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The Influence of Circadian Rhythm on Depression

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Abstract: Depression is a common mental disorder with key symptoms such as low mood, anhedonia, cognitive impairment, and sleep disturbances. The rising prevalence of depression underscores the need to investigate its relationship with circadian rhythm, which could enhance current treatment approaches, such as light therapy and melatonin supplementation. Many individuals with depression experience insomnia, delayed sleep phase, and fragmented sleep, which is related to circadian dysfunction. Circadian rhythm is typically controlled by the suprachiasmatic nucleus and other external clues, such as light or meal timing. An impact on genetic bases or external factors could disrupt circadian rhythm. Epidemiological, clinical, and animal studies have revealed the bidirectional relationship between circadian disruption and depression with supporting evidence. This essay focuses on the bidirectional relationship between depression and circadian rhythm. Furthermore, this essay will discuss how clock genes, neurotransmitters, the HPA axis, oxidative stress, and mitochondrial dysfunction induce depression and circadian disruption.

Keywords: Circadian rhythm, Depression, Insomnia, Oxidative Stress

1. Introduction

Depression is a mental disorder that disturbs people's emotions, cognition, and behavior, generally characterized by both psychological, social, and physical symptoms, such as no motivation, anhedonia, cognitive impairment, and reduced social interactions [1]. Globally, depression is becoming more prevalent, leading to a gradual increase in the number of people receiving treatment for it. For instance, in the United States, the percentage of Americans treated for lifetime depression has increased 9.4% from 2015 to 2023 [2]. Depression severely impacts quality of life and public health by increasing people's tendency to commit suicide and exist with comorbidities, such as cardiovascular disease, respiratory diseases, and arrhythmic circadian rhythm [3].

Circadian rhythm is a biological clock in the human body, which regulates numerous physiological and behavioral processes, including hormone release, internal body temperature regulation, appetite, digestion, and sleep pattern cycles. Acting as a central pacemaker, it synchronizes the peripheral clocks across the cardiovascular, endocrine, and immune systems. Both external factors and biological mechanisms can regulate circadian rhythm. For external factors, light exposure plays a crucial role in circadian rhythm. Morning light advances the clock, while evening light delays the clock because light activates photoreceptive ganglion cells in the inner retina, which transmit signals to the suprachiasmatic nucleus (SCN) in the hypothalamus [4]. Meal timing can also affect the clock. Late meal timing disrupts the alignment between the central clock and peripheral clocks in the liver and pancreas. Specifically, food intake can increase the level of glucose in blood, then trigger the

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insulin release, thereby altering metabolism in liver and pancreas organelles that delay the peripheral clock. Moreover, late-night exercise delays the clock by postponing the post-exercise cooling phase (sweating), which in turn disrupts sleep onset. At the molecular level, various clock genes are involved in regulating circadian rhythms, such as BMAL1, CLOCK, PER, and CRY. In the morning, two transcription factors, CLOCK and BMAL1, form a transcriptional complex that binds to enhancer boxes, which promotes the transcription of downstream genes, CRY and PER. As the day progresses, PER and CRY proteins are accumulating in the cytoplasm. By evening, CRY and PER proteins enter the nucleus and inhibit their own transcription by binding to the CLOCK-BMAL1 complex. During the night, PER and CRY proteins will gradually degrade, which contributes to the reactivation of the CLOCK and BMAL1 complex, forming a negative feedback loop that follows a 24-hour cycle [5].

As circadian rhythm follows a 24-hour cycle, mood disorders, including depression, also exhibit fluctuations within this timeframe. Evidence from multiple realms tries to explain the complex correlational relationship between circadian rhythm and depression. Various evidence from epidemiological, pharmacological, and animal studies shows the bidirectional and correlational relationship between circadian rhythm and depression. Epidemiological evidence highlights insomnia as a core symptom of depression, with most depressed patients experiencing circadian disturbances [6]. The coexistence of depression and circadian rhythm disruption demonstrates the correlation between circadian rhythm and depression. Additionally, pharmacological studies indicate that inadequate sleep is associated with treatment outcomes for depression. In a study of 553 adolescents diagnosed with major depressive disorder (MDD), 73% of them exhibited sleep disturbance, and others had either insomnia or hypersomnia. Those experiencing both conditions are showing more severe depressive symptoms [7]. Furthermore, sleep is also associated with emotional processing and mental health. Animal model studies indicate that sleep-deprived individuals at an early age contribute to unhealthy emotional development, which reduces their emotional instability and makes them more prone to depression [8]. Since circadian disruption is a key symptom in depression, understanding circadian involvement in individuals with depression could possibly alleviate their symptoms and provide a more rounded treatment targeting their major symptoms. This is achieved revealing the bidirectional relationship between circadian rhythm and depression. This review aims to identify the elements that facilitate the coexistence of circadian rhythm and depression while also highlighting the significance of addressing circadian rhythm in individuals with depression.

2. Neurobiological basis of circadian rhythm dysfunction in depression

2.1. Clock gene disruptions in depression

Although there is no conclusive evidence proving a causational relationship between circadian disruption and depression, scientists have identified the genetic pathway that links clock gene disruption to depression. Recent studies have found that antidepressants and electroconvulsive therapy for MDD modulate the phosphorylation of the GSK3 enzyme, which is crucial for various cellular functions, including regulation of circadian rhythm [9]. This may discover a shared genetic pathway that regulates both circadian rhythm and severity of depression. Moreover, nearly 90% of depressed patients share irregular sleep patterns, such as shorter time lag between the phase of rapid eye movement and sleep onset, increased duration of rapid eye movement sleep, and decreased slow-wave sleep [10]. Furthermore, circadian disruption increases the severity of depressed individuals by expressing positive symptoms, such as alertness and over-enthusiasm, and negative symptoms, such as guilt and disgust [10]. Additionally, epigenetic alterations driven by both mental health and lifestyle factors, such as circadian disruption, are frequently observed in depressed people. Epigenetic changes, such as histone modification and DNA methylation, are adaptive according to the environment. Anxiety sensitivity, particularly “Anxiety-sensitivity-Mental Incapacitation Concerns,”

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is strongly linked to mood disorders and depressive symptoms, as demonstrated in the G1219 twin study involving over 2,000 participants [11]. Furthermore, mental stress from depressed patients increases cortisol levels in humans. In an experimental study, mice with increased stress levels had lower DNA methylation of the FK506 binding protein 5 that regulates glucocorticoids and could thus potentially disrupt the circadian rhythm [12].

2.2. Hypothalamic-pituitary-adrenal (HPA) axis and cortisol rhythms

The hypothalamic-pituitary-adrenal axis (HPA) connects three organs—hypothalamus, pituitary gland, and adrenal glands—to regulate stress levels. Adrenal glands release cortisol that binds to either mineralocorticoid receptors (MRs) in the hippocampus or glucocorticoid receptors (GRs) in the brain. As cortisol has a higher affinity for MR than GR, it spreads influences mostly through the MRs in the hippocampus. Depression reflects an irregular or dysfunctional MR and GR within HPA. Specifically, 40-60% of depressed patients have disturbances in their HPA system, such as irregular circadian rhythm [13].

2.3. Neurotransmitter imbalances and circadian control

Depression and circadian rhythm have a reciprocal relationship with serotonin. The serotonergic system consists of neurons that control the release of serotonin or 5-hydroxytryptamine (5-HT). Serotonin is a neurotransmitter that regulates circadian rhythm, body temperature, appetite, and emotional processing, which has a precursor form as the amino acid tryptophan. Once tryptophan is ingested from the diet, it is converted to serotonin via reactions [14, 15]. When a threshold is reached, serotonin is released into the synaptic cleft and then bound to different subtypes of serotonin receptors on target neurons. One subtype of serotonin receptor is 5-HT_1A receptors that are found in the hippocampus, prefrontal cortex, and amygdala, which can reduce anxiety and depression. Its dysregulation contributes to the development of depressive symptoms [15]. Inadequate serotonin levels due to nutritional deficiencies or stress contribute to depression and disrupted circadian rhythms. An increase in serotonin neurotransmission results in a more positive recognition of emotional material and improved attention. By enhancing serotonin levels, the severity of depression symptoms and circadian disruptions is likely to be reduced. However, due to the complexity of the serotonergic system, with over hundreds of neurons and over 14 serotonin receptors, scientists are confounded by the behavior of serotonin in different receptors and face difficulties in advancing psychiatric drugs that regulate the serotonergic system [15, 16].

The dopaminergic system regulates the release of dopamine through four different dopaminergic pathways; each pathway regulates a specific area of the brain with distinct functions. The tuberoinfundibular pathway transmits dopamine from the hypothalamus to the pituitary gland and inhibits prolactin release; the mesolimbic pathway releases dopamine from the Ventral tegmental area (VTA) to amygdala and reinforces rewards; the mesocortical pathway releases dopamine from the VTA to the prefrontal cortex and regulates cognition and emotion; and lastly, the nigrostriatal pathway carries dopamine from the substantia nigra to the striatum by controlling voluntary movement [17]. As the “reward center” in the brain, dopamine is a neurotransmitter that controls motivational arousal, mood, and attention. It is synthesized from the amino acid tyrosine via tyrosine hydroxylase and DOPA decarboxylase. When an action potential is triggered by a threshold, a neuron releases chemical signals that release dopamine into the synapse to bind with postsynaptic dopamine receptors (D1-D5). The symptoms of lack of motivation and anhedonia in depression are often associated with reduced dopamine signaling. Depression is also associated with reductions of gamma-aminobutyric acid (GABA) and glutamate levels. GABA is a neurotransmitter that reduces neuronal excitability and inhibits nerve transmission, which produces a calming effect. Glutamate regulates

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relaxation, anxiety, and sleep. It is important for excitatory transmission to balance with inhibitory neurotransmission. With disrupted GABA and glutamate as proper inhibitory neurotransmitters, it induces symptoms of depression, such as depressed or manic mood states. Studies often show that depressed patients have lower levels of GABA due to their deficits in GABA receptors and GABA synthetic enzyme GAD67 [18].

2.4. Sleep-wake cycle and depression

Disrupted circadian rhythm, such as insomnia/hypersomnia and delayed sleep phase, can co-occur with MDD. Insomnia refers to the condition where patients have difficulty falling asleep. Hypersomnia is the condition of feeling excessive sleepiness due to inadequate sleep. Over 50% of MDD patients exhibit insomnia symptoms, which may be influenced by psychosocial factors such as lack of social support and severe depressive symptoms. There is sufficient evidence showing that CBT targets depression symptoms and insomnia severity even better than medication [19]. Rapid eye movement (REM) sleep disorder is a sleep disorder that includes unpleasant dreams and violent muscle movements during REM sleep. The latency of REM sleep lies between sleep onset and the first occurrence of REM sleep. Despite there being no sufficient explanation of sleep abnormality's role in depression, a shortened REM latency is found to be associated with depression, exacerbating main symptoms like depressed mood and cognitive dysfunctions [20]. Patients with major depressive disorders are associated with sleep abnormalities, such as fragmented deep sleep and decreased slow-wave sleep. Fragmented deep sleep refers to the short duration of deep sleep, preventing restorative and functional deep sleep that restores mental health and enhances immunity. Slow-wave sleep refers to the period when the body transforms into a more restorative rest, which typically lasts from 20 to 40 minutes. Fragmented and decreased deep sleep weakens patients' emotional resilience and thus induces the risk of depression [21].

3. Molecular and cellular mechanisms linking circadian rhythm and depression

Neuroinflammation refers to the uncontrollable chronic activation of the brain's immune cells, which leads to the release of pro-inflammatory cytokines and thus causes cell death and neurodegenerative disorders. Cytokines are small proteins produced in response to pathogens, and they recruit immune cells to aid the body's inflammatory response. Higher cytokine levels are shown to correlate with depressive symptoms' severity, such as fatigue and sleep disturbance. Studies have also shown that failure in SSRI treatment increases the baseline of tumor necrosis factor α (TNF- α) and interleukin 6 (lL-6) [22]. Free radicals regulate the immune system and control blood flow. But an excessive amount of radicals may target macromolecules and thus cause cell damage, which are normally killed by antioxidants to protect the cell from diseases and apoptosis. However, oxidative stress happens when the numbers of free radicals and antioxidants are imbalanced, which adversely affects people's health. Oxidative stress is known to play a role in depressed patients as it causes apoptosis, inflammation, and neurodegeneration [23]. Fewer dopaminergic neurons are associated with depression, which also contributes to alleviating oxidative stress' levels.

Disrupted Circadian control can impair immune response and brain function. Immune cells, including neutrophils, macrophages, and T cells, follow circadian rhythms, reaching peak production during the daytime in humans. However, circadian misalignment disrupts immune cell recruitment to weaken the defense against pathogens. Additionally, pro-inflammatory cytokines and anti-inflammatory signals regulate the balance of circadian rhythm. A disrupted rhythm hinders the capacity of the immune response and increases baseline inflammation. Moreover, misaligned circadian rhythms impact clock genes, which affect lipid metabolism and mitochondrial functions.

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As mitochondrial activity normally peaks during the daytime, aligning to the clock, a disrupted rhythm will impair its activity, which is involved in lipid metabolism, oxidation of pyruvate, and energy metabolism. Patients with MDD experience disrupted glucose metabolism, which is caused by oxidative stress, disrupted mitochondrial function, and insulin resistance [24]. Bidirectional relationships existed between metabolic disorders, such as obesity and diabetes, and circadian-linked depression. Depressive symptoms lessen physical activity and contribute to unhealthy eating. Antidepressants, such as SSRIs, a treatment for depression, have side effects, such as inducing weight gain, increasing triglyceride levels, and increasing the risk for diabetes. [25]. Obesity and diabetes also contribute to oxidative stress and insulin resistance, which adversely affect mitochondrial functions and the immune system and eventually contribute to depressive symptoms.

The gut-brain axis refers to the bidirectional pathway that connects the central nervous system (CNS) and the gut through endocrine and neural pathways. The gut contains 95% of the serotonin in our body and synthesizes GABA, both of which regulate mood through neurotransmitter signals. Gut microbiota function is closely linked to circadian rhythms, as microbial activity in intestinal epithelial and immune cells follows clock gene regulation and meal timing. Disruptions in circadian rhythm can impair gut microbiota function and balance, lead to reduced serotonin production and increased pro-inflammatory microbes, and heighten permeability to bacterial endotoxins. These disruptions may activate the hypothalamic-pituitary-adrenal axis (HPA), elevating cortisol levels and contributing to anxiety-related symptoms such as low mood, hypervigilance, and sleep disturbance.

4. Conclusion

Circadian rhythm and depression share a bidirectional relationship. Circadian rhythm disruption enhances reactive oxygen species, leading to neuron damage and exacerbating depressive symptoms. Additionally, it increases pro-inflammatory cytokine levels in the blood, which contributes to neuroinflammation and reduces neuronal resilience. Impaired circadian clocks also disrupt mitochondrial function by reducing ATP synthesis, which affects cellular energy metabolism. Since the central clock synchronizes peripheral clocks across organ systems, circadian disruption extends to gut microbiota, diminishing serotonin production and dysregulating the hypothalamic-pituitary-adrenal (HPA) axis. Moreover, misalignment decreases the availability of serotonin, dopamine, and norepinephrine synthesis that normally follows circadian patterns, which induces anhedonia and depressed mood. Despite the neurological imbalance associated with depression, circadian misalignment appears to be a fundamental underlying factor. Future research is needed to build the bridge between biology, neuroscience, immunology, and chronobiology to reveal more mechanisms to target depression by stabilizing circadian rhythm.

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