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Article *in* Seminars in Neurology · April 2005

DOI: 10.1055/s-2005-867079 · Source: PubMed

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Sleep and Pain: Interaction of Two Vital Functions

Timothy Roehrs, Ph.D.,[1,2] and Thomas Roth, Ph.D.,[1,2]

ABSTRACT

Disturbed sleep is a key complaint of people experiencing acute and chronic pain. These two vital functions, sleep and pain, interact in complex ways that ultimately impact the biological and behavioral capacity of the individual. Polysomnographic studies of patients experiencing acute pain during postoperative recovery show shortened and fragmented sleep with reduced amounts of slow wave and rapid eye movement (REM) sleep, and the recovery is accompanied by normalization of sleep. Objective assessments of sleep in patients with various chronic pain conditions have been less definitive with some studies showing fragmented and shortened sleep and others showing normal sleep. Although daytime fatigue is a frequent complaint associated with complaints of pain-related disturbed sleep, objective assessments of daytime sleepiness reveal minimally elevated levels of sleepiness and emphasize the importance of distinguishing sleepiness and fatigue. The pain-sleep nexus has been modeled in healthy pain-free subjects and the studies have demonstrated the bidirectionality of the sleep-pain relation. Given this bidirectionality, treatment must focus on alleviation of both the pain and sleep disturbance. Few of the treatment studies have done such, and as a result no clear consensus on treatment approaches, much less on differential etiology-based treatment strategies, has emerged.

KEYWORDS: Sleep disturbance, fatigue, sleepiness, pain

Objectives: On completion of this article, the reader will be able to discuss the sleep disturbances found in acute and chronic pain conditions.
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Disclosure: Statements have been obtained regarding the authors' relationships with financial supporters of this activity, use of trade names, investigational products, and unlabeled uses that are discussed in the article. The authors have nothing to disclose.

"Pain is a perceived threat or damage to one's biological integrity."[1] As such then, nociceptive information is essential to survival; when perceived by the organism as pain, defensive mechanisms are recruited to protect the organism from further damage. Recognition of the importance of pain is seen by the designation of pain measurement as the fifth vital sign. Sleep also serves biologically essential functions. Although the

Sleep in Neurological Practice; Editor in Chief, Karen L. Roos, M.D.; Guest Editor, Alon Y. Avidan, M.D., M.P.H. *Seminars in Neurology*, Volume 25, Number 1, 2005. Address for correspondence and reprint requests: Timothy Roehrs, Ph.D., Sleep Disorders and Research Center, Henry Ford Hospital, 2799 West Grand Blvd., CPF-3, Detroit, MI 48202. [1]Henry Ford Health System, Sleep Disorders and Research Center, Detroit, Michigan; [2]Department of Psychiatry and Behavioral Neuroscience, School of Medicine, Wayne State University, Detroit, Michigan. 0271-8235,p;2005,25,01,106,116,ftx,en;sin00349x.

exact nature of these functions is still not clear, any persistent deprivation or fragmentation of sleep increases the homeostatic sleep drive, inevitably producing a rapid sleep onset. Sleep cannot be avoided when the homeostatic sleep drive reaches its maximum; sleep intrudes into wakefulness in the form of brief microsleeps, resulting in automobile and workplace accidents. When these two vital functions, pain and sleep, interact, the biological and behavioral capacity of the individual is compromised.

This article will review the growing literature on the sleep disturbances found in acute and chronic pain conditions. The new literature on experimental models of pain and sleep and the few studies that have explored the bidirectionality of that association will also be reviewed. The neurobiological mechanisms underlying pain and sleep and their possible interactions will be described. Finally, various treatment issues and treatment approaches will be discussed.

An important methodological consideration in understanding the pain-sleep interaction relates to their measurement. Scales have been developed that can reliably measure various aspects of sleep and pain. However, sleep can be directly assessed with the simultaneous recording of multiple physiological systems (e.g., electroencephalography [EEG], electromyography, and electrooculography]). This method, termed polysomnography, is the standard for defining sleep and its stages. Polysomnography allows the investigator to objectively quantify sleep duration and awakening frequency, distinguish various types of sleep fragmentation, and identify primary sleep disorders. Research participants cannot accurately do this, in part because of the amnesic properties of sleep and in part because of the impact of primary sleep disorders. Thus, apnea patients who awaken hundreds of times a night to resume breathing are not aware of this and only report in the morning awakening tired. In contrast, insomnia patients typically underestimate their sleep duration and overestimate their sleep latency. Not surprisingly, subjective sleep data are vulnerable to bias.

In the case of sleep-pain research there are two potential biases. First, there is the expectancy that nocturnal pain will disturb sleep. Second, there is potential for a response bias, that is, complaining of one symptom will increase the likelihood of complaining of another. Thus, in evaluating results of the various studies more weight must be placed on polysomnographic assessments of sleep.

SLEEP IN CLINICAL PAIN CONDITIONS

Acute Pain

Epidemiological studies have reported sleep disturbances in persons experiencing acute and chronic pain.[2–4] But very few studies have polysomnographically assessed sleep in various conditions in which acute pain is experienced. The obvious problem is acute pain's unpredictable and short-lived nature. However, one clinical model of acute pain lending itself to polysomnographic study is that experienced during the postsurgery recovery period. A few studies of the sleep of postoperative patients (~100 total patients studied) after major abdominal surgery, herniorrhaphy, or minor undefined surgery have been done.[5–10] In these studies, sleep was recorded from 1 to 6 postoperative nights. Total sleep time was generally reduced for 1 or 2 night's duration and the sleep was fragmented with frequent arousals and awakenings. In most patients, regardless of the type of surgery, the duration of slow wave sleep was reduced for up to 4 nights. Typically, rapid eye movement (REM) sleep was absent on the first 2 postoperative nights with a "rebound" shown over subsequent nights.

Although sleep is clearly disrupted in these patients, determining the causal role of the various factors is extremely difficult. Rosenberg-Adamsen et al identified several factors that may contribute to the postoperative sleep disturbance.[11] Hospital-related environmental factors including noise, temperature, and light are important variables. The stress response to the surgical insult, which involves any number of hormones and biochemical reactions, must also be considered. Additionally, the medications used during the postoperative recovery, specifically type and dose of analgesics, are an important factor. The effects of one class of analgesics, the opiates, on sleep are discussed in detail below. Interestingly, studies of the efficacy of analgesic-sleep aid combination drugs have been done using assessments of pain and sleep in patients undergoing obstetric procedures, dental extraction, and bunionectomies.

Chronic Pain

The literature describing the sleep of patients experiencing chronic pain is much more extensive than that of acute pain, but again no more definitive. The diseases studied are diverse and include the various headache disorders and the peripheral neuropathies with associated pain such as diabetic neuropathy and postherpetic neuralgia. Sleep and fatigue in musculoskeletal diseases, including rheumatoid arthritis, osteoarthritis, and fibromyalgia, have also been studied, as have conditions in which pain is diffuse, nonspecific, and not related to structural pathology (i.e., chronic fatigue syndrome).

HEADACHE

The association of sleep and headache is well known in clinical medicine, and representative population surveys have reported a sleep and headache association. For

example, in the survey done by the Gallup Organization for the National Sleep Foundation, 25% of a population-based sample reported sleep and headaches as common problems.[12] The relation of disturbed sleep and headache was recently reviewed.[13] Sleep in patients with tension-type headaches is generally characterized polysomnographically by low sleep efficiency, frequent awakenings, and reduced amounts of slow wave sleep. However, in intermittent migraine, minimal sleep disturbance was reported, albeit in only one study.[14] The review makes the important point that primary sleep disorders such as apnea and periodic leg movements were often not ruled out in the studies. Morning headache is a frequent complaint in sleep apnea. A study of the relation of cluster headache and sleep apnea found 20 of 25 patients with cluster headache had sleep apnea syndrome.[15] Another study reported 55% of patients with headache had a primary sleep disorder.[16] Also, headache is a symptom associated with a variety of other medical and psychiatric disorders, which then have their own sleep-disruptive effects. Various drug treatments also are known to produce both headache and sleep disturbance. Some of the drugs used to treat headache may result in sleep disturbance. Quite clearly, the etiologies and manifestations of sleep disturbance in headache are complex and multifactorial.

NEUROPATHIC PAIN

Patients with various peripheral neuropathic pain conditions report persistent interruption of sleep. We are not aware of studies comparing the sleep disturbance in neuropathic pain with that of other chronic pain conditions or age-matched control populations. However, pharmacotherapeutic trials of different drugs have included pain assessments and ratings of sleep interference and have shown improvements in the subjective ratings of sleep interference.[17–19] The only available polysomnographic study assessed patients with diabetic and postherpetic neuropathy. Relative to historic age-matched controls, the 19 neuropathic pain patients had lower sleep efficiencies and fragmented sleep as reflected in reduced amounts of stages 3 and 4 and REM sleep and elevated stage 1 sleep.[20]

MUSCULOSKELETAL PAIN

Patients with rheumatic diseases frequently complain of disturbed sleep and daytime fatigue. Studies of sleep and daytime function in patients with rheumatic diseases and fibromyalgia recently were critically reviewed in two companion articles.[21,22] Polysomnographic studies have reported sleep efficiencies that are normal in some studies[23–25] and abnormally low in other studies.[26–28] Some studies have reported disrupted and fragmented sleep and an elevated prevalence of underlying primary sleep disorders. Alpha intrusions into non-NREM (NREM) sleep generally, and slow wave sleep specifically, have also been reported in some studies. This EEG anomaly is discussed in more detail below.

Fatigue is a major symptom in rheumatoid arthritis and is one of the five criteria for clinical remission. Unfortunately, fatigue has not been precisely defined or measured in the general population. It is not differentiated from daytime sleepiness, a condition with known morbidities attributable to reduced and fragmented sleep. Both in terms of etiology and reversal, fatigue and sleepiness are distinct conditions. Fatigue is caused by muscular or mental exertion (i.e., extended time-on-task) and reversed by rest. In contrast, sleepiness is caused by sleep fragmentation or sleep loss and is reversed by sleep. Rest does not improve level of sleepiness.

Sleepiness is objectively measured using the multiple sleep latency test (MSLT) in which sleep onset is measured polysomnographically on repeated opportunities throughout the day. MSLT norms and epidemiological data have been published.[29] The few studies that have measured sleepiness by MSLT in rheumatoid patients have reported normal or moderately elevated levels of sleepiness.[25,28,30] The patients all had fatigue complaints at study entry, but concurrent assessment with validated fatigue scales on the day of the MSLT were not done. Thus, it is difficult to differentiate sleepiness and fatigue in these studies and how this daytime sign-symptom complex relates to the disturbed nocturnal sleep.

In patients with fibromyalgia the amounts of slow wave sleep, REM sleep, and total sleep time are reduced relative to age-matched normals.[31–34] Also, the number of transient arousals and full awakenings are increased. The presence of α intrusions into slow wave sleep specifically and NREM sleep generally, referred to as α-delta sleep, is reported to be a prominent characteristic of the sleep of fibromyalgia patients.[35] It was described in fibromyalgia patients as an admixture of α EEG waves with delta EEG waves and later described also as phasic bursts of α activity during all the NREM sleep stages.

The α-delta anomaly is not specific to fibromyalgia. It is also reported in patients with rheumatoid arthritis, as noted above, and chronic fatigue syndrome.[36,37] Furthermore, its specific relation to chronic pain has been questioned. It is important to note that α-delta sleep was first described by Hauri and Hawkins[35] and identified as a feature of sleep in depressed patients. Also, in a study of 1076 consecutive patients at a sleep disorders center fewer than 40% of the patients exhibiting the α-delta anomaly had chronic pain.[38] The functional significance of this anomaly has also been disputed. Most authors have considered it evidence of disturbed and light sleep. However, multisite EEG recording with electronic signal processing has differentiated the occipital α of relaxed wake with eyes closed from the frontal-central α seen during sleep.[39] It is hypothesized that rather than being a sign of arousal

during sleep as suggested by occipital α, this frontal-central α is a sign of sleep-maintaining processes.

In several studies of patients diagnosed with chronic fatigue syndrome, in which pain is more diffuse and not structural, reductions in sleep efficiency and REM sleep have been reported.[38–40] However, it has been disputed as to whether sleep is disturbed in rigorously diagnosed chronic fatigue syndrome.[41] Furthermore, as in other pain conditions, the disturbed sleep may be attributable to comorbid depression rather than chronic fatigue. Finally, fatigue and sleepiness have not been well differentiated in this patient population.

The causal relation of pain and sleep loss and its consequence is difficult to determine in many of these chronic pain conditions. As noted above, much of this literature has not carefully distinguished fatigue and daytime sleepiness. Although reduction of sleep time and fragmentation of sleep clearly lead to increased daytime sleepiness, that relation has not been directly explored in chronic pain conditions.[29] Also, most of the studies have only used investigators' qualitative, not quantitative, assessments of sleep fragmentation and α intrusion. Systematic scoring rules for sleep fragmentation have been published[42] and electronic analysis for EEG α frequency can be used. In addition, many of these musculoskeletal conditions are heterogeneous, and only recently have diagnostic criteria been systematically applied. Thus, the rigor of the diagnostic criteria in these studies is often criticized.[41] Importantly, many of these patients have depression and anxiety disorders; additionally, some also have primary sleep disorders (i.e., apnea and periodic leg movements). Primary sleep disorders and psychiatric disorders can themselves cause sleep fragmentation and sleep loss.

An important issue that arises from these studies is the bidirectionality of the pain and sleep relation (i.e., poor sleep enhances pain and enhanced pain further disturbs sleep). In a prospective study, self-ratings of sleep and pain in patients with fibromyalgia showed that nights with poor sleep tended to be followed by days with greater pain, and days with greater pain were followed by nights with greater sleep disturbance.[43] Studies showing a correlation of the amount of α intrusion to measurements of pain and treatment-related reductions of α sleep leading to lowered levels of pain also support a bidirectional hypothesis.[41]

EXPERIMENTAL MODELS OF SLEEP AND PAIN

Disruptive Effects on Sleep of Experimental Pain

Studies have attempted to experimentally induce pain during sleep in healthy subjects using short, discreet stimuli. Three different nociceptive stimuli (i.e., muscle stimulation by infused hypertonic saline, mechanical pressure at the right proximal interphalangeal joint, and cutaneous stimulation with green-blue light) were presented during slow wave sleep.[44] Each stimulus during wakefulness was detected as painful and evoked ratings of "sharp, nauseating, and agonizing" pain. During the 10 seconds subsequent to the presentation of these stimuli during sleep, the EEG was characterized by increases in α and β frequencies and decreases in delta frequencies. Although all were sleep-disruptive, there were some differences among the three stimuli in their sleep-disruptive potencies and among results from the various EEG derivations studied.

Cortical arousal, using the American Sleep Disorders Association (ASDA) criteria to define arousal, was assessed in healthy, pain-free subjects. The ASDA criteria are a set of scoring rules that can be reliably applied in assessing the presence of EEG α and β activity.[42] Cold, neutral, or hot stimuli applied to shoulder skin were presented during sleep.[45] Cortical arousal to the cold and hot stimuli, which were rated as moderately painful in wake, was reduced in slow wave and REM sleep relative to stage 2 sleep. In a follow-up study, thermal stimulation that produced a rapid and transient rise in heart rate during wake produced a 7% increase in stage 2 sleep, 5% in stages 3 to 4, and 4% in REM.[46] In another study, ASDA-defined arousal threshold to heat stimuli applied to the forearm was higher in stages 3 and 4 and REM sleep compared with stage 2 sleep.[47] During wake the stimuli were rated as being burning, hurting, and at tolerance threshold for the higher intensities necessary to produce arousal during sleep. These studies clearly show that relative to wake, arousal responses to painful thermal stimuli are reduced in sleep, and within sleep, more so in stages 3 and 4 and REM than stage 2. To date these studies have not found a differential stages 3 and 4 versus REM sleep nociceptive arousal threshold. It should be noted that arousal threshold to acoustic stimuli in man is higher in stages 3 and 4 sleep relative to REM sleep and stage 2 NREM.[48]

The studies cited above all presented short, discreet painful stimuli. In clinical pain conditions the painful stimulus is persisting and not episodic; even in acute clinical pain the nociceptive stimulus often lasts for nights. An experimental model of deep muscle pain in healthy subjects utilized two types of weight lifting exercises, one designed to produce deep muscle pain and the other no pain.[49] Visual analog scale ratings of pain over the 84 hours of assessment validated the differential experience of pain in the two exercise conditions. However, a differential effect on the polysomnographically assessed sleep over 2 nights at 60 and 84 hours postexercise was not observed, despite the perceived differential pain ratings.

Sleep Loss and Pain Sensitivity

Nathaniel Kleitman, the father of modern sleep research, reported in his 1939 monograph that in sleep deprivation studies "cutaneous sensitivity to touch remained unchanged" whereas "that to pain showed a progressive increase [i.e., hyperalgesia] during the period of wakefulness."[50] This same observation has often been reported anecdotally in studies of sleep loss, but over all these years it has received little systematic evaluation.

Owing to the clinical description of the α-delta sleep anomaly in fibromyalgia patients, the majority of the few studies that have been done have focused on the deprivation or disruption of slow wave sleep. One early study deprived healthy subjects of slow wave sleep, producing slight reductions of sleep time, and three of the six subjects had reduced thresholds to mechanical pressure induced pain (i.e., showed hyperalgesia) the following day.[51] Two recent studies have done selective stage 3 to 4 deprivation in healthy subjects. Young adults were deprived of stage 3 to 4 sleep for 3 nights without reducing total sleep time (i.e., 6.8 hour per night on average), and pain threshold measured by dolorimetry was not significantly altered.[52] In contrast, a study of middle-age women similarly deprived stage 3 to 4 sleep and found that pain threshold measured by dolorimetry was significantly reduced on the second and third nights of deprivation.[53] In this study the total sleep time was initially reduced from 6.4 to 5.4 hour, although it returned to 6.4 hour by the third night of slow wave sleep deprivation. An important factor in the discrepant results between studies may be the reduced total sleep time associated with the deprivation. It also may be that age is an important factor; the subjects in whom deprivation of stage 3 to 4 sleep led to hyperalgesia were older (44 versus 23 years of age on average).

Total deprivation of sleep, as opposed to selective sleep stage deprivation, clearly has a hyperalgesic effect. Forty hours of total sleep deprivation reduced mechanical pain threshold by 8% in healthy, pain-free adults.[54] But again, disruption of REM or slow wave sleep for 1 night did not produce effects in this study, despite a concomitant reduction of sleep time to 5 hours in the disruption conditions. The subjects of this study also were somewhat younger, 31 years of age on average, than those of the study showing a hyperalgesic effect of slow wave sleep deprivation. These studies indicate that when stage 3 to 4 deprivation has a hyperalgesic effect, it occurs with concomitant reduction of sleep time and in middle-aged individuals.

To understand the relation of sleep deprivation to pain sensitivity a paradigm shift is necessary. Loss of specific sleep stages may not be critical to producing hyperalgesia; the extent, irrespective of sleep stage, in sleep time reduction and the subsequent level of sleepiness produced by the sleep time reduction is more likely the critical factor. Sleepiness is conceptualized as a physiological need state, produced by discrepancy between one's habitual sleep time and biological sleep need.[29] Reduction of nocturnal sleep time from the optimal 8 hours to 6, 4, and 2 hours in alert, healthy, young adults has a linear and positive relation to the level of sleepiness the following day as measured by the MSLT, and the sleep loss effects have been shown to accumulate over nights.[55,56] On the other hand, a longer sleep time produced by an extended bedtime increases MSLT scores in otherwise healthy individuals who are excessively sleepy.[57]

Sleep loss and increased sleepiness clearly has hyperalgesic effects. A study that used a radiant heat stimulus to assess pain threshold in young, healthy, pain-free adults found that total sleep deprivation (i.e., 1 night of sleep loss) reduced pain threshold by 27%.[58] This study also found that 4 hours of sleep loss reduced pain thresholds by half as much, 13.5%. Sleepiness as measured by MSLT was increased by the 8-hour sleep loss and approximately half as much by the 4-hour sleep loss. Furthermore, in this study the increased sleepiness that is typically shown over the midday after 8 hours in bed the previous night was associated with reduced pain thresholds.[59] Although it will yet be necessary to determine whether this midday hyperalgesia is due to other circadian factors or to sleepiness occurring over the midday, sleepiness due to reduced bedtime the previous night is associated with hyperalgesia.

The role of age in the hyperalgesic effect of sleep reduction is not clear. It has not been directly tested, but it can be discussed. Age probably has a direct impact on nociception, but it is also likely that age modifies the response to sleep time reductions. It is known that with age intolerance develops to the sleep schedule shifts required in shift or night work.[60] As one ages, intolerance to reductions of sleep time from one's biological sleep need may also develop. Thus, the potential for a hyperalgesic effect of sleep reduction may increase with age.

NEUROBIOLOGY AND PHARMACOLOGY OF PAIN AND SLEEP

The neurobiology and pharmacology of pain and sleep is an extremely complex interaction that has not been well described and is not well understood. It is not the purpose here to provide a complete description of the neurobiology of pain. The present intent is to describe the potential interactions of pain systems with sleep systems. It is also noted that in discussing chronic pain conditions, the source and etiology of the pain (i.e., peripheral versus central, inflammatory versus structural) may be very important with regard to the neurobiology of the pain-sleep interaction.

Pain Perception

Although the neurobiology of pain is complex, the basic systems and their neurochemistry can be described.[61] Pain is a complex perception resulting from the activation of peripheral nociceptors and the modulation of these sensations by several central mechanisms.[61] Nociceptive information is transmitted from the periphery to the dorsal horn of the spinal cord and from the spinal cord to the thalamus and the cerebral cortex along five major ascending pathways. As an example, thermal nociceptors (i.e., the system used in many of the studies cited in this review) transmit information along A-delta fibers to lamina I and V of the dorsal horn, ascending through the spinothalamic tract to the thalamus, to both central lateral and ventral posterior thalamic nuclei, and terminating at the somatosensory cortex. Glutamate and some neuropeptides (i.e., substance P, calcitonin gene-related peptide) are some of the transmitters used by this system. This system, using A-delta nociceptors and fibers, relates to what is characterized as first or sharp pain. A second system that relates to dull, burning pain, sometimes called second pain, uses C nociceptors and fibers. C fibers are known to release substance P in response to persisting injury. Although substance P has received the most extensive research attention, other neurochemicals may also be important.

Hyperalgesia

Hyperalgesia (e.g., enhanced pain sensitivity) can occur through both peripheral and central mechanisms. In the periphery the release of bradykinin, histamine, serotonin, substance P, prostaglandin, and acetylcholine can sensitize nociceptors. Centrally mediated hyperalgesia can occur through the opening of postsynaptic N-methyl-D-aspartate glutamate receptor gates at the dorsal horn. The C receptor and fiber system is known to fire repetitively in conditions with persisting pain and thereby hyperexcite dorsal horn neurons. Thus, pathways for a possible sleep loss–induced hyperalgesia exist. However, studies have yet to explore the mechanisms by which sleep loss produces its hyperalgesic effect.

Antinociception

Antinociception, the inhibition of nociceptive information, results from the modulation of A-delta fibers by nonnociceptor A-β fibers, according to the classical gate control theory of Melzack and Wall.[62] This inhibition occurs at the dorsal horn. Other descending inhibitory systems also suppress nociceptive neurons in the dorsal horn. One such inhibitory system originates in the midbrain periaqueductal gray, projects to the nucleus raphe magnus in the pons, and then along the dorsolateral funiculus to the dorsal horn of the spinal cord.[61] This is one system by which the opiates are thought to produce their analgesic effects.

Beyond the opioid system, other major nonspecific, inhibitory systems are active during sleep. The most current models of sleep-wake neurobiology posit major roles for the inhibitory neurochemicals, gamma-aminobutyric acid (GABA), and galanin.[63] During sleep GABAergic and galaninergic neurons of the ventrolateral preoptic nucleus inhibit the major cholinergic and monoaminergic ascending arousal systems. These neurons project caudally to the level of the posterior hypothalamus where they inhibit the ascending arousal system. GABAergic interneurons of the thalamus also inhibit all afferent input to the cerebral cortex, including nociceptive input.

Adenosine has sleep-promoting capacity and is considered by some to be the major neurochemical that operates as the sleep-wake homeostat.[64] Its level in the brain accumulates during sustained wakefulness and decreases during sleep, particularly slow wave sleep. Interestingly, adenosine receptor activation has also been shown to produce analgesia.[65] In part, the analgesic effects of morphine can be attributed to the fact that morphine induces release of adenosine. The role of adenosine in the sleep-pain nexus needs further exploration.

Evidence also indicates that acetylcholine has a critical role in antinociception and sleep. Animal studies have shown that cholinomimetics have an antinociceptive effect.[66,67] Clinical studies have also shown that cholinergic agonists can be used for pain control.[68,69] Acetylcholine has a prominent role in the generation of REM sleep.[70] Thus, acetylcholine may both promote antinociception and REM sleep. Opiates are potent REM-suppressing drugs in acute studies. Animal studies have shown REM suppression after morphine or methadone.[71] One study of heroin effects in drug-naive humans showed REM suppression,[72] and several studies of drug addicts have similarly reported REM suppression.[73,74] The impact of opioid-induced REM suppression on pain threshold is not clear.

A few studies have attempted to explore the nature of sleep-related antinociception in humans. A study used laser pulses applied to the skin to excite A-delta fibers during wake and sleep in healthy, pain-free subjects.[75] Evoked potentials recorded from the somatosensory cortex were markedly reduced during stage 2 sleep relative to wake. In another study a method of selectively stimulating C fibers was developed and evoked potentials from somatosensory cortex were recorded during sleep.[76] The amplitude of late occurring evoked potentials was markedly reduced during sleep. Studies to localize the pain-associated evoked potentials within the somatosensory cortex have also been done. A recent study used magnetoencephalography (MEG) to record evoked magnetic fields following painful electrical

stimulation of the index finger.[77] Late MEG signals were reduced in stage 2 sleep relative to wake, although early MEG signals were not altered. Early painful and nonpainful signals were localized to the primary somatosensory cortex, and the late painful signals were localized to the secondary somatosensory cortex. The authors speculate that the early MEG signals represent the nociceptive stimulus and the late MEG signals the experience of pain, its location, and intensity.

Chronic Pain and Sleep

In chronic pain conditions the question arises as to what adaptive mechanisms are recruited to protect sleep and what adaptations occur within the pain systems. Generally, humans show a rapid increase in arousal threshold (i.e., reduced arousability) with repeated stimulation during the night. The more sleep is fragmented, the more it is resistant to further disruption. Is the α-delta EEG anomaly a reflection of such an adaptive process protective of sleep? On the other hand, with the persisting intrusion of α activity into sleep are the restorative processes of sleep compromised? As discussed earlier, sleep loss, even in moderate amounts, leads to increased daytime sleepiness. As yet, the only studies that have assessed level of daytime sleepiness in a chronic pain condition found no clearly increased daytime sleepiness in arthritis patients.[25,28,30] Adaptations to the performance-impairing effects of experimental sleep loss in healthy subjects have been reported. One study found a slowly accumulated sleep loss (i.e., 2 hours per night for 4 nights) did not produce the same degree of performance impairment that a single night of 8 hours sleep loss did.[55] Whether adaptation to the impairing effects of sleep loss due to chronic pain associated disruption of sleep occur, and if so at what cost, is not known.

In chronic pain conditions, whether an adaptation to nociceptive information occurs and how such an adaptation occurs neurobiologically, is unclear. What does appear clear is that central mechanisms are recruited. The data in chronic pain patients suggest the central stress system, the hypothalamic-pituitary-adrenal axis (HPA), is activated in chronic pain. Several recent reviews have described the nature of HPA axis response to acute and chronic pain.[78,79] Of note for sleep is the fact that the corticotropin-releasing hormone and locus ceruleus-norepinephrine systems are activated in the stress response. Through various central and peripheral effector systems HPA activation has antisleep, antireproductive, antigrowth, immunosuppressive, and catabolic effects. The stress response is intended to be time-limited; in chronic stressful conditions (i.e., pain), its pathophysiology is expressed as hyperactivation or hypoactivation.

The sleep disturbance expressed in chronic pain is likely due to HPA dysregulation and not the direct nociceptive disruption of sleep. There is accumulating evidence that primary insomnia is the expression of a physiological "hyperarousal" associated with activation of the sympathetic nervous system (SNS) and HPA axis. A similar pathophysiology may underlie the sleep disturbance in chronic pain. Insomniacs show increased metabolic rates,[80] elevated levels of circulating catecholamines,[81] increased body temperature,[82] and altered heart rate variability[83] and pupillometry patterns.[84] The HPA augmentation in insomnia is indicated by elevated levels of urinary free cortisol proportional to the amount of wakefulness during the night.[81] An activated SNS and HPA axis suggests a central mechanism possibly involving corticotropin-releasing-factor neurons. Similar responses to the stress of chronic pain and a similar disruption of sleep may occur in chronic pain conditions. One proviso is that primary insomnia is often characterized by full wakefulness and not light fragmented sleep.

TREATMENT CONSIDERATIONS

The treatment of sleep disturbance due to acute or chronic pain has received very little systematic study. The studies are limited in the methodologies used to assess sleep, pain, and the associated daytime sleepiness and fatigue. The data have rarely shown improvement in both sleep and pain, much less in daytime function. Typically, studies show improvement in one domain with minimal or no improvement in the other. For that reason several drug classes have been evaluated, and no consensus on treating disturbed sleep in acute or chronic pain has arisen, much less differential etiology-based treatment strategies.

Analgesics

Analgesics are frequently used in treating chronic pain, but are not uniformly successful in improving sleep. Acetaminophen, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and opiates have been used. A placebo-controlled study of the NSAID tenoxicam in patients with rheumatoid arthritis found the drug improved the clinical condition of the patients but had no effect on the polysomnographically recorded sleep of the patients.[26] It should be noted that patients had primary sleep disorders that may have been the causal factor in the disturbed sleep. A placebo-controlled study of the opioid levorphanol in patients with neuropathic pain of various etiologies reported improvement in their daily pain ratings and a small improvement in their self-rated "ability to get enough sleep."[18]

Antidepressants

Tricyclic antidepressants are used to treat a variety of chronic pain conditions. A recent meta-analytic review

of tricyclic antidepressant treatment in patients with fibromyalgia concluded that in comparison to placebo the improvement in subjective assessment of sleep was greater than the improvement in measures of morning stiffness and tenderness.[85] Another review of treating sleep disturbance in neuropathic pain noted improvement of sleep in both depressed and nondepressed patients with neuropathic pain of various etiologies.[86] This observation raises the issue of the mechanism underlying the sleep improvement associated with the antidepressant treatment. These medications have sedating effects due to both their anticholinergic and antihistaminic activities. Their antinociceptive effect may be due to their capacity to release adenosine in the periphery and their central inhibition of the neuronal reuptake of adenosine.[65] The antinociceptive effect of adenosine was discussed above.

Hypnotics

Benzodiazepine receptor ligands, including the older benzodiazepine hypnotics and the newer drugs that act at the benzodiazepine receptor but are nonbenzodiazepine in chemical structure, have been used extensively in a variety of chronic pain conditions. In a survey of rheumatoid arthritis patients, ~30% of patients reported use of benzodiazepines for their sleep disturbance due to their pain, and the drug had been used for 4 years on average.[86] However, there is little systematic, placebo-controlled study of their efficacy in pain-associated sleep disturbance. One study of triazolam compared with placebo in patients with rheumatoid arthritis found improvement in polysomnographically measured sleep; morning stiffness and daytime sleepiness were also improved.[25] A dose-effect study of zolpidem in patients with fibromyalgia found self-rated sleep time, speed of sleep onset, frequency of awakenings, and daytime energy were all improved with the drug relative to placebo.[87]

Antiepileptic Agents

Recent research interest has focused on using the antiepileptic GABAergic drugs in treatment of neuropathic pain. Gabapentin, a structural analogue of GABA, has inhibitory activity on excitatory neurotransmitter systems, which are hypothesized to cause "windup" at dorsal horn neurons in models of neuropathic pain. Patients with spinal cord injury who experienced neuropathic pain were treated with gabapentin for 5 weeks.[19] After a 1-week dose titration, their self-rated pain and sleep interruption scores were improved relative to baseline. Another 8-week study of gabapentin in patients with diabetic neuropathy reported improvement in pain and sleep interference ratings relative to baseline.[88] Two large placebo-controlled studies of gabapentin in patients with postherpetic neuropathy have been conducted. A 7-week trial in the United Kingdom found improvement relative to placebo in ratings of pain and sleep interference over the trial but no difference between the low and high dose used.[89] The 8-week U.S. trial in postherpetic pain patients similarly found improved pain and sleep interference ratings relative to placebo with gabapentin.[17] However, what remains to be determined is the degree to which the drug directly impacts sleep and pain, as well as the degree to which improvement in sleep relates to improvement in pain.

CONCLUSIONS

Acute and chronic pain is associated with disturbed sleep. However, to date the specific nature of the sleep disturbance, its causal mechanisms, and its effective treatment have not been thoroughly explored. Acute pain following various surgical procedures is associated with reduced and fragmented sleep and diminished amounts of slow wave and REM sleep. In fact, the return of REM sleep may be a bellwether of the recovery process. In chronic pain the specific nature of the sleep disturbance and its pathological significance is not as clear. In part, the problem relates to the complexity and heterogeneity of the chronic pain conditions and their comorbidity with psychiatric conditions, typically depression and anxiety. Experimental models of the sleep-pain interaction have shown that the relation is bidirectional. In healthy, pain-free subjects sleep has an antinociceptive effect and the loss of sleep has a hyperalgesic effect. To date, the sleep stage specificity of this interaction has not been clearly demonstrated. As to treatment of acute and chronic pain, several drug classes have been evaluated and no consensus on treating disturbed sleep in acute or chronic pain has arisen, much less differential etiology-based treatment strategies.

ACKNOWLEDGMENTS

This work was supported by NIH (NIAAA) grant No. R01 AA11264 awarded to Dr. T. Roehrs, and NIH (NIMH) grant No. R01 MH59338 awarded to Dr. T. Roth.

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