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The Influence of Circadian Rhythm on Immune Disorder

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Abstract: In the era of rapid social development year by year, increasing work pressure has disrupted more and more people's normal sleep and activity cycles. Biorhythms are periodic rhythms that organisms have evolved to align with Earth's 24-hour rotation. Biorhythm, as a key regulatory system, has been the focus of research recently. It can not only affect the body's hormone secretion but also affect the body's cell function. This paper explores the role of the human immune system and the impact of biorhythms on the immune system. An immune disorder is a condition in which the immune system functions abnormally and can result in an overactive or underfunctioning immune system. In the case of a chaotic biological rhythm, the endogenous immune system will be overloaded, causing the body to suffer from immune diseases. Regulating biorhythms and mitigating their disturbances may offer a novel approach to addressing disorders of the immune system. Through extensive research, this review aims to understand the specific effects of biorhythms on immune diseases and explore potential preventive and therapeutic strategies through biological rhythms.

Keywords: Circadian rhythm, Immune cell, Immune disorder, Immune disorder disease

1. Introduction

The circadian rhythm is essential for maintaining human health, serving as an evolutionary mechanism that enables organisms to adjust to the 24-hour day-night cycle [1]. Disruptions in circadian rhythms are strongly linked to the pathogenesis of various diseases, such as diabetes and cardiovascular disorders. In the majority of mammals, circadian rhythms are governed by a hierarchical network comprising central and peripheral pacemakers. Situated in the anterior region of the hypothalamus, the suprachiasmatic nucleus (SCN) typically functions as the primary control center for the brain's circadian clock [1]. The SCN can transmit rhythmicity to other neural structures, so it can act as a circadian pacemaker. At the molecular level, biorhythms are controlled by certain clock genes, including Bmal1, PER, and CRY. These core circadian genes produce two essential transcription factors, BMAL1 and CLOCK. These factors form complexes that attach to specific E-box elements within the promoters of the PER and CRY genes [2]. This induces the production of Per 1 and 2 and Cry 1 and 2 factors, which then form complexes that inhibit the activity of the CLOCK/BAML1 complex. To reset the cycle, the CLOCK/BAML1 complex can be degraded via the ubiquitin-proteasome pathway, following the BMAL1 and CLOCK levels to rise again and restart the rhythm [2]. Environmental factors can also affect circadian rhythm. For example, the over-exposure of blue light to the SCN will inhibit the production of melatonin, thus affecting the body's normal sleep. The immune system is critical to maintaining our overall health. The immune system

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is broadly divided into innate and adaptive immunity. Innate immunity acts as the host's primary defense mechanism, reacting quickly and in a non-specific manner to danger signals [3].

Monocytes, macrophages, and dendritic cells are examples of typical innate immune cells that can perform immunological functions by secreting mediators [3]. For example, macrophages play a crucial role in immunity by engulfing antigens and viruses, thereby triggering immune responses. Adaptive immunity is a specific immunity that relies on activated T cells and B cells, which are essential components for adaptive immunity. Promoting T cell differentiation into effector T cells and inducing B cells to make certain antibodies are two steps in the adaptive immunity process [3]. T cell responses are driven by antigens. Upon recognizing an antigen, the antigen- presenting cells (APCs) will present it to the cell surface and then let the T cell recognize and bind it. This process stimulates the T cell's expansion and differentiation. B cells work differently than T cells. The B cell response is marked by antibody production. One type of B cell is the T-cell-dependent B cell, which requires help from follicular helper T (Tfh) cells to initiate an antibody response. Another type of B cell can secrete natural antibodies without T cell assistance, contributing to immune activity [3]. Apart from immune cells, certain hormones also play significant roles in the immune system. Cortisol is one of them. The primary biological clock in the suprachiasmatic nucleus controls the distinct circadian rhythm feature of cortisol secretion, which in turn sets off the hypothalamic-pituitary-adrenal (HPA) axis.

Circadian rhythms are involved in almost all biological activities, including metabolism, mood regulation, and immune responses. One of the typical examples is that immune cells that circulate throughout the body can be influenced by the circadian rhythm. Macrophages are innate immune cells, which convert their breeding into immune activity through a series of reactions induced by Toll-like receptors (TLRs) on the cell surface. However, the activation of TLR4 signals is controlled by circadian rhythm, making macrophage immune responses time-dependent. The disruptions of circadian rhythm often lead to abnormal secretion of hormones, immune factors, etc., which often leads to abnormal function of the immune system. Immune cells exhibit changes in circadian cycles and are regulated by genes associated with circadian rhythms. The impact of disrupting the circadian rhythm on immune system function is examined in this article.

2. Molecular and cellular basis of circadian regulation in immunity

2.1. Clock genes and immune regulation

Biological rhythms at the cellular level result from oscillations in the expression of CLOCK genes within the cell, and the most important genes in this loop are BMAL1 and CLOCK. They are responsible for the circadian rhythm regulation of many cells. Genes such as REV-ERB and ROR also exist, which are activated through the binding of the BMAL1-CLOCK heterodimer to the E-box site. These genes regulate the rhythm by inhibiting BMAL1. In the negative feedback loop, CLOCK and BMAL1 are able to form a heterodimer that directly interacts with E-box elements, leading to the enhanced expression of PER and CRY genes. As the PER/CRY protein complex builds up over time, it subsequently suppresses the activity of the BMAL1/CLOCK heterodimer. This regulatory cycle operates on a 24-hour rhythm. Moreover, these mechanisms also play a crucial role in immune regulation, influencing immune cell activity and inflammatory responses.

Griffin et al. observed that deletion of Rev-erbα in mice led to spontaneous microglial activation in the hippocampus and promoted a pro-inflammatory phenotype [4]. Macrophage-specific Bmal1 knockout mice also exhibited inhibited transcription of the clock gene Rev-erbα , resulting in a partial loss of the rhythmic immune response [5]. These findings suggest that disruption of circadian rhythms can contribute to inflammatory conditions. In cells and tissues, the transcriptional activator BAML1 and its dimer CLOCK regulate diurnal cellular functions and indirectly influence immune cell

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proliferation and activity. By regulating gene expression and transcriptional cytokines—such as nuclear factor κB (NF-κB), mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK-STAT)—they can indirectly enhance the specific proliferation of immune cells in an immunologically active host. Importantly, type 2 diabetes in humans is associated with decreased levels of BMAL1 and SIRT1 in pancreatic β cells, suggesting a potential link between pancreatic inflammation, disturbance of the circadian rhythm, and compromised β-cell function. These findings collectively underscore the role of circadian rhythm dysregulation in promoting inflammation and metabolic disease.

2.2. Hormonal and neural regulation

Cortisol suppresses innate and T cell-mediated cytokine production in whole blood from healthy individuals, patients with subarachnoid hemorrhage (SAH), and volunteers. However, it only inhibits cytokine production, but not the T cell-mediated immunity [6]. Melatonin, expressed in the brain as a hormone that affects the circadian rhythm, also has a certain synergistic effect on the regulation of the immune system. It regulates the circadian dependence of cell proliferation and differentiation by increasing the level of stem cell markers, thereby maintaining the homeostasis of adult neurogenic niches [7]. Beyond hormonal regulation, the suprachiasmatic nucleus (SCN) of the hypothalamus exerts a strong influence on circadian rhythms and immune function. The retinohypothalamic tract (RHT) sends light signals and other internal and external cues to the SCN. The SCN then controls many body systems, including the immune system. This control works through both direct and indirect neural and endocrine pathways, making sure that tissues on the outside are in sync with the circadian clock in the brain [8].

2.3. Immune cell trafficking and circadian oscillations

Toll-like receptors (TLRs) on macrophages—key components of the innate immune system—regulate their activity. Notably, TLR4 activity is influenced by the circadian clock, and splenic macrophages show rhythmic oscillations in Tlr and Tlr6 mRNA expression. Dendritic cells (DCs), which serve as antigen-presenting cells, have their activity modulated by circadian rhythms. And the lack of BMAL1 negatively affects the development of B cells, resulting in a decrease in the number of B cells in the blood and spleen of animals with BMAL1 knockout [9]. Cortisol regulates the expression of CXCR4 on T cells, which in turn regulates the level of initial T cells in the body. In general, initial T cells peak at night and are lower during the day [9]. Monocytes in the human body peak at rest and trough during active periods [10]. Since some organs play multiple roles, a lot of white blood cells stick to the vascular bank as they move through the vascular system [10]. This is because they are sentinels in blood vessels. Moreover, adhesion molecules exhibit diurnal changes following leukocyte circadian rhythms.

3. Circadian rhythm and immune disorder diseases

Rheumatoid arthritis (RA) is a genetically based inflammatory disease that is mediated by the immune system. One of the main symptoms of RA is morning stiffness, which is defined by joint pain, edema, and stiffness in the morning [11]. The poor fibrinolysis of fibrin deposits along the synovial neutrophils is linked to this symptom. The circadian clock, controlled by the Bmal1 gene, is crucial for maintaining immune homeostasis and reacting to inflammatory cues. Inflammatory arthritis is influenced by the circadian patterns of joint mesenchymal cells, including fibroblast-like synoviocytes (FLS). Deletion of Bmal1 in FLS leads to increased inflammation, highlighting the clock's role in inflammatory arthritis [12].

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The etiology of inflammatory bowel disease (IBD), a nonspecific chronic inflammatory disorder, remains unclear. Gastrointestinal flora play an important role in the human digestive system, and these microbiotas have a certain impact on individual physical and mental health. The biological clock controls the production of hormones and peptides released by the gut, which controls hunger in the body. If the circadian rhythm is thrown off, it can lead to an imbalance of the gut flora [13]. Researchers are increasingly recognizing sleep as a potential factor in the onset of IBD. If an organism's internal biological clock and external environmental stimuli are not synchronized, the circadian rhythm is out of whack, which will increase the risk of disease [14]. Even in modern society, people often work night shifts, and trying to regulate rest and work hours is also a beneficial way to reduce the incidence of enteritis.

Asthma is bronchial hyperresponsiveness leading to airway inflammation, bronchoconstriction, and "chest tightness" symptoms. Asthma usually worsens at night. The circadian system has an independent influence on lung function indicators, including airway resistance and FEV1, which influence the onset of asthma [15]. AR is a long-term nasal mucosal inflammation that results in symptoms similar to asthma and nasal hypersensitivity. Under the action of the light source, the circadian rhythm disturbance leads to fluctuations in the level of eosinophils, which leads to enhanced AR symptoms [16]. The disruption of the circadian rhythm has the potential to exacerbate asthma symptoms. Therefore, clinical medicine can enhance the attention to nighttime asthma patients and the use of related treatment machines or enhance drug remission during this period, perhaps to enhance asthma treatment. Multiple sclerosis is a chronic neurodegenerative disorder characterized by demyelination of central nervous system neurons. The main symptoms of the disease include movement disorders, various neurodegenerative vision, sensory, and other disorders, and even cognitive processing [17]. Research has demonstrated that the disease pathogenesis is driven largely by immune cell-resident cell interactions [17]. However, the abnormal secretion of melatonin caused by sleep disorders can also exacerbate the disease, and staying up late can shorten telomeres, which is why the disease is more severe in people with sleep disorders.

4. Conclusion

The body's immune system is significantly impacted by biorhythm, one of the primary endocrine system regulation mechanisms. Both the secretion of immune substances and the proliferation of immune cells cannot be separated from the regulation of circadian rhythm. If the circadian rhythm is disrupted, it will also cause a substantial burden on the body's immune system and even cause irreparable harm to people's bodies. Studies have found that many diseases in the human body are related to immune system disorders caused by biological rhythm disorders. Both autoimmune diseases and inflammatory diseases are related to the biological rhythm of the human body. Diseases such as asthma, which have a circadian rhythm, can be targeted by using the periodicity of day and night. Therefore, a regular biological rhythm and a properly functioning immune system are integral to a healthy body. The purpose of studying biorhythms is not only to understand the hormonal movement of the body and the periodic activity of cells, but also to prevent or further treat autoimmune disorders and inflammatory diseases. Confusing the biological rhythm can aggravate existing diseases and lead to the development of new immune diseases. This is why it is crucial to maintain biorhythms in all aspects of life. In the future, the regulation of biorhythms could be used as a treatment for these immune system diseases, and specific drugs could be studied through regulation in this respect.

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