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Circadian Clock Gene Dysregulation in Alzheimer's Disease: Insights and Implications

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Abstract:

Alzheimer's disease (AD), a progressive neurodegenerative disorder, is increasingly understood to involve not just traditional neuropathological hallmarks but also disruptions in systemic physiological processes, notably the circadian rhythms. The intersection of circadian clock gene dysregulation and the pathogenesis of AD, emphasizing both the insights gained and the potential therapeutic implications. Circadian rhythms, which govern daily physiological and metabolic processes, are regulated by core clock genes such as BMAL1, PER, CRY, and others. In AD, multiple studies have observed altered expression and function of these genes, which may contribute to the characteristic symptoms of the disease, including disrupted sleep patterns, changes in daily activity levels, and mood fluctuations. circadian dysfunction might exacerbate AD pathology through mechanisms such as increased amyloid-beta production, impaired clearance, and neuroinflammation. Furthermore, targeting circadian clock genes and their regulatory pathways might offer novel strategies for AD management, such as the timing of drug administration to coincide with optimal circadian phases, or the use of chronotherapeutics. Finally, identifing gaps in current knowledge and suggests directions for future research to better understand the role of circadian biology in AD and to harness this information for therapeutic benefit. This review not only underscores the importance of circadian rhythms in AD but also highlights the potential for circadian-based interventions to mitigate disease progression and improve quality of life for affected individuals.

Keywords: Circadian rhythms; clock gene; alzheimer's disease

1. Introduction

The internal clock has a crucial effect on the functioning of the human body, for example, changing the timing of sleep and wake, regulating body temperature, and controlling hormone production. It is named circadian rhythm [1]. The working principle of this internal clock is to maintain the same frequency as the external environment by being exposed to light and darkness. The circadian rhythm is related to the interrelated transcriptional translation feedback loop network, which is also one of the reasons for the complex molecular mechanisms of circadian rhythm, and a group of genes that exhibit daily fluctuations in expression levels are also an important part of circadian rhythm.. These genes encode for proteins that play critical roles in the regulation of circadian rhythms. For example, the CLOCK gene is a master regulator of the circadian system, and its mutations have been linked to various sleep disorders [2]. Other important genes include BMAL1, CRY1, and PER2, which form a heterodimer complex that activates the transcription of target genes [1]. The expression of these circadian genes is regulated by a variety of factors, including transcription factors, post-translational modifications, and epigenetic modifications [2]. For instance, the phosphorylation state of PER2 protein determines its stability and activity, thereby affecting the timing of the circadian cycle [1]. Epigenetic modifications, such as DNA methylation and histone modification, also play a role in the regulation of circadian gene expression [2].

The official explanation for Alzheimer's disease(AD) is the degeneration of the central nervous system, which is mainly manifested by memory impairment, loss of language ability, loss of cognition, and behavioral changes as people grow older. The exact mechanisms underlying AD are not fully understood, but research has identified several key processes that contribute to the development and progression of the disease. One of the primary mechanisms in AD is the accumulation of amyloid-beta plaques and neurofibrillary tangles in the brain. Amyloid-beta plaques are composed of aggregated amyloid-beta peptides, which are produced by the cleavage of amyloid-beta

precursor protein (APP). These plaques disrupt synaptic function and lead to neuronal death [3]. Neurofibrillary tangles, on the other hand, are formed by the hyperphosphorylation of tau protein, another component of APP. Tau tangles cause neurons to become dysfunctional and eventually die [4]. In addition to amyloid-beta plaques and neurofibrillary tangles, inflammation also plays a role in AD pathology. Microglia, the immune cells of the central nervous system, become activated in response to amyloid-beta plaques and release pro-inflammatory cytokines, such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α). This chronic inflammation can exacerbate neuronal damage and contribute to cognitive decline [5].

Another potential mechanism in AD is oxidative stress, which occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body‘s ability to detoxify them. ROS can damage cellular components, including lipids, proteins, and DNA, leading to cell death [4]. Elevated levels of ROS have been observed in AD brains, and it is thought that they may contribute to neurodegeneration by promoting amyloid-beta plaque formation and inflammation [6].

This review aims to clarify the complex relationship between circadian rhythms and the pathophysiological processes associated with AD. It will explore the molecular behavior of circadian genes and their regulatory mechanisms, and highlight how disturbances in these rhythms could contribute to AD. Additionally, the review seeks to set the stage for future research that might identify new therapeutic targets or interventions utilizing the circadian rhythm to alleviate the impact ofAD.2. The relationship between circadian rhythm imbalance and AD and new treatment ideas.

2. Mechanisms of Circadian Rhythm Affecting AD

2.1 The Genetic Mechanisms by Which Circadian Rhythm Regulatory Genes Affecting AD

The suprachiasmatic nucleus (SCN) acts as the master clock in circadian rhythms, synchronizing with light-dark cycles. Genetic mechanisms were discovered through studies in model organisms like fruit flies and mice. „Clock“ genes such as period (per) regulate protein accumulation and degradation. In mammals, core clock genes include Per1, Per2, and Bmal1. CLOCK-BMAL1 heterodimers activate clock genes, and resulting PER proteins repress CLOCK-BMAL1 activity, completing the feedback loop. Clock-controlled genes impact various physiological processes. Mutations in clock genes can cause circadian rhythm disorders. Understanding these genetic mechanisms improves our knowledge of internal timing, adaptation, and implications for human health.

2.1.1 Retinoic acid receptor-related orphan receptor α (RORα)

Retinoic acid receptor-related orphan receptor α (RORα) is a gene that encodes a nuclear receptor protein involved in the regulation of gene expression. The RORα nuclear receptors play a crucial role in the development of the cerebellum and are involved in the regulation of various cellular processes, such as maintaining circadian rhythms and controlling lipid metabolism. Researchers discovered that the staggerer mutant mouse, which is a model for cerebellar degeneration leading to ataxia due to impaired dendritic development and neurodegeneration of Purkinje cells, is caused by homozygous deletions within the RORα gene [7]. For example, using a model of APP/PS1 double transgenic mice were maintained under 12 hours to 12 hours light to dark cycles unless otherwise noted. Increased levels of RORα have been found to provide protection to neurons against apoptosis induced by oxidative stress [8]. RORα exerts its influence on gene transcription by binding to specific response elements. RORα overexpression protects neurons against oxidative stress-induced apoptosis, which is an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system, is implicated in AD. It may regulate the expression of genes involved in antioxidant defense mechanisms, thereby counteracting the damaging effects of oxidative stress in AD.

2.1.2 Period homolog 1/2

PER1/2 genes, known as Period homolog 1/2, play a crucial role in regulating the circadian clock. These genes form complexes that negatively inhibit the feedback loops involved in transcription and translation within the SCN, the master clock of the body [9]. The repressive effects of PER proteins on gene expression are released on a daily basis through a process involving progressive phosphorylation by casein kinase 1ε and δ. This phosphorylation marks PER proteins for degradation through the ubiquitin pathway. Additionally, the degradation of CRY1/2 proteins, which are also involved in the feedback repression, is facilitated by the SCF/Fbxl3 ubiquitin ligase complex. The expression of PER and CRY proteins, including their activation and subsequent repression, defines the circadian period, representing one complete cycle. When both PER1 and PER2 genes are deleted, it can result in disruptions in the circadian rhythm, leading to clock arrhythmia. Emerging evidence suggests a potential link between PER1/PER2 gene dysfunction and AD, a neurodegenerative

disorder characterized by cognitive decline and memory impairment. One specific point of interest is the role of PER1/PER2 genes in regulating the clearance of amyloid-beta (Aβ), a protein that forms plaques in the brains of AD patients.

The accumulation of Aβ plaques is a hallmark of AD and is thought to contribute to the pathogenesis of the disease. PER1/PER2 genes have been implicated in the regulation of Aβ production and clearance, which may influence the dynamics of Aβ accumulation in the brain [10]. Sleep disturbances and alterations in the sleep-wake cycle are associated with increased Aβ levels and impaired Aβ clearance. It is hypothesized that the dysregulation of PER1/PER2 genes in AD may contribute to disrupted sleep patterns, leading to impaired Aβ clearance and increased Aβ accumulation. Additionally, PER1/PER2 genes can modulate the expression and activity of enzymes involved in Aβ metabolism. For example, it has been suggested that PER1/PER2 proteins may interact with the enzyme neprilysin, which plays a crucial role in Aβ degradation. Dysfunction of PER1/PER2 genes could disrupt this interaction, impairing Aβ clearance and promoting plaque formation. Regarding drugs specifically targeting PER1/PER2 for AD treatment, as of my knowledge cutoff in 2021, there are no drugs available that directly modulate PER1/PER2 gene function for the treatment of AD. However, research is ongoing to explore interventions that target the circadian system as a potential therapeutic approach. These interventions include strategies aimed at improving sleep and circadian function, such as light therapy and melatonin supplementation. By restoring circadian rhythms and promoting healthy.

2.1.3 Reverse Erythroblastosis virus E26 oncogene homolog alpha (REV-ERBα)

REV-ERBα, also known as NR1D1, is a gene that belongs to the nuclear receptor superfamily. REV-ERBα functions as a transcription factor, meaning it can bind to specific DNA sequences and either activate or repress the expression of target genes [11]. It acts as a core component of the molecular circadian clock, helping to maintain the proper timing of physiological processes. REV-ERBα plays a regulatory role in several aspects related to AD, including circadian rhythm disruption, amyloid beta (Aβ) accumulation, and the inflammatory response. REV-ERBα controls the expression of clock genes and genes involved in regulating sleep and wakefulness. Reduced levels of REV-ERBα may lead to dysregulated expression of these genes, contributing to disrupted circadian rhythm and impaired sleep-wake cycles observed in AD. REV-ERBα has also been found to regulate the expression of genes involved in Aβ production and clearance [12]. Specifically, REV-ERBα controls the expression of beta-secretase (BACE1), an enzyme responsible for cleaving amyloid precursor protein (APP) and generating Aβ. Altered REV-ERBα expression levels may dysregulate BACE1 expression, leading to increased Aβ production. Moreover, REV-ERBα also influences the expression of genes involved in Aβ clearance mechanisms, such as the insulin-degrading enzyme (IDE). Disruptions in REV-ERBα function may disrupt the balance between Aβ production and clearance, contributing to Aβ accumulation in AD. Chronic inflammation is a hallmark of AD pathology. REV-ERBα regulates the expression of genes involved in immune and inflammatory responses [13]. Altered REV-ERBα expression can result in dysregulated immune responses and increased inflammation in the brain. For example, REV-ERBα controls the expression of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Dysregulation of REV-ERBα function may lead to an imbalance in the expression of these cytokines, promoting inflammation in the brain and contributing to AD pathology.

2.1.4 Brain and muscle ARNT-like 1(BMAL1) gene

The BMAL1 (Brain and Muscle ARNT-like 1) gene is a key component of the molecular circadian clock, playing a crucial role in regulating the timing of various biological processes. BMAL1 is a transcription factor that forms a heterodimer with CLOCK (Circadian Locomotor Output Cycles Kaput) protein. Together, BMAL1 and CLOCK bind to specific DNA regions called E-boxes, initiating the transcription of target genes involved in the circadian rhythm. The BMAL1 gene is expressed in various tissues, including the brain, liver, and skeletal muscle, where it regulates the expression of genes involved in metabolism, sleep-wake cycles, and other physiological processes. BMAL1 acts as a central coordinator of the circadian clock, influencing the timing of sleep, hormone secretion, metabolism, and other rhythmic behaviors. Emerging evidence suggests a potential link between BMAL1 dysfunction and AD. Disruptions in the circadian rhythm, which BMAL1 regulates, have been observed in AD patients, and alterations in BMAL1 expression have been implicated in the pathogenesis of the disease. BMAL1 can link to AD by its interaction with amyloid-beta (Aβ), a protein that accumulates in the brains of AD patients. Aβ can disrupt the circadian rhythm and suppress BMAL1 expression. Reduced BMAL1 levels can, in turn, impair the normal functioning of the circadian clock and lead to further Aβ accumulation, creating a vicious cycle [14]. This disrupted feedback mechanism between Aβ and BMAL1 may contribute to the progression of AD pathology. BMAL1 is involved in the regulation of various processes that are

disrupted in AD, including sleep-wake cycles, metabolism, and inflammation. Sleep disturbances are common in AD, and the disruption of BMAL1-mediated circadian regulation may be a contributing factor. Inadequate sleep and circadian rhythm disruption have been associated with increased Aβ production, impaired Aβ clearance, and increased tau pathology, which are key hallmarks of AD.

2.1.5 Cryptochrome 1 gene (CRY1)

The CRY1 gene is a key component of the molecular circadian clock, playing a crucial role in regulating the timing of biological processes. CRY1 belongs to a family of genes that encode proteins involved in the circadian rhythm. It functions as a negative regulator of the circadian clock by inhibiting the activity of CLOCK-BMAL1 transcriptional complexes. CRY1 protein levels oscillate over a 24-hour period, with higher levels during the daytime and lower levels at night. It binds to the CLOCK-BMAL1 complex, inhibiting its transcriptional activity and suppressing the expression of clock-controlled genes. This negative feedback loop is a fundamental mechanism in maintaining the circadian rhythm. CRY1 is involved in other physiological processes, such as DNA repair, metabolism, and development. It interacts with various signaling pathways and transcription factors, influencing cellular functions beyond circadian regulation. There is growing evidence suggesting a potential link between CRY1 and AD. Disruptions in the circadian rhythm, including alterations in CRY1 expression and function, have been observed in AD patients, indicating a potential role in the pathogenesis of the disease. CRY1 also interacts with amyloid-beta (Aβ). Studies have shown that Aβ can disrupt the circadian rhythm and alter the expression of CRY1 [15]. This disruption of CRY1 expression can, in turn, affect the normal functioning of the circadian clock, leading to further Aβ accumulation and potentially contributing to the progression of AD pathology. Moreover, CRY1 has been implicated in the regulation of sleep-wake cycles and neuronal plasticity [16], both of which are disrupted in AD. Sleep disturbances are common in AD, and alterations in CRY1 expression and circadian rhythm disruption may contribute to these sleep abnormalities. CRY1 may influence synaptic plasticity involves the modulation of N-methyl-D-aspartate (NMDA) receptor signaling. CRY1 interacts with proteins involved in NMDA receptor signaling pathways, potentially affecting the strength of synaptic connections and the ability of synapses to undergo plastic changes. Additionally, CRY1 has been found to modulate brain-derived neurotrophic factor (BDNF) signaling, which is crucial for synaptic plasticity. BDNF promotes the growth and survival of neurons and plays a key role in synaptic plasticity processes. CRY1 may regulate BDNF signaling pathways, potentially impacting the structural and functional changes that occur at synapses during learning and memory formation.

2.2 Other Mechanisms of Circadian Rhythm Influencing AD

2.2.1 Circadian rhythm associating hormone affecting AD

Besides genetic influence on AD, circadian rhythm disruption has been linked to the development and progression of ADthrough various mechanisms, including changes in hormone levels. For instance, melatonin, a hormone that regulates sleep-wake cycles, is decreased in AD patients and may contribute to cognitive decline [17]. Melatonin plays a crucial role in maintaining the body‘s internal clock and regulating various physiological processes, including immune function, antioxidant defense, and neurotransmitter synthesis [18]. Studies have shown that melatonin supplementation can improve sleep quality and reduce symptoms of depression and anxiety in AD patients [19].

2.2.2 Circadian rhythm regulating amyloid-beta precursor protein

Additionally, the circadian system influences the production and clearance of amyloid-beta, a protein that accumulates in the brains of AD patients and is believed to play a key role in neurodegeneration [20]. Amyloid-beta is produced by the cleavage of amyloid-beta precursor protein (APP), which is itself regulated by the circadian clock [21]. Disruption of the circadian system can lead to dysregulation of APP processing and increased production of amyloid-beta, contributing to its accumulation in the brain [22]. Furthermore, the clearance of amyloid-beta from the brain is also influenced by the circadian system, with peak clearance occurring during wakefulness and reduced clearance during sleep [23]. Targeting the circadian system may therefore represent a promising approach for the prevention and treatment of AD.

3. Novel Strategies of Circadian System to Treat AD

Circadian rhythm disruption has been linked to the development and progression of AD via different molecular biology mechanisms. As research deepens, the results indicate that targeting the circadian rhythm system may be a new approach for the early prevention and later treatment of AD. This paper will discuss potential new drugs that target the circadian system for the treatment of AD.

3.1 Chrono Biotics

These are drugs that help regulate the sleep-wake cycle

and improve sleep quality. Examples include melatonin receptor agonists, such as ramelteon, which is already approved for the treatment of sleep disorders. Chrono biotics may also have neuroprotective effects in AD models by reducing oxidative stress and inflammation [24].

3.2 Light Therapy

Light therapy is a promising treatment option for individuals suffering from sleep disorders and cognitive impairments. This therapeutic approach involves exposing the patient to bright light, which helps reset the circadian clock and improve sleep quality [25]. In recent years, light therapy has gained significant attention in the field of AD research due to its potential benefits in improving cognitive function and reducing the risk of developing AD [26]. Several studies have demonstrated the effectiveness of light therapy in treating sleep disorders such as seasonal affective disorder (SAD) and sleep-wake cycle disorders [27]. By simulating natural daylight, light therapy can help regulate the body‘s internal clock, also known as the circadian rhythm, which plays a crucial role in maintaining healthy sleep patterns [28]. This, in turn, can lead to improved sleep quality and overall well-being. In addition to its sleep-promoting effects, light therapy has also shown promise in enhancing cognitive function in patients with AD. Research has suggested that exposure to bright light can stimulate the production of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which are essential for maintaining healthy brain function [29]. Furthermore, light therapy has been found to reduce amyloid-beta levels, a protein that accumulates in the brains of AD patients and is believed to contribute to neurodegeneration [30].

4. Summary

In conclusion, the disruption of circadian rhythm genes plays a crucial role in the development and progression of AD. Circadian rhythm can also have a significant impact on the occurrence and development of AD through hormone secretion and affecting key AD-related proteins. Understanding the molecular biological mechanisms by which these circadian rhythms influence AD is very important for the understanding and treatment of AD. Future research should focus on elucidating the molecular mechanisms underlying this relationship and developing novel therapeutic strategies targeting circadian rhythm genes for AD prevention and treatment.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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