GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

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Circadian cycle genes and their association with depression

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GSC Biological and Pharmaceutical Sciences, 2024, 29(03), 017–021

Publication history: Received on 26 October 2024; revised on 02 December 2024; accepted on 04 December 2024

Article DOI: https://doi.org/10.30574/gscbps.2024.29.3.0454

Abstract

This work delves into the complex role of circadian-regulating genes and their relationship with depression, emphasizing key genes such as CLOCK, BMAL1, PER, and CRY that control biological rhythms. Genetic variations in these genes can lead to circadian disruptions, manifesting as insomnia, hormonal imbalances, and depression. This study highlights the critical role of melatonin, regulated by light exposure, in circadian alignment. Dysfunctional circadian regulation affects neurotransmitter secretion, particularly serotonin and dopamine, thereby impacting mood. This paper also discusses the influence of norepinephrine, GABA, glutamate, and genetic variants in serotonin pathways on mood disorders and their potential for targeted therapeutic interventions.

Keywords: CLOCK; Circadian cycle; Melatonin; Depression; Cortisol; Serotonin; Neurotransmitters; Genetic variants**.**

1. Introduction

The circadian cycle plays a pivotal role in regulating an individual's well-being through intricate interactions between environmental cues (light/dark cycles) and genetic mechanisms. The hypothalamus, specifically the suprachiasmatic nucleus (SCN), functions as the primary regulator of circadian rhythms by receiving light signals via the optic chiasm and modulating melatonin secretion from the pineal gland. This cycle synchronizes sleep-wake patterns and governs key physiological processes. Disruptions in circadian genes, such as CLOCK, BMAL1, PER, and CRY, can lead to sleep disturbances, hormonal imbalances, and mood disorders, including depression. Genetic variants may impair the release of critical neurotransmitters, resulting in heightened cortisol levels and a predisposition to stress and mood instability [1,2].

2. Expanded Physiology of the Circadian Cycle

The circadian rhythm operates on a roughly 24-hour cycle, influencing metabolism, hormone release, mood regulation, and cellular function [3]. The central nervous system (CNS) connects with the retina via the retinohypothalamic tract (RHT), conveying light-dependent signals to the SCN. This process regulates melatonin secretion, which decreases during daylight to promote wakefulness and increases at night to induce sleepiness (Figure 1). Melatonin is not merely a sleep-inducing hormone; its levels are inversely related to depressive symptoms [4,5].

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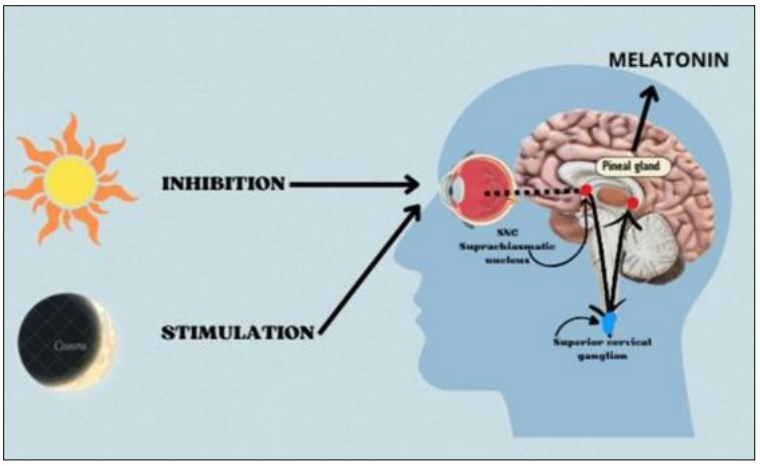

Figure 1 Circadian rhythm and sleep (modified from [15])

3. Molecular interactions in the circadian clock

The circadian gene network in **mammals** is regulated through multiple layers of genome-wide mechanisms. At its core, the transcription factors CLOCK and BMAL1 activate the **Per1, Per2, Cry1, and Cry2** genes (illustrated Figure 2) [3]. The protein products of these genes (PER and CRY) inhibit their own transcription. PER and CRY proteins are further regulated posttranslationally by distinct E3 ubiquitin ligase pathways, including FBXL3 and FBXL21 for CRY, and β-TrCP for PER. Additionally, PER levels are modulated by CK1 [3]. CLOCK and BMAL1 also control the expression of *Nr1d1* and *Nr1d2*, encoding the nuclear receptors REV-ERBα and REV-ERBβ, respectively. These nuclear receptors rhythmically suppress the transcription of *Bmal1* and *Nfil3*, two genes activated by retinoic acid-related orphan receptors

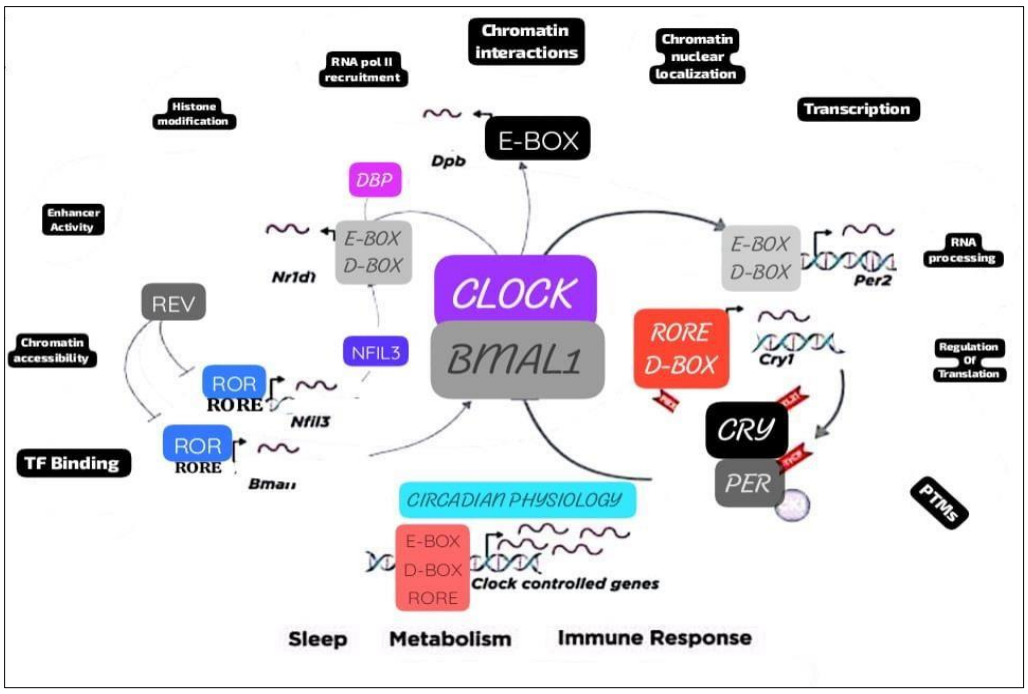

Figure 2 Molecular interactions in the circadian clock (modified from [18]).

(RORα/β). Furthermore, NFIL3, in coordination with D-box binding protein (DBP) and CLOCK/BMAL1, helps establish rhythmic expression patterns in REV-ERBα/β receptors [3, 18].These three interconnected transcriptional feedback loops collectively regulate most cycling genes, influencing rhythmic processes across various physiological systems, such as sleep, metabolism, and aging. For simplicity, regulatory elements like E-boxes, D-boxes, and RORE-binding regions, typically located upstream in gene promoters, are visually summarized as stacked boxes (Figure 2) [18].

Recent research has uncovered additional regulatory layers of circadian gene expression, including rhythmic histone modifications, recruitment of RNA polymerase II (Pol II), circadian chromosomal interactions, and post-translational modifications (PTMs). For a detailed summary of the studies contributing to this expanded understanding of the clock[18].The CLOCK and BMAL1 genes function as primary transcriptional activators, driving circadian rhythms by binding to E-box elements in circadian gene promoters. Their interaction with PER and CRY genes forms feedback loops that tightly regulate the cycle. Genetic variants can alter circadian timing and lead to desynchronization of hormonal and metabolic processes (Figure 2) [6,3].

4. Genetic Disruptions and Malfunctions in the Circadian Cycle

Genetic variant affecting circadian genes contribute to a wide spectrum of physiological and psychological disorders. For instance, mutations in CLOCK and PER genes have been implicated in major depressive disorder (MDD) and seasonal affective disorder (SAD). The CRY1 gene has been linked to delayed sleep phase syndrome, causing prolonged nocturnal activity and difficulty awakening at typical hours [7,8].

The hypothalamic-pituitary-adrenal (HPA) axis, crucial for stress response, exhibits disrupted cortisol rhythms in patients with circadian misalignments, exacerbating depressive symptoms.

Altered melatonin secretion patterns, common among patients with mood disorders, reinforce the connection between circadian dysfunction and psychiatric illnesses [9].

5. Genes of the Circadian Cycle and Mechanistic Insights

The CLOCK and BMAL1 proteins form complexes that initiate circadian gene transcription, regulating downstream genes through intricate feedback mechanisms [10]. The PER and CRY proteins, interacting with casein kinase 1 (CK1), modulate their stability, nuclear translocation, and degradation. This ensures circadian rhythms remain aligned with environmental changes. Additional regulatory elements, such as Rev-Erb, fine-tune circadian cycles through the modulation of BMAL1 expression [11,12]. Research using model organisms, including

Drosophila, has highlighted the evolutionary conservation of circadian regulatory mechanisms. These findings underscore the critical role of circadian genes across species and their impact on physiological processes, such as sleep, metabolism, and emotional regulation [13].

6. Influence of Circadian Genes on Depression and Mood Disorders

Disruption of circadian rhythms affects mood regulation through altered neurotransmitter synthesis and secretion. Genetic variants in CLOCK, BMAL1, PER, and CRY genes are strongly linked to depression, anxiety, and other mood disorders. Dysregulation of serotonin and dopamine, neurotransmitters critical for emotional balance, often accompanies circadian disturbances [14,15]. Elevated cortisol levels, a hallmark of chronic stress, further compound depressive symptoms. Notably, melatonin supplementation may improve sleep but has limited efficacy in alleviating mood disorders, emphasizing the complex nature of circadian regulation on mental health [16,17].

7. Feedback loop in the molecular clock.

This feedback mechanism is initiated trough the interplay of the CLOCK/BMAL1 transcriptional activator complex with its inhibitors (PER/CRY, REV-ERBα) or enhancers (RORα/β), establishing the molecular clock oscillator that regulates the expression of numerous clock-controlled genes (CCGs), including those involved in metabolism, signaling, and epigenetic regulation (Figure 3)[17].

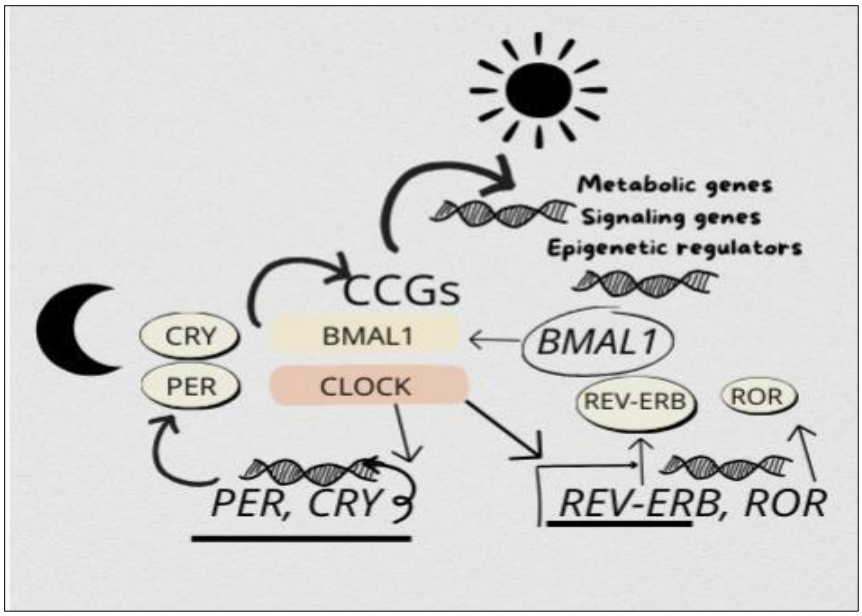

Figure 3 Circadian molecular clock mechanism (modified from [17])

8. Clinical Implications and Therapeutic Approaches

The study of circadian genes provides us with valuable information about therapeutic interventions for mood disorders. Chronotherapy, which aims to realign circadian rhythms through exposure to natural light and melatonin, has been shown to mitigate depression and improve mood [18]. Genetic testing to identify variants in circadian genes may pave the way for personalized pharmaceutical medicine, optimizing new treatment strategies based on individual genetic profiles [19]. Pharmacogenetics approaches targeting circadian regulators hold potential for future therapies. Modulating the activity of CLOCK and BMAL1, for example, may in the future promote a significant change to alleviate circadian rhythm-related mood disturbances. Similarly, lifestyle interventions, such as controlled exposure to natural light, minimization of blue light at night, and sleep schedules, can influence better circadian alignment and reduce depressive symptoms [20,21].

9. Perspectives on Epigenetics and Environmental Influences

Epigenetic modifications also play a critical role in circadian regulation. Environmental factors, including exposure to artificial light and stress, can influence gene expression through methylation and histone modification mechanisms. Understanding how these modifications interact with genetic predispositions offers further insights into the complex relationship between circadian rhythms and depression [21]

10. Conclusion

The circadian cycle is a fundamental regulatory system that governs a wide array of physiological and behavioral processes, significantly influencing human health. Its intricate interactions between core circadian genes, environmental cues such as light exposure, and neurotransmitter pathways underscore its complexity and importance. Genetic variations or polymorphisms in key genes like CLOCK, BMAL1, PER, and CRY have been shown to disrupt the natural rhythms of the cycle, potentially contributing to the development of mood disorders, including depression. These disruptions may alter sleep-wake patterns, hormonal regulation, and emotional stability, highlighting the critical role of genetic and environmental synchronization in maintaining mental well-being.

Emerging research into these genetic mechanisms opens new avenues for understanding the etiology of mood disorders, particularly their connection to circadian misalignment. This knowledge underscores the importance of comprehensive, interdisciplinary approaches to mental health care. Personalized therapeutic strategies, incorporating genetic insights and lifestyle modifications such as optimized sleep hygiene, light therapy, and chronotherapeutic interventions, are essential for addressing circadian-related disorders. By bridging the gap between genetic research and clinical application, we can develop more effective treatments that not only target symptoms but also address the underlying disruptions in circadian regulation, ultimately improving mental health outcomes on a broader scale.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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