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REVIEW

A Narrative Review of the Reciprocal Relationship Between Sleep Deprivation and Chronic Pain: The Role of Oxidative Stress

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Abstract: Sleep is crucial for human health, insufficient sleep or poor sleep quality may negatively affect sleep function and lead to a state of sleep deprivation. Sleep deprivation can result in various health problems, including chronic pain. The intricate relationship between sleep and pain is complex and intertwined, with daytime pain affecting sleep quality and poor sleep increasing pain intensity. The article first describes the influence of sleep on the onset and development of pain, and then explores the impact of daytime pain intensity on nighttime sleep quality and subsequent pain thresholds. However, the primary emphasis is placed on the pivotal role of oxidative stress in this bidirectional relationship. Although the exact mechanisms underlying sleep and chronic pain are unclear, this review focuses on the role of oxidative stress. Numerous studies on sleep deprivation have demonstrated that it can lead to varying degrees of increased pain sensitivity, while chronic pain leads to sleep deprivation and further exacerbates pain. Further research on the role of oxidative stress in the mechanism of sleep deprivation-induced pain sensitization seems reasonable. This article comprehensively reviews the current research on the interrelationship between sleep deprivation, pain and the crucial role of oxidative stress.

Keywords: sleep deprivation, pain, oxidative stress, antioxidants

Introduction

Sleep deprivation is a pivotal health concern in contemporary society, often caused by various factors including unhealthy lifestyle habits and sleep disorders such as insomnia, sleep-related breathing disorders, and central sleep disorders. Modern lifestyles have contributed to the prevalence of sleep deprivation and disorders, rendering it a prominent health issue in today's world. Sleep deprivation has a range of biological impacts, including altered neural autonomic control, elevated oxidative stress, increased inflammation, and disrupted coagulation responses.[1]

Sleep deprivation increases the body's pain sensitivity and affects the ability of the cerebral cortex to perceive the pain threshold and inhibit pain. Pain, an unpleasant sensation and intricate brain response, stands as the most prevalent and disabling symptom in medicine. The organism's perception of pain primarily occurs through spinal-thalamic transmission to the sensory cortex of the brain, eliciting a distinct sensation of discomfort. Individuals suffering from both pain and sleep deprivation often exhibit a range of overlapping symptoms, including sleep disturbance, pain, anxiety, depression and fatigue.[2–4] The impact of sleep disturbance on pain sensitivity is highly conserved across species. Total sleep loss, or sleep deprivation, particularly from prolonged wakefulness, is the main driver of the pain hypersensitivity response, as it preferentially increases pain perception.[5] Pain sensitivity follows a 24-hour rhythm and is largely

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regulated by the body's internal circadian rhythm system.[6] With the duration of sleep deprivation increasing, central nociceptive hypersensitivity and pain regulation decline, raising the risk of chronic pain.[7,8]

Chronic pain is a widespread health issue, often linked to sleep deprivation that increases the likelihood of acute pain becoming chronic.[9,10] Prolonged chronic pain can give rise to extended periods of sleep deprivation, ultimately resulting in a range of physical and emotional complications. Investigations have further demonstrated that sleep disorders can influence pain perception, with individuals suffering from such disorders exhibiting a greater likelihood of developing chronic pain.[9,10] Chronic pain can greatly exacerbate insomnia, and both chronic pain and mood disorders are significant factors in this relationship.[11] The relationship between sleep and pain is bidirectional, with pain disrupting sleep[12] and inadequate sleep or sleep disorders intensifying pain.[13] Previous studies have indicated that oxidative stress significantly affects the relationship between sleep and pain.[14] Oxidative stress, referring to an imbalance between oxidant production and antioxidant defense, disrupts biological systems. Research indicates that wakefulness increases oxidative stress, whereas sleep serves as a safeguard against its deleterious effects. Chronic sleep deprivation and disruptions in circadian rhythm can lead to increased pro-inflammatory cytokines and oxidative stress.[15]

Sleep deprivation has the potential to induce nociceptive sensitization, and patients suffering from chronic pain are more likely to develop sleep deprivation. Nevertheless, the connection between sleep deprivation and pain is bidirectional, meaning that they mutually influence each other. The prevalent belief is that pain disrupts the initiation or maintains the duration of sleep, resulting in daytime drowsiness. Numerous clinical and experimental studies in recent years have demonstrated the effect of sleep deprivation on pain sensitivity.[14,16] Thus, the intricate relationship between sleep deprivation and pain remains to be thoroughly investigated and elucidated. Ultimately, we will delve into the pivotal role of oxidative stress in this bidirectional association. Clinically, numerous patients suffer from different degrees of sleep deprivation and chronic pain, and these two factors complement each other, seriously affecting their life quality and psychological health. Our objective is to explore the potential mechanisms and dynamics of their interactions, aiming to offer insights for future research to address this longstanding issue. In summary, this review will explore the relationship between sleep deprivation and chronic pain, focusing on the impact of oxidative stress on both.

Sleep Affects the Onset and Progression of Chronic Pain

The crucial role of adequate sleep in maintaining normal physiological functions is universally acknowledged. Sleep deprivation, which is defined as the inadequate amount of sleep.[17] Sleep deprivation is prevalent in modern society, with a recent trend of decreasing sleep duration.[1,18] A particular brain structure is responsible for encoding chronic pain and regulating sleep.[19] Since this structure regulates both sleep and pain, it is likely that sleep deprivation influences pain and vice versa. Sleep enables the night-time recovery of various bodily functions, suggesting that it may help reduce pain hypersensitivity resulting from extended wakefulness.[5]

Epidemiological studies have established that poor sleep is associated with an increased risk of chronic pain. Sleep deprivation can make individuals more susceptible to pain. A study on sleep restriction in healthy adults found that sleep restriction was correlated with increased instances of new spontaneous pain.[7] There is strong evidence to suggest that sleep disturbances impair endogenous pain-inhibitory function and increase spontaneous pain in women.[20] Decreased sleep duration was linked to a higher frequency of pain reports,[21] and was associated with abdominal and lower-extremity pain among nurses following night work.[22] A meta-analysis showed that preoperative sleep disturbances had a negative impact on the onset and severity of chronic pain in postoperative patients.[23] Patients with obstructive sleep apnea syndrome[24] who experience sleep deprivation and potential nociceptive hypersensitivity, have been found to exhibit lower pain thresholds after effective interventions for sleep deprivation. These human-based studies and experimental research have demonstrated that sleep deprivation is associated with heightened pain sensitivity.

Evidence indicates that sleep deprivation influences pain sensitivity via various pathways and mediators, including compromised immunity, exacerbated inflammatory responses, and increased levels of cytokines (eg, interleukin 6, C-reactive protein, and cortisol) that enhance pain perception and modulate pain processes.[25,26] In numerous chronic diseases, these markers are present in elevated concentrations, thereby contributing to the emergence and persistence of chronic pain conditions.[27,28]

Chronic Pain Leads to Sleep Deprivation and Further Aggravates Pain

Pain is a necessary response that serves to protect the body from harm. However, if pain persists beyond the normal healing phase or occurs without injury, it becomes pathological. Unlike acute pain, which serves a protective function, chronic pain signifies a dysfunction of the nociceptive system, causing physical and emotional suffering and reducing quality of life.[29–31] This condition impacts a considerable portion of the global population, resulting in substantial healthcare expenses and reduced productivity.

Adults suffering from chronic pain frequently experience sleep disturbances, including shortened sleep duration or compromised sleep quality.[12,32] Sleep disorders are a common issue and are significantly more prevalent among individuals with chronic pain. It is widely believed that sleep deprivation often results from chronic pain.[33] A meta-analysis has revealed that the prevalence of sleep disorders in patients with chronic pain can be as high as 70% or higher compared to those without chronic pain.[12] Among US veterans with chronic non-malignant pain, sleep disorders were found to be associated with poorer pain outcomes.[34] The coexistence of chronic pain and sleep deprivation can lead to additional impairments, further compromising the health and quality of life of these patients.

Clinically, it is often observed that patients reporting higher levels of pain intensity also exhibit greater degrees of sleep deprivation.[35] This creates a vicious cycle between sleep deprivation and pain in the chronic pain population, where poor sleep exacerbates pain which in turn disrupts sleep, perpetuating this cycle over time. The bidirectional relationship between sleep deprivation and chronic pain can be attributed to the fact that sleep deprivation has been shown to lower pain thresholds.

Sleep Deprivation is a Risk Factor for Pain and Good Sleep Helps Relieve Pain Perception

Sleep deprivation can result in an elevation of pain sensitivity, subsequently disrupting sleep and giving rise to a vicious cycle. This intricate and bidirectional relationship between sleep and pain has been thoroughly explored in numerous studies. Although the interplay is complex, it seems that sleep deprivation exerts a more profound influence on pain sensitivity than the converse. A study of adults and children revealed that the quality of nighttime sleep was a stronger predictor of the following day's pain sensitivity compared to the ability of pain intensity to predict subsequent sleep quality.[36] Edwards et al conducted a study involving 971 healthy adults over a period of one week and discovered that self-reported sleep duration from the previous night significantly predicted pain symptoms the following day. Although pain symptoms also predicted subsequent sleep duration, their impact was only half as strong as that of sleep duration on pain sensitivity. Furthermore, the quality of sleep from the preceding night has been identified as a predictor of the subsequent day's pain threshold. Research indicates that sleeping less than 6 hours per night is associated with increased pain sensitivity the following day.[37] It has been demonstrated that sleep deprivation, whether caused by short sleep duration or poor sleep quality, predicts the onset of future pain experiences.[20,38] In a study on patients with knee osteoarthritis, both subjective and objective measures of total sleep time were used to predict pain response at the 6-month follow-up. Results showed that sleep duration was the strongest predictor of pain severity.[39] A follow-up study involving 12,350 healthy women revealed that self-reported sleep issues doubled the risk of a fibromyalgia diagnosis one year later.[40] This implies that sleep not only predicts the next day's pain response, but also the likelihood of long-term pain. The evidence supports the hypothesis that sleep has a greater impact on pain symptoms than pain has on sleep.

Recent studies suggest that good sleep quality can predict pain relief. The increased sensitivity to pain caused by sleep deprivation can be mitigated through naps[41] and effective treatment of sleep disorders.[24] Roehrs et al have demonstrated that longer durations of sleep can lead to a decrease in pain sensitivity, while poor sleep quality serves as a risk factor for the development of chronic widespread pain.[42,43] A population-based study further revealed that restorative sleep, as reported by individuals, is independently associated with the alleviation of chronic widespread pain and the reinstatement of musculoskeletal health.[44] Another 5-year prospective study also suggested that disturbed sleep may predict the onset of multisite pain, and undisturbed sleep may be associated with pain relief.[45]

The findings of numerous studies indicate that sleep deprivation can increase the risk of developing pain and that sleep has a greater impact on pain than pain has on sleep. Short-term pain sensitivity and long-term pain onset can be

predicted by assessing nighttime sleep quality and duration, while good sleep quality may predict short-term pain alleviation. This supports the hypothesis that sleep plays a significant role in the management of pain and ought to be taken into account in clinical treatments for pain.

The Role of Oxidative Stress in the Relationship Between Sleep and Chronic Pain

Maintaining a balance between oxidants and reductants is crucial for normal functioning. Oxidative stress occurs when there is an imbalance between the reactive oxygen species within the body and its antioxidant system. This imbalance disrupts normal physiological functions, triggering a series of adaptive responses.[46] When the balance between reactive oxygen and the body's antioxidant system is disrupted, peroxides and free radicals are produced, leading to cytotoxic effects. Research has demonstrated that oxidative stress plays a pivotal role in various diseases, including atherosclerosis, chronic obstructive pulmonary disease, Alzheimer's disease, and cancer, highlighting the diverse mechanisms through which oxidants can inflict cellular damage.[47] There are two primary mechanisms underlying the contribution of oxidative stress to disease pathogenesis: (1) The direct oxidation of macromolecules, such as membrane lipids, structural proteins, enzymes, and nucleic acids, by reactive substances involved in oxidative stress (eg, -OH, ONOO-, and HOCL). This leads to abnormal cellular function and cell death. (2) Abnormal redox signaling that occurs when signaling proteins interact with hydrogen peroxide or other electrophiles, acting as secondary messengers. To defend against oxidative damage, organisms have evolved several defense mechanisms, including antioxidant enzymes, substrate availability, and damage repair. The main components of the antioxidant defense system include: (1) enzymes such as superoxide dismutases, which neutralize hydrogen peroxide and lipid peroxides; (2) the synthesis of thioredoxin reductase, glutathione, and glutathione reductase through the action of thioredoxin, glutamate-cysteine ligase, and glutathione synthase; and (3) the repair or removal of oxidized macromolecules.[48]

The various biomarkers indicative of oxidative stress and redox status exhibit significant circadian rhythms.[49] Research on healthy volunteers has shown that the activity of superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), glutathione reductase (R-GSSG), and the concentration of glutathione (GSH) are regulated by circadian rhythms.[50] Similarly, circadian rhythm regulation of the balance between oxidation and antioxidants has also been observed in Daphnia pulex.[51] A previous study indicated that sleep deprivation can exert a significant influence on pressure pain thresholds and plasma oxidative stress markers among healthy adult residents, even after just one night of sleep deprivation.[14] Moreover, studies have shown that sleep deprivation can have an impact on the oxidative stress status of the body in animal experiments. A study on mice found that sleep deprivation caused increased nociceptive sensitivity, which was accompanied by increased levels of oxidative stress and inflammation markers in the cerebral cortex and striatum. However, the antioxidant and anti-inflammatory compound naringenin was able to counteract the nociceptive sensitivity and reduce the levels of oxidative stress and inflammation markers.[52] Oxidative stress can be triggered in the brain, liver, and pancreas of animals experiencing sleep deprivation.[53,54] Sleep deprivation leads to alterations associated with oxidative stress, such as the accumulation of reactive oxygen species in the gut, causing death in fruit flies and mice.[55] The cerebral cortex is pivotal to the perception and regulation of pain, and the medial prefrontal cortex is a key region associated with pain modulation and with the development of chronic pain.[56] Not only does sleep deprivation harm the brain, but it also affects peripheral tissues to varying degrees. Studies have shown that sleep deprivation reduces antioxidant capacity in peripheral tissues of animals that have been deprived of sleep for 5 and 10 days.[57] Sleep deprivation leads to cellular stress, disrupting multiple physiological processes.[58,59] This hypothesis suggests that sleep plays a crucial role in mitigating oxidative stress and restoring the antioxidant system in the body, thereby averting the generation and accumulation of reactive oxygen species.

Sleep deprivation, by disrupting the normal physiological processes of sleep, gives rise to elevated levels of oxidative stress and lipid peroxidation in both central and peripheral tissues, hindering the proper functioning of the body.

The mechanisms underlying the decreased pain thresholds observed in sleep deprivation remain incompletely understood. However, growing evidence suggests a correlation between sleep deprivation and pain, mediated by oxidative stress and inflammation. The imbalance triggered by sleep deprivation between oxidant and antioxidant defense systems leads to increased levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are key contributors to pain development.[60] However, the exact role that oxidative stress plays in regulating pain is still

unknown. The increased levels of reactive oxygen species have been found to contribute to sleep deprivation-induced nociceptive hyperalgesia through activation of microglia and enhancement of NLRP3 inflammasome activity in the dorsal horn of the spinal cord.[61] A single night of total sleep deprivation has been demonstrated to disrupt the downstream nociceptive pathway, promote spinal cord excitability, and sensitize peripheral nociceptors to cold and pressure pain.[62] Melatonin has been shown to alleviate oxidative stress, activation of the NF-κB pathway, neuroinflammation, and apoptosis in mice subjected to sleep deprivation.[63] Sleep deprivation gives rise to heightened levels of reactive oxygen species within the body, and the accumulation of these species may increase neuronal excitability by reducing inhibitory transmission to GABAergic neurons located in the spinal cord.[64] Activation of neuronal NMDA receptors has been shown to trigger the release of superoxide from neighboring neurons and astrocytes, ultimately leading to an oxidative stress response.[65]

A meta-analysis has revealed that sleep disturbance is associated with elevated levels of systemic inflammation markers.[25] Furthermore, this systemic inflammation has been found to decrease the pain threshold among study participants.[66] Chronic sleep deprivation has been shown to cause nociceptive hyperalgesia in mice, and this phenomenon is accompanied by an increase in oxidative stress and levels of inflammatory markers in the cerebral cortex and striatum. The administration of antioxidants and anti-inflammatory substances effectively reduces nociceptive hyperalgesia, as well as the oxidative stress and inflammation marker levels.[52] Intrathecal injection of antioxidants has been found to alleviate nociception in sleep deprivation animals, while the opposite effect was seen with the intrathecal injection of reactive oxygen species, inducing hyperalgesia in normal animals.[67] In rapid eye movement sleep deprivation rat models, there was a significant positive correlation between oxidative stress levels in the thalamus and pain behavior scores. The use of drugs to reduce oxidative stress has been shown to decrease pain behavior scores in these rats.[16] Additionally, oxidative stress in the spinal cord has been identified as the underlying mechanism responsible for the development of mechanical hyperalgesia and neurological damage due to sleep deprivation. Antioxidant compounds may disrupt this vicious cycle between pain and sleep deprivation.[68]

Previous systematic reviews and meta-analyses have consistently concluded that sleep deprivation exerts a moderate to large influence on pain perception in healthy individuals. These conclusions were derived from a range of sleep deprivation paradigms and pain outcome measures.[38] Similarly, reviews have shown that full and partial sleep deprivation, as well as sleep fragmentation, can enhance spontaneous pain intensity or lower pain thresholds and tolerances in individuals, whether or not they have chronic pain.[69] In this review, we propose that sleep modulates the emergence and development of pain. Conversely, the persistent state of pain prompts sleep deprivation, which in turn exacerbates pain perception. This exacerbation of pain by sleep deprivation subsequently impacts sleep quality, creating a vicious cycle where oxidative stress may play a significant part (Figure 1). Notably, this review did not delve into the effects of sleep deprivation on pain perception in specific life contexts, such as noise-induced sleep deprivation or sleep deprivation

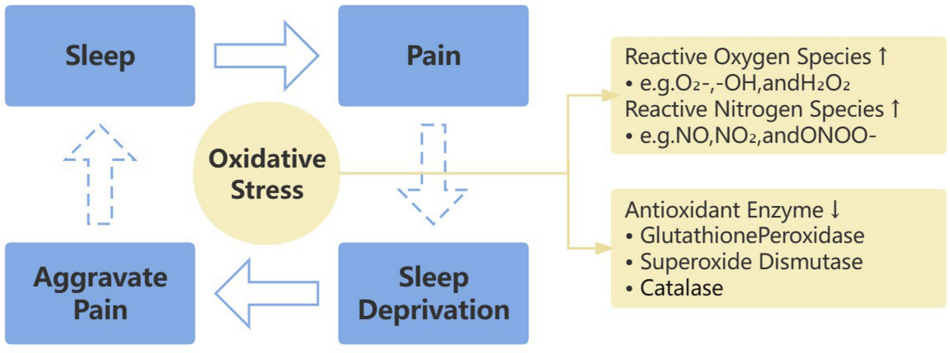

Figure 1 Hypothesis about the role of oxidative stress in sleep and chronic pain. Sleep affects the onset and progression of chronic pain. The persistent state of pain triggers sleep deprivation, which further aggravates pain perception. In turn, exacerbated pain affects sleep quality, creating a vicious cycle. The solid and dashed arrows in the figure indicate that this review suggests that sleep deprivation has a more definite and pronounced effect on pain perception than pain has on sleep quality. Oxidative stress may play an important role in the complex reciprocal relationship between sleep and chronic pain.

experienced by medical personnel and other professionals during shifts. Future research should focus on exploring the impact of sleep deprivation on pain perception across various real-life scenarios.

In conclusion, current research on the reciprocal relationship between sleep deprivation and pain has highlighted the important role of oxidative stress in mediating this relationship. It indicates that sleep disturbances can lead to pain, and this process is modulated by oxidative stress, as shown in Figure 1. Nevertheless, further exploration is warranted to comprehensively grasp the underlying mechanisms governing this relationship. The findings of the study have implications for the development of new strategies for managing sleep disturbances and pain, and for the design of future research aimed at exploring the role of oxidative stress in the relationship between sleep and pain.

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Disclosure

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