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The impact of circadian rhythm on bipolar disorder

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Abstract. This review mainly focuses on the role of circadian rhythm in both causation and treatment of bipolar disorder (BD). Circadian rhythm is an essential modulator that makes our body function in tune with the 24-h cycle, controlling the metabolic and endocrine processes. In terms of the causation and the development of BD, disrupted circadian rhythms might play a crucial part. It would be discussed from the dysregulation of neurotransmitters such as dopamine, serotonin, norepinephrine and melatonin, which are modulated by the clock and contribute to BD. The clock genes like Circadian locomotor output cycles kaput (CLOCK), Period (PER), and Cryptochrome will also be discussed, since their expressions operate the clock and their polymorphisms could lead to abnormal circadian rhythm and make people present certain symptoms. Furthermore, it can be inferred that regulating circadian rhythm might be an efficacious treatment for BD, including the administration of lithium and light therapy, both of which target regulating circadian rhythm by modulating the elements of the clock.

Keywords: Circadian rhythm, bipolar disorder, neurotransmitters, clock genes.

1. Introduction

Circadian rhythm is an internal 24-h cycle that controls the metabolism, endocrine system, sleep-wake pattern, etc. It is modulated by both internal oscillator and external cyclic signals. The internal oscillator is made up of 20,000 circadian pacemaker neurons located in the suprachiasmatic nucleus (SCN) of the hypothalamus and is run by multiple transcription/translation feedback loops of clock genes [1]. The environmental signal is caught by one of the retinal neurons called photosensitive retinal ganglion cells (ipRGCs), which contain melanopsin, and transported to the SCN. As a result, the central clock in SCN would modify our internal oscillators according to the outside signals and then synchronize the peripheral circadian clocks, allowing cells in peripheral tissues to follow the same clock.

Bipolar disorder (BD) is characterized by the recurrent state of mania and depression. It is one of the most severe and prevalent mental diseases. Based on relative data, bipolar disorder is ranked at the fourth place of the global burden of mental, neurological and substance-use disorders [2]. Besides, studies suggest that the outcome of BD treatment is not favorable. To be specific, almost 60% of BD patients have difficulties in at least one area of functioning over time, while more than one-half of patients are rehospitalized in the following one or two years [3].

Studies have found that the disruption of circadian rhythm, such as the misalignment of internal oscillator and external signals and the polymorphisms of certain clock elements, might be a fundamental contributor to BD [4]. Therefore, this review summarizes the significance of circadian rhythm in BD from both the causation and development and the treatment aspects. When it comes to the causation and

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development, the review mainly discussed the regulation of certain neurotransmitters like dopamine, serotonin, norepinephrine and melatonin, which are secreted following circadian rhythm, and clock genes like Circadian locomotor output cycles kaput (CLOCK), aryl hydrocarbon receptor nuclear translator like (ARNTL), Period (PER) and Cryptochrome (CRY), whose expression could affect the whole clock. Moreover, it is found that different episodes of BD are characterized by different circadian disturbances. To be specific, patients show longer circadian rhythm during depression, shorter circadian phase in mania, and delayed sleep-wake phase during euthymia [5]. Thus, the review will also analyze the existing treatments of BD from the circadian-regulated perspective, such as lithium administration and light therapy, which aim at different episodes of BD.

Previous studies have already delved into multiple perspectives on the relationship between BD and circadian rhythm. However, there is not a general conclusion to sort out those numerous findings. Therefore, it is hoped that this review could provide convenience for future studies and provide novel ideas for further investigations in the treatments of bipolar disorder.

2. The relationship between circadian disruption and bipolar disorder from the molecular perspective

2.1. Neurotransmitter regulation

Bipolar patients usually show abnormal sleep patterns such as insomnia and sleep phase delay. This kind of circadian disruption is suggested to connect with aberrant neurotransmitter regulation. Dopamine, serotonin, norepinephrine (noradrenaline) and melatonin are the four key neurotransmitters in bipolar disorder. The disturbance of the circadian rhythm might cause their dysregulation, and in turn, the abnormal regulation could further disrupt the circadian rhythm, which might prompt the development of bipolar disorder. Studies have found that depression episode is tied to low levels of norepinephrine, melatonin and dopamine, while mania episode is tied to high levels of norepinephrine, melatonin and dopamine [6]. In addition, low levels of serotonin are found in both states.

2.1.1. Dopamine. Dopamine is one of the most important neurotransmitters in bipolar disorder. According to the animal experiments, increased dopamine1 (D1) receptors in the limbic system were found among sleep-deprived rats. The increased amount of D1 receptors could cause the increased activity of dopamine-stimulated adenylate cyclase [7], which might be a contributor to the bipolar-mania state. Moreover, a significant decrease in relative basal ganglia dopamine2 (D2) receptor occupancy is found after the sleep deprivation of depressed patients, suggesting that sleep deprivation may aggravate depression [8]. As a result, sleep deprivation might cause bipolar disorder by changing the amount of dopamine receptors and therefore modifying the normal regulation.

2.1.2. Serotonin. Serotonin is also a key neurotransmitter. Serotonin secretion follows the circadian rhythm. It reaches the peak during the day, lowering during the night. According to relative research, circadian genes are expressed in serotonergic raphe neurons, and the expression of serotonergic genes also follows the clock. Moreover, key serotonin signaling molecules like the 5-HT reuptake transporter (SERT) and the 5-HT1B, 5-HT7, and 5-HT2C receptors are all expressed in the SCN biological clock nucleus, suggesting that the regulation of serotonin might be mediated by light signals and the regulation of serotonin could also affect circadian rhythm [9]. Therefore, the disturbance of the circadian rhythm could lead to the abnormal secretion of serotonin, and in turn impacts the circadian rhythm, which may further aggravate bipolar disorder.

2.1.3. Norepinephrine. Norepinephrine is in charge of bipolar disorder. Norepinephrine secretion shows an obvious circadian pattern, whose peak is found around noon and remains low during sleep time. The circadian pattern of norepinephrine is often abolished completely during sleep deprivation. Also, the circadian rhythm of norepinephrine secretion is highly exogenous under normal sleep or wake

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conditions [10]. Therefore, circadian disruption could be a leading factor in bipolar disorder, since the level of norepinephrine is contributive to the mania/depression episodes.

2.1.4. Melatonin. Abnormal melatonin regulation could cause circadian disruption, which is exhibited by bipolar patients. Studies have found that bipolar patients usually suffer from sleep abnormalities, among which the most prevailing characteristics involve melatonin, including decreased nocturnal melatonin level, increased light-induced melatonin suppression, delayed dim-light melatonin onset, and abnormal melatonin synthesis [11]. Low levels of melatonin could be caused by mainly two ways.

The exposure to light, especially short-wavelength light, is suggested to suppress the regulation of melatonin. Being exposed to light, including natural light and artificial light, at inappropriate time would cause the disrupted suppression of melatonin synthesis and secretion, which would affect the circadian rhythm. Besides, the level of norepinephrine and serotonin could also influence endogenous melatonin secretion, since norepinephrine participates in the transcription pathway for melatonin biosynthetic enzymes [12], and serotonin N-acetyltransferase decides melatonin synthesis.

2.2. Circadian genes.

Clock genes work together to regulate circadian rhythm. Therefore, the mutation or the epigenetic modification of certain clock genes would cause the disruption of circadian rhythm, leading people to present certain symptoms. Thus, the polymorphisms of clock genes could be an essential cause of bipolar disorder.

2.2.1. CLOCK. Studies have found that the substitution of thymine (T)and cytosine (C) in position 3111 of CLOCK gene, which brings about the presence of two alleles--3111C and 3111T, could affect bipolar disorder. Bipolar-depressed patients who carry 3111C variants were observed to show higher evening activities and phase delays, as well as a higher proportion of insomnia and sleep complaints during their lifetimes [13]. Moreover, C/C homozygotes own a higher recurrence rate of illness episodes, which could be surmised to be attributed to the triggering effect of sleep deprivation [14]. What is worth mentioning is that there is temporarily no insomnia reported among healthy C allele carriers.

2.2.2. ARNTL. According to the investigation, the methylation of the clock gene ARNTL is much higher among BD patients. It might be attributed to its role in regulating neurotransmitter levels via regulating the gene expression of monoamine oxidase A (MAOA). Thus, the epigenetic modification of the clock genes is likely to be a factor of bipolar disorder's causes [15].

2.2.3. PER and CRY. Period genes and Cryptochrome genes also play an indispensable role. The mutation of PER gene is responsible for the altered sleep-wake cycle and advanced sleep phase, while CRY1 and CRY2 are associated with the advance and the delay of sleep phase, respectively [16].

3. The treatment of bipolar disorder by regulating circadian rhythm

3.1. Lithium

Lithium is the most well-known medicine in treating bipolar disorder so far. It mainly focuses on circadian regulation by modifying elements in circadian pathways, among which glycogen synthase kinase-3β(GSK3β) and the neurotransmitters melatonin are primarily targeted.

3.1.1. GSK3β. GSK3β is indicated to be a clock modulator. The administration of lithium is linked to the inhibition of GSK3β. Experiments have shown that the GSK3β-haploinsufficient mice model shows a lengthened circadian locomotor activity compared to the wild-type littermates. Moreover, it is suggested that GSK3 isoforms are connected to the regulation of certain clock genes. For example, it is found responsible for the phosphorylation and stabilization of BMAL1(ARNTL) protein, and also PER2's phosphorylation and the transfer to the nucleus. Therefore, the inhibition of GSK3β may cause

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the phase delay of circadian rhythm. Besides, GSK3β also mediates the phosphorylation and stabilization of REV-ERBα, which can then modulate ARNTL gene expression. As a result, the inhibition of GSK3β would induce a lengthened circadian rhythm[17]. In conclusion, lithium could modulate the circadian clock by inhibiting GSK3β and therefore cause a delayed and lengthened circadian rhythm.

3.1.2. Melatonin. Melatonin is a fundamental hormone that is produced by the pineal gland and is responsible for promoting sleep. Its synthesis depends on serotonin N-acetyltransferase (AANAT) activity. According to the relative studies, chronic lithium treatment contributes to the suppressed amplitude and peak of AANAT diurnal activity cycle, which consequently results in the restricted synthesis of melatonin and induces a delay of acrophase [18]. There are also experiments suggesting that the mean levels of pineal and serum melatonin are lower in the lithium-treated group than in the control group during the dark. The nocturnal peak is lower and has a delay. The duration of the nocturnal peak is also shortened as well [19]. In conclusion, lithium treatment could lead to a reduced level of melatonin and a delayed acrophase, suggesting its prospective function of mediating circadian rhythm.

3.2. Light therapy

Light therapy is a kind of non-pharmacologic treatment that aims to cure neuropsychiatric diseases. It is typically conducted by making patients exposed to bright light using fluorescent light boxes or fluorescent ceiling units.

Our circadian rhythms are the results of the interplay between our endogenous oscillators and the external cyclic signals, which is also referred to as Zeitgeber. We catch the light signals by our eyes. One of our retinal neurons called intrinsically photosensitive retinal ganglion cells (ipRGCs) contain melanopsin, a light-sensitive pigment, therefore are able to receive light signals and transport them to the suprachiasmatic nucleus, where the central clock is. After that, our bodies are able to adapt themselves to the environment and mediate the regulation of different chemicals, including hormones that are responsible for mood. The misalignment of Zeitgeber and endogenous oscillators seems to be a main contributor to the dysregulation of the circadian rhythm, which may therefore lead to the formation of mood disorders.

Therefore, administering light therapy to mood disorder patients might modify their circadian rhythms and is a prospective treatment, which does not have strong side effects and tolerance compared to psychiatric treatment. Research has found that morning or midday bright light can cause a phase advance in circadian rhythms. For bipolar-depressed patients, which is characterized by the delayed circadian rhythm, light treatment in the morning and midday is efficacious in improving euthymia and sleep parameters, including the advanced sleep phase, increased nocturnal melatonin secretion, and reduced insomnia [20].

4. Limitation

So far, the treatment of bipolar disorder still remains several drawbacks. Firstly, the treating methods are limited. Nowadays, the most prevalent treatments are pharmacotherapy and psychosocial treatments. However, the effectiveness of medication is relatively low. Lithium is the first agent to be used in treating BD. Although the lithium response is reckoned across full-spectrum, patients with mixed states of depression and mania only have a 30-40% lithium response rate, while patients with four or more affective episodes show only a 20-30% lithium response rate. Moreover, it also has side effects like excessive thirst, polyuria, tremor, and cognitive impairment [20]. For psychotherapies, the effects could only be seen over a long period, which might be slight. Therefore, it is hoped that new and efficacious treatments could be invented.

5. Conclusion

To sum up, the disruption of circadian rhythm might play an indispensable role in both causation and treatment of bipolar disorder.

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From the molecular perspective, a disrupted circadian rhythm is tied to the dysregulation of neurotransmitters and the polymorphisms of clock genes. Neurotransmitters like dopamine, serotonin, norepinephrine and melatonin are all secreted and regulated following the circadian rhythm and are all responsible for mood regulation, some might even further control the circadian rhythm. Therefore, the disturbance of circadian rhythm would cause the dysregulation of those neurotransmitters, which could lead to bipolar disorder or aggravate it. Besides, the polymorphisms of clock genes are closely tied to BD. For example, the substitution of T and C in position 3111 of CLOCK and the mutation of PER and CRY are linked to BD symptoms. Among BD patients, the methylation level of ARNTL is much higher.

Moreover, by analyzing existing treating methods like lithium and light therapy, it can be concluded that one of their main targets is to regulate circadian rhythm. To be specific, lithium could inhibit GSK3β, lower the peak, and cause a delayed acrophase of melatonin secretion, therefore lengthening and delaying the circadian rhythm. Thus, it is an effective medicine to treat acute mania. Furthermore, light therapy conducted in the morning or the midday is responsible for advancing the circadian rhythm and improving sleep, which helps alleviate the symptoms of bipolar-depression. In conclusion, regulating circadian rhythm is a primary target of existing BD treatment.

It is anticipated that this review could lead to a deeper understanding of BD and provide inspiration for more efficacious BD treating methods.

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