Mechanisms By Which Sleep Disturbance Contributes to Osteoarthritis Pain: A Conceptual Model

Michael T. Smith, PhD, CBSM, Phillip J. Quartana, PhD, Renata M. Okonkwo, PhD, and Adeel Nasir, MD

Corresponding author
Michael T. Smith, PhD, CBSM
Johns Hopkins Bayview Medical Center, 5510 Nathan Shock Drive, Suite 100, Baltimore, MD 21224, USA.
E-mail: msmith62@jhmi.edu

Current Pain & Headache Reports 2009, **13:**447–454
Current Medicine Group LLC ISSN 1531-3433

Sleep disturbance is prevalent in aging and painful rheumatologic populations, but it has largely been a neglected dimension of the routine clinical care of arthritis patients. Pain associated with osteoarthritis (OA) is a leading cause of disability worldwide, and factors that contribute to pain in OA are poorly understood. Sleep disturbance is not only a consequence of pain, it is also likely to play an integral role in pain expression. Emerging research suggests that many patients with OA demonstrate signs of generalized hyperalgesia and faulty central pain modulatory processing similar to other idiopathic pain disorders, such as fibromyalgia. Sleep disruption is increasingly recognized as a direct contributor to both hyperalgesia and impaired endogenous pain modulation. This article reviews the extant literature on sleep disturbance and hyperalgesia in patients with OA. We propose a conceptual working model describing pathways by which sleep disturbance interacts directly with central pain processing mechanisms and inflammatory processes, and indirectly with mood and physical functioning to augment clinical OA pain. The clinical and research implications of the model are discussed.

Introduction

Osteoarthritis (OA) is extremely prevalent and a leading cause of pain and disability worldwide [1]. In the United States, more than 21 million adults suffer from painful degenerative joint diseases, and this number is expected to increase sharply as the population ages. OA is characterized by loss of articular cartilage, synovitis, and joint capsule thickening, with the most prevalent symptoms being pain in weight-bearing joints, reduced range of motion, and insomnia [2]. In addition, OA is associated with decrements in physical function and quality of life [2], which are linked to substantial health care costs [3]. Age, obesity, and joint misalignment are major risk factors for OA. The knees and hips are the most common and disabling joints to be impacted by OA. Although sometimes referred to as *noninflammatory arthritis*, particularly in comparison to rheumatoid arthritis, research is increasingly focusing on the role of both local and systemic proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, as mediators of the onset, maintenance, and progression of OA [4••].

Pain is the primary reason that OA patients seek treatment, and severe pain is a major risk factor for disability, disease progression [5], and joint replacement surgery [2,5]. In general, knee pain has been found to be a more robust predictor of disability than radiographic signs of joint disease [6]. The mechanisms of pain in knee OA, however, are complex and poorly understood. Moreover, numerous studies have documented that radiographic markers of disease severity are relatively weak correlates of pain severity and disability [7]. Because clinical pain severity is the primary driver of disability, impaired quality of life, and health care burden in OA, investigations aimed at identifying and treating the causes of clinical pain are needed. Although recent reviews have focused on psychosocial factors and neuroplastic changes as contributors to OA pain, insomnia and sleep disturbance have been largely neglected in the OA literature. Insomnia, however, is increasingly recognized as a risk factor for medical and psychiatric morbidity. Importantly, emerging research indicates that dysregulated sleep may causally induce hyperalgesia and predict the development of chronic pain following acute injury, independent from

other recognized psychosocial risk factors such as depression and anxiety [8]. This review aims to highlight sleep as a potentially significant risk factor for the development and maintenance of pain associated with OA, with particular focus on linkages between sleep and alterations of central pain processing and inflammation that have mechanistic implications for developing novel prevention and treatment approaches.

Sleep Disturbance in Chronic Pain

Sleep is a significant problem for the majority of patients with chronic pain, with self-report estimates of sleep disturbance ranging from 50% to 88% among heterogenous pain conditions [9,10]. Although limited by small samples, polysomnographic (PSG) studies in mixed pain samples have corroborated self-report studies demonstrating longer sleep latencies, reduced total sleep time, increased awakenings, and reduced sleep efficiency in individuals with chronic pain as compared to controls without chronic pain [11,12]. In addition to sleep continuity disturbance, significant microstructural abnormalities are evident in individuals with chronic pain, most notably reduced delta activity (slow wave activity) and/or increased alpha activity [12]. Early work by Moldofsky and Scarisbrick [13] identified an "alpha–delta" non–rapid eye movement (NREM) sleep electroencephalogram (EEG) pattern in which higher frequency alpha waves associated with arousal (8–12 Hz) are superimposed onto slower frequency (0.5–3.5 Hz) delta activity, a pattern that correlates with more daytime muscle pain and fatigue [13], EEG patterns that have also been observed in a variety of rheumatologic populations, including individuals with fibromyalgia and back pain, respectively. Interestingly, these patterns have been observed in samples composed of depressed individuals and as well as asymptomatic controls. The significance of these EEG findings remains unclear and continues to be elucidated.

These cross-sectional studies, which have included OA patients, have consistently found that sleep disturbance positively correlates with clinical pain severity [14,15]. In addition, poor sleep is also associated with mood disturbance, inactivity, and presleep cognitive rumination [16], phenomena similarly experienced by individuals with primary insomnia. In addition to pain, cognitive–behavioral factors such as poor sleep hygiene, behaviorally conditioned hyperarousal to the bedroom environment, and maladaptive attitudes and beliefs about sleep may contribute to the maintenance of insomnia in chronic pain. For example, recent work by our group in patients with temporomandibular joint disorder (TMD) found that 40% of patients satisfied research diagnostic criteria for primary insomnia [17]. These findings taken together suggest that insomnia occurring in the context of chronic pain may share similarities with primary insomnia. Psychosocial factors, however, do not entirely explain the sleep–pain relationship, as several investigations have found that sleep disturbance is associated with pain severity independent from these factors [14–16].

Sleep Disturbance in Osteoarthritis

Consistent with the general chronic pain literature, epidemiologic surveys report that at least 50% of patients with OA suffer from significant disturbances initiating or maintaining sleep [18–20]. Results from the Osteoarthritis Southern Italy Study (OASIS), a large epidemiologic study, indicated that 58% of knee OA patients sampled complained of problems maintaining sleep at least 3 nights per week [18]. A separate, more recent epidemiologic study found that 25% of individuals with arthritis (primarily OA) reported sleep continuity disturbance "most of the time," and that pain was the most robust correlate of insomnia, explaining the majority (59%) of the variance in the relationship between arthritis and sleep problems. A study of 48 hip arthroplasty candidates found significant presurgical sleep maintenance disturbance with diary and actigraphy average sleep efficiency estimates of approximately 78%, well below the widely accepted "normal" minimum of 85% [21]. Many other studies have corroborated that prolonged middle-of-the-night awakening is the most common form of insomnia reported by patients with chronic pain. All of the studies describing sleep disturbance in individuals with knee OA report a robust relationship between pain severity and sleep disturbance (eg, [18]).

A major gap in the literature is the scarcity of objective sleep measurement among individuals with OA. One small PSG study, however, found that 14 OA patients demonstrated an increase in NREM stage I, a decrease in NREM stage II, and more wake after sleep onset time compared with controls [22]. A report comparing 10 patients with fibromyalgia to 10 patients with OA found both groups demonstrated similar sleep disturbance profiles, including prolonged sleep latency, prolonged middle awakenings, and frequent alpha intrusion (microarousal) during NREM stage II [23]. These small studies suggest that the sleep of patients with OA may be "lighter" than normal. Due to the lack of PSG studies in patients with OA, rates of sleep disorders requiring PSG for diagnosis remain largely unknown. The relative absence of such investigations is particularly alarming given that obesity and older age are risk factors for both OA and sleep-disordered breathing, a serious medical condition. In addition to fragmenting sleep and altering sleep microstructure, sleep apnea exposes patients to chronic intermittent hypoxia and dramatically increases risk for cardiovascular disease and mortality. We are aware of only one study that addressed the issue of sleep apnea in 254 hip and knee OA patients awaiting arthroplasty [24]. This investigation reported PSG-documented rates of sleep apnea to be approximately 7%, well above the population norms typically reported between 2% and 4% [25].

Reciprocal Interactions Between Sleep Disturbance and Pain

Investigators of several longitudinal studies in a variety of pain disorders have reported that baseline sleep disruption predicts subsequent increases in pain severity, and that increased pain also predicts subsequent sleep disturbance [26,27]. Reports of acute insomnia symptoms have also been shown to predict development of chronic pain among individuals who have suffered serious burn injury and to predict the development of widespread pain in a general population sample. Few longitudinal studies, however, have been conducted exclusively in OA populations. Recent data from 110 knee OA patients undergoing total knee arthroplasty is an exception. The former reported that sleep disturbance 1 month after surgery partially mediated the relationship between pain and functional limitations at 3 months. In the only longitudinal PSG study, increased wake after sleep onset time and reduced slow wave sleep (SWS) independently predicted 6-month pain reports in individuals with rheumatoid arthritis. Several diary studies, using multilevel data models, have reported bidirectional, day-to-day relationships between sleep and pain in fibromyalgia, rheumatoid arthritis, and healthy subjects [28]. These studies suggest that the sleep and pain relationship may be described as a reciprocal, vicious cycle; however, these investigations are limited by the lack of objective sleep measurement.

Sleep Disturbance–induced Hyperalgesia

More direct evidence for a reciprocal relationship between pain and sleep is based on several experimental studies demonstrating that total sleep deprivation [29] or selective sleep-stage perturbations [30] decrease pain threshold or tolerance, although only a few studies have used control groups [29,30]. One recent study reported that total sleep deprivation decreased thermal pain threshold, but did not alter detection of innocuous thermal stimuli, suggesting the specificity of sleep deprivation to pain processes rather than general somatosensory function [29]. Several other studies have proposed that SWS disruption might have a specific effect on sensitivity to mechanical stimuli [13]. In support of Moldofsky's classic early work, these findings suggest the possibility that sleep disturbance may contribute to the development and maintenance of OA pain by contributing to generalized hyperalgesia.

Local and Generalized Hyperalgesia in Osteoarthritis

Hyperalgesia, or enhanced responsiveness to painful stimuli, is a feature of many rheumatologic diseases, most notably fibromyalgia, but also rheumatoid arthritis. Although less widely studied via psychophysical pain testing methods, patients with OA have been found to demonstrate local, and in some cases, generalized hyperalgesia relative to control groups [31]. For example, recent work has indicated that knee OA patients rate suprathreshold mechanical stimuli on the upper body as more intensely painful than controls [31]. Enhanced pain responses at unaffected sites support suggestions that OA pain involves the central nervous system (CNS) [31,32•], in addition to peripheral mechanisms. Most of the data in knee OA, however, are based on findings of reduced pain threshold or tolerance, measures that do not provide information about specific aberrant CNS pain modulatory processes. Furthermore, pain thresholds are often only modestly associated with pain severity in OA and other painful conditions [33]. Other noninvasive psychophysical pain tests should be used to more directly assess central pain modulation, as such measures may be more robustly associated with clinical pain. These measures are only beginning to be applied to study OA pain.

Central Pain Modulatory Deficits in Chronic Pain and Osteoarthritis

Chronic pain is increasingly conceptualized as a disease of the nervous system that includes reorganization of spinal cord circuitry and supraspinal neural pathways that respond to persistent peripheral input. Dysregulated central pain inhibitory and facilitatory mechanisms have been implicated in pathophysiologic models of chronic pain. Several noninvasive methodologies for studying pain modulation in humans have been developed and applied to study the pathophysiology of chronic pain. Two of the most widely used paradigms are diffuse noxious inhibitory controls and temporal summation.

Diffuse noxious inhibitory controls

One well-studied pain inhibitory process with demonstrated clinical relevance is diffuse noxious inhibitory controls (DNIC). DNIC refers to the phenomenon whereby one noxious stimulus inhibits the pain produced by a second noxious stimulus (ie, counter-conditioning) [34]. In animal models, DNIC circuitry involves a spinobulbo-spinal negative feedback loop mediated by a supraspinal link in the medullary subnucleus reticularis dorsalis [35]. DNIC effects are demonstrated by assessing responses to a phasic noxious stimulus before and then during heterotopic application of a tonic noxious stimulus. Generally, responses to the phasic noxious stimulus are reduced during concurrent administration of the tonic stimulus to a distant body site, with the magnitude of the reduction (decreased sensitivity) serving as a measure of the efficacy of central inhibitory, analgesic systems [36]. Human studies of DNIC have demonstrated that increases in pain threshold during the tonic application of the painful stimulus are not simply mediated by a diversion of attention. Animal and human research using morphine, naloxone [37], and neuroimaging [38] have shown that DNIC relies upon opioid-mediated supraspinal mechanisms. Serotonin and norepinephrine are also important neurotransmitter systems known to drive descending pain

inhibition. Impaired DNIC has been demonstrated in multiple chronic pain conditions, including fibromyalgia [39], low back pain [40], TMD [41], tension headache [42], and irritable bowel syndrome, suggesting the possibility of pathophysiologic role of DNIC mechanisms in the onset or maintenance of persistent pain. Pain inhibitory capacity has also been shown to be negatively associated with age, suggesting that impaired DNIC may play a role in age-related pain disorders such as OA.

Notably, we are aware of one longitudinal study of DNIC in OA, which evidenced that knee OA patients awaiting surgery lacked measurable DNIC, but, when tested 9 months later, the pain-free knee OA patients demonstrated normal DNIC values (comparable to controls). Other studies have also found DNIC to be negatively associated with clinical pain severity [36].

Diffuse noxious inhibitory controls and sleep disruption

Some animal work suggests that sleep deprivation blocks DNIC-like effects in animals, and sleep deprivation decreases opioid receptor binding in the limbic system, which would presumably disrupt endogenous opioid analgesia [43]. We recently reported results of a clinical experiment to study the effects of partial sleep deprivation and DNIC in healthy, pain-free women. We found that sleep disruption induced by forced awakenings significantly impaired DNIC and was associated with development of spontaneous pain [44•]. We have subsequently found that PSG-recorded sleep efficiency and total sleep time is positively associated with DNIC in a clinical sample of patients diagnosed with painful TMD. TMD patients with a greater percentage of wake time during the sleep period and reduced total sleep time demonstrated impaired pain inhibitory capacity during the day, even after controlling for multiple potential confounds [45•].

Temporal summation

Temporal summation, or "windup," is another common psychophysical phenomena thought to index central pain facilitation. Temporal summation refers to the enhancement of pain caused by repeated noxious stimulation; animal studies have shown that it involves sensitization of second-order dorsal horn neurons in the spinal cord [46]. In humans, temporal summation is thought to reflect endogenous pain modulatory processes arising from supraspinal structures. Like DNIC, temporal summation has also been implicated in pathophysiologic models of chronic pain. Temporal summation depends on *N*-methyl-D-aspartate (NMDA) receptor activation [46], with some work suggesting that the medullary dorsal reticular nucleus may play a role in this spinal sensitization [47]. Inflammatory mediators, such as proinflammatory cytokines and substance P, may play an important role in the temporal summation effect. Measures of temporal summation, involving either mechanical or thermal stimulation, are sensitive to between-group differences in pain, with temporal summation demonstrated in women relative to men [48], fibromyalgia patients [49], and TMD patients relative to controls. Increased temporal summation has been found to be associated with increased subclinical pain complaints in healthy subjects (headache and back ache frequency) [50]. To our knowledge, however, no studies have evaluated whether temporal summation is enhanced in knee OA, or whether sleep disturbance enhances temporal summation—both important topics in need of research investigation.

The Potential Role of Systemic Inflammation in Central Sensitization in Osteoarthritis

Systemic inflammation has long been recognized to play a pathophysiologic role in rheumatoid arthritis, but research increasingly demonstrates that proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6 may also mediate the onset, maintenance, and progression of OA [4••]. These cytokines have been linked to dysfunction in synovium, cartilage, and subchondral bone. IL-6, as well as C-reactive protein (CRP), an acute-phase protein marker of systemic inflammation, have been linked prospectively to OA progression in at least two studies [4••,51]. Considerable animal studies demonstrate that TNF-α, IL-1β, and IL-6 have direct and indirect receptor-mediated sensitizing effects on afferent nociceptive pathways in spinal dorsal horn and dorsal root ganglia [52], and these cytokines mediate muscle and joint hyperalgesia [53]. When tissue damage occurs, a cascade of inflammatory signals is released from cells at peripheral nerve terminals, leading to nociceptor sensitization. When noxious inputs persist, central sensitization contributes to protracted changes in sensory ganglia and dorsal horn neurons, which mobilize the release of TNF-α, IL-1β, and IL-6 via CNS [53,54] and "satellite" glia [55]. Glial release of these cytokines increases conductivity of NMDA receptors and the quantity of these receptors on sensory neuron surfaces [53]. Thus, TNF-α, IL-1β, and IL-6 are hypothesized to mediate molecular alterations promoting hyperalgesia and temporal summation among individuals with OA. It should be noted, however, that associations between circulating inflammatory markers and enhanced temporal summation have yet to be demonstrated in human studies.

Sleep Loss, Insomnia, Inflammation, and Spontaneous Pain

Experiments in healthy adults demonstrate that even mild, short-term sleep loss activates gene transcription factors that initiate inflammatory signaling [56] and elevations in IL-6, TNF-α, and CRP [57••]. In a recent study of middle-aged adults, a short habitual sleep time (< 5 hours per night) was associated with increased circulating CRP and IL-6 [58]. A small PSG study of healthy adults found that age was associated with increased wake after sleep onset time, reduced SWS, and increased circulating IL-

6 over a 24-hour period [59]. An important experiment by Haack and colleagues [60] in healthy, pain-free adults demonstrated that sleep restriction to 4 hours per night over 10 days increased circulating IL-6, and IL-6 was correlated ($r = 0.67$) with spontaneous pain ratings, independent of fatigue. These investigators also reported that total sleep deprivation increases circulating prostaglandin (PG) activity, specifically PGE_2, in subsequent studies. Consistent with the literature regarding the pain and inflammatory mediating effects of PGs, changes in PG levels were positively correlated with changes in spontaneous pain complaints ($r = 0.52$) in the aforementioned study [60]. Animal work indicates that PGs stimulate glutamate release in the spinal cord, which acts on NMDA receptors to facilitate nociceptive neurotransmission (central sensitization) [61]. Vgontzas et al. [62] reported that compared with controls, individuals with chronic primary insomnia displayed an association with a shift in circadian IL-6 and TNF-α secretion from nighttime to daytime, postulating that daytime elevations in these cytokines may explain increased fatigue and mood-related symptoms associated with insomnia.

Inflammation, Mood Disturbance, Decreased Physical Function, and Sleep

The observation that proinflammatory states impact mood and fatigue highlights several indirect pathways by which sleep disturbance–induced inflammation might also contribute to clinical pain augmentation in OA other than by directly augmenting heightened central pain processing mechanisms. As indicated previously, cross-sectional studies in heterogeneous samples of patients with chronic pain have found that inactivity and depressed mood are also associated with enhanced pain severity. Sleep disturbance is a widely recognized risk factor for depression, for example, and inactivity, including daytime napping, is an important sleep hygiene factor that weakens the homeostatic drive for sleep, which may contribute to perpetuation of insomnia symptoms. Two recent cross-sectional studies have also demonstrated that objective actigraphy measures of wake after sleep onset time are inversely associated with walking speed and time to complete chair stands in older adults independent of a number of potential confounds [63,64]. Longitudinal studies demonstrating that poor sleep increases risk for diminished physical activity or that decreased physical activity predicts development of poor sleep have yet to be rigorously investigated. Data suggest, however, that both negative mood and decline in physical functioning are linked with systemic inflammation.

Inflammation and negative mood

Inflammation is increasingly recognized as a central mediator of emotional experience [65,66]. Most notably, markers of innate immunity (eg, TNF-α, IL-1β, and IL-6) and CRP have been shown to co-vary with depressive symptoms across the severity spectrum [67]. Treatment of medical conditions such as hepatitis C and cancer with cytokine therapy often fosters significant mood disturbance [67–69]. Administration of vaccines promoting inflammation in healthy young adults causes behavioral and mood profiles that substantially overlap with depressed mood [70]. A recent study highlighted the intriguing possibility that inflammation and exogenous psychosocial stress synergistically foster mood disturbance [70]. Specifically, healthy volunteers exposed to both a *Salmonella typhi* vaccination and a psychosocial stressor reported greater mood disturbance compared with those exposed to either the stressor or the vaccine alone. For OA patients, arguably, the most common stressor experienced is pain. Days (or weeks) with elevations in self-reported pain are associated with mood disturbance in rheumatic disease, including OA [71,72]. Indeed, clinically significant mood disturbance is commonly experienced by those with OA [73], possibly via inflammation [74].

Inflammation and physical function

In addition to negative mood, circulating levels of inflammatory markers have also been inversely associated with physical function in older adults [75]. Moreover, inflammation predicts declines in performance-based measures of physical function and disability onset [76]. Chronic, even low-level, systemic inflammation might diminish physical function via a number of pathways, including increased muscle catabolism, anhedonia, and fatigue. Importantly, several studies of older adults demonstrate independent effects of inflammation on physical activity even after controlling for multiple age-related confounds (eg, medical conditions, adiposity) [75]. None of these studies, however, evaluated the potential role of sleep disturbances among these associations, and surprisingly little work has examined interrelationships between inflammation and physical function in older adults with OA. A single cross-sectional study of knee OA reported inverse associations between IL-6 and TNF-α with walking speed and self-reported function, respectively [77]. In a clinical trial, weight loss–related changes in soluble TNF receptor 2 have been noted to correlate with 6-minute walk test performance improvements at 6-month follow-up, suggesting that inflammation may mediate physical function in older adults [78].

Conclusions

Based on the above review, Figure 1 provides a simplified, working conceptual model describing both direct and indirect pathways by which sleep disturbance is likely to contribute to the expression of clinical pain in OA. The data suggest that many of the relationships are bidirectional, which heighten the potential benefit of intervention efforts aimed at disrupting vicious cycles that accelerate disease processes via synergistic interactions. Inflammation plays a central role in the model as: 1) it

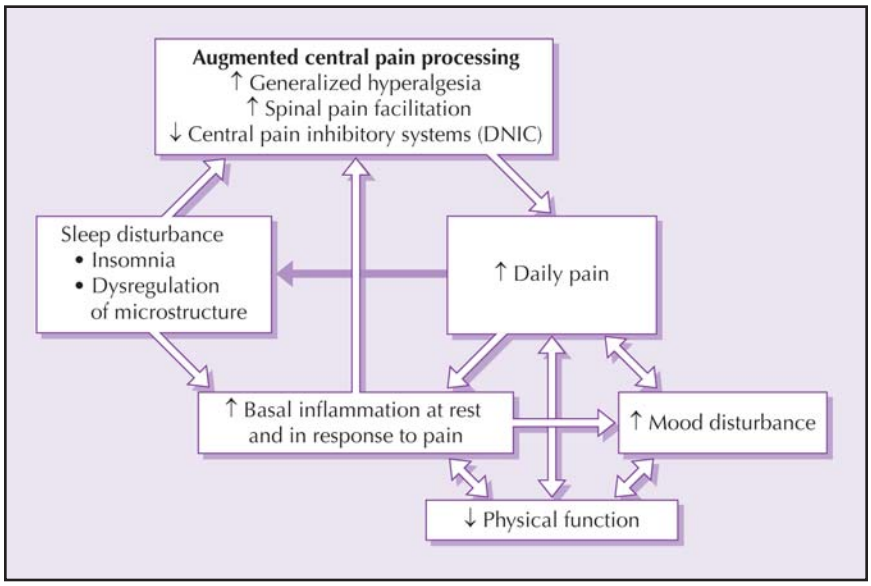

Figure 1. Hypothetical model of sleep disturbance–induced pain augmentation: a central role of inflammation. DNIC—diffuse noxious inhibitory controls.

is the most well-studied candidate mechanism to date; 2) emerging data identify heightened, albeit low-grade (relative to rheumatoid arthritis), inflammation broadly in OA and sleep-disrupted samples; and 3) basic science work has confirmed the role of inflammatory mediators in both peripheral and central sensitization. While the relationships between factors in the proposed model require more research to clarify and elaborate specific mechanistic pathways, research is also needed on large samples to confirm the overall model, establishing the multiple causal pathways and the relative weight and timeframe by which they may contribute to pain expression and possibly even disease progression in OA. Additional mechanisms in the model, besides aberrant inflammation known to impact central pain processing, are very much in need of study in OA. As shown in the diagram, an impaired pain inhibitory system is a particularly promising pathway that has been linked to sleep disruption and clinical pain via animal and human experiments. At least one study has identified failed pain inhibitory capacity in presurgical knee OA patients. Pain inhibitory systems are driven by descending opioidergic, serotonergic, and noradrenergic pathways, linking brainstem inhibitory centers, for example, rostroventral medulla, and periaqueductal gray to dorsal horn afferents. It is unclear how aberrant inflammatory processes may interact with these inhibitory circuits in human models of OA, but endogenous opioids are well known to regulate neuroendocrine function, particularly the hypothalamic-pituitary-adrenal axis. The preceding suggests that aberrant inflammatory processes may not only contribute to pain augmentation via glutamatergic spinal sensitization, but also via effects on descending pain inhibition. This potential interaction, however, has yet to be directly investigated.

Although research on the mechanisms by which sleep disturbance augments pain in general and OA in particular is in its infancy, the clinical implication of the extant research is clear: aggressive management of sleep disorders should be a critical component of the comprehensive treatment of rheumatologic patients and older adults. With rates of sleep disorders in older adults approaching 50% [79], identification and treatment of sleep disturbance is a largely unrecognized opportunity for disease prevention that may improve endogenous central pain modulatory systems, mood, physical function, and ultimately the degree and persistence of pain in OA.

Acknowledgments

This work was supported by the National Institutes of Health: grants R01 AR05487 (MTS), K23 NS4716 (MTS), and T32 MH075884 (PJQ).

Disclosure

Dr. Michael T. Smith has received investigator-initiated research funding from Sepracor, Inc.

No other potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Lawrence RC, Helmick CG, Arnett FC, et al.: **Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States.** *Arthritis Rheum* 1998, **41:**778–799.
2. Dominick KL, Ahern FM, Gold CH, Heller DA: **Health-related quality of life and health service use among older adults with osteoarthritis.** *Arthritis Rheum* 2004, **51:**326–331.
3. Centers for Disease Control and Prevention (CDC): **Impact of arthritis and other rheumatic conditions on the health-care system: United States, 1997.** *MMWR Morb Mortal Wkly Rep* 1999, **48:**349–353.

4.•• Livshits G, Zhai G, Hart DJ, et al.: **Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: the Chingford study.** *Arthritis Rheum* 2009, **60:**2037–2045.
This large-scale study demonstrates that circulating proinflammatory cytokines predict the development of radiographic knee OA 5 years downstream.
5. Hochberg MC: **Prognosis of osteoarthritis.** *Ann Rheum Dis* 1996, **55:**685–688.
6. Hopman-Rock M, Odding E, Hofman A, et al.: **Physical and psychosocial disability in elderly subjects in relation to pain in the hip and/or knee.** *J Rheumatol* 1996, **23:**1037–1044.
7. Creamer P, Lethbridge-Cejku M, Hochberg MC: **Where does it hurt? Pain localization in osteoarthritis of the knee.** *Osteoarthritis Cartilage* 1998, **6:**318–323.
8. Smith MT, Klick B, Kozachik S, et al.: **Sleep onset insomnia symptoms during hospitalization for major burn injury predict chronic pain.** *Pain* 2008, **138:**497–506.
9. Smith MT, Haythornthwaite JA: **How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature.** *Sleep Med Rev* 2004, **8:**119–132.
10. Wilson KG, Watson ST, Currie SR: **Daily diary and ambulatory activity monitoring of sleep in patients with insomnia associated with chronic musculoskeletal pain.** *Pain* 1998, **75:**75–84.
11. Wittig RM, Zorick FJ, Blumer D, et al.: **Disturbed sleep in patients complaining of chronic pain.** *J Nerv Ment Dis* 1982, **170:**429–431.
12. Schneider-Helmert D, Whitehouse I, Kumar A, Lijzenga C: **Insomnia and alpha sleep in chronic non-organic pain as compared to primary insomnia.** *Neuropsychobiology* 2001, **43:**54–58.
13. Moldofsky H, Scarisbrick P: **Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation.** *Psychosom Med* 1976, **38:**35–44.
14. Morin CM, Gibson D, Wade J: **Self-reported sleep and mood disturbance in chronic pain patients.** *Clin J Pain* 1998, **14:**311–314.
15. Wilson KG, Eriksson MY, D'Eon JL, et al.: **Major depression and insomnia in chronic pain.** *Clin J Pain* 2002, **18:**77–83.
16. Smith MT, Perlis ML, Smith MS, Giles DE: **Pre-sleep cognitions in patients with insomnia secondary to chronic pain.** *J Behav Med* 2001, **24:**93–114.
17. Smith MT, Wickwire EM, Grace EG, et al.: **Sleep disorders and their association with laboratory pain sensitivity in temporomandibular joint disorder (TMD).** *Sleep* 2009, **32:**779–790.
18. Wilcox S, Brenes GA, Levine D, et al.: **Factors related to sleep disturbance in older adults experiencing knee pain or knee pain with radiographic evidence of knee osteoarthritis.** *J Am Geriatr Soc* 2000, **48:**1241–1251.
19. Gallup Organization: *Adult public's experiences with nighttime pain.* National Sleep Foundation; 1997.
20. Power JD, Perruccio AV, Badley EM: **Pain as a mediator of sleep problems in arthritis and other chronic conditions.** *Arthritis Rheum* 2005, **53:**911–919.
21. Edinger JD, Bonnet MH, Bootzin RR, et al.: **Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group.** *Sleep* 2004, **27:**1567–1596.
22. Leigh TJ, Hindmarch I, Bird HA, Wright V: **Comparison of sleep in osteoarthritic patients and age and sex matched healthy controls.** *Ann Rheum Dis* 1988, **47:**40–42.
23. Doherty M, Smith J: **Elusive "alpha-delta" sleep in fibromyalgia and osteoarthritis.** *Ann Rheum Dis* 1993, **52:**245.
24. Harrison MM, Childs A, Carson PE: **Incidence of undiagnosed sleep apnea in patients scheduled for elective total joint arthroplasty.** *J Arthroplasty* 2003, **18:**1044–1047.
25. American Academy of Sleep Medicine: *The International Classification of Sleep Disorders: Diagnostic and Coding Manual,* edn 2. Westchester, IL: American Academy of Sleep Medicine; 2005.
26. Affleck G, Urrows S, Tennen H, et al.: **Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia.** *Pain* 1996, **68:**363–368.
27. Raymond I, Nielsen TA, Lavigne G, et al.: **Quality of sleep and its daily relationship to pain intensity in hospitalized adult burn patients.** *Pain* 2001, **92:**381–388.
28. Totterdell P, Reynolds S, Parkinson B, Briner RB: **Associations of sleep with everyday mood, minor symptoms and social interaction experience.** *Sleep* 1994, **17:**466–475.
29. Kundermann B, Spernal J, Huber MT, et al.: **Sleep deprivation affects thermal pain thresholds but not somatosensory thresholds in healthy volunteers.** *Psychosom Med* 2004, **66:**932–937.
30. Roehrs TA, Hyde M, Blaisdell MS, et al.: **Sleep loss and REM sleep loss are hyperalgesic.** *Sleep* 2006, **29:**145–151.
31. Bradley LA, Kersh BC, DeBerry JJ, et al.: **Lessons from fibromyalgia: abnormal pain sensitivity in knee osteoarthritis.** *Novartis Found Symp* 2004, **260:**258–270.
32.• Clauw DJ, Witter J: **Pain and rheumatology: thinking outside the joint.** *Arthritis Rheum* 2009, **60:**321–324.
This article highlights the potential role of CNS factors in OA pain expression.
33. Wolfe F, Ross K, Anderson J, Russell IJ: **Aspects of fibromyalgia in the general population: sex, pain threshold, and fibromyalgia symptoms.** *J Rheumatol* 1995, **22:**151–156.
34. Willer JC, De Broucker T, Le Bars D: **Encoding of nociceptive thermal stimuli by diffuse noxious inhibitory controls in humans.** *J Neurophysiol* 1989, **62:**1028–1038.
35. Lima D, Almeida A: **The medullary dorsal reticular nucleus as a pronociceptive centre of the pain control system.** *Prog Neurobiol* 2002, **66:**81–108.
36. Edwards RR, Ness TJ, Weigent DA, Fillingim RB: **Individual differences in diffuse noxious inhibitory controls (DNIC): an association with clinical variables.** *Pain* 2003, **106:**427–437.
37. Le Bars D, Willer JC, De Broucker T: **Morphine blocks descending pain inhibitory controls in humans.** *Pain* 1992, **48:**13–20.
38. Wilder-Smith CH, Schindler D, Lovblad K, et al.: **Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls.** *Gut* 2004, **53:**1595–1601.
39. Kosek E, Hansson P: **Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects.** *Pain* 1997, **70:**41–51.
40. Peters ML, Schmidt AJ, Van den Hout MA, et al.: **Chronic back pain, acute postoperative pain and the activation of diffuse noxious inhibitory controls (DNIC).** *Pain* 1992, **50:**177–187.
41. Maixner W, Fillingim R, Sigurdsson A, et al.: **Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: evidence for altered temporal summation of pain.** *Pain* 1998, **76:**71–81.
42. Pielsticker A, Haag G, Zaudig M, Lautenbacher S: **Impairment of pain inhibition in chronic tension-type headache.** *Pain* 2005, **118:**215–223.
43. Ukponmwan OE, Rupreht J, Dzoljic MR: **REM sleep deprivation decreases the antinociceptive property of enkephalinase-inhibition, morphine and cold-water-swim.** *Gen Pharmacol* 1984, **15:**255–258.
44.• Smith MT, Edwards RR, McCann UD, Haythornthwaite JA: **The effects of sleep deprivation on pain inhibition and spontaneous pain in women.** *Sleep* 2007, **30:**494–505.
This study experimentally demonstrates, for the first time, that sleep disruption impairs endogenous pain inhibitory processes, which are conceptually linked to the pathophysiology of idiopathic pain.
45.• Edwards RR, Grace E, Peterson S, et al.: **Sleep continuity and architecture: associations with pain-inhibitory processes in patients with temporomandibular joint disorder.** *Eur J Pain* 2009 Jan 23 (Epub ahead of print).
This is the first study to show that sleep disturbance is associated with impaired pain inhibitory processes in a clinical pain sample.

46. Eide PK: **Wind-up and the NMDA receptor complex from a clinical perspective.** *Eur J Pain* 2000, **4:**5–15.
47. Dugast C, Almeida A, Lima D: **The medullary dorsal reticular nucleus enhances the responsiveness of spinal nociceptive neurons to peripheral stimulation in the rat.** *Eur J Neurosci* 2003, **18:**580–588.
48. Fillingim R, Maixner W, Kincaid S, Silva S: **Sex differences in temporal summation but not sensory-discriminative processing of thermal pain.** *Pain* 1998, **75:**121–127.
49. Price D, Staud R, Robinson M, et al.: **Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients.** *Pain* 2002, **99:**49.
50. Edwards RR, Fillingim RB: **Effects of age on temporal summation and habituation of thermal pain: clinical relevance in healthy older and younger adults.** *J Pain* 2001, **2:**307–317.
51. Spector TD, Hart DJ, Nandra D, et al.: **Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease.** *Arthritis Rheum* 1997, **40:**723–727.
52. Segond von Banchet G, Boettger MK, Fischer N, et al.: **Experimental arthritis causes tumor necrosis factor-alpha-dependent infiltration of macrophages into rat dorsal root ganglia which correlates with pain-related behavior.** *Pain* 2009, **145:**151–159.
53. Milligan ED, Watkins LR: **Pathological and protective roles of glia in chronic pain.** *Nat Rev Neurosci* 2009, **10:**23–36.
54. Ren K, Dubner R: **Neuron-glia crosstalk gets serious: role in pain hypersensitivity.** *Curr Opin Anaesthesiol* 2008, **21:**570–579.
55. Takeda M, Takahashi M, Matsumoto S: **Contribution of the activation of satellite glia in sensory ganglia to pathological pain.** *Neurosci Biobehav Rev* 2009, **33:**784–792.
56. Irwin MR, Wang M, Ribeiro D, et al.: **Sleep loss activates cellular inflammatory signaling.** *Biol Psychiatry* 2008, **64:**538–540.
57.•• Haack M, Sanchez E, Mullington JM: **Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers.** *Sleep* 2007, **30:**1145–1152.

This experiment suggests that one possible mechanism for sleep disturbance–induced pain sensitivity may be systemic inflammation.

58. Miller MA, Kandala N, Kivimaki M, et al.: **Gender differences in the cross-sectional relationships between sleep duration and markers of inflammation: White Hall II Study.** *Sleep* 2009, **32:**857–864.
59. Vgontzas AN, Zoumakis M, Bixler EO, et al.: **Impaired nighttime sleep in healthy old versus young adults is associated with elevated plasma interleukin-6 and cortisol levels: physiologic and therapeutic implications.** *J Clin Endocrinol Metab* 2003, **88:**2087–2095.
60. Haack M, Lee E, Cohen DA, Mullington JM: **Activation of the prostaglandin system in response to sleep loss in healthy humans: potential mediator of increased spontaneous pain.** *Pain* 2009, **145:**136–141.
61. Nishihara I, Minami T, Watanabe Y, et al.: **Prostaglandin E2 stimulates glutamate release from synaptosomes of rat spinal cord.** *Neurosci Lett* 1995, **196:**57–60.
62. Vgontzas AN, Zoumakis M, Papanicolaou DA, et al.: **Chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime.** *Metabolism* 2002, **51:**887–892.
63. Dam TT, Ewing S, Ancoli-Israel S, et al.: **Association between sleep and physical function in older men: the osteoporotic fractures in men sleep study.** *J Am Geriatr Soc* 2008, **56:**1665–1673.
64. Goldman SE, Stone KL, Ancoli-Israel S, et al.: **Poor sleep is associated with poorer physical performance and greater functional limitations in older women.** *Sleep* 2007, **30:**1317–1324.
65. Howren MB, Lamkin DM, Suls J: **Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis.** *Psychosom Med* 2009, **71:**171–186.
66. Miller AH, Maletic V, Raison CL: **Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression.** *Biol Psychiatry* 2009, **65:**732–741.
67. Majer M, Welberg LA, Capuron L, et al.: **IFN-alpha-induced motor slowing is associated with increased depression and fatigue in patients with chronic hepatitis C.** *Brain Behav Immun* 2008, **22:**870–880.
68. Raison CL, Broadwell SD, Borisov AS, et al.: **Depressive symptoms and viral clearance in patients receiving interferon-alpha and ribavirin for hepatitis C.** *Brain Behav Immun* 2005, **19:**23–27.
69. Raison CL, Borisov AS, Broadwell SD, et al.: **Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction.** *J Clin Psychiatry* 2005, **66:**41–48.
70. Brydon L, Walker C, Wawrzyniak A, et al.: **Synergistic effects of psychological and immune stressors on inflammatory cytokine and sickness responses in humans.** *Brain Behav Immun* 2009, **23:**217–224.
71. Smith BW, Zautra AJ: **The effects of anxiety and depression on weekly pain in women with arthritis.** *Pain* 2008, **138:**354–361.
72. Smith BW, Zautra AJ: **Vulnerability and resilience in women with arthritis: test of a two-factor model.** *J Consult Clin Psychol* 2008, **76:**799–810.
73. Rosemann T, Laux G, Szecsenyi J, et al.: **Pain and osteoarthritis in primary care: factors associated with pain perception in a sample of 1,021 patients.** *Pain Med* 2008, **9:**903–910.
74. Cremeans-Smith JK, Soehlen S, Greene K, et al.: **In-hospital levels of C-reactive protein and IL-6 predict post-operative depressive symptoms among patients undergoing total knee replacement surgery.** *Brain Behav Immun* 2009 Jun 24 (Epub ahead of print).
75. Hsu FC, Kritchevsky SB, Liu Y, et al.: **Association between inflammatory components and physical function in the health, aging, and body composition study: a principal component analysis approach.** *J Gerontol A Biol Sci Med Sci* 2009, **64:**581–589.
76. Ferrucci L, Penninx BW, Volpato S, et al.: **Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels.** *J Am Geriatr Soc* 2002, **50:**1947–1954.
77. Penninx BW, Abbas H, Ambrosius W, et al.: **Inflammatory markers and physical function among older adults with knee osteoarthritis.** *J Rheumatol* 2004, **31:**2027–2031.
78. Miller GD, Nicklas BJ, Loeser RF: **Inflammatory biomarkers and physical function in older, obese adults with knee pain and self-reported osteoarthritis after intensive weight-loss therapy.** *J Am Geriatr Soc* 2008, **56:**644–651.
79. Vitiello MV, Moe KE, Prinz PN: **Sleep complaints cosegregate with illness in older adults: clinical research informed by and informing epidemiological studies of sleep.** *J Psychosom Res* 2002, **53:**555–559.