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Circadian rhythms and depression: A review of mechanisms, effects and treatment strategies

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Abstract. Circadian rhythms play an important role in the temporal co-ordination of many physiological processes such as the sleep-wake cycle, hormone release or metabolism. Major depressive disorder is associated with severe disruption of these rhythms. This review discusses the basic functions of circadian rhythms and how they control various physiological systems and maintain homeostasis in the body. It also explores epidemiological data linking circadian rhythm disruptions such as insomnia, jet lag, and shift work to a high risk of depression. The review also notes that circadian rhythm disruption can exacerbate depression, reduce treatment response, and lead to more frequent relapses. The review identifies treatments such as phototherapy, melatonin supplements, and sleep stage interventions as potential strategies for restoring circadian rhythm function in patients with depression, thereby improving clinical care. The aim of this review is to provide direction for future research and development of circadian rhythm-based treatments for depression.

Keywords: Circadian rhythms, major depressive disorder, sleep-wake cycle, light therapy.

1. Introduction

As the core regulator of behavioral rhythms, circadian rhythm is responsible for the regulation of time-dependent activities in organisms such as sleep-wake cycles, hormonal secretion, body temperature and metabolic processes to enable an organism to adapt its physiology to cope with 24 h changes in its environment so that physiological homeostasis can be established. Circadian rhythms are intrinsic to the 24-hour self-regulating cycle that exists in almost all life forms [1] and serve to harmonize the physiology of organisms with the Earth's Day/night cycle. In addition, circadian neurons cooperate with the molecular clocks of peripheral tissues through complex signaling pathways to ensure that the metabolic processes of different organs and tissues are synchronized with the environment at the appropriate circadian phase, thus working together to achieve systemic regulation of the body [2]. Nevertheless, a disturbed biological clock has been linked with several psychiatric diseases — most evidently Major Depressive Disorder (MDD) Multiple studies have indicated that disturbances of circadian rhythms not only negatively impact sleep, mood and behavior [3], but also are implicated in the pathophysiology of depression, with symptoms of delayed sleep phase and dysregulated circadian activities abnormally expressed in depressed individuals; these abnormal clock functions are thought to not just aggravate depressive symptomology, but could alter patient responsiveness to standard treatments as well as further elevate relapse rates [4]. The purpose of this paper is to summarize the

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effects of circadian rhythms on depression, and therapeutic strategies based on circadian modulation [5], for future research and clinical treatment.

2. Circadian rhythm: fundamental mechanisms

Circadian rhythms in mammals are centrally coordinated by the suprachromaffinic nucleus (SCN) of the brain located in the anterior aspect of the hypothalamus, which is a key location for the control of the biological clock [6] and receives light inputs from the retina, which generates output signals directly through neural signals and indirectly through hormonal factors that affect multiple systems throughout the body Output signals. In this way, the SCN controls many physiological functions in animals, including sleep and wake cycles, thermoregulation, hormone secretion, and metabolism to help maintain body homeostasis.

The proper functioning of circadian rhythms requires a variety of endogenous and exogenous regulators; light is the most powerful external signal. Melatonin secretion is regulated by the SCN, and light influences the activity of the SCN through inputs from the retino-hypothalamic bundle. Melatonin is a hormone secreted by the pineal gland, and its secretion increases with the onset of darkness, thus serving as a sleep inducer and initiator of nocturnal physiology. In addition, circadian rhythms are also largely regulated by clock genes (e.g., CLOCK, BMAL1, PER, CRY, etc.). On a biological scale, clock genes enable the robustness of the circadian clock at the molecular level, a behavior that arises from the interactions between these genes and gene products and adaptive responses to changes in the external environment, forming a self-regulating transcriptional-translational feedback loop, also known as the TTFL (transcriptional-translational negative feedback loop) [6]. In addition to melatonin secretion, light can influence the expression of clock genes during the biological clock cycle, thereby directly regulating rhythms. In summary, complicating this system may allow organisms to better adapt to circadian changes and seasonal cycles in environments suitable for normal functioning.

Circadian rhythms affect many physiological systems in the body in addition to their important function of regulating the sleep-wake cycle [7]. Second, circadian rhythms are key clock genes for metabolic processes [8], which regulate energy intake and expenditure, glucose metabolism, and lipid metabolism to maintain a balanced metabolic state. One of the hallmarks of metabolic syndrome, obesity, and type 2 diabetes is disrupted circadian rhythms [8]. A second important aspect is that circadian rhythms also affect parameters of cardiovascular function such as blood pressure, heart rate, and vascular tone. One study found that a disrupted circadian rhythm is one of the risk factors for hypertension and atherosclerosis [9]. In addition, the immune system is also closely linked to circadian rhythms; the immune system controls the behavior of immune cells, inflammatory responses, and resistance to disease. Dysregulation of circadian rhythms increases the risk of infections, chronic inflammation and even autoimmunity due to impaired immune responses.

This paper may help lay an important foundation for further exploration of the complex relationship between circadian rhythm disruption and depression, provide a more detailed understanding of the physiological background of circadian rhythms, the major regulators, and their myriad impacts on numerous systems in the human body, and deepen the understanding that circadian rhythms are critical for maintaining health.

3. Epidemiological associations between circadian rhythm disruptions and depression

3.1. Insomnia and shift work-related circadian disruptions

Circadian rhythm disruption is diverse, but it can disrupt the body's internal biological clock in several ways, leading to different conditions. A common epidemiologic association associated with circadian rhythm disruption is insomnia. Insomnia is the most common sleep disorder resulting in an inability to fall asleep, awakening from sleep too early, or not being able to fall asleep upon awakening, and the inability of the patient to compensate for the lack of sleep by resuming daily activities. Chronic insomnia disrupts circadian rhythms, causing the body's biological clock to become disconnected from the environment and increasing the risk of depression. It is more common among shift workers and those

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who travel across time zones. Studies have shown that night shift workers have significantly higher rates of depression than those who work normal hours [10]. This is because they need to adjust their circadian rhythms to accommodate work schedules that do not coincide with ambient light and darkness. Individuals who frequently travel across time zones have poor jet lag recovery, which can lead to sleep disturbances and depression [11].

3.2. The influence of age and gender on circadian rhythm susceptibility

Numerous epidemiologic studies have found a strong association between circadian rhythm disruption and the onset or course of depression [12]. Circadian rhythm disorders such as insomnia, shift work, and traveling through different time zones significantly increase the risk of depression in the general population compared to those with chronic sleep disorders. Additionally, the study found that individuals with circadian rhythm disorders were more susceptible and had a higher prevalence of depression in women than in men. Additionally, age plays an important role, with adolescents and older adults having relatively fragile biological clocks and being more susceptible to circadian rhythm disruption in the development of depressive mood [13]. Their epidemiologic evidence provides a basis for addressing the relationship between circadian rhythm disruption and depression and suggests that there are some differences in the patterns of response to circadian rhythm disruption across populations.

3.3. Circadian rhythm disruptions as a risk factor for depression

To explore this issue, numerous researchers have conducted several studies that have furthered our understanding of how circadian rhythms affect depression. Most studies have shown that circadian rhythm disruption is an important risk factor for precipitating depression. Both in clinical populations and in the general population, circadian rhythm disruption has shown a strong association between circadian rhythm disruption and the onset and progression of depression [14]. For example, circadian rhythm disruption is nearly ubiquitous in patients with clinical depression, including altered sleep patterns and abnormal circadian physical activity levels. Similarly, circadian rhythm disruption may further transform mild depressive syndromes into major depressive syndromes, generating new episodes of MDD in a sustained manner (reciprocal causation). Currently, epidemiologic data have confirmed the relationship between circadian rhythm disruption and depression but elucidating its biological basis and understanding which types of disruption lead to which pathophysiologic consequences remains a hot area of research.

4. Impact of circadian rhythm disruptions on depression symptoms

4.1. Depression and its physical and emotional symptoms

Major depressive disorder (MDD) is a complex mental disorder with symptoms that include depressed mood, loss of interest, and low cognitive functioning. Its characteristics can affect the patient's daily life and social functioning. When we talk about depression, the most important thing is low mood, when you are in a state of sadness, you feel hopeless and helpless. Similarly, depression can cause significant physical manifestations, including difficulty sleeping, changes in eating habits, and significant changes in weight. They often have trouble falling asleep, stay asleep for short periods of time, or wake up too early. Appetite may also change drastically, leading to significant weight gain or loss.

4.2. The role of circadian rhythms in depression-related sleep and mood disruptions

Circadian rhythms are disrupted, and appetite changes can occur; mood changes can also be very pronounced [10]. First, sleep disturbances have been a major symptom of depressed patients since the clinical description of melancholia, with internal clock disorders leading to difficulties in falling asleep or staying asleep at the right time, as evidenced by shorter sleep duration or reduced sleep quality. In addition, the resulting chronic sleep deprivation reduces mood, triggers fatigue, and impairs cognitive performance, thus creating a vicious cycle. Circadian rhythms also affect the production of certain hormones in the body, including cortisol and melatonin [15]. This can directly affect a patient's appetite,

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leading to binge eating or anorexia. Similarly, when irregularities in one's circadian rhythm can also lead to mood swings [16]. Since circadian rhythms control the production and release of serotonin (5-hydroxytryptamine) and dopamine, an erratic biological clock can lead to abnormal levels of these neurotransmitters, which can exacerbate feelings of mood instability, anxiety, and despair.

4.3. The link between delayed sleep stages and circadian activity changes in depression

This circadian rhythm abnormality in depressed individuals typically includes delayed sleep onset and alterations in various circadian activity endpoints. Delayed sleep stages are characterized by sleep onset and awakening significantly later than normal. This is particularly common in young, depressed patients. On the other hand, altered levels of circadian rhythm activity are characterized by a significant reduction in daytime activity [17]. These circadian rhythm disturbances are not only part of the depressive symptoms but may also be one of the factors that aggravate depression. Circadian rhythm disruptions are closely related to depressive symptoms and their onset (e.g., sleep, appetite), as well as other aspects of mood regulation. This finding may contribute to a more successful treatment program for people with depression to help them restore normal circadian rhythms and reduce depressive symptoms.

5. Potential mechanisms linking circadian rhythm and depression

5.1. Neurobiological mechanisms in neurotransmitter regulation

Circadian rhythms are major regulators of neurotransmitter synthesis and release and therefore play a crucial role in the onset/development of depression. Mood Stability - Mood is largely influenced by certain neurotransmitters, including 5-hydroxytryptamine (serotonin), dopamine, and norepinephrine [18], all whose metabolism and functioning are largely regulated by circadian rhythms. For example, serotonin synthesis and release peaks during the day and decreases at night to maintain emotional homeostasis. However, if circadian rhythms are disrupted, levels of these neurotransmitters can become abnormal, leading to mood swings, anxiety conditions, and depressive symptoms. Circadian dysregulation has also been shown to regulate cortisol secretion by interfering with the SCN and the hypothalamic-pituitary-adrenal (HPA) axis, which is critical to the pathophysiology of depression due to its role in stress hormone fluctuations [19]. In addition, the severity of depression has been associated with melatonin dysregulation [20], and peak melatonin secretion usually occurs at night, but their secretion may not only be delayed in depressed patients, but also insufficient to regulate sleep or mood.

5.2. Genetic and molecular mechanisms of clock genes

The circadian rhythms acted upon by clock genes are critical to the regulation of behavior in depressed individuals, and thus variation in these genes is a likely pathway to depression. These clock genes, including CLOCK, BMAL1, PER, and CRY, may function as transcriptional-translational feedback loops to maintain their stability and precision [21]. However, when clock genes are mutated or improperly expressed, circadian rhythms are disrupted, and the risk of depression is increased. For example, mutations in the CLOCK gene are strongly associated with sleep disturbances and circadian rhythm desynchronization in depressed patients. Other studies have shown that mutations in the PER gene may also elongate or narrow the biological clock cycle, which in turn triggers the core symptoms of depression. This supports a role for gene-environment interactions in circadian rhythms and depression. For example, differences in some clock genes are thought to increase vulnerability to environmental changes (e.g., low light exposure and social dissonance) and, along with circadian rhythm disruption, affect susceptibility to depression.

5.3. Environmental and behavioral influences on circadian disruption

Circadian rhythms, environmental and behavioral factors largely mediate their effects on depression. Light is the most important inducer of circadian rhythms and reduced or irregular light fluctuations can directly disrupt the functioning of biological rhythms, thereby exacerbating depressive symptoms. For example, during the winter months, reduced light hours are also an important trigger for seasonal

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affective disorder (SAD), and in fact, half an hour of light therapy per day has been shown to be effective in alleviating such depressive symptoms. Conversely, this disruption of social rhythms can disrupt circadian rhythms during irregular work schedules and rapid socialization changes [17]. Similarly, the all-encompassing use of electronic devices today, especially during nighttime screen time, can lead to sleep disturbances and disrupted circadian rhythms, which pose a risk for depression.

The onset of depression is subject to multiple modulations by different aspects of the circadian rhythm, in which environmental and behavioral factors, neurobiological mechanisms, and genetic and molecular mechanisms interact to influence the development of depression, and which provide many new feasible and prospective perspectives for the treatment of depression today.

6. Circadian rhythm-based treatment strategies for depression

6.1. Principles and applications of bright light therapy

Light therapy treats depression in a non-pharmacological way by regulating circadian rhythms. It involves regulating the biological clock through high levels of standardized artificial light consistent with natural conditions. Light therapy is thought to act directly on the SCN through organic signaling pathways [22]. This could address sleep and mood disorders associated with circadian rhythms by matching the SCN to local time zones through light stimulation. Previous research has shown that light therapy can be effective in alleviating depressive symptoms in both SAD patients and non-SAD patients [23]. In clinical applications, patients receive 30-minute to 2-hour doses of light early in the morning to coincide with the acute effects on the SCN and to advance the biological clock clock time, thereby improving mood on the same day and maintaining a state of wakefulness for rest and activity on the following day. Light therapy is a widely recommended adjunctive therapy for depression because of its well-recognized tolerability and minimal side effects [24], with the most common side effects in systematic reviews being mild headache or eyestrain.

6.2. Effectiveness and applicability of melatonin supplementation therapy

Melatonin is a hormone secreted by the pineal gland that helps regulate the circadian sleep cycle (the body's internal clock) and circadian rhythms. In healthy conditions, melatonin secretion peaks at night and serves to promote sleep. However, people with depression often have abnormalities in melatonin secretion, experiencing delayed or decreased secretion, which can lead to sleep disorders. Melatonin supplementation therapy is designed to correct the biological clock by providing exogenous melatonin [25], thereby re-establishing normal sleep patterns. Clinical findings suggest that melatonin supplementation is effective in improving sleep quality in patients with depression, as well as reducing depressive symptoms by indirectly affecting neurotransmitter homeostasis [26]. However, the effects of melatonin supplementation are very specific for different types of depressed patients and vary from person to person. In addition, melatonin, as a hormone, is naturally derived and usually has fewer adverse effects, but more research is needed to determine its safety and indications for long-term use.

6.3. Sleep phase delay therapy

Therapies such as delayed sleep phase are temporal therapies that restore synchronization to unsynchronized biological rhythms, but may be less effective for depressive symptoms more directly related to circadian rhythm disruption. This approach gradually delays the patient's bedtime until his or her internal circadian rhythms are synchronized with the external environment, ultimately improving sleep quality and reducing depressive symptoms. The basic idea behind sleep stage delay therapy is to normalize the patient's sleep schedule by effectively pressing the reset button on the internal biological clock. In addition, it is combined with light therapy and melatonin supplementation therapy to make the treatment even more beneficial.

In addition, other therapeutic options for regulating circadian rhythms have garnered increasing interest. For example, "social rhythm therapy" aims to restore balance in the biological clock by stabilizing daily activities and social interactions. Research also indicates that exercise therapy and

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cognitive behavioral therapy (CBT) can improve patients' sleep and mood states. These therapies reset the clock through a variety of pathways, and the results provide a rich approach to treating depression holistically.

7. Future research directions and challenges

In recent years, significant progress has been made in research on the relationship between circadian rhythms and depression, but there are limitations. First, many studies have limited sample sizes and therefore cannot be statistically generalized beyond the populations studied. Second, the predominance of cross-sectional studies in research design may hinder the elucidation of the causal relationship between circadian rhythm disruption and depression. In addition, current measurement tools have limitations. Circadian rhythm measurements are usually obtained through self-report questionnaires, which may lead to subjective bias and measurement error. While the use of biomarkers may provide a higher degree of objectivity than subjective evaluations, their expensive and cumbersome nature prevents their use in large-scale studies.

To better understand the link between circadian rhythm disruption and depression, future studies should employ higher order models and longer time spans [27]. These types of study designs are uniquely able to capture the temporal dynamics associated with circadian rhythms and their ongoing effects on antecedent stress susceptibility in the context of depression. In addition, differences in the role of circadian rhythm disruption in different subtypes of depression (recurrent vs. first-episode depression) need to be further investigated in future studies [14]. Developing personalized treatment strategies will also be a key area for future research [28]. Going back to the previous point, it is not enough to rely on genetics as a marker; if it is combined with neurobiology and environmental science, researchers will be able to design more targeted treatments for individual patients. This would not only improve efficacy, but also help reduce adverse effects and overcome drug dependence.

Understanding the relationship between our rhythms and depression requires a broad multidisciplinary approach. From a psychological perspective, research can provide insight into the effects of circadian rhythms on mood and behavior, while neuroscience can shed light on the mechanistic pathways by which circadian disruption causes or exacerbates depressive symptoms in the brain. Identifying susceptibility genes associated with circadian rhythms could provide substantial evidence as to why some susceptible individuals experience circadian rhythm disruption and depressive symptoms even under the same environmental stressors. In addition, research in the social sciences and public health can facilitate the implementation and dissemination of circadian rhythm regulation interventions in mental health. Through such collaborations, we can gain a deeper understanding of the impact of circadian rhythms on depression and work to improve treatment and prevention methods.

8. Conclusion

In conclusion, circadian rhythm disruption plays a pivotal role in both the onset and progression of depression, making it a crucial target for treatment. As research continues to highlight the intricate connection between biological rhythms and mood regulation, therapeutic approaches that focus on restoring circadian balance, such as light therapy and melatonin supplementation, hold great promise for improving depressive symptoms. Moving forward, personalized interventions that consider individual genetic, environmental, and behavioral factors are likely to enhance treatment outcomes, offering a more precise and effective approach to managing depression and enhancing overall well-being.

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