The Immunological Impairments Caused by Chronic Sleep Deprivation and Circadian Misalignment

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Abstract. The lifestyle of staying up late, centered around chronic sleep deprivation and irregular circadian rhythms, has become a widespread public health hazard worldwide. This article provides a systematic review of research on circadian immune regulation and sleep induced immune damage. Numerous studies have confirmed that the normal maintenance of immune homeostasis strictly depends on a complete sleep cycle and regular circadian oscillations. During physiological sleep, the body achieves the functional reset and reserve of immune cells through precise regulation of neuroendocrine signals, including rhythmic activation of T lymphocytes and natural killer cells, as well as regular secretion of cytokines. The research results indicate that long-term sleep disorders disrupt the fine balance of immune homeostasis through multiple neuroendocrine immune pathways, such as melatonin and glucocorticoid signaling dysregulation, downregulation of circadian clock gene expression, and excessive accumulation of injury related molecular patterns, ultimately leading to a dual immune deficiency state. On the basis of sorting out the core immunological changes caused by chronic sleep deprivation, this article clarifies the limitations of current research, in order to provide theoretical basis for formulating evidence-based sleep health intervention strategies for modern populations.

Keywords: Chronic sleep deprivation, circadian misalignment, immune homeostasis, innate immunity, adaptive immunity.

1. Introduction

The chronic sleep deprivation and circadian rhythm disorder represented by staying up late have widely penetrated into the lifestyle of modern industrialized society, with over 30% of adults worldwide suffering from long-term sleep deprivation of less than six hours per day. This habitual disturbance of work and rest is not an isolated lifestyle problem. A large number of epidemiological cohort studies have clearly linked it with the increase in the incidence rate of a variety of immune related diseases. Especially in areas such as increased susceptibility to infection, worsening of autoimmune diseases, and weakened tumor immune surveillance function, the immune damage caused by sleep deprivation is becoming increasingly prominent, posing a public health hazard that urgently needs to be thoroughly analyzed[1].

Previous studies have fully confirmed that the core processes of immune system development, circulation, activation, and cytokine release are all precisely regulated by the internal biological clock network, and physiological sleep, especially the slow wave deep sleep stage, provides a critical time window for the functional recovery of immune cells. At the same time, there is a bidirectional regulatory steady-state feedback loop between sleep and immunity.

Inflammatory factors may prolong sleep out of a desire for defence; however, too much sleep can also suppress serious inflammation. However, most of the existing evidence comes from fixed-duration animal sleep-deprivation experiments, and there is a lack of a systematic comparison of the dynamic changes in different immune cell subpopulations under gradient sleep deprivation. More importantly, some of the molecular mechanisms discovered in rodent models are difficult to directly apply to humans, and large-scale human clinical trials and translational studies are still lacking; thus, an all-encompassing understanding of the sleep immune-regulatory network has not been achieved[2][3].

Therefore, this paper systematically reviews related studies on the connection between circadian immune homeostasis and immune damage induced by chronic sleep deprivation, focusing on the

gradual changes in innate and adaptive immune cells during prolonged sleep deprivation, and explains the molecular mechanism of circadian rhythm disorders that lead to immune dysfunction and inflammatory overactivation via multiple neural-endocrine-immune pathways. Build an all-encompassing analysis system in this study to explore how abnormal sleep behaviour systematically disrupts the immune system and address the deficiency of previous research that has only focused on single-cell types or isolated signalling pathways. In addition, this study hopes to provide a biological basis for sleep behaviour intervention and the prevention and control of immune-related diseases through rhythm adjustment, offering practical references for the construction of public health strategies based on rhythm adjustment.

2. Regulation of the Circadian Rhythm of Normal Immune Function

2.1. Regulation of the Circadian Rhythm of Innate Immunity

The innate immune system is the primary barrier for the body to resist the invasion of pathogenic microorganisms, and its various functional indicators exhibit stable diurnal fluctuations. The phagocytic ability of macrophages, the directed migration of neutrophils, the killing activity of natural killer cells, and the secretion level of type I interferon all undergo regular changes with the alternation of day and night. These rhythmic phenomena are both autonomously driven by intrinsic clock genes within innate immune cells and co regulated by systemic hormone circadian signals[4].

Natural killer cells, as the main cytotoxic innate lymphocyte population, play a crucial role in clearing virus-infected cells and early malignant transformation cells. The effector function of this cell is most active during the nighttime sleep phase, and this enhanced process relies on melatonin signaling and transcriptional regulation of rhythmic clock genes. In the normal sleep wake cycle, natural killer cells upregulate the expression levels of perforin and granzyme during resting periods, thereby enhancing the clearance efficiency of target cells[5]. At the same time, the elevated cortisol levels during the day moderately inhibit the excessive expression of cytotoxic activity to prevent unnecessary tissue inflammatory damage. Both resident macrophages and dendritic cells follow a precise circadian rhythm program, increasing the expression density of virus pattern recognition receptors (including RIG-I, MDA-5, and TLR3) during sleep, enabling the body to initiate a faster recognition response when faced with pathogen invasion at night[3][6].

The release process of hematopoietic stem cells from the bone marrow to the peripheral circulation is also regulated by the circadian rhythm oscillation mechanism. The nighttime rest phase helps maintain a stable mobilization state of hematopoietic progenitor cells to supplement the reserve of innate immune cells in the circulating blood, ensuring that the body has basic innate immune monitoring ability at all times of the day. The normal operation of all rhythmic physiological processes mentioned above relies on a complete and uninterrupted sleep cycle to maintain their normal oscillation amplitude. When chronic sleep deprivation occurs, these daily immune fluctuations gradually flatten out, and the enhanced effect of innate defense function at night also disappears.

2.2. Regulation of the Circadian Rhythm of Adaptive Immune Response

The adaptive immune response mediated by T lymphocytes and B lymphocytes also highly relies on a complete sleep process and accurate circadian rhythm timing to achieve effective antigen-specific responses. Each subpopulation of CD4+helper T cells, CD8+cytotoxic T cells, regulatory T cells, and B cells carries their own intrinsic molecular clock system, which is responsible for regulating cell migration distribution, differentiation direction, and cytokine synthesis.

During deep sleep, CD4+T cells circulating in the blood migrate directionally to secondary lymphoid organs (including lymph nodes and spleen) to promote effective antigen presentation and clonal expansion. This process is a necessary prerequisite for the production of memory T cells after vaccination or natural infection. The data from clinical human vaccination studies shows that the concentration of antigen-specific antibodies produced by subjects who maintain normal nighttime

sleep is about twice that of volunteers who sleep less than five hours. This result strongly indicates that sleep plays an indispensable role in maintaining a strong humoral immune response mediated by B cells.

The circadian rhythm signal also affects the direction of the division for CD4+T cell differentiation into different helper subsets. A regular sleep cycle can reduce excessive polarisation of Th17 cells and keep the proportion of regulatory T cells to Th17 cells at a healthy level, thus preventing autoimmune damage. Prolonged sleep deprivation will disturb the body's circadian rhythm and thus increase the disease-causing ability of Th17 cells through the IL-23 pathway. At the same time, the immune-suppressive function of regulatory T cells is abnormally enhanced, resulting in a contradictory immune status of both systemic inflammation and overactive antigen-specific adaptive defence capabilities. The two immunodeficiencies are likely responsible for some of the increased risks of chronic inflammatory autoimmune diseases and serious viral infections in sleep-deprived individuals[7][8].

2.3. Neuroendocrine Mediators Linking Sleep, Circadian Rhythm, and Immunity

Melatonin and glucocorticoids are the two main hormone-signaling factors linking the sleep-wake cycle with the immune circadian rhythm. Melatonin is produced and released in the blood by the pineal gland only during the dark hours of the night under normal sleeping circumstances. This hormone can bind to specific receptors on the surface of almost all immune cells and thus has various immune-regulatory functions, such as promoting the activity of natural killer cells, stimulating the expression of type I interferon, inhibiting the inflammatory signaling pathway that involves nuclear factor kappa B, and regulating the balance between regulatory T cells and Th17 cells. In the case of prolonged sleep deprivation, the peak release of melatonin at night will be lower, and thus this required mediator with anti-inflammatory and immune-modulating properties will be lacking.

As a primary endogenous glucocorticoid of the body, circulating cortisol generally shows a circadian rhythm in its concentration, reaching a peak in the morning and falling to a minimum during the night of sleep. A relatively low level of nocturnal cortisol is favourable for the high-level secretion of immune factors by the body during sleep; otherwise, high basal cortisol will be maintained throughout the night. Prolonged elevation of cortisol suppresses lymphocyte proliferation, inhibits antibody production, and reduces the migration of white blood cells to tissues; thus, a state of chronic immunosuppression is formed. The loss of the immune-protective effect of melatonin and the extended immunosuppressive effect of glucocorticoids are the main neuroendocrine mechanisms underlying immune dysfunction due to sleep deprivation[9].

3. Immune Damage Caused by Chronic Sleep Deprivation

3.1. Changes in Innate Immune Cells after Long-Term Sleep Deprivation

Multiple clinical studies and preclinical experiments have shown that chronic sleep deprivation can lead to widespread suppression of innate immune function. The number and cytotoxic activity of natural killer cells showed a stepwise decreasing trend related to the duration of sleep restriction. In a strictly controlled study on human sleep restriction, participants slept only four hours per night for six consecutive nights, and their natural killer cell perforin release ability and target cell killing efficiency decreased by 30% to 40%. This functional impairment gradually improved after several days of returning to normal sleep patterns.

Under chronic sleep deprivation, there is a moderate increase in the counts of monocytes and neutrophils in peripheral blood, but the phagocytic function and pathogen clearance ability of these cells are actually impaired. The above-mentioned innate immune cells gradually shift towards pro-inflammatory polarization and secrete a large amount of tumor necrosis factor alpha, interleukin-1 beta, and interleukin-6, but do not enhance the actual defense efficacy of the body against pathogens. This condition constitutes a sterile inflammatory state, where the levels of inflammatory markers in the circulation continue to rise without corresponding improvement in anti infective ability. Over

time, this can promote the occurrence and development of cardiovascular system, metabolic system, and autoimmune tissue damage.

Long term disruption of circadian rhythm can also cause damage to the hematopoietic homeostasis of the bone marrow. Persistent sleep fragmentation can alter the epigenetic modification pattern of hematopoietic stem cells, reduce the diversity reserve of downstream innate immune cell progenitor cells, and weaken the body's ability to replenish defensive white blood cells in the event of pathogen invasion. This epigenetic reprogramming can result in persistent immune dysfunction, which may not be immediately reversed after sleep recovery, thus becoming a persistent threat to health caused by long-term irregular sleep patterns[3].

3.2. Adaptive immune Dysfunction Induced by Sleep Deprivation

The suppression of the adaptive immune system constitutes another important characteristic of chronic sleep deprivation, which is manifested by impaired T cell activation processes and deficiencies in B cell-mediated humoral immune responses. The total number of CD3 positive T cells in peripheral blood of sleep deprived individuals is significantly reduced, with a particularly significant decrease in CD8 positive cytotoxic T cells responsible for virus clearance and tumor clearance. The T cells remaining in the circulation exhibit delayed proliferation response after antigen stimulation, and the secretion levels of antiviral cytokines interferon gamma and interleukin-2 also decrease accordingly[2].

The ratio of regulatory T cells to effector T cells is abnormal in the sleep-deprived state. The proportion of regulatory T cells in the peripheral blood was relatively high; thus, they inhibited the activation of antigen-specific T cells and impaired the formation of adaptive immune memory. At the same time, there is an abnormal expansion of Th17 cells that drives tissue damage in autoimmune diseases through the interleukin-23-Th17 inflammatory pathway and increases the risk of such diseases. Both sides of this dual imbalance at the level of T cell subpopulations result in a conflicting immune phenotype, namely a reduction in the body's specific defence against foreign pathogens and an excessive inflammatory reaction in its own tissues[10].

Humoral immunity is also compromised due to insufficient sleep. The human vaccination trials against hepatitis A virus and influenza virus showed that subjects with long-term sleep deprivation produced significantly lower titers of specific IgG antibodies after vaccination compared to normal sleepers. This indicates that the differentiation process of B cells into plasma cells is disrupted, and the storage function of immune memory is also weakened. This discovery has clear public health implications, as people who habitually stay up late have relatively lower protective efficacy from routine vaccination, and their likelihood of encountering breakthrough viral infections increases as a result[10].

4. Limitations and Challenges

Although existing evidence has fully confirmed the damaging effects of chronic sleep deprivation on the immune system, most mechanistic conclusions stem from fixed duration rodent sleep deprivation models, and systematic comparative studies on the dynamic changes of various immune cell subpopulation gradients under different continuous sleep deprivation durations are scarce. It is currently difficult to determine whether mild short-term sleep restriction only causes reversible immune changes, and whether severe long-term sleep fragmentation leads to permanent epigenetic immune remodeling. Furthermore, there is a significant lack of research on the bridge between animal experiment results and human physiological conditions. There are significant species-specific differences in circadian rhythms and immune regulatory pathways between rodents and humans, and large sample multicenter cohort studies tracking changes in immune indicators in populations with long-term sleep disorders are still scarce. Finally, the synergistic effects of sleep deprivation and other lifestyle risk factors (such as sedentary behavior, high-fat diet, and psychological stress) on immune function have not been fully integrated and examined in existing research frameworks.

5. Conclusion

A large amount of preclinical and clinical research evidence confirms that chronic sleep deprivation and circadian rhythm disorders can disrupt the inherent circadian rhythm of the innate and adaptive immune systems, thereby inducing a state of double immunodeficiency. This deficiency manifests as a decrease in the body's ability to defend against pathogens and tumors, accompanied by persistent low-grade systemic inflammatory response. The neuroendocrine immune axis, regulated by the circadian rhythm signals of melatonin and glucocorticoids, plays a central mediating role in connecting irregular sleep patterns with the breakdown of immune homeostasis.

Existing research has shown the main phenotypic changes in immune cell subsets under sleep deprivation conditions, but systematic gradient comparative studies and large-scale human transformation experiments for different sleep deprivation durations are still relatively scarce. If future research can dynamically track immune changes under different durations of sleep deprivation and conduct large-scale validation in populations, it will help deepen our understanding of the relevant mechanisms and promote the development of precise sleep health intervention strategies for modern populations with chronic sleep deprivation.

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