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The Influence of Circadian Rhythm on Bipolar Disorder

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Abstract: Circadian rhythm disorder is one of the main symptoms of bipolar disorder. The circadian rhythm disorder in bipolar disorders is caused by the combined effects of genes, neurotransmitters, hormones, etc. It can manifest as a gene expression disorder, a sleep-wake cycle disorder, and other metabolic disorders of the body. Its influencing factors include season, light intensity, working mechanism, and social pressure. Treatment of bipolar disorder often begins with addressing circadian rhythm disorders, thus giving rise to various therapies, ranging from drugs to psychological and behavioral therapies. This article mainly summarizes the information regarding the introduction of circadian rhythm, the interplay between bidirectional regulation and circadian rhythm, and the association between circadian rhythm disorders and their respective treatment strategies. Moreover, this review aims to generate insights for future research on novel therapeutic approaches and drug development for the bipolar disorder treatment.

Keywords: Bipolar disorder, Circadian rhythm, Circadian disorder

1. Introduction

Bipolar disorder (BD) is a mixed psychiatric disorder characterized by depression or mania. These two symptoms can occur alone or in mixed episodes [1], and they are always divided into two types: BD I is severe depression with manic episodes, and BD II is hypomania [2]. Its seriousness and complexity are reflected in multiple psychological and physiological disorders that are caused by it. The normal disorders are circadian rhythm disorder, migraine headache, obsessive-compulsive disorder, anxiety, etc. [3]. Circadian rhythms, which are 24-hour patterns, regulate biological functions such as biological behavior, organ activity, and cell activity to adapt to predictable environments [4]. It plays a role in light stimulating the suprachiasmatic nucleus (SCN), which is responsible for processing and accepting the information from light. The SCN regulates protein secretion and neurotransmitter distribution to control circadian rhythms [5]. In humans, circadian rhythms regulate some important parts, for example, the intestinal flora [4]. On a psychiatric and psychological level, circadian rhythm disorder is related to BD, depression, seasonal affective disorder (SAD), autism, and anxiety. These mood disorder's susceptibility is connected to the sleep state in the circadian rhythms. The poor sleep state undermined psychological health, which increased the susceptibility to psychiatric disorders [6]. Recently, the circadian rhythm in BD patients has been significantly considered in diagnosis and treatment. Because of the unbalanced sleep demand in depression and mania, BD patients sleep-wake rhythms are abnormal. This alternation of states also influences sleep quality, as the REM sleep in a manic state is more. Because of that, sleep disorders are the main manifestation of circadian rhythm disorders in bipolar disorders. These sleep disorders,

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which are led by circadian rhythm disorders, always obviously appear in genes, the melatonin and cortisol secretion, the light sensitivity of SCN, and society [7]. Nowadays treatments are always fundamental to these functions. For example, the reason for using lithium to treat BD is that it can correct the circadian rhythm. However, the treatment methods that aim to correct circadian rhythms to treat bipolar disorder still need to be expanded. Due to the global incidence rate of BD increasing substantially and the incidence structure being younger, lower side effects and more convenient therapies need to be developed [8]. The aim of this article is to analyze the mechanism of circadian rhythm disorders in BD and summarize the existing therapies to provide ideas on developing potential treatments.

2. Mechanisms linking circadian dysfunction to bipolar disorder

2.1. Neurotransmitter dysregulation

Circadian dysfunction has a strong connection with neurotransmitter dysregulation. The motivational-reward system represented by dopamine plays a significant role in it. The disorder of the dopamine system can be caused by serotonin (5-HT) deficiency [9], an increase of corticotropin-releasing factor (CRF), and GC receptor inactivation [10]. And dopamine system disorder will lead to psychotic symptoms in BD's circadian system. Such as, overexcited dopamine neuronal activity or dopamine circadian rhythm loss will cause manic symptoms. And the lower the activity of it, the more it will cause depression and hypersomnia [9]. The other system is called the orexin/melanin-concentrating hormone neuronal system, which plays a role in emotion regulation, sleep-wake state, eating behavior, and metabolism. These functions decide its connection in some of BD's symptoms. Such as depression regulation and regulation of binge eating and anorexia states. Also, it has a connection with the dopamine reward system, which can regulate the circadian system on both sides.

2.2. HPA axis and stress response

The HPA axis is a key part of the CNS responding to stress. The main byproduct of it, cortisol, plays an important role in affecting responsive environmental stimulation, cognitive and emotional processes, and maintaining circadian systems [11]. HPA axis activities abnormal in BD are common to see, and this is a reason for the circadian rhythm disorder in BD. The abnormal activities performed in the HPA axis are cortisol disorders, such as cortisol parasecretion, answering abnormality, and cortisol rhythm disorder [11]. The circadian rhythm closely correlates with the cortisol rhythm disorder. First, clock gene expression alteration in the SCN will have a negative influence on the HPA axis, and the HPA axis abnormality is a direct factor in cortisol disorder [12]. Second, sleep time decreases, and sleep-wake cycle changes affect the diurnal cortisol slope (DCS) [12]. In the HPA axis itself, it can perform in abnormal molecular mechanisms and also the gene of the HPA axis. The abnormal molecular mechanisms in BD's HPA axis include GR hypofunction, which can be measured in GR protein reduction and mRNA binding of GR to DNA reduction [11].

2.3. Inflammatory pathways and metabolic implications

Higher inflammatory markers can be observed in severe mental disorders, such as depression and bipolar disorders. Also, the higher inflammatory marker level can be seen as a potential factor in the risk of mental illness. However, this connection is unsubstantial because little evidence can prove there exists a causal relationship [13]. Some inflammatory markers have been demonstrated to have a certain correlation in BD, such as CRP, BDNF, and IL-6 [13]. But there is no evidence showing the connection of the aforementioned markers in BD and circadian rhythm. Evidence suggests a connection between circadian clocks and inflammatory pathways. The circadian oscillator can

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prevent different components of the immune system from synchronously activating by suppressing innate immunity [14]. This process includes regulation of cortisol. Additionally, the inflammatory pathways in the HPA axis have been proven to be connected to BD [11]. This might be a way to study the connection in the three parts. Research has proven that the circadian rhythm interacts with redox homeostasis in metabolism. It shows in the molecular interaction and neuronal excitability in SCN neurons [14]. And in bipolar disorder, redox state disorder is one of its mechanisms. For instance, mitochondrial failure, mitochondrial distortion, calcium homeostasis disruption, higher lactate levels in the brain, and reduced pH [15]. One study shows melatonin therapy for patients with circadian rhythm disorders and BD. That shows the mitochondrial regulation can be a target of circadian rhythm disorder and BD treatment [16]. However, there are still only a few research focuses on this aspect. In the future, we can expand on this area and thereby gain a more profound understanding of this mechanism.

3. Circadian rhythms and mood regulation

3.1. Clock gene abnormity in BD

A series of studies revealed that there is a close connection between dysphrenia and circadian rhythm, particularly in the sleep state. And also found that clock genes contribute to the association between mental health and chronotype. In a study conducted by Lee, a significant correlation was observed between clock gene difference and bipolar disorder. This research shows the difference in CLOCK 3111T/C single nucleotide polymorphism (SNP; rs1801260) and the connection in circadian type and BD. The research proves that the C allele frequency in the T3111C SNP as a high-risk gene in bipolar disorder is significant. C allele is associated with the extreme evening type. This is genetic-level evidence of circadian rhythm disorder in BD [17]. The other research by Bengesser offered another piece of evidence about ARNTL (which is related to BMAL 1 [18]) and the MAOA gene (which is related to stress response [19]). By analyzing the ARNTL and MAOA gene expression in peripheral mononuclear blood from BD and healthy people's fasting blood samples, this research proves that the expression of the ARNTL and MAOA genes will change in different emotional states. That is to say, the clock gene expression changes in different states of BD, and this offers another gene expression state in circadian rhythms in BD. ARNTL gene expression was higher in the euthymia state in BD than in depression and hypomania, and MAOA gene expression in peripheral mononuclear blood was lower in BD compared to healthy controls [20]. These two studies prove that BD itself and the different emotional states in BD will all influence gene expression in the circadian system, which provides a basic theoretical basis for circadian rhythm disruption in bipolar disorder.

Sleep disorder is a main part of circadian rhythm disorder, and it is a significant symptom in BD. For example, BMAL1 has been reported to be related to somnipathy, including the amount of sleep fragmentation, the sleep architecture changing, and sleep deprivation increasing [21]. In BD, the methylation of ARNTL increases its silence rate, and as a result, its expression decreases [20]. Because of the connection between BMAL1 and ARNTL, BMAL1's lack or lower expression will lead to somnipathy in BD [20, 21]. And many studies have reported that, besides BMAL1, the other clock gene lacks or has a decreased expression in BD. PER3 polymorphism influenced the total sleep time and was always a target of lithium treatment. CRY1 and CRY2 are involved in the regulation of sleep, which significantly contributes to its progression [22]. The single or multiple variations of these clock genes will have a profound impact on the circadian rhythm of BD.

3.2. Sleep-wake cycle alterations

The sleep-wake cycle is determined by sleep homeostatic processes and the circadian system. These two systems influence each other to keep the cycle balanced. In BD patients, these cycle disorders

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always perform in circadian preference change and somnipathy. The circadian change also led to the sleep-wake cycle change. Many studies indicate that BD patients' circadian preference is to the evening type, and it has been proved that this condition is a high risk of mental illness. One reason for these findings is the close connection between the evening type and somnipathy [22]. This is because the two systems each regulate different physiological states: the circadian rhythm system is primarily associated with the state of wakefulness, while the sleep homeostatic regulation mechanism is responsible for initiating and maintaining the sleep state. During the daytime, the circadian system through the neurotransmitters, hormones, and circadian regulators is represented by the SCN to keep the wake activities. This system peaks in daytime off and decreases by the night increase. And the sleep homeostatic system increases sleep pressure through the wake time and decreases in the sleep state. Because the sleep pressure increases, people will feel sleepy in the evening [23]. But the evening type broke this balance. Evening type will cause the sleep pressure to increase slowly in the wake state and decrease hard in the sleep state, which leads to subjective hypersomnia, insomnia, and sleep deprivation [24]. The other reason for it is emotion regulation. Evening types show inadequate emotion regulation and have more negative emotions, such as depression [2, 25]. The bad mood regulation in BD will lead to depression and manic mixed episodes, which aggravate the cycle disorder. Somnipathy in different patients has a different performance. In mania, it exhibits a sleep-needing decrease (DSPS). However, in depression, hypersomnia and insomnia are more common [4]. These can be explained by delayed sleep phase syndrome [26]. DSPS is a condition characterized by an imbalance in the sleep-wake cycle. A phase delay in melatonin rhythm is the main research part in these two illness mechanisms and treatments. Both the symptoms of DSPS and BD can be alleviated by using light therapy and drug therapy on BD, and this is one reason for using melatonin as a treatment mechanism in treating BD's circadian disorder [26].

3.3. Environmental and behavioral triggers

Besides the gene and internal regulatory mode of the body, the environment and behavior are other triggers leading to the circadian rhythm disorder in BD. Research shows that higher social pressure, shift work, and daily negative emotion stimulation all are contributing factors. Higher social pressure and negative emotion stimulation will influence external time cues and internal circadian rhythm. All these factors are interrelated. And some research has discovered that the circadian rhythm disorder will begin before the BD; this will lead to the manic and depression breaking out [27]. Shift work as an external factor directly induced the occurrence of circadian rhythm disorder in BD [4]. Furthermore, the seasonal factor is an important cause of the circadian rhythm in BD. Due to the light change seasonally, the changes in the body's absorption of vitamin D have triggered mood changes and circadian rhythm alterations in bipolar disorder, manifesting the symptoms of seasonal affective disorder (SAD) [28].

4. Therapeutic implications and future directions

Light therapy plays a role in advancing and stabilizing circadian rhythms and also in improving mood and energy. This is because of the character of SCN and the absorbing and transitioning of the light in the body. The most used method is morning bright light exposure combined with the 'triple chronotherapy, which is a beneficial method to treat depression in BD. However, morning bright exposure can aggravate the manic. So, it needs to be combined with a placebo. Dark therapy is a beneficial way to treat the manic in BD. Its method is avoiding the blue ray light in the evening, which can stabilize and shorten the sleep time. Drug treatment in both BD and circadian rhythm disorder is always used in clinical therapy. The most famous drug is lithium-based pharmaceuticals. Lithium can correct the circadian rhythm by acting on the PER3 gene expression, thereby preventing and treating

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bipolar disorder. The other drug, which now is widely used in clinical practice, is quetiapine, which has sedation that can help patients fall asleep. Cognitive behavior therapy (CBT) is nowadays recommended treatment. From treating circadian dysfunction, it can be an effective treatment for chronic insomnia and also can regulate and improve the negative emotion in BD. CBT combined with motivational therapy, socialization therapy, and chronotherapy can exert therapeutic effects in multiple aspects. And reduce the possibility of recurrence and enhance sleep and emotional regulation functions. Furthermore, through CBT, it can improve the initiative of BD patients to increase physical activity, outside activity, and social activity. This can change from the root of BD patients habits and lifestyles, which can lead them to find the best way to live [8, 29].

5. Conclusion

The circadian rhythm disorders in bipolar disorder are mostly manifested as various sleep disorders, abnormal expression of corresponding genes, and emotional regulation disorders. These three aspects interact with each other in various ways. At present, clinical research mainly focuses on the study of manifestations of sleep disorders and the related research on clock genes. However, neurotransmitters, brain region activities, brain structure changes, and sleep structure determination pose significant challenges due to strict research conditions, so there are relatively few studies on these aspects. In the therapeutic section, although the research on phototherapy has increased in recent years, there are still many aspects that need improvement and additional treatment methods that can be developed. The brain, as an important central nervous tissue of human beings, is expected to see more research focusing on the activities and structures of brain regions in the future. Moreover, it is hoped that more convenient and effective gene therapy methods targeting clock genes can be developed.

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