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Review

The relevance of sleep abnormalities to chronic inflammatory conditions

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Abstract. Sleep is vital to health and quality of life while sleep abnormalities are associated with adverse health consequences. Nevertheless, sleep problems are not generally considered by clinicians in the management of chronic inflammatory conditions (CIC) such as asthma, RA, SLE and IBD. To determine whether this practice is justified, we reviewed the literature on sleep and chronic inflammatory diseases, including effects of sleep on immune system and inflammation.

We found that a change in the sleep-wake cycle is often one of the first responses to *acute* inflammation and infection and that the reciprocal effect of sleep on the immune system in acute states is often protective and restorative. For example, slow wave sleep can attenuate proinflammatory immune responses while sleep deprivation can aggravate those responses.

The role of sleep in CIC is not well explored. We found a substantial body of published evidence that sleep disturbances can worsen the course of CIC, aggravate disease symptoms such as pain and fatigue, and increase disease activity and lower quality of life. The mechanism underlying these effects probably involves dysregulation of the immune system. All this suggests that managing sleep disturbances should be considered as an important factor in the overall management of CIC.

Keywords: Sleep–Immune system–Inflammation–Asthma–Rheumatoid arthritis – Systemic Lupus Erythematosus – Inflammatory bowel disease

Introduction

Adequate quantity and quality of sleep are required for optimal health and daytime functioning. For one thing, recent research suggests that individuals with sleep abnormalities are at increased risk of all-cause mortality and serious adverse health and economic consequences [1]. For another, chronic insomnia and sleep deprivation are associated with work absenteeism, greater health care utilization, hypertension, autonomic nervous system dysfunction, impairment of glucose control and increased inflammation [1–3].

Despite these negative effects, sleep quantity and quality are often ignored by medical professionals. To gain insight to whether, this practice is justified, we reviewed the literature on interaction between sleep and inflammation. We found may reports suggesting that sleep disturbances are relevant to chronic inflammatory conditions, particularly asthma, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) [4–8]. Nevertheless, it is unclear whether sleep alterations in patients with these diseases are :1) the result of factors associated with disease such as pain, stress or depression [9], 2) a consequence of drug treatment or 3) the result of disease-related immune changes. It is also possible that sleep disturbances contribute directly to the pathogenesis of the disease. We then further focused our literature review on normal sleep physiology its links to immune system function and explored how sleep disturbances might interact with the immune system and exacerbate chronic inflammatory conditions, and thus be a logical part of disease course, management and pathophysiology.

Searches of Medline and PsycLit databases were performed using a combination of search terms: sleep and health, sleep and inflammation, sleep and cytokines, sleep and hormones, sleep and any of several different chronic inflammatory conditions. Reviewing was restricted to articles on human and animal studies published recently in English language journals (1990 to the present). Only those studies which used standard, validated, subjective or objective evaluations of sleep parameters were selected for review (N = 60). We made the assumption that the four chronic inflammatory conditions we chose to focus on asthma, RA, SLE and IBD were representative of chronic inflammatory conditions in general.

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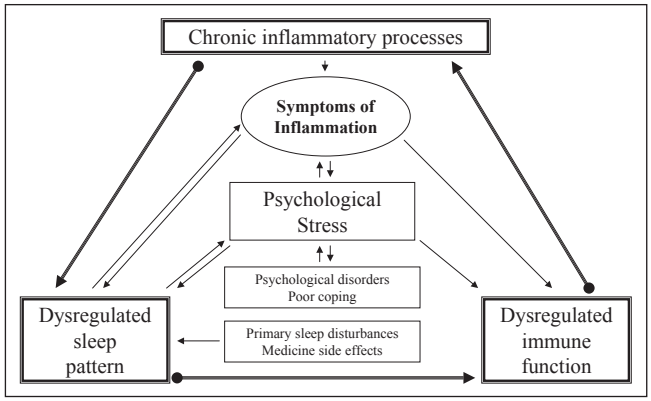

Figure 1. Possible connections between sleep and inflammatory disorders.

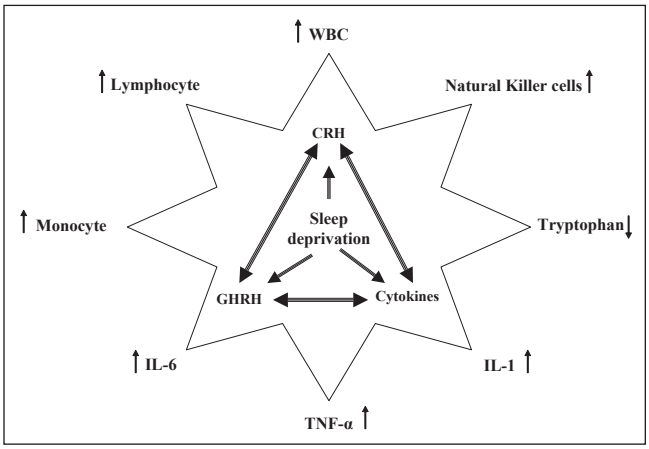

Figure 2. Sleep deprivation alters immuno-endocrine factors that are associated with inflammation
CRH = corticotropin releasing hormone, GHRH=growth hormone releasing hormone

1. Normal sleep behavior

Briefly, sleep is a reversible behavioral state of perceptual unresponsiveness to the environment. Based on changes in the electroencephalogram (EEG), the electromyogram (EMG), and the electro-oculogram (EOG), sleep has been divided into non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep [10]. NREM sleep is conventionally subdivided into four stages (stages 1–4); this includes a quiet stage of sleep (slow wave sleep) in which both heart and respiratory rates are slow, and blood pressure is low. REM sleep is defined by EEG activation, and bursts of rapid eye movements, and is accompanied by dreaming Some hormonal events, such as an increase in growth hormone (GH) secretion, occur during NREM sleep, while others such as increases in prolactin and glucocorticoids occur during REM sleep. Periods of REM and NREM sleep occur in 90 min cycles with the REM sleep duration progressively becoming longer later during any given sleep period. NREM sleep, especially slow wave sleep (SWS), which includes stages 3 and 4, is thought to provide physiological restoration more than other stages of sleep [11, 12]. It has also been shown that sleep parameters change with age. For example time spent in SWS decreases in older adults [13, 14].

2. Sleep and inflammatory mediators

Sleep and the immune system appear to have a reciprocal relationship. Indeed, in recent reviews [15, 16], the role of sleep in modulating the immune system has been described. This relationship is supported by research demonstrating that: 1) activation of the immune system disturbs sleep patterns [17, 18] and 2) sleep disturbances affect immune function [19, 20] (Fig. 1).

2. 1. Immune and neuroendocrine mediators alter sleep behavior

Increased sleepiness and fatigue are among the cardinal manifestations of acute inflammatory disorders. In particular, circulating cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) are the cytokines that make significant contributions to these immune-mediated acute phase responses (APR) [17] (Fig. 2). Because vast majority of cytokines are released during early inflammatory reactions, it is difficult to determine the unique contribution of each of these cytokines to systemic events in the acute phase response [17].

The most extensively studied inflammatory cytokines in sleep regulation are IL-1B and TNF-α [18, 21, 22]. It has been shown that injection of IL-1 and TNF in animal model increases time spent in NREM sleep. Further, blocking the effect of either of these two substances inhibits both spontaneous sleep and sleep rebound that normally occurs after sleep deprivation [23]. TNF-α has been linked to fatigue and sleepiness in rheumatoid arthritis and in obstructive sleep apnea patients [21, 22]. By using a TNF receptor fragment (TNFRF) as a TNF inhibitor, and an IL-1 receptor fragment (IL-1RF) as an IL-1 inhibitor, Takahashi et al. showed that TNF and IL-1 could influence each other's somnogenic effects [18]. In that study, intracerebroventricular injection of a combination of TNFRF and IL-1RF significantly reduced spontaneous NREM sleep in rabbits. In addition, pretreatment of rabbits with this combination attenuated NREM sleep rebound after sleep deprivation.

Studies have also shown that these cytokines dose-dependently increase NREM sleep time while decreasing REM sleep time [24]. Immune system activation through host defense mechanisms and the associated increases in proinflammatory cytokines result in increased body temperature, longer SWS periods and reduced wakefulness. In contrast to early phase of the acute inflammatory condition, with activation of the hypothalamic-pituitary-adrenal (HPA) in advanced stages of inflammation, the sleep-promoting effects of cytokines diminish and can result in reduced NREM sleep and increased wakefulness [25].

Another important cytokine associated with both the immune system and sleep behavior is IL-6. In one study, human volunteers were given IL-6 parenterally at a dose sufficient to reach levels associated with systemic infection. After 6.5 h, IL-6 caused significant subjective fatigue and resulted in a marked increase in C-reactive protein (CRP) compared

to placebo. There was also a significant suppression of REM sleep, and while total SWS time was similar to the placebo group, SWS time did decrease significantly during the first half of the sleep period and increase during the second half [17]. Interestingly, levels of other inflammatory cytokines did not increase after IL-6 injection [17], suggesting that among cytokines, IL-6 is particularly relevant to alterations in sleep patterns. This data is supported by the study of Vgontzas et al. who showed that overnight sleep deprivation increases daytime IL-6, which is responsible for daytime somnolence and fatigue [26]. Animal studies using a rat model, however, failed to show that IL-6 has a somnogenic effect [27].

There is some evidence that other hormones and neurotransmitters link sleep and inflammation. There is a close link between growth hormone releasing hormone (GHRH) and IL-1 with respect to their somnogenic mechanisms [28, 29]. In fact, because of the modulatory effects of corticotropin releasing hormone (CRH) on GHRH containing neurons [30], the somnogenic activities of GHRH and IL-1 may be related to a shared CRH feedback signal. It seems that inhibition of GHRH and IL-1B can inhibit NREM sleep while inhibition of CRH enhances NREM sleep [28, 31, 32]. In one study, Zhang et al. showed that GHRH mRNA in rats increases and somatostatin (SRIH) mRNA decreases during 8-hour sleep deprivation but return to normal levels after 1 to 2 h of recovery [31]. These findings support the concept that GHRH plays an important role in sleep homeostasis and suggest that these neuropeptides may interact reciprocally in modulating sleep, much like they do in control of growth hormone secretion [33].

Research also suggests that the hypothalamus, rather than the pituitary gland, is the main site of action of GHRH in sleep deprivation. Gardi et al. showed that there is a down-regulation of GHRH receptors in the hypothalamus but not in the pituitary gland after 8-hours of sleep deprivation in rats [34]. Therefore, it is likely that the sleep promoting action of IL-1 and GHRH are mediated via anterior hypothalamus neurons. These neurons are likely receptive to such substances and are influenced by other substances such as TNF-α and CRH [35]. Opp suggested that CRH might also be a modulator of physiologic waking [36]. This is supported by a study by Chang et al. [37], who administered CRH antagonists into the cerebral ventricle of rats and showed that CRH antagonists dose-dependently reduced, the amount of time the rats were awake. Subsequently, the authors showed that the mediator for this action is IL-1 [31]. In their study, astressin, a CRH antagonist, caused an increase in SWS and IL-1A and IL-1B mRNA expression, and resulted in a decrease in corticosterone and IL-6 and TNF-α mRNA expression in the brain [31]. Furthermore, pretreatment with anti-IL-1B resulted in elimination of the increases in SWS and decreases in waking time in rats. Thus, they concluded that IL-1 is a mediator of astressin-induced alterations in sleep behavior.

In summary, the literature suggests that TNF-α, IL-1 and IL-6 are important proinflammatory cytokines that are associated with alterations in the sleep-wake cycle.

2.2. Sleep deprivation effects on immune function

It appears that sleep deprivation alters immune system functions (Fig. 2). In one study, prolonged sleep deprivation in rats caused an unexplained hyper-catabolic state, symptoms of secondary malnutrition, and death [20]. Furthermore, post-mortem examination revealed no specific metabolic, morphologic or histological changes, suggesting that prolonged sleep deprivation can have a direct, life threatening effect on host defense mechanisms [36]. Other studies have shown that circulating white blood cells (WBC), particularly granulocytes and monocytes, are elevated during sleep deprivation [19, 38]. Prolonged sleep deprivation in humans for 64 h has also been linked to an increase in the activity of natural killer (NK) cells and monocytes, the primary source of inflammatory cytokines [38]. Redwine et al. showed that overnight sleep deprivation in humans can lead to enhanced nocturnal plasma IL-6 activity, and these changes in immune function occur independent of cortisol circadian rhythm, which remains unchanged [39]. Born et al. showed that sleep following sleep deprivation is associated with a decrease in monocytes, NK cells and lymphocytes and an increase in production of IL-2 [19]. Again, this effect was independent of changes in cortisol, which also has the potential to affect sleep patterns through alteration of circadian rhythms.

Prolonged periods of wakefulness can also result in an increase in IL-6 and TNF soluble receptors [40]. One study shows that a primary sleep disorder associated with depression can impair immune function [41]. The availability of tryptophan to the brain and hence synthesis of 5-hydroxytryptophan (5-HT) plays a modulatory role in regulation of sleep in normal individuals and in those with primary sleep disorders [42]. In fact, decreased availability of plasma tryptophan, which can also result in an alteration of inflammatory responses, has been proposed as the pivotal link connecting primary sleep disturbances to immune system dysfunction [41]. In that study, the ratio of tryptophan to tryptophan-competing amino acids was significantly correlated to increases in inflammatory cytokines such as IL-6 and IL-8 [41].

It is evident that sleep abnormalities can result in disruptive alterations in immune system function. However, the exact mechanism through which this occurs has yet to be elucidated. Given this link between proinflammatory cytokines, host immune function and the sleep-wake cycle, we hypothesized that sleep disruption plays a significant role in immuno-inflammatory cascades that cause or contribute to chronic inflammatory conditions, including those that are the focus of this review. Indeed, the current literature demonstrating sleep disturbances in asthma, RA and SLE, and our recent findings for IBD, support this hypothesis.

3. Sleep in chronic inflammatory conditions

3.1. Asthma

Asthma is an inflammatory disease that has been commonly associated with sleep disturbances [4, 43, 44]. Asthma can be associated with decreased quality of sleep, increased daytime sleepiness [4], and early morning awakenings. In one study, early morning awakenings were about twice as common and increased daytime sleepiness was about 50 % more common in asthmatics than in controls [4]. Polysomnographic (PSG) data have also shown that asthmatics have more awake time

Table 1. Sleep parameters that are abnormal in chronic inflammatory conditions.

Chronic Inflammatory Condition	Subjective parameters			Objective parameters (PSG)				
	Sleep Latency	Frequent awakening	Daytime sleepiness	NREMS (SWS)	Sleep latency	PLMI	RDI	Sao2(min)
Asthma	+	+	+	+	+			
Rheumatoid Arthritis	+	+	+	+	+	+		
Systemic Lupus Erythematosus	+	+	+	+	+	+	+	+

PSG = (Polysomnography); NREMS = NON REM Sleep; SWS = slow wave sleep; PLM = periodic leg movement; RDI = respiratory disturbance index; sao2 (min) = oxygen desaturation

during the night, longer latency to sleep onset and less SWS time [45] than controls (Table 1).

Conversely, sleep disturbances are one of the major modifiers of asthma that can affect the course and the severity of the disease. The physiologic changes that occur during sleep disturbances can adversely affect respiration, arousal responses and airway clearance of asthmatics [44]. Potential mechanisms include a prolonged supine posture, alterations in sympathetic and parasympathetic "balance", sleep-induced reduction in lung volumes, intrapulmonary pooling of blood, and increased compliance of the upper airway [43]. Thus, it is not surprising that sleep and its disturbances can play a crucial role in the pathogenesis of nocturnal asthma.

Animal studies have shown that nocturnal asthma is most often associated with REM sleep and is mainly due to autonomic nervous system imbalances [46]. Interestingly, 36-hour sleep deprivation had no effect on ventilatory and occlusion pressure responses to bronchoconstriction. However, this model of sleep deprivation did significantly raise the arousal threshold for bronchoconstriction [47].

3.2. Rheumatoid Arthritis

Sleep disturbances are common amongst patients with RA [48, 49]. In fact, as many as half of RA patients are reported to suffer from one or more sleep problems [50]. Fatigue, one of the major clinical manifestations of active disease in RA patients, was found to be mainly due to sleep disturbances [51] rather than to disease activity [48]. It seems that the reciprocal relationship of disease activity and sleep disturbances may reflect a cycle of pain, fatigue, inflammation and non-restorative sleep (Fig. 1). However, the effect of sleep on RA is an unexplored area. Theoretically, sleep problems in this population can decrease pain thresholds, which in turn could aggravate the sleep problem and together cause a vicious cycle. Modification of the immune system by release of cytokines induced by pain or sleep disturbances could increase the complexity of this interaction [50].

Although pain can certainly be associated with sleep problems in the absence of chronic disease [49], underlying disease activity could also explain both poor sleep [49] and pain [50] in this population. Sleep disturbances reported by RA patients include longer latency to sleep onset, numerous awakenings during the night, early morning awakenings, and increased daytime fatigue [8, 49]. PSG recordings have documented sleep problems in RA patients including increased sleep fragmentation and prominent EEG alpha activity during NREM sleep as the primary sleep abnormalities [48–51]. Prominence of EEG alpha activity during NREM sleep in RA patients has also been linked to increased morning stiffness [49, 50]. According to the PSG studies of Drewes et al, RA patients have more sleep stage shifts, spend more time in NREM stage 3 sleep, and experience more frequent periodic leg movements than do controls [49]. Such sleep fragmentation can lead to daytime somnolence in addition to other physiological consequences. Other studies also demonstrate a complex association between (a) morning stiffness, pain, and joint inflammation and (b) sleep pattern [49, 50, 52]. In these studies there were abnormal patterns of wakefulness, NREM sleep, and REM sleep in RA patients (Table 1). In a longitudinal study, Drewes et al. showed an increase in SWS and wakefulness following a period of pain and morning stiffness during increased disease activity [49, 52].

It is difficult to determine whether all of the sleep disturbances associated with RA are secondary to the patients' symptoms or, if in fact, they are contributing to the underlying disease process and disease activity. There are data to suggest that the latter is possible. When sleep in RA patients with low back pain was compared to the sleep of chronic low back pain patients without RA, actigraphic measurement of sleep showed poorer sleep quality in the RA patients [53]. Another study suggested that the severity of sleep disturbances in RA does not correlate well with disease activity and that most sleep disturbances were related to a primary sleep disorder rather than to the disease itself [48]. Drewes et al. found that, although there was a significant difference in PSG parameters in RA patients compared to normal controls, there were no differences between the PSG parameters of patients with active vs. inactive RA [49]. Interestingly, treatment with infliximab, a TNF-α antibody that serves as an anti-inflammatory medication, reduced sleep disturbances in RA patients independent of amelioration of joint discomfort, suggesting that sleep disturbances were indeed related to an underlying inflammatory process rather than to the mere presence of symptoms of inflammation [54]. This effect was attributed to the reversal of the effect of TNF-α on the central nervous system [54]. We noted above that glucocorticoids have the potential to adversely affect sleep. However, when RA patients were treated with steroids, there was no deleteri-

ous effect on their sleep pattern [49]. This observation again supports the notion that active inflammatory process in RA is an important cause of sleep disruption in these patients.

3.3. Systemic lupus erythematosus

The cause of abnormal sleep parameters in subjects with SLE is still not well understood. As in the case of asthma and RA, sleep disruption may be related to disease symptoms such as pain, sweating, palpitations and shortness of breath, or to the effects of the disease on CNS function [5]. Regardless of the cause, subjective and objective assessments of sleep in patients with SLE demonstrate poor sleep quality in these patients. This includes more frequent awakenings, restlessness, daytime sleepiness and fatigue when compared with healthy subjects, as well as increases in the periodic leg movement index (PLMI), an increased respiratory disturbance index (RDI) and oxygen desaturation [55]. Gudbjornsson et al. showed that while the total amount of sleep in SLE patients is normal, this group does experience more frequent sleep disruptions [5]. McKinley et al. reported more fatigue, longer sleep latency and total sleep time in subjects with SLE compared to control subjects, after controlling for depression [56].

3.4. Inflammatory Bowel Disease

While it has been long recognized that sleep disturbances are a common extra-intestinal manifestation of functional gastrointestinal disorders such as irritable bowel syndrome (IBS), and that these sleep disturbances affect intestinal function and symptoms [8, 57–60], roles for sleep disturbances in inflammatory bowel diseases (IBD) have been relatively unexplored. Only a few studies have addressed this issue. We were the first to show a relationship between sleep abnormalities and quality of life in IBD patients using a validated sleep questionnaire [8]. We showed that IBD subjects report significantly prolonged sleep latency, more frequent sleep fragmentation, higher rates of sleeping pill use, decreased day-time energy, increased tiredness and overall poor sleep quality compared to healthy controls on the Pittsburgh Sleep Quality Index, a validated measure of sleep quality [8]. When compared to subjects with IBS, we found that sleep was similarly disturbed in IBD patients. In addition, the reported sleep quality was inversely correlated with IBD disease severity score [8]. Both IBD and IBS subjects in this study thought that sleep and their disease status were correlated [8]. In another study by our group, we assessed objective measures of sleep in IBD patients and found that polysomnographic abnormalities are well-correlated with subjective sleep parameters in subjects with IBD [7]. Further studies are needed to determine the mechanism of sleep disruption in IBD and to determine whether treatment of disrupted sleep can affect the course of IBD.

Conclusion

Our review of the literature uncovered evidence for relationships between sleep, inflammation and the immune system. In fact, alterations in the sleep-wake cycle are often one of the first responses to inflammation and infection. Whether this phenomenon is a simple defense mechanism designed to conserve energy during periods of systemic inflammation, or has a reciprocal effect causing immune system activation, is not fully established. However, it is known that sleep modulates immune function. Slow wave sleep can reduce immune cell activation while sleep deprivation activates the immune system, increasing levels of proinflammatory cytokines including IL-1, IL-6 and TNF-α and immune cells including WBC, natural killer cells and monocytes. Neuroendocrine hormones, particularly GHRH and CRH, also play a central role in sleep-wake behavior patterns through their effects on cytokines. GHRH promotes NREM sleep while CRH has the opposite effect. Minor activation of the immune cascade is not associated with activation of the HPA system and is associated with increases in NREM sleep. However, stronger stimuli that activate host defense systems in conjunction with the HPA system can result in reduced NREM sleep and increased wakefulness.

Given this close association between sleep, the immune system and inflammation, it is not surprising that sleep disturbances exacerbate chronic inflammatory conditions. Although it is not yet possible to determine the cause and effect relationship between sleep disorders and these chronic inflammatory conditions, it seems logical to consider sleep disturbances as an important factor that adversely influences chronic inflammation and that it may play a role in disease exacerbation in those chronic inflammatory diseases with waxing and waning disease courses. Further randomized, controlled studies are needed to see if treatment of sleep disturbances in chronic inflammatory disorders can improve disease severity and decrease the rate of disease flare ups.

Future research should, therefore, explore the possibility that effective pharmacological and behavioral treatments for sleep disturbances may be a useful adjunct in the management of chronic inflammatory conditions and could positively impact patient quality of life as well as disease course.

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