Proceedings of ICBioMed 2024 Workshop: Computational Proteomics in Drug Discovery and Development from Medicinal Plants
DOI: 10.54254/2753-8818/65/2024.LA18097

The Role of Circadian Rhythm Disruptions in Alzheimer's disease Progression: Mechanisms, Implications, and Therapeutic Strategies

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Abstract. Circadian rhythm disruptions have emerged as a critical factor in the development and progression of Alzheimer's disease (AD). These disruptions affect key processes such as beta-amyloid (Aβ) aggregation, tau protein hyperphosphorylation, and impaired protein clearance, all of which contribute to neurodegeneration. Melatonin, a hormone that regulates the circadian cycle, plays a neuroprotective role but decreases with age, especially in AD patients. Research suggests that melatonin supplementation may help mitigate the effects of Aβ accumulation, tau-related pathology, and oxidative stress. Additionally, bright light therapy (BLT) has been shown to improve circadian rhythm regulation, enhancing sleep quality and cognitive function in individuals with AD. This review highlights the intricate relationship between circadian rhythm disruptions and AD pathology and examines therapeutic interventions such as melatonin and BLT that offer potential benefits in managing the disease.

Keywords: Alzheimer's disease, circadian rhythm, mechanisms, therapy.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative condition where cognitive and functional abilities progressively decline as individuals age [1]. It was first identified by Alois Alzheimer in 1906, based on his observations of a patient he encountered in 1901[2]. Since then, diagnostic criteria have evolved, allowing doctors to recognize the disease even in its early stages before symptoms appear, using biomarkers. Initially, Alzheimer described the main brain changes associated with the disease, but by the mid-1980s, the definition expanded to include other brain abnormalities contributing to dementia. Over time, individuals with AD experience genomic deterioration, loss of protein balance, and decline in cellular function as they age [1]. The disease disproportionately affects minority populations. In its early stages, individuals with AD struggle with forming and retaining new memories. As the disease progresses, their thinking and behavior also deteriorate due to the buildup of specific proteins in the brain, particularly beta-amyloid and tau [2]. These proteins disrupt neural connections, leading to memory loss and brain cell damage. In later stages of AD, factors like metabolism, blood flow, and inflammation contribute to worsening symptoms, including severe memory loss, disorientation, mood changes, confusion about events and places, and other cognitive declines. AD typically lasts from 1 to 20 years or more, significantly reducing life expectancy for those diagnosed.

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Circadian rhythms, the internal biological clocks that regulate various bodily functions, are controlled by a part of the brain called the Circadian Clock. These rhythms oversee key functions such as feeding and sleeping patterns. As people age, circadian rhythms weaken, compromising temporal coordination [3]. Evaluating an individual's internal clock in a clinical setting helps understand their circadian rhythms and assess the extent of disruptions [4]. Disruptions in circadian rhythms are closely tied to sleep disorders, which become more prevalent in older adults. Common sleep issues include chronic insomnia, disruptions in the natural sleep-wake cycle, movement disorders during sleep, and breathing problems such as sleep apnea. Diagnosis typically involves taking a detailed sleep history, using questionnaires, or keeping a sleep log. Polysomnography, a type of sleep study, is not generally recommended unless unusual behaviors occur during sleep or treatments are ineffective. Treatment for sleep disorders depends on the underlying cause and can include both non-drug and drug-based approaches \. Non-drug treatments for chronic insomnia and other sleep disorders may involve cognitive behavioral therapy, relaxation techniques, light therapy, and sleep hygiene education [5]. Since evidence supporting drug treatments is generally weak, any use of medication should be carefully considered between the patient and the doctor, with a focus on minimizing prescriptions.

2. Circadian rhythms disrupted in AD

The brain regulates the human sleep-wake cycle through key regions, including the brainstem, midbrain, thalamus, hypothalamus, and basal forebrain. These areas are responsible for controlling arousal, managing different sleep phases, and maintaining circadian rhythms [6]. Research indicates that weaker circadian rhythms are associated with lower cognitive function, especially in older individuals. For example, slower circadian rhythms in older women significantly increase the risk of developing mild cognitive impairment (MCI) and dementia [1,6].

Sleep disturbances are not only a result of neurodegenerative diseases like Alzheimer’s and Parkinson’s (PD) but may also precede their onset by many years or even decades [1]. Irregular sleep cycles, therefore, are not just symptoms but also major risk factors for these diseases. As such, maintaining a healthy sleep schedule has become a key strategy in preventing and managing AD [6].

The link between sleep disorders and AD has gained increasing attention in recent years. Most people with AD experience some form of sleep disruption, and growing evidence supports the association between sleep disturbances and neurodegenerative diseases such as AD, multiple sclerosis, and PD. Sleep problems may appear before cognitive decline becomes evident, serving as early indicators of neurodegeneration [6] follow these instructions as carefully as possible so all articles within a conference have the same style to the title page. This paragraph follows a section title so it should not be indented.

3. Mechanisms of circadian rhythm disruptions in AD development

As people age, the body’s circadian rhythms—natural 24-hour cycles—undergo significant changes [7]. These changes may manifest as weakened or inconsistent rhythms, shifts in timing that no longer align with environmental cues, and reduced coordination among the body's internal systems. These disruptions become more pronounced in neurodegenerative diseases like AD. Evidence suggests that alterations in circadian rhythms may precede the onset of Alzheimer’s symptoms by many years, indicating their potential role in the disease's progression [2]. Fragmented daily patterns of rest and activity in older adults, even those without dementia, have been linked to earlier cognitive decline, increased risk of Alzheimer's, and early indicators of Alzheimer's-related brain changes [1,7]. This highlights the possibility that circadian rhythm disturbances may contribute to both the development and worsening of AD.

3.1. Circadian rhythm and beta-amyloid (Aβ) aggregation in AD

Circadian rhythms significantly influence the production, clearance, and aggregation of Aβ, a key protein involved in AD. During sleep, the brain's glymphatic system effectively clears waste products, including Aβ. Disrupted circadian rhythms, particularly due to poor or irregular sleep, impair this clearance process, leading to an accumulation of Aβ [1], which can form plaques associated with AD.

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Furthermore, circadian dysregulation increases Aβ production by altering the normal fluctuations of Aβ levels that occur with the sleep-wake cycle, keeping production elevated during prolonged wakefulness. In addition, circadian rhythms also regulate the activity of enzymes involved in processing amyloid precursor protein, from which Aβ is derived [8]. Disruption in these rhythms can shift the balance toward increased Aβ production. Combined with impaired immune responses, such as reduced microglial activity, circadian disruption leads to both increased Aβ aggregation and decreased clearance, contributing to the progression of Alzheimer's disease.

3.2. Circadian Rhythm affecting tau levels leading to AD onset

Research has demonstrated that the progression of dementia in AD(AD) is more closely linked to the presence of neurofibrillary tangles than to amyloid plaques [9]. Upon examining the brains of individuals who had died from AD, scientists isolated these tangles and identified them as being made up of a protein with a molecular weight of around 50 KDa [3]. This protein was later identified as tau, a microtubule-associated protein that plays a critical role in maintaining the structural integrity of cells. In the context of AD, tau undergoes abnormal hyperphosphorylation, where an excessive number of phosphate groups are added to it. As a result, tau loses its ability to support microtubule assembly, instead forming aggregates that sequester normal tau, much like prions. This leads to further cellular dysfunction and damage [9].

Circadian rhythm dysregulation further amplifies the pathological effects of tau in Alzheimer's disease. The circadian clock plays a key role in maintaining homeostasis within the brain, including the regulation of protein synthesis and degradation. When circadian rhythms are disrupted, the normal clearance processes of misfolded proteins, including tau, are impaired. Studies have shown that disturbances in the sleep-wake cycle can increase tau aggregation, as sleep is essential for glymphatic clearance—the brain's system for removing waste, including excess tau. Additionally, circadian disruption affects the regulation of key enzymes involved in tau phosphorylation, such as glycogen synthase kinase-3 (GSK-3), which can further exacerbate tau hyperphosphorylation [10]. This increased tau burden, in conjunction with reduced clearance, accelerates the formation of neurofibrillary tangles, leading to greater neuronal damage and contributing to the cognitive decline observed in Alzheimer's patients. Thus, the interaction between circadian rhythm disturbances and tau pathology creates a vicious cycle, where impaired tau clearance leads to worsened neurodegeneration in the context of AD.

3.3. The role of melatonin in AD under circadian dysregulation

Melatonin, a hormone produced by the pineal gland, has gained significant attention as a potential treatment for sleep disturbances in neurodegenerative diseases such as AD [1]. Research has demonstrated that melatonin possesses antioxidant and anti-apoptotic properties, initially observed in studies involving neuroblastoma cells exposed to proteins linked to AD. As people age, melatonin levels naturally decline, and this decrease is even more pronounced in individuals with AD [11]. Circadian rhythm disruptions exacerbate this reduction, further impairing sleep and brain function in Alzheimer's patients. Melatonin plays a key role in circadian regulation, and its decline disrupts the synchronization of the sleep-wake cycle, which worsens cognitive function. Furthermore, studies have shown that melatonin protects neuronal cells from beta-amyloid-mediated oxidative stress and inhibits the formation of amyloid fibrils in vitro. Although the direct relationship between melatonin and the biochemical pathway of AD is still under investigation, experimental evidence suggests that administering melatonin to transgenic mice genetically predisposed to AD reduces beta-amyloid accumulation, prevents protein damage, and extends lifespan [11]. These protective effects are particularly relevant under conditions of circadian dysregulation, where the body’s natural processes for clearing harmful proteins and maintaining neural integrity are impaired. Melatonin supplementation helps mitigate these effects by regulating circadian rhythms and providing neuroprotective benefits, offering a promising avenue for treating sleep-related and neurodegenerative aspects of AD.

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4. Promising treatments associated with circadian rhythms in AD

4.1. Bright light therapy

Non-drug interventions are commonly prioritized for treating AD, particularly in managing sleep-related issues. A review of studies has indicated that bright light therapy (BLT) can be an effective method for addressing sleep disturbances in AD patients [1]. BLT works by influencing specific neurons in the eye that contain light-sensitive pigments, which transmit signals to the brain's suprachiasmatic nucleus (SCN), the region responsible for regulating the body's internal clock and melatonin production [2]. Light exposure affects melatonin levels, a hormone critical for synchronizing the body's circadian rhythms When light reaches the retina, it alters neurotransmitter and hormone activity, which can significantly impact the mental state and behavior of AD patients. The visual pathway involves specialized retinal cells that send signals to the hypothalamus, influencing various physiological functions, including melatonin secretion [12]. As a result, BLT has been shown to enhance sleep quality, mood, and biological rhythm regulation in individuals with AD.

4.2. Melatonin therapy

Subsequent studies on melatonin revealed that its antioxidant properties not only improved behavioral symptoms in AD mouse models but also demonstrated anti-tau activity, targeting another key protein involved in AD pathology. These animal studies showed that melatonin reduced Aβ levels, alleviated neuroinflammation, and helped protect neuroplasticity, particularly in the hippocampus, an area critical for memory formation [13]. Recent research has further highlighted melatonin's role in regulating circadian rhythm disturbances through the modulation of clock genes. By influencing signalling pathways such as GSK3 and CDK5, melatonin has been shown to reduce Aβ accumulation and prevent tau hyperphosphorylation, both major contributors to neurodegeneration in AD [14-15].

In human studies, melatonin has had mixed results. A short-term study involving elderly individuals with mild cognitive impairment found that melatonin supplementation improved sleep, mood, and cognitive performance [16]. However, clinical trials involving AD patients did not show significant improvements in sleep outcomes, although melatonin was useful as part of a broader sleep therapy approach. Some other studies have also failed to find a clear benefit of melatonin for improving sleep quality in AD patients, likely due to factors such as the short duration of trials and variations in the stages of dementia among participants. These mixed results underscore the need for further research to fully understand the relationship between melatonin, sleep disorders, and Alzheimer's disease, especially over longer periods and in more diverse patient populations.

5. Conclusion

Circadian rhythm disruptions play a significant role in exacerbating the pathological processes of Alzheimer's disease, including *Aβ* accumulation, tau hyperphosphorylation, and impaired protein clearance. These disruptions, along with decreased melatonin production in aging and AD patients, contribute to worsening cognitive decline and disease progression. While therapeutic interventions such as melatonin supplementation and BLT offer promising avenues for mitigating circadian-related disruptions, current clinical evidence presents mixed results, particularly in human trials. Future research should focus on long-term studies and a deeper exploration of circadian regulation mechanisms to better understand the potential of these treatments. Targeting circadian rhythms may present a valuable strategy for improving the quality of life and slowing the progression of Alzheimer's disease.

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