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Circadian Rhythms and Depression: Exploring the Connection

Shizhong Zhang

School of Biological Sciences, University of California, Irvine. 5120 Natural Sciences II, Irvine, CA 92697, USA

shizhonz@uci.edu

Abstract. Circadian rhythms, which regulate sleep-wake cycles, mood, and various physiological processes, are tightly linked to mental health. Disruptions in circadian rhythms are commonly observed in individuals with depression, manifesting as insomnia, early awakening, or excessive sleepiness. These disturbances can exacerbate depressive symptoms by affecting neurobiological mechanisms, including hormone regulation and neurotransmitter balance. Research indicates that insomnia is not only a consequence of depression but also a potential precursor, highlighting the bidirectional relationship between circadian rhythm disorders and mood disorders. Genetic factors, such as variations in clock genes, further contribute to circadian disruptions and increase susceptibility to depression. Therapeutic approaches targeting circadian rhythms, such as melatonin supplementation, light therapy, and wearable technology, offer promising solutions for managing both circadian disturbances and depressive symptoms. Future research should explore individualized treatment individualized treatment strategies and genetic interventions to prevent and treat depression by aligning circadian rhythms with external environmental cues. Understanding the complex interaction between circadian rhythms and depression could lead to more personalized and effective therapies.

Keywords: Circadian rhythms, Sleep disorders, Depression, Mechanism.

1. Introduction

Circadian Rhythm is an intrinsic biological rhythm exhibited by an organism during an approximately 24-hour cycle. This rhythm is controlled by the endogenous biological clock and is capable of functioning in the absence of external time signals such as changes in light and darkness. Circadian rhythms regulate a variety of physiological processes, including sleep-wake cycles, hormone secretion, body temperature fluctuations, and metabolism. External environmental factors, such as light, are important regulators of circadian rhythms and can synchronize an organism's rhythms with the timing of the external environment by influencing the biological clock. There is a strong relationship between circadian rhythms and mental health. The biological clock regulates many of our body's functions, including sleep, mood, hormone production, and metabolism, and when circadian rhythms are out of whack, these functions may be compromised, which in turn affects mental health. Here are some key aspects of the relationship between circadian rhythms and mental health: if the biological clock is not aligned with the actual sleep schedule, this may lead to decreased sleep quality, insomnia, and circadian problems. And chronic sleep disorders are closely linked to mental health issues such as depression and

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anxiety. Circadian rhythms directly affect mood states by regulating the secretion of mood-related hormones such as cortisol and melatonin. Circadian rhythm disruption may lead to mood instability and increased risk of depression and anxiety. Studies even have shown that people with schizophrenia often exhibit significant circadian rhythm disturbances, such as abnormalities in the sleep-wake cycle. Such rhythm disturbances may exacerbate symptoms and compromise treatment outcomes. Depression is a serious and common mood disorder that not only manifests itself in persistent low mood and diminished interest in daily activities, but may also affect an individual's thinking, feeling and behavior. Its causes are complex and involve a variety of factors such as genetics, environmental stressors, and neurochemical imbalances. Common symptoms of depression include persistent feelings of sadness, changes in sleep and appetite, decreased energy, cognitive impairment, social withdrawal, and suicide risk. Diagnosis is usually based on the duration of symptoms and the impact on daily functioning, ruling out other possible physical illnesses. Treatment includes medication, psychotherapy, other interventions, and lifestyle modifications. With professional intervention, depression is treatable, and many people are able to return to normal life.

The importance of exploring that the link between the condition that patient's circadian rhythms and the trigger of the depression is that this relationship sheds light on the underlying pathogenesis of depression and provides new perspectives on diagnosis, treatment, and prevention. Depression is often accompanied by disruptions in circadian rhythms, such as sleep disturbances and abnormal thermoregulation. These disorders may cause or exacerbate depressive symptoms ... Certain antidepressant medications may work by affecting the biological clock, and understanding the characteristics of patients' circadian rhythms can help optimize medication selection. In addition, the sleep management component of cognitive behavioral therapy can be adapted to an individual's biological rhythms to improve treatment outcomes. Maintaining a regular schedule, moderate light exposure, and healthy habits can help maintain a stable circadian rhythm, thereby reducing the risk of depression. Especially for people who are predisposed to depression, focusing on the health of circadian rhythms can be part of preventive measures.

2. The Relationship Between Circadian Rhythms and Depression

Studies have shown that people with depression often exhibit significant disruptions in circadian rhythms. are very common in people with depression. These problems are often associated with disruptions in the biological clock. For example, abnormalities in melatonin production may lead to difficulty falling asleep, while abnormalities in cortisol levels may lead to early waking. Circadian rhythms not only affect sleep, but also regulate mood states. Studies have found that people with depression often have mood swings that are inconsistent with circadian rhythms. For example, they may feel most depressed in the early morning, which is inconsistent with normal cortisol rhythms. Disturbed circadian rhythms may lead to an imbalance of mood-related neurotransmitters in the brain such as serotonin, norepinephrine and dopamine. Serotonin is strongly associated with depression, and disruption of circadian rhythms may affect the synthesis and secretion of serotonin, thereby exacerbating depressive symptoms.

2.1. The relationship between insomnia and depression

Circadian rhythm disorders, including insomnia, early awakening, and delayed sleep phase syndrome, have been found to have a strong association with the onset and progression of depression. Disruptions in the body's natural sleep-wake cycle can lead to imbalances in mood regulation and overall mental health, increasing the risk of depressive symptoms. Many depressed patients report sleep problems, which are considered a marker of circadian rhythm disruption. More than 90% of people with depression complain of difficulty in falling asleep, frequent nighttime awakenings, and early morning awakenings. As a result, depression is considered one of the leading causes of insomnia. According to an article by Berger and colleagues: patients with severe insomnia are four times more likely to develop depression, and insomnia may be a significant risk factor for the subsequent development of depression. [1]

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Epidemiological research has demonstrated that individuals with mood disorders are significantly more likely to experience sleep disturbances compared to the general population. These sleep issues often persist even during periods of remission. Conversely, people suffering from insomnia are ten times more likely to develop depression than those who sleep normally. Moreover, those who have chronic or persistent insomnia are at a much higher risk of developing new-onset depression compared to individuals without sleep problems. According to the findings of Ford and Kamerow, there is a strong link between ongoing sleep disturbances and the risk of depression. This suggests that sleep issues are not just a symptom of mood disorders, but in some cases, they might act as a contributing factor to the onset of these emotional conditions. [2].

2.2. Common Expression of Circadian Rhythm Disruption in Depressed Patients

Conventional beliefs suggest that symptoms of depression are the cause of various sleep problems, including insomnia or excessive sleepiness, and therefore depression is often treated with the assumption that as the depression subsides, so do the sleep problems. However, a large body of research in recent years has shown that sleep disorders may begin long before symptoms of depression appear and may increase a person's risk of that developing the depression and other related condition in their future. In an article by Benca and colleagues, they propose that insomnia may serve as an independent risk factor for the development of depression. Over time, research has consistently shown a bidirectional relationship between sleep disturbances and depression, where one can influence the other. However, the ongoing question is whether insomnia acts as a precursor, a premorbid feature, or a separate risk factor for depression. Despite significant advances in understanding the connection between sleep and mood disorders, much remains unknown about the underlying neurobiological mechanisms that link the two. Further exploration into this shared neurobiology is needed before the precise nature of this relationship can be fully understood. [3]

Studies have shown that serum brain-derived neurotrophic factor (BDNF) levels are significantly lower in patients with insomnia, with a similar trend in short-term sleepers. Animal experiments further support the conclusion that chronic sleep deprivation leads to decreased BDNF levels. Some researchers have proposed that the relationship between the experience of stress and serum BDNF levels in patients with insomnia may be mediated by a sleep disorder. Sleep disorders may be a neurobiological stressor that activates the stress system, leading to a decrease in BDNF levels, which negatively affects 5-hydroxytryptamine (5HT) signaling, synaptic plasticity, and neurogenesis. [4]

2.3. High prevalence of insomnia in depression

A systematic review and meta-analysis suggest that insomnia symptoms significantly increase the risk of depression. About 10% of adults suffer from insomnia on a chronic basis, and another 20% experience insomnia occasionally. The prevalence of insomnia is higher among people with depression, especially among women, older adults, and those with poor economic status. Insomnia tends to be a chronic problem, with about 40% of patients continuing to experience insomnia five years later. [5]

A study featured in Translational Psychiatry explored data from a population cohort with an average age of 65, uncovering a significant association between reduced sleep duration and the emergence of depressive symptoms. This research sheds light on the intricate relationship between sleep and mental health, particularly in older adults. Odessa S. Hamilton, the lead author from University College London’s Institute of Epidemiology and Health Care, highlighted an ongoing challenge in understanding this connection, stating, “There exists a longstanding chicken-and-egg dilemma in the relationship between insufficient sleep and depression. These conditions frequently coexist, making it difficult to ascertain whether one causes the other. Which factor precedes the other is still a matter of debate.” [6]

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3. Genetic and Molecular Mechanisms

3.1. Genetic basis of circadian rhythms

The genetic basis of circadian rhythms lies in the regulation of the biological clock by specific genes, often referred to as “clock genes”. These genes control the 24-hour cycle of physiological, behavioral, and metabolic processes in organisms. The circadian clock is controlled by a transcriptional-translational feedback loop (TTFL) in which clock genes and their protein products regulate each other's expression in a rhythmic manner.

3.2. Role of biological clock genes

Several studies have outlined how TTFL are critical for regulating these biological clocks. BMAL1 and CLOCK proteins form a complex that drives the expression of key circadian genes, such as PER and CRY. The proteins encoded by these genes repress their own transcription by interacting with the CLOCK-BMAL1 complex, creating a negative feedback loop that recurs approximately every 24 hours. Other regulatory loops involving proteins such as REV-ERBα and RORα fine-tune the system by controlling the expression of BMAL1, thus ensuring stable circadian rhythms [6].

The article "Genetics of circadian rhythms and sleep in human health and disease" by Jacqueline M. Lane et al., published in *Nature Reviews Genetics* (2023), explores the intricate relationship between circadian rhythms, sleep, and their genetic underpinnings. Studies have found that biological clock genes (e.g., PER3 and ARNTL2) affect circadian rhythm preferences and sleep patterns, which are strongly associated with mood disorders. Variants in these genes can lead to circadian rhythm disruption, which can increase the risk of depression. These gene variants affect an individual's sleep, mood, and overall daily rhythms [7].

According to Parsons and their colleague, they find that SNP rs10462020 in the PER3 gene was found to be significantly associated with circadian preference, suggesting that this gene may play a role in regulating circadian preference. rs922270, a SNP in the ARNTL2 gene, was also found to be associated with circadian preference for the first time, although the mechanism is unclear. These genes may directly influence circadian preference by affecting the molecular clock. In addition, SNP rs5443 in the GNβ3 gene was significantly associated with global sleep quality, which may be related to the enhanced signaling it triggers. SNP rs2304672 in the PER2 gene was associated with sleep duration, which is consistent with its previous association with late sleep phase syndrome. In terms of sleep onset latency, variants in both the ARNTL2 and DBP genes were nominally significantly correlated, but combined analyses showed that the ARNTL2 association was not independent. Finally, rare SNPs in the FBXL3 and PER2 genes were associated with sleep quality [8].

3.3. Gene Related Circadian Rhythm Disruption and Increased Risk of Depression

The relationship between circadian rhythm disruption and depression has been extensively studied. Rhythm disruption affects neurotransmitters, hormone levels, and the immune system in the brain, thereby increasing the incidence of mood disorders: specific cases of certain genetic mutations further illustrate the association between circadian rhythm disruption and depression. For example, mutations in the PER2 gene have been linked to progressive sleep phase syndrome, and people who carry this mutation not only sleep earlier but are also more likely to suffer from depression. In addition, polymorphisms in the BMAL1 gene are strongly associated with mood disorders, especially winter depression [7].

3.4. Effects of circadian genes on sleep and mood

Circadian rhythm genes (e.g., PER, CRY, CLOCK, and BMAL1) regulate the sleep-wake cycle through feedback loops. Studies have shown that mutations in the PER2 gene are associated with Familial Early Sleep Phase Disorder, which causes individuals to fall asleep earlier in the evening and wake up too early in the morning, and that mutations in the CRY1 gene are associated with Delayed Sleep Phase Disorder (DSPD), which interferes with the normal cycle of circadian rhythms and delays an individual's

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sleep. Circadian genes not only affect sleep but are also closely linked to the regulation of mood. dysfunction in genes such as BMAL1, PER and CRY may lead to mood disorders such as depression and anxiety. Mutations in genes may interfere with the balance of neurotransmitters (e.g., 5-hydroxytryptamine and dopamine), which in turn affects the brain's regulation of mood Disturbances in circadian rhythms (e.g., due to irregular rest and relaxation or jet lag) can further exacerbate mood problems, especially in people with pre-existing depression or anxiety disorders For example, a dysfunction of the biological clock can lead to increased anxiety, depressed mood, and impaired cognitive functioning of the brain [9] .

4. Therapeutic Approaches

Circadian rhythms, which regulate our sleep-wake cycles, body temperature, and various physiological processes, have become an important focus for therapeutic interventions. These biological clocks, driven by a network of core clock genes like BMAL1, CLOCK, PER, and CRY, control not only sleep patterns but also mood regulation, metabolism, and immune function. Dysregulation of these rhythms—whether through genetic mutations, lifestyle factors like shift work, or environmental changes—can lead to a range of health problems, including insomnia, depression, metabolic disorders, and chronic illnesses like cardiovascular disease and cancer.

4.1. Regulate Circadian Rhythms

Melatonin is a hormone secreted by the pineal gland and released primarily at night to help regulate the sleep-wake cycle. Utilizing exogenous melatonin supplements has become a common treatment for regulating circadian rhythms, improving sleep disorders and adjusting the biological clock. Melatonin can be particularly effective in people suffering from DSPD and jet lag by shortening the time to fall asleep and lengthening sleep duration. Melatonin regulates the biological clock in the circadian rhythm by binding to melatonin receptors in the brain. It is particularly suited to those with misaligned biological clocks, such as travelers across time zones, night shift workers, and those who suffer from sleep phase delays. Melatonin not only improves sleep but may also play a role in regulating mood and immune function [10].

Recent research has illuminated the potential of circadian-based therapies for treating these conditions. For example, light therapy and melatonin supplements are commonly used to correct sleep phase disorders by realigning the circadian clock. Chronotherapy, which involves adjusting the timing of sleep, meals, and medication, has also shown promise in enhancing treatment efficacy for both sleep disorders and conditions like hypertension and cancer, where the timing of medication can significantly impact outcomes. Furthermore, emerging pharmacological interventions targeting circadian clock genes and proteins, such as REV-ERB agonists, show potential in managing metabolic diseases and cancer. These interventions focus on synchronizing the body's internal clocks with external cues, improving health by restoring the natural rhythms that govern human biology [11]

4.2. Utilizing wearable devices for therapy

By collecting continuous data, these wearables offer real-time feedback that can help individuals better regulate their sleep patterns, detect misalignments, and even predict the onset of mood disorders such as depression. For example, actigraphy has been widely used to monitor sleep in natural living conditions, and advancements in technology have allowed more accurate predictions of sleep stages and circadian phases. These wearables have been particularly effective in detecting circadian disruptions among shift workers and people with insomnia [12]. According to Shapiro and their colleague, they suggest that Doctors can provide Fitbit to psychiatric patients and track their circadian rhythms. Once a phase shift in the circadian rhythm is monitored (e.g., a delayed or advanced phase associated with depressive or manic episodes), the doctor can intervene early. This intervention can include adjusting the patient's daily routine or providing medication to prevent or alleviate episodes of mood disorders [13].

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Further, in therapeutic applications, wearables can support interventions by reminding users to adjust their behaviors (e.g., exposure to natural light or melatonin intake) to realign their circadian rhythms. Additionally, these devices could be integrated into broader treatment plans, which has been shown to improve sleep quality when combined with wearable technology [14].

5. Conclusion

While substantial progress has been made in understanding the intricate relationship between circadian rhythms and depression, much remains to be explored. Future research should focus on clarifying whether circadian disruptions are a cause or consequence of depression, as well as investigating how individual differences, such as age, gender, and genetic predispositions, influence this relationship. There is also a growing interest in developing novel therapies aimed at regulating the biological clock, with promising potential in gene-editing techniques like CRISPR that could target clock genes responsible for circadian rhythm disruptions. This could prevent the onset of depression in individuals genetically predisposed to the disorder. Additionally, pharmacological approaches focusing on circadian proteins such as BMAL1 or PER2 may offer a more personalized treatment for depression, allowing for synchronization of the biological clock to improve outcomes. Non-invasive strategies, such as light therapy and melatonin supplements, could also be refined as we gain more understanding of circadian variability among individuals. Integrating circadian regulation into existing treatment protocols for depression is crucial, especially when considering methods like chronotherapy, which adjusts sleep and activity patterns in alignment with an individual's biological rhythms. Moreover, the timing of medication could be tailored to fit each patient's circadian profile, potentially enhancing therapeutic efficacy. Behavioral therapies, such as cognitive behavioral therapy for insomnia, combined with circadian interventions, offer a comprehensive approach that may significantly improve depression management. In conclusion, the link between circadian rhythms and depression not only provides new insights into the underlying mechanisms of mood disorders but also paves the way for innovative, circadian-focused treatments. As research advances, addressing circadian health will likely become a vital component of depression treatment and prevention strategies, offering personalized care that aligns with an individual’s biological clock.

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