Targeting Circadian Rhythm Genes: A Novel Therapeutic Strategy for Patients with Comorbid Depression, Anxiety, and Sleep Disorder

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Abstract. In contemporary society, the prevalence of mental disorders is on the rise and has gradually become an increasingly prominent public health issue. Among them, depression and anxiety disorders are the most common, and they often coexist with sleep disorders. There is a complex bidirectional correlation between the two. Rhythm genes play a core role in regulating the sleep-wake cycle and disease states. Abnormal expression or polymorphism of some rhythm genes may further participate in the comorbidity mechanism of sleep disorders and mental illnesses by influencing the circadian rhythm, neurotransmitter or hormone secretion. The current intervention methods mainly include psychotherapy, drug therapy, and several rhythm regulation strategies that are still in the exploration stage. It is worth noting that both of the latter two treatment methods may alleviate related clinical symptoms by regulating the expression of rhythm genes. However, existing research still has some limitations, such as a small sample size and an unclear mechanism of action. Therefore, in the future, it is necessary to explore the mechanism of action of rhythm genes more deeply and develop precise intervention strategies to reduce the burden of such diseases on individuals and society.

Keywords: Depression; Anxiety; Sleep Disorder; Rhythm Genes.

1. Introduction

In today's fast-paced society, the problems caused by mental disorders can no longer be ignored. According to the data disclosed in the World Mental Health Report, approximately one eighth of the world's population suffers from mental disorders. Mental disorders include many different types, such as depression, anxiety, etc. According to statistics in 2019, approximately 280 million people suffered from depression, 310 million from anxiety disorders, and some patients also suffered from multiple mental and psychological disorders simultaneously. The incidence rates of different types of mental disorders vary by gender and age. The incidence of depression among women is much higher than that among men of the same age, which may be related to the menstrual cycle of women or the pressure of social responsibility. A research report in the international academic journal The Lancet Psychiatry shows that among people aged 10 to 24, mental and psychological disorders account for at least 45% of the total diseases worldwide. Study pressure, social problems and excessive Internet use are all the main factors that induce psychological unhealthiness among teenagers. Mental and psychological disorders seriously reduce mental well-being. They not only lead to common problems such as loss of interest, social avoidance, and sleep disorders, but also generate desires for self-harm and suicide, thereby causing negative impacts. Moreover, from a social perspective, the loss in productivity and the resulting indirect social expenses will far exceed the medical costs.

Most mental and psychological problems are accompanied by sleep disorders of varying degrees, such as insomnia and fragmented sleep. At the same time, multiple pieces of evidence-based evidence and clinical cases have shown that sleep disorders and mental disorders are mutually causal: on the one hand, poor sleep quality and disrupted sleep time can exacerbate an individual's mental state; On the other hand, mental symptoms can lead to insufficient sleep and interfere with the regulatory process of the circadian rhythm. Night shift work can seriously affect the body's sleep-circadian system, thereby increasing the risk of depression and anxiety. Another study shows that about 8% of people with depression experience a deterioration in their mood in winter, indicating that mental

disorders are closely related to natural factors such as shorter daytime duration and changes in light exposure [1].

Rhythm genes play a crucial role in regulating the biological clock and maintaining the stability of the sleep-wake cycle. Abnormal expressions of genes such as PER, CLOCK, and BMAL1 can all cause disorders in sleep rhythms and further associate them with mental and psychological disorders. Abnormal expression of the PER2 gene may lead to delayed sleep phases, thereby exacerbating the low mood of patients with depression. Mutations in the CLOCK gene may be associated with the occurrence of anxiety disorders to some extent by influencing the circadian rhythm. In the genes encoding the core components of the molecular clock, multiple single nucleotide polymorphisms (SNPS) have been proven to be associated with depression, bipolar disorder and schizophrenia.

Therefore, it is of extremely important practical significance to deeply explore the frequent occurrence of mental illness in today's society and its bidirectional interaction with rhythm genes. This thesis aims to deeply explore the core role of rhythm genes in the association between mental and psychological disorders and sleep disorders. First, elaborate on the core rhythm genes and their molecular regulatory networks; Secondly, analyze the specific manifestations and pathogenic mechanisms of rhythm gene dysregulation in sleep disorders and mental illnesses respectively; The focus is on how rhythm disorders, as a common pathway, mediate the high comorbidity between sleep disorders and mental illnesses (especially depression and bipolar disorder). Finally, the intervention strategies based on rhythm regulation and their clinical transformation prospects are discussed, and the future research directions are prospected.

2. Depression Disorder

2.1. Epidemiological Character

Depression is one of the most common mental disorders, with a lifetime prevalence rate of approximately 16% [2]. The main manifestations are prolonged depression, loss of interest, social difficulties, etc. According to WHO data, it is estimated that about 3.8% of the global population suffers from depression, among which 5% are adults, 5.7% are people over 60 years old, and the rest are teenagers.

Depressive episodes are different from normal mood swings. They occur almost every day and last for at least two weeks. Depending on each individual's situation, it can be classified into mild, moderate and severe levels, and there will be many different symptoms, such as inability to concentrate, changes in appetite, sleep disorders. In severe cases, due to a sense of insufficient self-worth, thoughts of self-harm or suicide may even occur. It can also be classified based on the number of episodes: patients with their first and only episodes are diagnosed with single-episode depressive disorder; those with at least two episodes of depressive disorder are called recurrent depressive disorder; and there is a special type, namely bipolar disorder, which is mainly characterized by alternating episodes of depression and manic symptoms.

2.2. Depression and Rhythm Genes

Sleep is divided into rapid eye movement sleep and non-rapid eye movement sleep. During rapid eye movement sleep, the level of norepinephrine significantly decreases compared to the waking state and the non-rapid eye movement sleep state, reaching a minimum value [3]. Norepinephrine and the process by which the body and mind regulate emotions are both related. Therefore, sleep disorders are one of the most prominent symptoms of patients with depression, with approximately 90% of them experiencing sleep discomfort. Through sleep electroencephalogram research, it was found that the specific manifestations of sleep disorders in patients with depression include difficulty falling asleep, frequent awakenings after falling asleep, and reduced non-rapid eye movement sleep time, etc. Sleep disorders are not only the precursor manifestations of depression but also regarded as one of the symptoms caused by depression. Patients with depression will find that there are abnormal

parameters in multiple stages during sleep, especially during rapid eye movement sleep. These abnormal parameters are even regarded as one of the biomarkers for diagnosing depression [4].

Dysregulation of clock genes is an important factor in the development of sleep disorders and depression. CLOCK genes (such as BMAL1, Clock, etc.) maintain biological rhythms through a complex transcription-translation feedback loop, which involves the transcription of proteins such as PER and CRY and regulates the expression of cyclical genes. If there is a disorder or mutation, it will disrupt the homeostasis, not only leading to internal cyclical variations but also damaging the emotional regulation function; It simultaneously affects the secretion of hormones such as glucocorticoids and serotonin, disrupts emotional homeostasis, and increases the risk of depression [5].In addition, changes in single nucleotide polymorphisms of numerous clock genes are significantly associated with depression, as single nucleotide polymorphisms are involved in the regulation of gene function and expression.

2.3. Intervention

Psychotherapy is the preferred treatment for depression, including talk therapy with professionals or supervised non-professional therapists. Moderate and severe patients will need a combination of psychotherapy and antidepressants, while mild patients only need psychotherapy. However, most antidepressants have significant side effects, and different antidepressants may also cause various sleep disorders, such as nightmares, teeth grinding behavior and RLS. Among them, SSRIs, SNRIs and activated TCA will increase the latency of rapid eye movement sleep and interfere with sleep continuity. And most antidepressants will rebound the duration of rapid eye movement sleep after a few weeks. For instance, nortriptyline can have an inhibitory effect on rapid eye movement sleep, but studies have shown that after withdrawal, the rebound will be higher than before [4].

Melatonin is a physiological hormone that is closely related to rhythm genes, and its secretion and function are regulated by rhythm genes. Exogenous melatonin can improve the sleep latency of primary insomnia. From the perspective of rhythm gene mediation, melatonin and its receptor agonists can affect the sleep cycle by regulating the expression and function of rhythm genes. In clinical practice, there have been studies exploring its application in the intervention of sleep-rhythmic-related depression. For instance, a study that provided therapeutic intervention to over 300 patients with depression accompanied by sleep disorders demonstrated that the melatonin receptor agonist rametinib could improve sleep disorders by regulating the expression of Per1/Per2. Meanwhile, the study also found that the level of 5-HT rose by 22% compared with the baseline, alleviating depressive symptoms and providing effective evidence-based evidence for clinical application [6].

In addition, phototherapy based on circadian rhythm theory also has certain effects on depression. Phototherapy uses light of specific wavelengths to stimulate the retina, thereby influencing the production of 5-HT and hormones in the brain and altering the retinal-vlGN circuit to alleviate depressive symptoms [7]. From a mechanism perspective, phototherapy may reshape the disrupted circadian rhythm by regulating the expression of rhythm genes such as Clock and Bmal1.

Sleep deprivation can also manage depression, that is, not getting any form of sleep for 36 hours, but the effect will disappear when sleep is restored the next day. If sleep deprivation is repeatedly implemented, the effect usually weakens gradually within a few weeks after returning to normal sleep [2]. From the perspective of rhythm genes, sleep deprivation can temporarily interfere with the expression of rhythm genes, such as shifting the peak and trough of the expression of rhythm genes like Rev-erb α, temporarily enhancing the utilization efficiency of 5-HT in the brain, and generating an antidepressant effect. However, this kind of interference is short-term and unstable. As sleep resumes, the expression of rhythm genes will gradually rebound, and the antidepressant effect will fade. Long-term and repeated deprivation leads to a higher recurrence rate due to the disorder of rhythm genes.

3. Anxiety Disorder

3.1. Epidemiological Character

The main characteristics of anxiety disorder are excessive fear and worry about things and the generation of related behavioral disorders. It can be classified into several types, such as generalized anxiety disorder, panic disorder, social anxiety disorder, separation anxiety disorder and other types. Its symptoms usually begin in childhood or adolescence and persist into adulthood. But their performances each have their own characteristics. The most common disorder among teenagers is social anxiety disorder, which can be related to academic pressure, peer relationships or confusion about self-identity. Anxiety disorders among the elderly are very likely to be masked by physical symptoms and thus missed. Generally, women are more prone to anxiety disorders than men. According to data from the WHO, 4% of the global population suffers from anxiety disorders. The physical tension and overactivity of the nervous system caused by anxiety disorders are also known risk factors for diseases such as cardiovascular diseases. In addition, many patients with anxiety disorders are often accompanied by other mental illnesses, such as depression. According to the WHO statistics, approximately 60% of patients with anxiety disorders also suffer from depression, which may even trigger suicidal thoughts and behaviors, which deserve attention.

3.2. Anxiety and Rhythm Genes

Abnormal expression of rhythm genes can induce or aggravate anxiety symptoms by affecting the hypothalamic-pituitary-adrenal axis (HPA axis). If the circadian rhythm is disrupted by inhibiting the expression of BMAL1, it will lead to excessive activation of the HPA axis and an increase in cortisol levels, thereby enhancing the anxiety response. Animal studies have found that knocking out the PER2 gene can reduce the sense of despair and anxiety in mice, cause changes in the neurotransmitter system, and thereby affect the emotion-related behaviors of mice. In addition, the polymorphism of the PER3 gene is significantly associated with susceptibility to generalized anxiety disorder. Individuals carrying specific genotypes are more prone to sleep disorders and anxiety.

The combination of rhythm genes is also a key factor influencing the risk of anxiety disorders. Through machine learning and statistical analysis, it was found that the combination of single nucleotide polymorphisms of core rhythm genes, such as CRY1, CRY2, PER3 and ZBTB20, is significantly associated with the occurrence of anxiety disorders [8]. Taking the rs1123 locus of the CRY1 gene and the variable number tandem repeat (VNTR) polymorphism of the PER3 gene as examples, when the CRY1 mutant is combined with the long repeat sequence of PER3, they will jointly inhibit the expression of the neurotrophic factor BDNF circuit, which is crucial for emotion regulation in the preprecortex-hippocampus of the brain. This leads to excessive activation of the amygdala when facing stress, increasing the risk of anxiety disorders by 2.3 times. At the same time, some studies have shown that the ARNTL2 gene has a potential association with social phobia, but the specific mechanism remains to be further explored [9].

3.3. Intervention

Although there are currently effective methods for treating anxiety disorders in clinical practice, only 27.6% of patients are still willing to receive treatment. Psychological intervention is a fundamental treatment for anxiety disorders. These intervention measures can help people learn new ways of thinking and dealing with or understanding the anxiety. Learning stress management skills, such as relaxation techniques and mindfulness techniques, can help reduce the symptoms of anxiety disorders. Cognitive behavioral therapy (CBT) can help patients adjust their negative perceptions of rhythm disorders, such as correcting the unreasonable belief that "insomnia inevitably leads to increased anxiety." Combining mindfulness meditation can enhance patients' awareness of emotions and reduce physical anxiety symptoms caused by rhythm disorders.

In terms of drug treatment, antidepressants such as selective serotonin reuptake inhibitors (SSRI) can be used to treat anxiety disorders in adults. Although benzodiazepines are commonly used drugs,

they are prone to cause dependence and cannot be used for long-term treatment. Generally, they are not recommended as a routine regimen.

In terms of rhythm regulation, phototherapy can not only alleviate depressive symptoms but also improve anxiety. By simulating the light cycle of natural light, the expression rhythm of rhythm genes can be altered, which is particularly suitable for anxiety patients accompanied by seasonal mood fluctuations. There are also some targeted treatment directions that have shown anti-anxiety effects in animal experiments. For instance, antagonists targeting overexpression of the CLOCK gene can reduce cortisol levels by inhibiting the overactivation signal of the HPA axis [10]. In addition to phototherapy, social rhythm therapy has also attracted much attention: this therapy helps patients establish regular social activities and synchronously regulate the expression of rhythm genes to reshape disordered circadian rhythms.

4. Conclusion

Mental and psychological disorders are prominent public health issues in today's society. Among them, depression and anxiety disorders are common and have a high comorbidity rate, and there are obvious differences in the incidence among different populations. Such diseases are highly harmful, causing emotional, physical problems and even suicide risks to individuals, while also imposing a burden on society that far exceeds medical costs.

The core of the high comorbidity rate between sleep disorders and mental illnesses lies in the mediating role of rhythm disorders. Research has confirmed that sleep disorders and mental and psychological diseases have a two-way influence: poor or disordered sleep quality can aggravate disease symptoms, while mental disorders can disrupt the sleep cycle, forming a vicious cycle and serving as the pathological basis for comorbidities. The core mechanism behind this is closely related to rhythm genes. Abnormal expression of core genes such as PER, CLOCK, and BMAL1 can participate in the disease process by altering sleep structure. For instance, abnormalities in the PER2 gene may lead to delayed sleep phases and exacerbate depression. Mutations in the CLOCK gene are associated with anxiety disorders.

For these mechanisms, the existing treatment methods are highly diversified. In the treatment of depression, melatonin receptor agonists alleviate depression accompanied by sleep disorders by regulating Per1/Per2. Intervention targeting rhythm genes in anxiety disorders is gradually becoming known to patients. Emerging data also enhances the effectiveness of rhythm regulation strategies. For instance, phototherapy can up-regulate the expression of Clock and Bmal1 by stimulating the retina with light of specific wavelengths, thereby simultaneously improving sleep and mood. Its efficacy in treating seasonal depression has been verified in numerous trials.

However, current research still has many limitations. If the clinical sample size is small, there is insufficient evidence-based evidence, and the mechanism of action of some genes such as ARNTL2 remains unclear. Meanwhile, in clinical research, there is a lack of basis for personalized intervention, and data on long-term efficacy is scarce. In the future, the sample size should be expanded, focusing on analyzing the mechanism of action of rhythm genes in specific brain regions, and further developing targeted drugs.

In conclusion, in-depth exploration of the connection between mental and psychological disorders and rhythm genes can provide new directions for clinical treatment and is of great significance for alleviating personal suffering and reducing the burden on society. In the future, it is necessary to further clarify the gene regulatory mechanism, develop personalized rhythm regulation plans, and enhance the intervention effect.

References

[1] Meyer, N., Lok, R., Schmidt, C., Kyle, S. D., McClung, C. A., Cajochen, C., Scheer, F. A. J. L., Jones, M. W., & Chellappa, S. L. (n.d.). The sleep–circadian interface: A window into mental disorders.

Proceedings of the National Academy of Sciences of the United States of America, 121(9), e2214756121. https://doi.org/10.1073/pnas.2214756121

[2] Fang, H., Tu, S., Sheng, J., & Shao, A. (2019). Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment. Journal of Cellular and Molecular Medicine, 23(4), 2324–2332. https://doi.org/10.1111/jcmm.14170

[3] Goldstein, A. N., & Walker, M. P. (2014). The Role of Sleep in Emotional Brain Function. Annual Review of Clinical Psychology, 10, 679–708. https://doi.org/10.1146/annurev-clinpsy-032813-153716

[4] Wang, Y.-Q., Li, R., Zhang, M.-Q., Zhang, Z., Qu, W.-M., & Huang, Z.-L. (2015). The Neurobiological Mechanisms and Treatments of REM Sleep Disturbances in Depression. Current Neuropharmacology, 13(4), 543–553. https://doi.org/10.2174/1570159X13666150310002540

[5] Zou, H., Zhou, H., Yan, R., Yao, Z., & Lu, Q. (2022). Chronotype, circadian rhythm, and psychiatric disorders: Recent evidence and potential mechanisms. Frontiers in Neuroscience, 16, 811771. https://doi.org/10.3389/fnins.2022.811771

[6] De Berardis, D., Marini, S., Fornaro, M., Srinivasan, V., Iasevoli, F., Tomasetti, C., Valchera, A., Perna, G., Quera-Salva, M.-A., Martinotti, G., & di Giannantonio, M. (2013). The Melatonergic System in Mood and Anxiety Disorders and the Role of Agomelatine: Implications for Clinical Practice. International Journal of Molecular Sciences, 14(6), 12458–12483. https://doi.org/10.3390/ijms140612458

[7] Cui, L., Li, S., Wang, S., Wu, X., Liu, Y., Yu, W., Wang, Y., Tang, Y., Xia, M., & Li, B. (2024). Major depressive disorder: hypothesis, mechanism, prevention and treatment. Signal Transduction and Targeted Therapy, 9, 30. https://doi.org/10.1038/s41392-024-01738-y

[8] Ventresca, C., Mohamed, W., Russel, W. A., Ay, A., & Ingram, K. K. (2023). Machine learning analyses reveal circadian clock features predictive of anxiety among UK biobank participants. Scientific reports, 13(1), 22304. https://doi.org/10.1038/s41598-023-49644-7

[9] Partonen T. (2012). Clock gene variants in mood and anxiety disorders. Journal of neural transmission (Vienna, Austria : 1996), 119(10), 1133–1145. https://doi.org/10.1007/s00702-012-0810-2

[10] Nader, N., Chrousos, G. P., & Kino, T. (2010). Interactions of the circadian CLOCK system and the HPA axis. Trends in endocrinology and metabolism: TEM, 21(5), 277–286. https://doi.org/10.1016/j.tem.2009.12.011