NEUROPSYCHOPHARMACOLOGY REVIEWS

Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications

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Pain can be both a cause and a consequence of sleep deficiency. This bidirectional relationship between sleep and pain has important implications for clinical management of patients, but also for chronic pain prevention and public health more broadly. The review that follows will provide an overview of the neurobiological evidence of mechanisms thought to be involved in the modulation of pain by sleep deficiency, including the opioid, monoaminergic, orexinergic, immune, melatonin, and endocannabinoid systems; the hypothalamus-pituitary-adrenal axis; and adenosine and nitric oxide signaling. In addition, it will provide a broad overview of pharmacological and non-pharmacological approaches for the management of chronic pain comorbid with sleep disturbances and for the management of postoperative pain, as well as discuss the effects of sleep-disturbing medications on pain amplification.

INTRODUCTION

Chronic pain is highly comorbid with sleep that is deficient in duration or quality, such as is seen in sleep disorders. Moreover, the pain-sleep relationship is a bidirectional one: pain can disrupt sleep, and short or disturbed sleep in turn lowers pain thresholds and increases spontaneous pain.

Epidemiological studies have shown that poor sleep quality and insufficient sleep duration are risk factors for the development of chronic pain [1]. Furthermore, there is strong evidence that having short or disturbed sleep can cause hyperalgesia (i.e., an increased sensitivity to painful stimulation) and the development or exacerbation of spontaneous pain symptoms (e.g., muscle pain, headache) [2]. This association has been demonstrated in a number of experimental models of sleep loss, where sleep is restricted or disrupted over one or more days, and effects are assessed using subjective pain reports and/or quantitative sensory testing. This bidirectional relationship between sleep deficiency and pain serves to perpetuate and amplify sleep deficiency and pain via a vicious cycle in chronic pain populations; for example, a bad night's sleep enhances pain, which in turn disturbs sleep, and the cycle then perpetuates and amplifies over time.

In spite of this well-established bidirectional relationship between deficient sleep and pain, there is very little scientific knowledge about the basic neurochemical mechanisms underlying this reciprocal relationship. Such understanding is sorely needed to spur the development of new drugs and perhaps behavioral interventions that could help to manage or alleviate pain, potentially through targeting shared pathways modulating both sleep and pain.

POTENTIAL MECHANISMS UNDERLYING THE RELATIONSHIP BETWEEN SLEEP DEFICIENCY AND CHRONIC PAIN

Our current understanding of the neurobiological mechanisms of pain [3] implicate involvement of neuronal, as well as non-neuronal, components of the opioid, monoaminergic, orexinergic, immune, melatonin, and endocannabinoid systems; the hypothalamus-pituitary-adrenal axis; and adenosine and nitric oxide signaling, among others. These systems that have been hypothesized to mediate the effects of deficient sleep on pain are reviewed below.

Opioid system

Opioids exert their pharmacological actions through three opioid receptors (mu, delta and kappa), which can be activated by endogenous opioid peptides, including enkephalins, dynorphins, and endorphins. Both opioid receptors and associated peptides are broadly expressed throughout the peripheral and central nervous system. Opioid receptors can also be activated by exogenous opioids, such as morphine. In addition to the opioid system's central role in pain modulation, it is also involved in the regulation of multiple other systems, including the stress response, immune function, and emotional modulation (for reviews, see [4, 5]).

With respect to opioid-regulated nociception and analgesia, experimental studies in healthy adults using PET imaging have shown that endogenous opioid peptides are released in various brain areas in response to experimentally-induced sustained pain, and that the degree of mu-opioid receptor activation is associated with reduced pain intensity and unpleasantness ratings [6]. In addition, PET imaging studies demonstrate that patients with chronic pain have decreased mu-opioid receptor transmission in response to painful challenges compared to a control condition [7]. It has been hypothesized that decreased central nervous system (CNS) opioid receptor availability leads to the reduced ability to inhibit pain, thereby facilitating chronic pain conditions [8].

A potential role of the opioid system in sleep deprivation induced pain hypersensitivity was first hypothesized in the late 1970s [9]. More recently, the analgesic effects of the mu-opioid

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agonist morphine and enkephalinase inhibition have been shown to decrease in rodent models of REM sleep deprivation [10, 11]. While the role of the opioid system in sleep-wake regulation and in mediating the hyperalgesic effects of deficient sleep has not been directly tested in humans, some studies have investigated the effects of sleep deprivation or disruption on the descending pain inhibition system. This system is in part mediated by the endogenous opioid and monoaminergic systems, and it has been shown that acute experimental sleep disruption in healthy individuals impairs the endogenous pain inhibition system [12]. Diminished pain inhibition capacity has also been observed in patients with insomnia disorder (i.e., a disorder of difficulty falling asleep or maintaining sleep that is associated with impairment in daytime functioning [13]). Together, these findings suggest that inadequate sleep deteriorates functioning of the opioid anti-nociceptive system.

Monoaminergic system

The monoaminergic (serotonin, norepinephrine, dopamine) and opioid systems are closely related and can interact to modulate neurobiological functions such as nociception. The monoamine *serotonin* is widely distributed in the periphery and the central nervous system. Along with noradrenergic neurons, the seroto-nergic system appears to be necessary for mu-opioid analgesic function involved in endogenous pain inhibition [14]. The involvement of serotonin receptors in the modulation of pain is further suggested by the effectiveness of serotonin reuptake inhibitors in the management of various clinical pain conditions, such as fibromyalgia [8]. While serotonin can exert analgesic as well as proalgesic effects in the CNS, it is well established for its proalgesic effects in the periphery and is an active ingredient of the 'inflammatory soup' (i.e., a combination of proinflammatory mediators that stimulates and sensitizes nociceptors [15]). Dual actions of serotonin with proalgesic effects in the periphery and pro- and/or analgesic effects in the CNS are likely related to the type of receptor(s) activated by serotonin, emphasizing the complex role of the serotonergic system in pain modulation [16].

The serotonergic system is also important for the control of sleep-wake behavior. In the 1970s, it was thought that serotonin initiated and maintained deep non-REM sleep; however, recent studies have shown that serotonin predominantly functions to promote wakefulness and to inhibit REM sleep [17]. The inhibition of serotonin through systemic administration of serotonin $2_A/2_C$ antagonists (e.g., ritanserin) increases deep non-REM sleep in laboratory animals, healthy sleepers, as well as in patients with insomnia [17]. Sleep deficiency has also been associated with changes in the serotonin system. In animals, acute sleep deprivation increased extracellular serotonin metabolites in the basal forebrain [18], while more chronic forms of sleep restriction reduce the sensitivity of the serotonin 1A receptor (reviewed in [19]). In humans, acute sleep deprivation has been reported to increase serotonin plasma metabolites, which have been sug-gested to mediate the antidepressive effect of acute sleep deprivation [20].

Given the involvement of the serotonergic system in both pain and sleep-wake control, disturbances of this system may mediate the hyperalgesic effects of deficient sleep; however, this hypoth-esis warrants further investigation.

Norepinephrine (also called noradrenaline) functions as a neurotransmitter in the brain, where it is synthesized by neurons located in the locus coeruleus (LC) and a few other nuclei with projections to many other brain areas. In the periphery, norepinephrine is produced and released from the adrenal glands into the bloodstream as a hormone, and also functions as a neurotransmitter in the sympathetic nervous system. Norepi-nephrine activates adrenergic receptors and, depending on the receptor subtype (alpha- or beta-adrenergic), causes an increase in vigilance, readiness for action, vasoconstriction, increase in heart rate, among many other effects. Thus, norepinephrine plays a key role in promoting wakefulness and arousal (reviewed in [21]).

With respect to the sleep-wake cycle, noradrenergic neurons in the LC are active during wake, less active during non-REM sleep, and almost silent during REM sleep of rats [22]. In humans, norepinephrine levels in the blood circulation decline with sleep onset and are lower during sleep compared to wakefulness (reviewed in [19]. Experimental induction of sleep deprivation increased the levels of norepinephrine transporter mRNA in the LC of rodents [23] and of norepinephrine in the blood circulation in rodents and humans [24, 25]. Increased activity of the noradre-nergic system in the LC is incompatible with sleep and may contribute to insomnia and conditions characterized by elevated arousal, such as stress-related disorders (reviewed in [21]).

With respect to nociception, preclinical data suggest that enhancement of norepinephrine transmission has an analgesic effect in murine models of persistent or neuropathic pain, with a stronger analgesic effect produced when both noradrenergic and serotonergic transmissions are enhanced. In accordance, medica-tions that inhibit the reuptake of both norepinephrine and serotonin (e.g., the serotonin-norepinephrine reuptake inhibitors [SRNI] duloxetine) are efficacious agents in the treatment of various chronic pain conditions, including fibromyalgia and chronic headaches (reviewed in [26, 27]).

The involvement of the noradrenergic system in mediating the pain-promoting effects of sleep deficiency has not been directly addressed. However, it has been demonstrated that experimentally-induced neuropathic pain in rodents increase the activity of noradrenergic neurons in the LC, which may underlie the sleep disturbances caused by neuropathic pain [28]. However, based on our current knowledge, it is unlikely that this system contributes to the pain-promoting effect of sleep disturbances, given that deficient sleep appears to increase activity in this system, which would suggest an analgesic effect.

Several findings implicate that *dopamine* signaling may play a mechanistic role in linking sleep deficiency and pain [29]. Dopamine is a wake-promoting mediator, and pharmacologically induced increases in dopamine tone (e.g., through administration of amphetamines or modafinil) have potent wake-promoting effects (reviewed in [30]).

In mice, administration of modafinil normalized sleep depriva-tion induced increases in pain sensitivity, while administration of the anti-inflammatory drug ibuprofen and the opiate morphine did not [31]. A recent study extended these findings by showing that the hyperalgesic effect of acute REM sleep deprivation in rats relates to decreased activity at dopamine D_2 receptors in the nucleus accumbens, which is involved in both pain and sleep-wake cycle control [32]. Experimental administration of a D_2 agonist is shown to block the hyperalgesic effect of sleep deprivation, indicating that sleep deprivation increases pain by decreasing dopaminergic activity. Clinically, such findings suggest that in patients with chronic pain comorbid with sleep dis-turbances, the responsiveness to analgesic drugs may be enhanced by co-administration of dopaminergic drugs [32]. Given the wake-promoting properties of dopamine, proper timing of drug administration may play a crucial role in preventing amplification of sleep disturbances by dopamine.

Adenosine signaling

Adenosine is a neuromodulator that is involved in the regulation of a wide array of diverse functions, including energy metabolism, inflammatory and immune responses, sleep-wake regulation, and nociception. It physiological effects are mediated by action on four distinct adenosine receptors that are widely expressed in cells and tissues throughout the body (reviewed in [33]). The adenosine A_{2A} receptor, for example, is located on both neurons and glia cells in the CNS and on immune cells in the periphery [34]. Adenosine has sleep-regulatory and sleep-promoting properties,

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and extracellular adenosine levels in the basal forebrain and cortex have been shown to increase in proportion to wake time (reviewed in [30, 35]). Additionally, adenosine levels in the basal forebrain have been shown to increase in response to sleep fragmentation in rats, demonstrating a potential mediating effect of adenosine in the context of sleep disturbances [36].

With respect to the role of adenosine in nociception, the effects of adenosine receptor agonists and antagonists have been examined in multiple inflammatory and neuropathic pain models. Proalgesic and analgesic effects of the adenosine A_{2A} receptor have been reported, such that systemic administration of a selective A_{2A} receptor antagonist has been shown to produce an analgesic profile in several preclinical pain models, but also to block the analgesic effect of opioids (reviewed in [37]).

To our knowledge, three animal studies have addressed the mechanistic role of adenosine in linking sleep deficiency with increased pain sensitivity. In mice, administration of caffeine, a nonselective adenosine receptor antagonist widely used as a waking stimulant, reversed pain hypersensitivity caused by sleep deprivation [31]. Caffeine also prevented the postsurgical pain hypersensitivity in rats caused by sleep deprivation prior to surgery [38]. In the same study, microinjection of a adenosine A_{2A} receptor antagonist into the median preoptic nucleus, an area involved in sleep regulation, blocked postsurgical pain hypersensitivity caused by pre-surgical sleep deprivation, and prevented pain hypersensitivity caused by sleep deprivation alone [38]. In accordance, the hyperalgesic effect of acute REM sleep deprivation in rats correlated with increased activity at adenosine A_{2A} receptor in the nucleus accumbens, and administration of an A_{2A} receptor antagonist prevented the hyperalgesic effect of sleep deprivation [32]. These findings suggest that one pathway through which sleep deficiency enhances pain is through increased adenosinergic activity.

Nitric oxide signaling
Nitric oxide (NO), formed by the oxidation of nitrogen, is a potent vasodilator produced by cells in the central and peripheral nervous system that are involved in regulating immune, cardiovascular and nervous system functions. In the immune system, NO is produced by phagocytic white blood cells such as macrophages, and is involved in the killing of engulfed host-invading bacteria. In the cardiovascular system, NO is induced by a number of triggers and is synthesized in vascular endothelium by the enzyme endothelial nitric oxide synthase (eNOS) and produces smooth muscle relaxation, vasodilation, resulting in slowing of heart rate and lowering of blood pressure.

With respect to nociception, a study using a mouse genetic knockout of nitric oxide synthase (NOS), found that neuronal NOS (nNOS), particularly in the dorsal root ganglion (DRG), is very important for mechanical hypersensitivity after nerve injury. These investigators found further, that in these knockout animals systemic or spinal administration of pharmacological nNOS inhibitors attenuated the hypersensitivity. Interestingly, the nerve injury led to upregulated nNOS protein expression in the DRG but not the spinal cord, suggesting the DRG is a key site for the development of hypersensitivity [39]. The treatment of patients with complex chronic neuropathic pain with DRG stimulation is an area where clinical interventions are currently under development (reviewed in [40]).

Studies have shown that NO is another important player in the homeostatic regulation of sleep and wakefulness; in murine models, markers of NOs level in the basal forebrain were found to double during sleep deprivation [41, 42]. It was further discovered that NO production occurs upstream of adenosine increases [42]. These investigators also found that inducible NOS (iNOS) produced in wake-active neurons in the basal forebrain is positively correlated with sleep pressure [43], and that basal forebrain NO increases during sleep deprivation begin before

frontal cortex increases in iNOS and NO, and are followed by increases in adenosine [44]. These results demonstrate that changes in the NO system appear to occur in advance of changes in the adenosine system and together regulate sleep pressure.

Damasceno and colleagues [45] investigated REM sleep deprivation to modulate nociception in the rat and found that NOS was increased in the periaqueductal gray matter area (PAG) in the brainstem as a result of sleep deprivation. Other studies have shown spinal level modulation of pain due to REM sleep deprivation in rats [46–48]. In addition, in a rat model of chronic pain, Tomim and colleagues [49] found that descending pain inhibitory and pain facilitatory activity in the brainstem PAG was intensified by REM sleep deprivation.

While we are aware of no studies that have investigated the role of sleep deprivation or disruption on the development of spontaneous pain or pain hypersensitivity in the genetic NOS knockout mouse model, the existing literature suggests that NO increases in the basal forebrain and frontal cortex during sleep deprivation and that it is also an important mediator of pain in the PAG. Studies of NOS knockout mice in conjunction with pharmacological testing may be helpful in furthering our site-specific understanding of how sleep disruption impacts the development of chronic pain.

Orexinergic system
Discovered in the late 1990, the orexinergic system consists of two neuropeptides (orexins A and B—also known as hypocretins 1 and 2) and the orexin-1 and -2 receptors. Orexin-producing neurons are located in the lateral hypothalamic area and project to multiple brain regions, many of which are involved in the regulation of sleep and wakefulness [50], as well as to the spinal cord [51]. Indicative of orexin's role in sleep-wake regulation are findings of orexin deficiency associated with the sleep disorder narcolepsy in animals and humans (reviewed in [52]). Orexins are also involved in a broad range of other physiological and behavioral functions, including pain control. In the following, associations of the orexinergeric system with sleep-wake states and with pain control will be outlined.

Across the sleep-wake cycle, orexin neurons are active during wake and almost silent during sleep. This finding has been demonstrated in both murine and canine animal models [53]. Photo- and chemical stimulation of orexin neurons have been linked to wakefulness and inhibition of orexin neurons have been shown to promote sleep in animal models, supporting the hypothesis that the activity of orexin neurons is related to the behavioral states of sleep and wake [54, 55].

Experimental REM sleep deprivation in animals increases orexin A in discrete brain regions [56]. In humans, cerebrospinal fluid (CSF) orexin concentration increased after several nights of experimental sleep restriction [57], further supporting its involvement in maintaining wakefulness. Conversely, sleep fragmentation in atherosclerosis-prone mice has been recently shown to decrease expression of orexin in the hypothalamus, with a corresponding decrease of orexin A levels in plasma and bone marrow [58]. These findings suggest that sleep deficiency affects the orexinergic system, and that short and disturbed sleep may potentially have differential effects on this system. Clinically, orexin receptors are a target in the pharmacological treatment of narcolepsy and insomnia disorder. The dual orexin receptor antagonists suvorexant, for example, is currently approved for the treatment of insomnia disorder in the US and Japan [59].

Orexins neurons innervate brain regions that are also involved in nociception, such as the periaqueductal grey [60]. Further, orexin A immunoreactive fibers have been found in layers of the spinal dorsal horn, making it likely that the orexinergic system is also involved in pain transmission and modulation. Indeed, several studies have shown that intrathecal injection of orexin A produces anti-hyperalgesic and anti-allodynic effects in neuropathic,

postsurgery, and inflammatory pain models in animals (reviewed in [61]. Furthermore, it has been demonstrated that the analgesic effect can be reversed by administration of a selective orexin-1 receptor antagonist, but not, for example, by administration of the opioid antagonist naloxone [62–64]. These findings indicate that the analgesic effect is mediated by activation of the orexin-1 receptor. Destruction of orexin neurons in narcolepsy patients has also been shown to be associated with a pro-inflammatory immune signature, including increased production of pro-inflammatory cytokines by T cells [65]. In light of the proalgesic effects of inflammatory molecules, the orexin-immune connection may underlie the link between sleep deficiency and pain. However, orexin neurons in the perifornical area (PeF) do not receive direct nociceptive input from the lamina I nociceptive second order neurons in the spinal cord [66], and a recent study by Asano and colleagues [67], suggested that the nociceptive information from the spinal cord is transmitted to the PeF in hypothalamus via the glutamatergic lateral parabrachial (LPB) neurons. A subpopulation of the LPB neurons that express the calcitonin gene related peptide (CGRP) encodes and processes many noxious and aversive stimuli like cutaneous pain, aversive food [68], and hypercapnia [69]. These neurons are then involved in sensory processing of these signals by its projections to the forebrain areas [68, 69]. This newly discovered circuitry to PeF via LPB and the role of the descending pain pathways in modulating pain and arousal warrants further investigations.

Collectively, these findings suggest that the orexinergic system is involved in pain transmission and modulation. Accordingly, orexin peptides and their receptors offer opportunities for developing analgesic drugs [70]. In light of the involvement of the orexinergic system in both pain and sleep-wake control, the orexinergic system may mediate the hyperalgesic effects of sleep deficiency, a dual effect yet to be investigated.

Hypothalamus-pituitary-adrenal axis
The Hypothalamus-pituitary-adrenal (HPA) axis mediates the response to both physical and psychological stress. The release of corticotropin-releasing hormone (CRH) from the hypothalamus stimulates the secretion of adrenocorticotropin hormone (ACTH) from the pituitary, which then stimulates the secretion of glucocorticoids from the adrenal cortex (cortisol in humans and corticosterone in rats). The HPA axis is tightly inter-related with the immune system such that pro-inflammatory cytokines activate the HPA axis resulting in increased production of cortisol [71]. Cortisol, in turn, inhibits pro-inflammatory cytokine production, such as interleukin (IL)-1 and IL-6, which are known to sensitize nociceptors in the periphery or pain transmission neurons in the CNS (reviewed in [72]). Thus, cortisol and synthetic glucocorticoids (e.g., prednisolone and dexamethasone) are likely to modulate the nociceptive system indirectly through changes in the secretion of proinflammatory and proalgesic cytokines and prostaglandins (for details on cytokines and prostaglandins, see section g. Immune System).

In patients with chronic pain conditions, such as rheumatoid arthritis, fibromyalgia, headaches, or low-back pain, a dysfunctional HPA axis has been reported, including HPA hypo-reactivity and basal hypocortisolism, as well as HPA hyper-reactivity and basal hypercortisolism (reviewed in [73]). Such dysfunctions disrupt the balance between the HPA and immune systems and result in weakened immunoregulation and a state of low-grade inflammation in the body. Further, most studies in human have shown that sleep deficiency causes small elevations of basal cortisol levels (reviewed in [74]) and a greater surge of cortisol response to stress [75]. For example, an experimental study design consisting of restricting sleep on weeknights and catching up on sleep over the weekend over a three-week period progressively increased morning cortisol levels in healthy participants [76]. In these healthy participants, the monocytes were much more

sensitive to the counter-inflammatory cortisol signal, but this did not inhibit them from producing less of the pro-inflammatory IL-6 signal, suggesting a marked disruption in the interplay between the HPA and the immune system caused by recurrent episodes of sleep restriction and recovery [76].

Among individuals suffering from insomnia symptoms, mild increases in basal cortisol levels (reviewed in [74]) and a hyper-reactivity of the HPA axis to stressors [77] have been reported. Of interest, such hyper-reactivity has been found to mediate the relationship between deficient sleep and higher pain sensitivity [78]. This suggests that dysregulations of HPA axis responses may potentially serve as a marker for chronic pain risk associated with chronic deficient sleep.

Immune system
The immune system's response to infection and tissue injury is inflammation and includes the production of inflammatory mediators such as prostaglandins and cytokines. Small elevations of these inflammatory mediators (identified as low-grade inflammation) can also be found in the absence of the classical inducers of a typical inflammatory response (i.e., infection and tissue injury), and are likely due to cellular stresses and malfunction (reviewed in [79]). An upregulation of inflammatory mediators can be observed in various types of pain conditions, and in response to short or disturbed sleep, as discussed below.

Prostaglandins. Prostaglandins (PGs) are classic inflammatory markers that mediate some of the cardinal symptoms of inflammation, such as fever and pain. Their involvement in the production of such symptoms is demonstrated by the therapeutic effects of nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or acetylsalicylic acid (aspirin), which primarily prevent the synthesis of PGs through inhibition of cyclooxygenase (COX-1 and/or COX-2 enzymes [80]). With respect to the effects of PGs on sleep, inhibition of PG production by COX-2 inhibitors reduced spontaneous and cytokine-induced increases in non-REM sleep in animals [81]. In humans, inhibition of PG production through acute administration of aspirin at the recommended daily dose range has been shown to disrupt sleep (i.e., decreased sleep efficiency, increased number of awakenings) and decrease slow-wave sleep (SWS) [82, 83], supporting a role of PGs in sleep modulation. The effects of *chronic* administration of NSAIDs on sleep are unknown Recently, the PG system has been shown to not only promote inflammation, but also to play a role in the resolution of inflammation [84]. Thus, under certain circumstances, inhibiting this system by NSAIDs may contribute to ongoing inflammation and potentially disturb sleep. Given that a large proportion of the population uses NSAIDs on a regular basis [85], future research should address their long-term effects on sleep.

Regarding the effects of sleep deficiency on prostaglandin production, experimental sleep deprivation leads to increased levels of various PGs in the CSF of animals [86] and to increased urinary PGE_2 metabolite levels in humans [87]. The latter increase was associated with greater pain reporting, suggesting that PGE_2 mediates the hyperalgesic effects of sleep deficiency.

Cytokines. In addition to PGs, cytokines (e.g., IL-1, IL-6, tumor necrosis factor [TNF] alpha), have also been identified as potent pronociceptive factors capable of sensitizing peripheral sensory and central nociceptive neurons, thereby promoting hyperalgesia [72]. IL-6, for example, is a small protein that is produced mainly by circulating monocytes and macrophages but also by CNS immune cells, such as glial cells. Elevations in IL-6 in the periphery and spinal cord have been shown in various animal pain models [88]. Administration of IL-6 can lead to hyperalgesia, and IL-6 blockers (e.g., IL-6 receptor antibody tocilizumab) can reduce pain hypersensitivity [88], supporting an important role of IL-6 in the induction or amplification of pain. With respect to sleep, IL-6 and

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other inflammatory cytokines increase in response to short or disturbed sleep, and such cytokine elevations indicate a state of low-grade inflammation in the body [79]. Ongoing or chronic low-grade inflammation is thought to increase risk of a number of chronic health diseases, including cardiovascular, metabolic, neurodegenerative, and chronic pain conditions [79]. In the human experimental setting, elevations in blood IL-6 levels correlate with increased pain reporting after prolonged sleep restriction [89]. Thus, low-grade inflammation may constitute a mechanism that links short or disturbed sleep to chronic pain; however, causality is yet to be demonstrated.

Pineal melatonin system

The synthesis of melatonin, the main hormone secreted by the pineal gland, is stimulated by darkness and suppressed by light. In humans, peak melatonin levels occur during the night. The threshold to suppress melatonin has been estimated to be as low as 30 lux [90], which is well below normal fluorescent light of about 300–400 lux. Decreased suppression at night has been observed in shift workers exposed to artificial lighting at night, but also in individuals using light-emitting electronic devices, such as smartphones or tablets, before bedtime [91].

Melatonin has many actions and properties, including anti-inflammatory, analgesic, and sleep-promoting effects (reviewed in [92]). For example, melatonin can downregulate inflammatory mediators including prostaglandins and cytokines (reviewed in [93]), both markers known for their pain-sensitizing actions. Mechanisms of melatonin's analgesic properties are not entirely clear but appear to involve endorphins, GABA receptor, opioid receptors, and the nitric oxide-arginine pathway [94]. Potentiating the melatonin signal with exogenous melatonin administration can have a beneficial effect on sleep in certain sleep disorders, including insomnia disorder (i.e., a disorder of difficulty falling asleep or maintaining sleep that is associated with impairment in daytime functioning) and circadian rhythm sleep disorder of the delayed sleep phase type (i.e., a disorder characterized by delayed habitual bedtime and delayed rising time that is in conflict with work or lifestyle requirements (reviewed in [95]. In these patients, melatonin improves sleep by reducing sleep onset latency or by regulating sleep-wake times (reviewed in [95].

In patients suffering from chronic pain conditions, such as fibromyalgia and irritable bowel syndrome, exogenous administration of melatonin has been shown to reduce subjective pain [96, 97] and improve endogenous pain inhibition in fibromyalgia [98]. In animals, the administration of melatonin attenuated the development of neuropathic pain following nerve injury [99], suggesting that the melatonin system presents another potential mechanism through which deficient sleep facilitates pain.

Endocannabinoid system

The endocannabinoid system is a phylogenetically ancient system that appears to date back to the unicellular common ancestor of animals and plants. Endocannabinoids are lipid mediators that bind to cannabinoid receptors expressed in the central and peripheral nervous system. Besides endogenous cannabinoids (e.g., anandamide), exogenous cannabinoids target these receptors, including constituents of the cannabis plant (i.e., the psychoactive delta(9)-tetrahydrocannbinol [THC] and the nonpsychoactive cannabidiol [CBD]). The endocannabinoid system is involved in the regulation of a wide range of biological functions, including the modulation of pain and sleep, as reviewed below. Recently, cannabinoids have been increasingly used in the treatment of chronic pain. The cannabinoid system is known to play a modulating role in analgesia and sleep. A recent systematic review including over 6000 chronic pain patients showed that the average number of patients who reported a reduction in pain of at least 30% was greater with cannabinoids than with placebo [100].

In preclinical studies using diverse inflammatory and neuropathic pain models, cannabinoids have been found to exert antinociceptive effects [101]. The endocannabinoid system has been shown to attenuate the inflammatory response in inflammatory pain models, suggesting that inflammation constitutes a pathway by which endocannabinoids reduce the experience of pain (reviewed in [101]. Cannabinoids appear to also have an opioid-sparing action. For example, cannabinoid receptor agonists reduced the opioid dose needed to produce anti-nociception in pre-clinical inflammatory pain models (reviewed in [102]). This suggests an interplay between endogenous opioid and cannabinoid systems. However, the opioid-sparing effect of cannabinoids is less clear from the findings of large controlled clinical trials (reviewed in [102]). Whether the promotion of the endocannabinoid system is an effective therapeutic strategy to reduce opioid use is still an open question.

The endocannabinoid system has been shown to exhibit a diurnal rhythm across the normal sleep-wake cycle, with higher levels during wakefulness (reviewed in [103]. Furthermore, sleep restriction increased circulating levels of endocannabinoids in healthy humans [104, 105]. This increase may explain greater appetite induced by deficient sleep. However, it may not explain greater pain reporting and pain sensitivity commonly observed in response to deficient sleep [2], suggesting that mediators other than cannabinoids contribute to pain amplification following sleep deficiency.

Research on exogenous cannabinoids on sleep is still in early stages and the results to date have been inconsistent. Preliminary findings suggest that the cannabinoid cannabidiol (CBD, the nonpsychoactive constituent of cannabis), does not affect sleep parameters in healthy sleepers [106]; however, it may have a beneficial effect in the treatment of insomnia disorder. For example, high-dose CBD (unlike low-dose CBD) has been shown to increase total sleep time and reduce arousal frequency in individuals suffering from insomnia disorder (reviewed in [107].

Some studies have addressed the potential role of cannabinoids in patients with chronic pain conditions comorbid with sleep disturbances. Based on a recent systematic review, 22 out of 29 randomized clinical trials showed that cannabinoid use is associated with a modest analgesic effect in the management of chronic non-cancer pain, with some trials reporting a concomitant improvement in subjective sleep [108]. For example, in patients with diabetic peripheral neuropathic pain, the synthetic cannabinoid nabilone was associated with improvements in pain relief and subjective sleep when compared to placebo [109]. Similarly, in various neuropathic pain conditions, a THC and CBD oromucosal spray treatment improved pain and sleep quality when compared to placebo treatment [110]. Administration of THC also appears to have a beneficial effect on muscle stiffness, pain and sleep in multiple sclerosis patients [111]. Further, Sativex, a 1:1 TCH/CBD compound, has demonstrated significant beneficial effects on both pain and sleep quality among a small sample of patients with rheumatoid arthritis [112]. In summary, the research of cannabinoids effect on sleep and pain is relatively new and controlled longitudinal studies are needed to better understand both the underlying mechanisms and their clinical implications.

Figure 1 summarizes findings on the effects of sleep deficiency on neurobiological systems and mediators with predominantly analgesic, hyperalgesic, or dual analgesic and hyperalgesic properties. Collectively, sleep deficiency appears to have a de-activating effect on several systems/mediators with predominantly analgesic properties, including the opioid system, the orexinergic system, the melatonin system, and dopamine signaling, while activating systems/mediators with predominantly hyperalgesic properties, including NO and adenosine signaling, and inflammatory mediators of the immune system.

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Analgesic	Analgesic and/or Hyperalgesic	Hyperalgesic
Opioid system	**Monoaminergic - Serotonin**	**Adenosine signaling**
↓ Responsivity to opioids	↓ Serotonin 1A receptor sensitivity	↑ Adenosine (A2A receptor mediated)
Monoaminergic - Dopamine	↑ Extracellular serotonin in basal forebrain	**Nitric oxide signaling**
↓ Dopamine D2 receptor activity	↑ Plasma serotonin metabolites	↑ NO in basal forebrain, PAG, cortex
Monoaminergic - Norepinephrine	**HPA axis**	**Immune system**
↑ Norepinephrine transporter mRNA in LC, norepinephrine levels in blood	↑ Cortisol (indirect effects on pain through interplay with immune system)	↑ Prostaglandins (PGE2)
Orexin signaling		↑ Cytokines (IL-1, IL-6, TNF)
↓ Orexin-A in hypothalamus, plasma, bone marrow		
↑ Orexin-A in hypothalamus, LC, cortex, CSF		
Melatonin		
↓ Melatonin levels in blood (mediated through light exposure at night)		
Endocannabinoids		
↑ Endocannabinoids in blood		

System/mediator property:
- Analgesic
- Analgesic/hyperalgesic
- Hyperalgesic

Effect of sleep deficiency on system/mediator:
- ↑ Activating
- ↓ Deactivating

Fig. 1 Effects of sleep deficiency on neurobiological systems/mediators with predominantly analgesic or hyperalgesic properties. Systems/mediators with predominantly analgesic properties are presented in blue, those with analgesic and/or hyperalgesic properties (depending on site of action and receptors involved) are presented in purple, and those with predominantly hyperalgesic properties are presented in red. The effect of sleep deficiency on systems/mediators is indicated by up- and down- arrows, with up-arrows reflecting an activating influence and down-arrows reflecting a deactivating influence on systems/mediators. For example, activation of the opioid system has analgesic effects (blue), and sleep deficiency leads to reduced responsivity to exogenous opioids (down-arrow), suggesting that the pain-promoting effect of sleep deficiency is mediated by the opioid system. Not depicted are the many interactions between these systems and mediators, further emphasizing the complexity of the neurobiological mechanisms involved in the pain-promoting effects of sleep deficiency. LC: Locus coeruleus; CSF: cerebrospinal fluid; HPA: hypothalamus-pituitary adrenal; NO: nitric oxide, NOS: NO synthase; PAG: periaqueductal gray; IL: interleukin; TNF: tumor necrosis factor

CLINICAL IMPLICATIONS
In the following section, clinical implications of the bidirectional relationship between sleep and pain and its underlying mechanisms will be discussed, including behavioral and pharmacological approaches to manage chronic pain comorbid with sleep disturbances, interventional approaches to reduce postoperative pain, as well as sleep-disturbing and sleep promoting medications to be considered in pain management (Fig. 2). This domain is of great clinical interest, as demonstrated by a large scale study demonstrating that short term improvements in insomnia symptoms predict long-term improvement in both sleep and pain, regardless of the treatment modality pharmacological or non-pharmacological [113]. This finding emphasizes the hypothesis that improving sleep might yield a better pain relief, particularly as sleep appears to be a more reliable predictor of pain than pain is that of sleep [114].

Interventions to manage chronic pain comorbid with sleep deficiency
Non-pharmacological approaches. Non-pharmacological sleep interventions, such as sleep hygiene (i.e., good sleep habits), mindfulness, and relaxation training, are effective strategies to improve sleep quality in populations reporting poor sleep health (reviewed in [115]). In clinical populations meeting diagnostic criteria for insomnia disorder, cognitive behavioral therapy for insomnia (CBT-I), is considered the first-line treatment [116]. CBT-I is a multi-component intervention that includes sleep hygiene education, time in bed restriction, stimulus control, targeting of negative cognitions about sleep, and relaxation tools; and has been shown to be an effective intervention in populations with both chronic pain and insomnia. For example, in patients with comorbid insomnia and osteoarthritis, CBT-I led to objective reductions in the time spent awake during the night, which in turn predicted reductions in clinical pain [117]. In patients with comorbid insomnia and fibromyalgia, combined CBT-I and CBT-P (P stands for pain) was found to improve both subjective sleep measures and pain severity [118].

In recent years, studies on CBT-I have begun to incorporate physiological assessments, which allows for a better understanding of biological changes associated with CBT-I. In adults suffering from insomnia disorder, CBT-I has been found to result in lower levels of C-reactive protein (CRP), an acute phase protein regulated by IL-6, and this decrease was associated with remission of insomnia [119]. Additionally, TNF and IL-6 expression by monocytes were lower post-CBT-I treatment, and gene transcripts involved in inflammation were downregulated [120]. These immune effects suggest that CBT-I in adults suffering from insomnia disorder reduces both insomnia symptoms and inflammation. Recently, the impact of CBT-I on immune markers has also been investigated in populations with insomnia comorbid with chronic pain. In patients with osteoarthritis knee pain, improvement of insomnia was paralleled by improved physical functioning, a decline in knee pain, and a reduced IL-6 response to an experimental pain challenge [121]. These findings suggest that improving sleep has a beneficial effect on various inflammatory mediators, which may underlie the observed improvement of chronic pain following CBT-I. However, further research is needed to substantiate the mechanistic role of these and other mediators in the association between sleep deficiency and pain.

Pharmacological approaches
Pharmacological interventions targeting sleep: Pharmacological interventions in the treatment of insomnia include GABA$_A$ receptor agonists non-benzodiazepine hypnotics (e.g., zolpidem,

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Fig. 2 Clinical implications and research opportunities based on current knowledge of the sleep-pain relationship

zopiclone), melatonin receptor agonists (e.g., ramelteon), anti-depressants (e.g., trazodone, doxepin), orexin receptor antagonists (e.g., suvorexant), $GABA_A$ receptors agonists benzodiazepines (e.g., lorazepam), and gabapentin-receptor $\alpha_2\delta$ subunit antagonist gabapentinoids, such as gabapentin and pregabalin [59]. Several studies have investigated the effects of pharmacotherapy on both sleep and pain in patients with sleep disturbances comorbid with chronic pain, and addressed the question whether successfully managing sleep disturbances can improve pain symptoms (reviewed in [122]). For example, in patients with rheumatoid arthritis, the non-benzodiazepine zopiclone improved sleep, but this effect was not paralleled by an improvement in pain, while the benzodiazepine triazolam improved both sleep and pain parameters (reviewed in [123]. These discrepant results could be related to the more targeted impact of non-benzodiazepine selective agonists at $GABA_A$ receptors in sleep-promoting neural domains compared to the broader impact of benzodiazepines in the brain. In patients with temporomandibular joint dysfunction, melatonin has been shown to improve sleep quality, decrease pain scores, and reduce analgesic consumption [124]. To date, sleep promoting pharmacotherapy studies have not shown consistent improvement in comorbid chronic pain, suggesting a potentially complex reciprocal sleep-pain relationship across chronic pain disorders.

Recently, cannabinoids have been increasingly used in the treatment of chronic pain. The cannabinoid system has been proposed to play a favorable modulating role on analgesia and sleep. A recent systematic review including over 6000 chronic pain patients showed that the average number of patients who reported a reduction in pain of at least 30% was greater with cannabinoids than with placebo [100]. A review on the effects of cannabinoids on objective sleep measures showed inconsistent findings in the general population, though in clinical populations, findings suggest that cannabinoids may improve sleep via reducing pain [125]. The research of cannabinoid effects on sleep in pain conditions is relatively new and controlled and long-itudinal studies are needed to advance our understanding and clinical implications.

Pharmacological interventions targeting inflammation: Few studies have targeted inflammatory pathways in the management of chronic pain, with some also assessing the effects on sleep. Immune dysregulation plays a pathophysiological role in various chronic pain conditions and can be the cause or the consequence

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of deficient sleep (reviewed in [79]). Consequently, immunotherapy may not only be effective to improve disease activity, but also to improve sleep. In patients with inflammatory bowel diseases (i.e., Crohn's disease and ulcerative colitis), administration of the anti-inflammatory agents anti-integrin (vedolizumab) or anti-TNF (infliximab or adalimumab) resulted in improved sleep quality within six weeks of therapy initiation, although associations with pain intensity were not reported [126]. Similarly, in patients with ankylosing spondylitis, a chronic inflammatory disease affecting the axial skeleton, thoracic cage, and muscle-joint pain, anti-TNF therapies improved subjective sleep quality, and this improvement was associated with a reduction in disease activity and pain [127]. In patients with rheumatoid arthritis, a chronic progressive autoimmune disease involving excessive production of various cytokines, in particular TNF, several studies have reported subjective and objective (polysomnography) sleep improvements in response to anti-TNF therapy. For example, anti-TNF infusion treatment with infliximab in patients with active disease decreased time to fall asleep and increased sleep efficiency, but these sleep improvements did not relate to joint pain amelioration. Thus, the effect on sleep may independently resulted from the inhibition of TNF actions in the CNS [128]. Treatment with an IL-6 receptor inhibitor (tocilizumab) in rheumatoid arthritis patients with active disease improved self-reported sleep quality and daytime sleepiness. The observed sleep improvement could not be explained by a reduction in disease activity, further suggesting a direct effect of cytokines on sleep regulation that is independent of disease activity [129].

The above findings suggest that cytokine therapy has a beneficial effect on sleep in chronic inflammatory diseases, which may be independent from its effect on improvement in disease activity in certain conditions and populations.

Interventions to reduce postoperative pain
Postoperative pain is a major health care challenge that remains undermanaged (reviewed in [130]). Sleep patterns in the postoperative period can be severely disrupted and shortened with a suppression of both slow-wave and rapid-eye-movement (REM) sleep [131]. The quantity and quality of sleep after surgery are influenced by a multitude of factors, including hospital-related environmental factors (e.g., noise, light), interruptions in sleep due to nurse checks or other medical interventions, the extent of tissue injury, the effectiveness of the analgesics, and the activation of the surgical stress response, as well as pain [132].

Patients experiencing postsurgical pain are often provided with analgesic medication. *Opioids*, while a potentially effective form of short term pain management, have significant risks for both dependence and mortality [133]. Opioids also have a broad physiological action, including both significant sedative effects [134] and sleep-disruptive effects (reviewed in [135, 136]). This suggests opposing actions of opioids alleviating pain while also disrupting sleep. Opioids also potentially aggravate pain by inducing pain hypersensitivity, or hyperalgesia, via administration of select short-acting opioids or intermediate-acting opioids when administered in high doses or for extended time [137]. It has also been observed that opioids may specifically exaggerate postoperative sleep disturbances [131], thereby potentially contributing to greater postoperative pain observed following opioid treatment [138]. A mild sleep-disrupting effect has been reported for acute treatment with NSAIDs (e.g., aspirin, ibuprofen). Given their beneficial effect in acute pain management [138], the potentially mildly sleep disturbing effect of NSAIDs is outweighed by the effect of reducing the interference of pain in sleep processes.

Gabapentinoids (gabapentin, pregabalin) have been reported to improve postoperative pain management as demonstrated by reduced opioid consumption and pain scores [138], and have also been shown to improve insomnia symptoms in patients with

fibromyalgia and anxiety disorders [59]. In a clinical study that investigated the effects of perioperative use of pregabalin on both sleep and pain in patients after intracranial surgery, preoperative sleep quality improved and postoperative pain scores and analgesic usage were reduced compared to placebo [139]. However, the relationship between changes in sleep quality and pain was not examined (e.g., whether improvements in sleep preceded reduced analgesic use or vice versa). Of note, both gabapentin and pregabalin are associated with significant side effects, including sedation and dizziness [140], which need to be considered in balancing the clinical benefits and risks in the management of acute postoperative pain.

Several studies have investigated the effect of *melatonin* on sleep in the postoperative period, and most of those studies reported a beneficial effect on sleep [141]. In breast cancer patients, for example, melatonin administered pre- and post-operatively increased sleep efficiency as objectively measured by actigraphy; however, subjectively assessed postoperative pain did not differ between melatonin and placebo administration [142]. Given melatonin's favorable side effect profile and its sleep promoting and analgesic properties reported in many studies, rigorous and methodologically well-designed clinical investigations are needed to better understand the role of melatonin on the relationship between sleep and postoperative pain.

Preoperative sleep disturbances the night before surgery have also been shown to increase postoperative pain. In breast cancer patients, lower sleep efficiency the night prior to surgery was associated with higher self-reported pain after surgery, and this association was independent of factors such as use of perioperative analgesics, psychosocial distress, or depression [143]. In animals, sleep loss the night prior to surgery caused a marked increase in mechanical hypersensitivity after surgery and prolonged postoperative recovery time [38]. Thus, obtaining good quantity and quality sleep the night prior to surgery may serve as an interventional target in the management of surgical pain.

In summary, pre- and postoperative sleep and pain management with pharmacological and non-pharmacological approaches are likely to improve sleep, reduce postoperative pain, and accelerate recovery processes with variable influences on the relationship between pain and sleep. However, there are risks of some medications (e.g., opioids) for both increasing daytime sedation as well as disrupting nighttime sleep. In view of the complex influence of the extent of tissue injury and the perioperative psychosocial factors on both pain and sleep, further investigations are needed to better understand the complex biological nature of a combination of nociceptive, neuropathic and inflammatory processes and psychosocial factors on postoperative pain and its relationship to sleep disruption.

Sleep-disturbing medications and pain management
A number of medications for the treatment of various diseases have sleep disturbing effects, thereby potentially augmenting pain in patients with acute and chronic pain. Sleep disturbing or altering effects have not only been shown for some analgesics (in particular opioids; see above), but also other classes of drugs, including psychotropic medications (e.g., antidepressants), cardiovascular drugs (e.g., beta-blocking agents), and corticosteroids (reviewed in [144]). As mentioned earlier, despite transient benefits for pain management, chronic and acute *opioid* use generally disrupt sleep, as indicated by reduced slow wave sleep, REM sleep suppression, and increased awakenings and arousal during sleep [144]. In addition to the known risks for dependence and abuse, chronic opioid use increases both daytime sedation and the prevalence of breathing-related disorders, particularly central sleep apnea.

Antidepressants used in the treatment of chronic pain conditions can have variable effects on sleep, depending on the drug class and dose. For example, low-dose tricyclic antidepressants (e.g.,

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amitriptyline, doxepin) have sleep-promoting effects, including increased slow wave sleep and sleep continuity, while activating tricyclic antidepressants (e.g., imipramine) have sleep-disrupting properties (reviewed in [145]. Mirtazapine, a medication with antihistamine, α$_2$-blocker and antiserotonergic activity is effective for both treatment of depression and insomnia, albeit in different dose ranges [146], has been demonstrated to be effective on both sleep and pain in patients with fibromyalgia [147]. Reported side effects of *beta-adrenergic blocking agents* (e.g., propranolol, atenolol) include insomnia. These agents also inhibit melatonin production, thereby interfering with melatonin's sleep-promoting and circadian phase regulatory properties, which may underlie the sleep-disturbing effect of beta-blocker [148].

Corticosteroids (e.g., cortisone, prednisone) are used as an immunosuppressant drug in a wide array of medical conditions, including certain inflammatory and autoimmune diseases and some types of cancer. Greater endogenous cortisol secretion and/or dysregulation of the diurnal cortisol rhythm have been frequently reported in insomnia and may be responsible for insomnia symptoms [149]. Based on cross-sectional studies, about 50% of patients exposed to systemic corticosteroids report sleep disturbances [150, 151]. Currently, there are no studies on objectively measured sleep changes in response to corticosteroid therapy in patients, or how these changes may depend on dose and duration of use.

To summarize, adjustments of dosage and timing of pharmacological treatments for both pain and sleep should be considered in chronic pain patients with multiple comorbidities in order to keep associated sleep-disturbing effects at a minimum, thereby preventing or reducing the pain-augmenting effect of sleep disturbances.

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS
Sleep deficiency affects various systems known to influence nociceptive processing, including the opioid, monoaminergic, orexinergic, immune, melatonin, and endocannabinoid systems; the hypothalamus-pituitary-adrenal axis; and adenosine and nitric oxide signaling, among others. Based on our current knowledge, sleep deficiency appears to have a de-activating effect on several systems/mediators with predominantly analgesic properties, including the opioid system, the orexinergic system, the melatonin system, and dopamine signaling, while activating systems/mediators with predominantly hyperalgesic properties, including NO and adenosine signaling, and inflammatory mediators of the immune system.

Within the highly complex and reciprocal interactions among these organized neurobiological systems, potential modulating pathways may exist by which short and disturbed sleep promote pain amplification. The current knowledge on the interplay between sleep and pain apparently plays a role in enhancing pain in various clinical acute and chronic conditions. As described, clinical implications are that both behavioral and pharmacological approaches are necessary for the optimal management of the coexistence of chronic pain with insomnia. Interventional approaches in the management of acute postoperative pain is complicated by the release of proinflammatory mediators, nociception, psychosocial and environmental stressors, as well as confounded by the administration of sleep disturbing analgesics, therefore requiring multimodal management. In chronic pain disorders, CBT-I is most effective in addressing sleep disturbance. The incorporation of physiological measures (e.g., immune mediators) in interventional studies will further our understanding of mechanisms through which interventions influence sleep and pain. Clarification of these mechanisms is crucial for the development of more refined therapeutic strategies to improve both sleep and pain control in future research.

ADDITIONAL INFORMATION

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