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EDITORIAL

How does sleep influence asthma through immunity?

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1. Introduction

Asthma is a chronic respiratory disorder characterized by airway inflammation and narrowing, affecting over 330 million people worldwide and leading to hundreds of thousands of fatalities annually [1]. Asthma 'endotypes' refer to the biological mechanisms or pathways leading to its manifestation, while 'phenotypes' describe its visible manifestations such as clinical characteristics or symptoms; both terms reflect growing recognition of asthma's heterogeneity across multiple studies highlighting different disease presentations and mechanisms. It can be categorized into five phenotypes: allergic asthma, non-allergic asthma, adult-onset asthma, asthma with persistent airway limitation, and obesity-associated asthma [2]. Given its multifaceted origins, which include genetic, environmental, and lifestyle factors, sleep has emerged as a pivotal feature influencing asthma's progression and management [3].

Clock genes play a central role in regulating mast cell activation and T-cell responses in allergic conditions, specifically by modulating the expression of high-affinity (FceRI) and interleukin-33 receptor ST2 on mast cells, thereby altering IgE-dependent or IL-33-dependent mast cell activation over time [4]. Additionally, CD4+ T cells exhibit robust clock gene rhythms, which correlate with variations in interleukin production (IL-2, IL-4, and IFN-g production post-stimulation) as well as CD40L expression post-stimulation, supporting the circadian regulation of T-cell responses and underpinning their circadian regulation in allergic settings [5].

Sleep and immunity are deeply intertwined. Poor sleep quality can lead to both increased systemic and bronchial inflammation, which in turn can influences an individual's vulnerability to asthma [6]. The current studies offer valuable insights into sleep's crucial role in modulating cytokines and T-cell responses, which are central to asthma's pathophysiology [6]. However, these findings represent just the tip of the iceberg. Many aspects, such as the impact of sleep deprivation on specific immune cells, factors linking sleep patterns to asthma exacerbations, and the potential of sleep-based interventions in asthma management, remain largely unexplored.

This editorial aims to bridge this knowledge gap by thoroughly examining the role of sleep in asthma, focusing on its influence on immune cells and pathways. By shedding light on these complex interactions, we aspire to pave the way for more holistic, patient-centric approaches to asthma management.

2. Sleep and immunity

Sleep-wake cycles play an integral role in orchestrating our biological circadian rhythm, governed by cellular clocks and regulated by the hypothalamic pacemaker, the suprachiasmatic nuclei [7]. This regulatory system has profound effects on immunological functions. Sleep offers a reprieve from stress-inducing hormones, such as cortisol and catecholamines. In the initial phases of sleep, there's a noticeable reduction in these stress-related hormones, especially cortisol and catecholamines [7]. Simultaneously, levels of pro-inflammatory hormones and cytokines rise, creating an optimal environment for immune cell activation and Th1 immune responses, which are essential for establishing lasting immunological memory. While this surge in pro-inflammatory agents can bolster adaptive immune responses, especially post-vaccination, it also introduces risks. Chronic disruptions in sleep patterns can upset this delicate equilibrium, leading to persistent low-grade inflammation and immunodeficiency, thereby heightening vulnerability to infectious agents [8].

The respiratory system, a primary barrier against external pathogens, is underpinned by robust immune responses [9]. During the deep stages of non-rapid eye movement (NREM) sleep, there's a marked increase in pro-inflammatory cytokines, notably interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These cytokines serve as a protective shield, preparing the respiratory system for potential daily challenges [9].

Proinflammatory mediators such as leukotrienes, histamine, and acetylcholine (ACh) are pivotal in orchestrating inflammatory responses. Leukotrienes (LTs), primarily produced by leukocytes and part of the eicosanoid family, act as potent inflammatory mediators with a critical role in inflammation. Their production can be triggered by both immunological and non-immunological stimuli including antigens, immune complexes, and cytokines [10]. Histamine, released by basophils, which also produce leukotrienes, suggests a connection between histamine and leukotrienes in inflammatory responses [10].

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Cysteinyl leukotrienes (CysLTs), a subclass within the leukotriene family, are derived from arachidonic acid by various cells such as eosinophils and hold multifaceted roles during allergic reactions [11]. Leukotrienes share a close relationship with eosinophils since certain leukotrienes stimulate the generation and release of reactive oxygen species (ROS) as well as EDN release by these cells, these interactions are crucial in understanding their biology and sleep-mediated immunological processes [11].

At the intersection of Type 2 immunity, neuroinflammation, and sleep disorders lies a nuanced narrative for understanding immune-mediated neurological responses. Central to this narrative are inflammatory cytokines such as interleukin-1 beta and tumor necrosis factor-alpha, which play an essential role in sleep regulation while exhibiting bidirectional links with neuroinflammatory processes [12]. Sleep deprivation may exacerbate neuroinflammation, which in turn disrupts sleep patterns [12]. The loss of sleep also significantly impacts immune function; deprivation could aggravate the adaptive arm of the immune system while also affecting the innate arm, thereby disrupting both arms [12].

The intimate connection between sleep and respiratory inflammation is exemplified by nocturnal asthma. Individuals with this condition often experience symptom exacerbations at night, peaking in the early morning hours. This pattern is believed to be influenced by the circadian rhythm's impact on inflammatory mediators, coupled with a natural tendency for bronchoconstriction at dawn [13].

3. Current evidence of sleep, immunity, and asthma

Several studies have illuminated the relationship between sleep duration and asthma. A pivotal study by Hu et al. analyzed 538 asthmatics and found that shorter sleep durations were linked to an increased risk of asthma in individuals with central obesity [14]. Additionally, animal studies have shown that sleep deprivation can intensify airway inflammation, resulting in neutrophilic lung inflammation. This supports the hypothesis that insufficient rest might be a potential risk factor for neutrophilic asthma [3].

Furthermore, the quality of sleep has been shown to have direct implications on the respiratory health of asthmatics. Those who experience shorter sleep durations exhibit diminished lung function and decreased FeNO levels compared to individuals who get adequate sleep. Moreover, a higher percentage of blood eosinophils, a marker of inflammation, was observed in asthmatics with reduced sleep [3,15].

In a broader context, a comprehensive study using U.K. Biobank data revealed a compelling connection between sleep patterns, genetic predisposition, and asthma risk. Adults with both poor sleep habits and a strong genetic predisposition were found to have more than double the risk of developing asthma over an 8-year period. While the exact causal relationship between sleep and asthma remains to be definitively established, the data strongly suggests that enhancing sleep quality might serve as a preventive strategy against asthma, particularly for those with a genetic predisposition [16].

Further emphasizing the importance of sleep in asthma management, a U.S.-based study highlighted that asthmatic adults with short sleep durations not only experienced more frequent asthma attacks but also had increased healthcare usage and a diminished quality of life. On the other hand, those who slept longer than the recommended duration reported greater limitations in their daily activities [17].

Evening chronotype and night shift work are two factors commonly linked with poor sleeping habits, yet they hold distinct implications for asthma risk [18,19]. Individuals exhibiting an evening chronotype tend to fall asleep later than average and experience misalignments of circadian rhythms due to working night shifts; these misalignments can increase the susceptibility to inflammation-based diseases like asthma. Furthermore, permanent night shift workers have been found to have higher odds of moderate to severe asthma compared to day workers, suggesting a direct relationship between night shift work schedules and respiratory health [19].

Lastly, a study from Saudi Arabia delved into the link between sleep patterns and the immune system in bronchial asthma patients [20]. The findings revealed that patients in the asthma group had elevated levels of various immune markers, longer wakefulness after sleep onset, and increased latency to REM sleep compared to the control group. Moreover, these patients also reported shorter overall sleep durations and decreased sleep efficiency.

4. Expert opinion

Asthma, sleep, and the immune system share a complex and deeply intertwined relationship. Asthma is characterized by chronic airway inflammation, which often intensifies during sleep.

A significant factor in this phenomenon is the heightened activity of our immune system during sleep. This period sees an increased release of pro-inflammatory cytokines, such as Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-α). While these cytokines are vital defense mechanisms against infections, they can amplify the inflammation that asthma patients experience. Such disruptions compromise their quality of sleep and further exacerbate asthma symptoms. This cyclical relationship means that asthma can degrade sleep quality, and in turn, disrupted sleep can become a persistent feature of their condition.

Sleep holds an undeniable influence over immune function and, by extension, asthma symptoms. Chronic sleep deprivation correlates with low-grade systemic inflammation. This not only exacerbates asthma symptoms but also weakens one's immunity against infections. Respiratory infections are of particular concern as they can precipitate severe asthma attacks.

Central to this interplay is the immune system. Its reactions, heavily influenced by sleep patterns and external factors, can either alleviate or intensify asthma symptoms. A persistent lack of proper rest can attenuate immune responses, making our bodies more vulnerable to infections and other triggers that worsen asthma symptoms.

To truly understand the intricate relationship between sleep and asthma progression, it's essential to delve into its

underlying mechanisms. Some theories suggest that the adverse effects of insomnia on asthma, primarily an inflammatory condition, might stem from chronic inflammation induced by inadequate sleep. Moreover, certain sleep characteristics, such as 'chronotype,' snoring, and overall sleepiness, are linked to specific inflammatory responses, suggesting these patterns might indirectly influence asthma risk through inflammation-mediated pathways. Sleep chronotypes classify people based on their natural sleeping and wake preferences into three main groups. Morning Chronotypes tend to wake early and feel most active in the morning; Evening Chronotypes have night owl tendencies but feel most energetic later in the evening; and Intermediate Chronotypes tend to fall between these extremes in terms of energy level.

However, the current body of research examining the interplay between asthma, sleep, and immunity leaves gaps. Many studies prioritize two of these elements, often overlooking the third; some suffer from limitations like the absence of blinded interventions, constrained sample sizes, or potential biases. The reliability of self-reported sleep data is debatable, and confounding factors, like concurrent chronic diseases, can obscure true results.

A comprehensive examination of the connections among sleep, immunity, and asthma demands thorough, targeted research. It's vital to assess the impact of sleep deprivation on distinct immune cells and evaluate the potential of sleep-centric interventions for effective asthma management. Given the multifaceted nature of both asthma and sleep disorders, isolating the effect of one variable on asthma progression becomes a challenging endeavor.

As our understanding of asthma's genetic basis expands, research is likely to veer toward individualized sleep interventions for asthma management. Advancements in wearable technology and health-focused innovations are poised to play a pivotal role in monitoring and fine-tuning sleep patterns for those with asthma.

Currently, the convergence of genetic predispositions, sleep patterns, and asthma risk presents an intriguing research avenue. By leveraging extensive genomic databases combined with comprehensive sleep data, we might be on the cusp of uncovering personalized patterns, paving the way for bespoke asthma management strategies.

5. Conclusion

Sleep, immunity, and asthma represent an increasingly important area of medical research and practice that impacts millions worldwide. Due to its chronic nature and intricate connections with both the immune and sleep systems, effective care must consider multiple facets. Current research underscores the profound influence of sleep on asthma progression, mainly through its impact on immunity. However, we still lack comprehensive insight into this domain, with many angles yet to be explored. As technology and our understanding of genetics evolve, there is immense potential for personalized interventions, like sleep optimization, to enhance asthma management. The challenge remains in converting this knowledge into actionable strategies. However, with sustained research and innovation, we might witness revolutionary breakthroughs in holistic asthma management.

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• **This study is important because it addresses the relationship between asthma, sleep, and immunity. Hence, provide an evidence of this link between asthma and sleep through immunity.**