episodes during night sleep when compared to healthy control subjects. However, the increased frequency of arousal episodes was strongly related to the occurrence of respiratory abnormalities. Thus, what are causes at the first glance may be consequences at the second one. Similarly, depression has to be considered as a mediating factor because of its well-known association with sleep disorders and chronic pain.¹⁵

There is also evidence that disturbed sleep augments acute pain. Raymond et al.¹⁶ 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 or other factors facilitate subsequent pain. However, it is not clear whether a change in sleep architecture, a complete interruption of sleep or a deprivation of certain sleep stages are critical for this facilitatory effect. The next section provides a systematic review of experimental data on the effects of sleep deprivation on pain perception in order to address this question.

Experimental analysis of the effect of sleep deprivation on pain perception

This review of the literature is based on a medline research for the years 1962 to February 2005 using the keywords 'sleep', 'sleep deprivation', '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 behavioral measure of pain as dependent variable. Furthermore, only studies that meet minimal methodological demands, regarding sample size and description, control of sleep deprivation, quality of pain measurement and suitability of statistics, were reviewed.

Human data

A total of 8 human studies met the inclusion criteria (Table 1). The pioneering study in this field is the one of Moldofsky et al.,⁹ the clinical aspects of which were already reported in the preceding section. Since the authors proposed that NREM sleep interruption causes myalgic pain as in fibromyalgia, they subjected six healthy men to a selective (stage 4) sleep deprivation for three consecutive nights. During stage 4 NREM sleep deprivation period both pressure pain sensitivity and the likelihood of occurrence of musculoskeletal pain increased. The validity of this study is hampered by the fact that a control group was missing. Thus, the changes observed might be due to unfamiliar sleeping conditions in a laboratory or result from any kind of sleep disruption and not necessarily from deprivation of sleep stage 4.

Parts of these objections were addressed in a second study by Moldofsky and Scarisbrick¹⁷ by adding the results of a second group to the data of Moldofsky et al.⁹ Seven healthy individuals were deprived selectively from 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 NREM sleep deprivation were not replicated by REM sleep deprivation.

In contrast to these studies, Drewes et al.¹⁸ analyzed the effects of total instead of selective sleep deprivation on pain detection (for pressure and heat) and tolerance thresholds (for pressure) in 10 healthy individuals without a control condition. The repeated measurements at short intervals of 2 h (starting at 11 p.m. and ending at 7 a.m.) with an additional assessment the next day (at 11 p.m.) indicated no changes in pain detection and tolerance thresholds. Accordingly, the finding of a generalized hyperalgesia was seemingly not replicated as far as uncontrolled studies provide evidence.

The study of Older and colleagues¹⁹ is one of the few controlled ones comparing 3 days of noise-induced disruption of slow wave sleep in 13 subjects and 3 days with 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 latter idea was derived from observations on fibromyalgia patients, who tend to have low IGF-1 levels. Whereas pressure pain thresholds and IGF-1 serum levels did not change, somatic complaints increased after the third night of sleep deprivation. Although again evidence for a

generalized hyperalgesia could not be accumulated, a heightened vulnerability to pain appeared to result from prolonged periods of disrupted sleep.

The findings of Drewes et al.¹⁸ and Older et al.¹⁹ are in contrast to the results of Lentz and colleagues,²⁰ who also investigated the effects of 'slow wave sleep disruption' over 3 nights. Although the study was uncontrolled, the comprehensive assessment of pain highlights this study in comparison to others. At the tender points designated for the diagnosis of fibromyalgia, the pressure pain thresholds decreased after 2 and 3 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 tenderness and pain, which represent anatomically generalized changes in pain sensitivity. In contrast, an interest in the regional pain of temporomandibular disorder (TMD) inspired the study of Arima et al.²¹ conducted in 10 healthy men. A variety of tests for TMD-like symptomatology (e.g. pressure pain threshold above the temporomandibular joint, occlusal force, electromyography of the M. masseter 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 EEG-controlled sound stimulation). The meaning of these findings is not definite because no substantial reduction of slow wave sleep could be achieved in the second and third night of sleep deprivation and in the first night no compensatory increase of NREM sleep stages 1 and 2 was observed.

An outstanding study, using current standards of methodology in this field, is the one of Onen et al.²² Sleep deprivation was accomplished in its total form, as 'slow wave' and REM sleep deprivation. The authors made use of a cross-over design, in which nine healthy men run through a night of total sleep deprivation for 40 h, and then either through two consecutive nights with 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 to 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

Table 1 Human experiments on the effects of sleep deprivation on pain.

Author	Subjects	Treatment	Design	Pain-related measurements	Main results
Moldofsky et al., 1975 ⁹	Healthy males, N = 6	SW-SD for 3 consecutive nights	Repeated measures over 7 days with the conditions <ul style="list-style-type: none"> • Baseline • SW-SD • Recovery 	Pain thresholds: <ul style="list-style-type: none"> • mechanical (at 26 sites, which are found to be often tender in fibromyalgia patients) 	Decreased mechanical pain thresholds after SW-SD More musculoskeletal symptoms after SW-SD
Moldofsky and Scarisbrick, 1976 ¹⁷	Healthy subjects, N = 13 (12 males, 1 female)	SW-SD vs REM-SD for 3 consecutive nights	Comparison of two independent groups (SW-SD vs REM-SD) including repeated measures over 7 days with the conditions: <ul style="list-style-type: none"> • Baseline • SW-SD or REM-SD • Recovery 	Subjective ratings of body complaints Pain thresholds: mechanical (at 26 sites, which are found to be often tender in fibromyalgia patients)	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 to the REM-SD group
Drewes et al., 1997 ¹⁸	Healthy subjects, N = 10	Total SD for one night	Repeated measures during the night and the following day <ul style="list-style-type: none"> • Baseline • SW-SD or REM-SD • Recovery 	Subjective ratings of body complaints Pain thresholds: <ul style="list-style-type: none"> • 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 ¹⁹	Healthy subjects, N = 19	SW-SD for 3 consecutive nights	Controlled comparison of two independent groups (SW-SD vs. untreated controls) including	Pain thresholds:	(1) No differences in pain thresholds within or between groups

<p>repeated measures over 7 days with the conditions:</p> <ul style="list-style-type: none"> • Baseline 	<ul style="list-style-type: none"> • mechanical 	<p>(2) More body complaints after 3rd SW-SD night compared to controls</p>
<p>SW-SD or control nights</p> <ul style="list-style-type: none"> • Recovery 	<p>Subjective rating of body complaints (VAS) Assessment of insulin-like growth factor (IGF-1) Pain thresholds:</p>	<p>(3) No changes of IGF-1 after SD</p>
<p>Repeated measures over 5 days with the conditions:</p> <ul style="list-style-type: none"> • Baseline 	<ul style="list-style-type: none"> • mechanical: thresholds were assessed on 16 specific sites, which are found to be often tender in fibromyalgia patients, and on two additional control sites 	<p>(1) Decreased tender point pain thresholds after the 2nd and 3rd SW-SD night compared to baseline</p> <p>(2) Pain thresholds on control sites were decreased after 3rd SW-SD night</p>
<p>SW-SD for 3 consecutive nights</p>	<ul style="list-style-type: none"> • Treatment 	<p>(3) Higher skinfold tenderness after the 3rd SW-SD night</p> <p>(4) Increased vasodilatation to mechanical stimulation (inflammatory flare response) after the 3rd SW-SD night</p>
<p>Healthy females, N = 12</p>	<p>Skinfold tenderness</p> <p>Skin reactive Hyperemia</p>	<p>(5) More musculoskeletal discomfort after the 3rd SW-SD night</p>
<p>Repeated measures over 6 days with the conditions:</p> <ul style="list-style-type: none"> • Baseline 	<p>Subjective ratings of body complaints</p> <p>Pain thresholds:</p> <ul style="list-style-type: none"> • mechanical (M. masseter) 	<p>(1) No effects of SW-SD on pain thresholds</p> <p>(2) No effects of SW-SD on EMG activity, maximum voluntary occlusal force and VAS-ratings</p>
<p>SW-SD for 3 consecutive nights</p>	<p>Repeated measures over 6 days with the conditions:</p> <ul style="list-style-type: none"> • Baseline 	<p>(1) No effects of SW-SD on pain thresholds</p> <p>(2) No effects of SW-SD on EMG activity, maximum voluntary occlusal force and VAS-ratings</p>
<p>Healthy males, N = 10</p>	<p>Healthy males, N = 10</p>	<p>(1) No effects of SW-SD on pain thresholds</p> <p>(2) No effects of SW-SD on EMG activity, maximum voluntary occlusal force and VAS-ratings</p>
<p>Lentz et al., 1999²⁰</p>	<p>Arima et al., 2001²¹</p>	<p>Arima et al., 2001²¹</p>

Table 1 (continued)

Author	Subjects	Treatment	Design	Pain-related measurements	Main results
Onen et al., 2001 ²²	Healthy males, N = 9	Total SD for one night, the following two nights <ul style="list-style-type: none"> • REM-SD or • SW-SD 	<ul style="list-style-type: none"> • Treatment • Recovery Controlled crossover-study with a counter-balanced order of REM- and SW-SD (two sequences). Repeated measures over 6 days with the conditions: <ul style="list-style-type: none"> • Baseline • Treatment • Recovery 	EMG (M. masseter) Maximum voluntary occlusal force Subjective rating of body complaints (VAS) Pain thresholds: <ul style="list-style-type: none"> • 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
Kundermann et al., 2004 ²³	Healthy subjects, N = 20 (11 males and 9 females)	Total SD for two nights with an interval of two days	<ul style="list-style-type: none"> • Treatment • Recovery Independent groups (Total SD vs. untreated controls) including repeated measures for overnight and between-session effects	Pain thresholds: <ul style="list-style-type: none"> • thermal Thermal sensitivity thresholds	(1) Heat pain thresholds were decreased after total SD, cold pain thresholds tended towards the same effect (2) Thermal sensitivity thresholds were unchanged after total SD

SD, sleep deprivation; SW-SD, slow wave-sleep deprivation; REM-SD, rapid eye movement-sleep deprivation; IGF-1, Insulin-like growth factor 1.

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. In our own laboratory we investigated the effects of two nights of total sleep deprivation separated by two recovery nights in comparison to two nights of undisturbed nocturnal sleep.²³ Twenty healthy subjects were assigned either to sleep deprivation or to control. Heat pain thresholds decreased significantly overnight after sleep deprivation with a rebound after recovery nights. A similar finding was obtained for cold pain thresholds although this method of pain induction tended to produce less reliable results. The pain specificity of our results could be established by assessing thermal sensitivity to non-painful stimuli (warmth and cold thresholds), with absolutely no indication of an effect of sleep deprivation.

While only a few human studies on the effects of sleep deprivation on pain perception have as yet become available, with still inconsistent findings, there is nevertheless a tendency of the results to indicate that sleep deprivation produces hyperalgesic changes in healthy subjects (5 out of 8 studies showing hyperalgesic changes with the remaining three studies showing no effect and no study showing hypoalgesic changes). In this regard, 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 have appeared to exert this effect, while results on the effects of selective REM sleep deprivation remain unclear. The findings of Onen et al.²² 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. In contrast to our study with a big sample and the use of heat pain thresholds,²³ the hyperalgesic action of slow wave sleep deprivation was observed in small samples only when tested by pressure pain stimulation. This suggests that the size of effect of sleep deprivation on pain perception is bigger when tested by experimental use of pressure pain than by use of heat pain. 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.²⁴ Muscle nociception is likely to be influenced to a much stronger degree by the

descending pain inhibitory control system than skin nociception.²⁵ 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 and not a regional one. The findings of Lentz et al.²⁰ and Onen et al.²² corroborate the idea of a systemic change in pain sensitivity as similar results were obtained when testing multiple sites.

It should be critically noted that individual factors (e.g., age or gender 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. However, our study²³ excluded general changes in somatosensitivity as underlying hyperalgesia after sleep deprivation because a similar pattern of changes was not observed for sensitivity to non-painful stimuli. Finally, since 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.²⁶ were among the first, who conducted experiments 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.²⁷ showed that REM sleep deprivation for 4 days decreases nociceptive thresholds as long as 96 h after termination of the sleep deprivation procedure.

Ukponmwan et al.²⁸ examined the relationship between REM sleep and opioidergic activity. They deprived Wistar rats selectively from REM sleep. The animals in the control groups were either pre-stressed or untreated. After a treatment period of 96 h, anti-nociceptive opioidergic mechanisms were activated either by stress produced by swimming for 5 min in ice-cold water, by the intracerebroventricular (icv) application of the

Table 2 Animal experiments on the effects of sleep deprivation on pain.

Author	Animals	Treatment	Design	Pain-related measurements	Main results
Hicks et al., 1978 ²⁶	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)	(1) Decreased nociceptive thresholds immediately, 3 h and 24 h after REM-SD (2) Effect of decreased nociceptive thresholds was independent from the length of REM-SD
Hicks et al., 1979 ²⁷	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)	(1) Decreased nociceptive thresholds immediately, 24 h and 96 h after REM-SD
Ukponmwan et al., 1984 ²⁸	Wistar rat, N = 3 × 70	REM-SD for 4 consecutive days	3 groups (REM-SD vs. pre-stress vs. controls) under the following conditions: cold- water-swim analgesia or phosphoramidon or morphine	Nociceptive thresholds: ● electrical (tail electric shock test)	(1) Condition a, b and c produced antinociceptive effects in pre-stressed and untreated (control) rats
Ukponmwan et al., 1986 ²⁹	Wistar rat, N ≥ 171	REM-SD for 4 consecutive days	2 groups (REM-SD vs. controls) under different pharmacologic conditions: (a) Deprenyl (b) β-phenylethylamine (c) Phosphoramidon(d) Deprenyl+phosphoramidon (e) β-phenylethylamine+phosphoramidon (f) Deprenyl+β-phenylethylamine+phosphoramidon	Nociceptive thresholds: ● mechanical (paw pressure test)	(1) REM-SD decreased basal nociceptive thresholds (without pharmacological intervention) compared to untreated (control) rats (2) No antinociceptive effect of condition a, b and c in sleep-deprived animals
				Nociceptive thresholds: ● mechanical (paw pressure test)	(1) REM-SD decreased basal nociceptive thresholds (without pharmacological intervention) compared to untreated (control) rats (2) Condition c, d, e and f produced increased nociceptive thresholds in the control group compared to the sleep deprived group (3) No differences in nociceptive thresholds between REM-SD and control group under condition a and b

Asakura et al., 1992 ³⁰	ddY mouse, N = 20	REM-SD for 2 consecutive days	Comparison of two independent groups: REM-SD vs. untreated controls	Nociceptive thresholds:	(1) No difference in the hot-plate test between the groups
Onen et al., 2000 ³¹	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: <ul style="list-style-type: none"> • Baseline • REM-SD or control nights • Recovery 	Nociceptive thresholds: <ul style="list-style-type: none"> • thermal (hot plate test) 	(1) Decreased nociceptive thresholds after 48h and 72h REM-SD
Onen et al., 2001 ³²	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: <ul style="list-style-type: none"> • Baseline • REM-SD or control nights 	Nociceptive thresholds	(1) REM-SD increased number and intensity of vocal responses to electrical stimuli
:				<ul style="list-style-type: none"> • 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) 	(2) REM-SD increased number and intensity of vocal responses to electrical stimuli
Dametto et al., 2002 ³³	Wistar rat, N = not stated	REM-SD for 4 consecutive days (in groups of 6 rats)	3 × 2 factorial design: <ul style="list-style-type: none"> • REM-SD vs. two different control groups with no REM-SD • Social stable vs social unstable conditions 	Nociceptive thresholds:	(3) No differences in the formalin test between or within groups
				<ul style="list-style-type: none"> • electrical foot shocks with assessment of flinch response and/or vocalization 	(1) No difference between the groups in flinch responseNo difference between the groups in flinch response
					(2) REM-SD deprived animals showed higher vocalization-thresholds
					(3) No interaction of REM-SD with social stress during SD

SD, sleep deprivation; REM-SD, rapid eye movement–sleep deprivation.

enkephalinase-inhibitor phosphoramidon or morphine. All three opioidergic treatments increased the thresholds for paw-pinch in the control and in the pre-stressed animals. However, in the rats deprived from REM sleep these effects were not present.

In a subsequent study, Ukponmwan et al.²⁹ tested whether the potentiation of opioidergic anti-nociception by monoamines can be prevented by REM sleep deprivation. Consequently, they did not only induce opioidergic anti-nociception 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 anti-nociceptive effects of phosphoramidon. This effect was abolished by 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 and colleagues³⁰ investigated the consequences of REM sleep deprivation over 48 h in mice using a variety of behavioral and neurochemical tests. Accordingly, the test of nociception was not the primary incentive to set up the study. They found no impact of REM sleep deprivation on nociceptive sensitivity as assessed by the hotplate test, a finding, which contrasts with almost all other animal data available.

Onen et al.³¹ assessed the vocalization threshold to noxious mechanical stimuli 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 h with a tendency to 'overshoot' towards increased nociceptive thresholds. This observation of an 'early' normalization contrasts with the findings of Hicks et al.,^{26,27} who continued to observe enhanced nociception even after a period of 48 h of recovery sleep. In a succeeding study, Onen et al.³² examined the effect of REM sleep deprivation over 3 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.³³ investigated the effects of REM sleep deprivation in Wistar rats over 96 h with a focus on performance in different

conditioning tasks. They assessed also nociceptive thresholds (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 ('modified multiple platform technique; MMPT), 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 behavior. The indication of even an anti-nociceptive 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, just the two studies^{30,33} with a wider scope, which did not exclusively focus on nociception, failed to find pro-nociceptive effects of REM sleep deprivation.

In summary, the experimental animal data are much more consistent than those obtained from studies in humans. REM sleep deprivation was observed to increase nociceptive behavior in almost all studies. This suggests a hyperalgesic action of REM sleep deprivation. 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 depriving NREM sleep stages. (The exclusive interest in REM sleep deprivation so far has very likely had methodological reasons because REM sleep deprivation is easy to accomplish in rodents.) 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 perception has been descriptive and does not allow for pinpointing 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.²⁸ According to their results, the analgesic action of endogenous and exogenous opioids is dependent on undisturbed sleep architecture or undisturbed sleep continuity as 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 synthesis³⁴ or/and a reduced affinity of μ - and δ -opioid receptors.³⁵

The potentiation of the opioidergic analgesic effects, produced by the application of enkephalinase-inhibitors and a MAO-B inhibitor or by MAO-B substrates, can be nullified by REM sleep deprivation.²⁹ This suggests the involvement of further neurotransmitter systems. The MAO-B inhibitor deprenyl stimulates dopaminergic but also serotonergic activity,³⁶ 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 the potency of morphine in producing analgesia.³⁷ This effect is due to the neurochemistry of the descending pain inhibitory control system, which contains opioidergic and monoaminergic (serotonergic, noradrenergic) links.³⁸ Furthermore, decreased levels of 5-HT and 5-hydroxyindole acetic acid in different brain areas were found in rats after REM sleep deprivation of 96 h.^{38,39} One can speculate that REM sleep deprivation or a disruption of sleep continuity in general render 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 (>72 h) were investigated.^{38,39} In contrast, shorter periods of sleep deprivation (<24 h) have appeared to enhance 5-HT activity in animals in various cerebral structures.⁴ However, a recent study of Bjorvatn et al.⁴⁰ 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 pre-synaptic (release, turn-over) or post-synaptic 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 neuroimmunologic factors (particularly the interleukins⁴¹) 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 predominantly pressure pain sensitivity and to induce muscle pain as shown in this review. Muscle nociception is much more subject to the descending pain inhibitory system than skin nociception as explained earlier in this review.^{24,25}

Future research

Besides more descriptive studies on the active part of sleep deprivation (which type and stages of sleep have to be deprived in which form?) when it affects pain perception studies focusing on the mechanisms of action are badly needed in the future. To achieve the latter, experiments, which are designed to examine specific mediating factors (such as opioidergic and serotonergic neurotransmission) and which are capable of delineating 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.

Conclusion

In this review evidence was examined for the hypothesis that the deprivation or the disturbance of sleep enhances pain sensitivity and causes pain. Pain disturbs sleep by inducing arousal and triggering all other neurobiological sequels of stress, which 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 maintain or even augment each other. Accordingly, sufficient management of disturbed sleep might alleviate pain.³ On the other hand, better pain relief may promote more restorative sleep, which then further assists in long-term pain relief.

Practice points

Concurrent management of disturbed sleep and pain in patients with chronic pain is advisable because:

1. Pain enhances arousal and disrupts sleep.
2. Sleep deprivation and sleep disruption increase pain sensitivity and vulnerability to pain.
3. A vicious circle with sleep disorder and chronic pain maintaining and augmenting each other may result.

Research agenda

Future research should focus on:

1. Determination of the active part of sleep deprivation regarding its effect on pain perception (e.g. total, NREM or REM sleep deprivation).
2. Determination of the part of the pain system affected by sleep deprivation (e.g. spinal or cerebral parts, excitatory or inhibitory parts, certain neurotransmitter systems).
3. Determination of potential mediators of the relationship between sleep deprivation and pain perception (e.g. vigilance, mood, autonomic and endocrine changes).

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