Dysregulation of the Circadian Rhythm and its Effect on Alzheimer's Disease

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Abstract

Sleep, a fundamental physiological behavior, is primarily controlled by the circadian clock, an internal mechanism in the body that regulates the physiologically appropriate time of day for sleep. Dysregulation of circadian rhythms significantly contributes to pathogenesis in several neurodegenerative diseases, including Alzheimer's disease, affecting millions worldwide. However, how this dysregulation of the circadian rhythm contributes to the onset of Alzheimer's disease is still unknown, and there is no effective treatment or cure for this neurodegenerative disease. In this paper, we comprehensively review the literature to understand how dysregulation of circadian rhythms may contribute to the onset of Alzheimer's disease. First, we investigated the relationship between circadian rhythms and sleep deprivation. The risk of developing Alzheimer's disease was higher in patients with sleep disturbances, which suggests that sleep disturbances and Alzheimer's disease might be linked. Preventative measures can be made to prevent the onset of Alzheimer's disease. Second, we investigated the impact of abnormal protein buildup in Alzheimer's disease. Studying these proteins is the first step towards understanding the relationship between the dysregulation of the circadian rhythm and the onset of Alzheimer's disease. Lastly, we investigated the dysregulation of circadian genes in Alzheimer's disease, which plays a significant role in the onset of Alzheimer's disease. Sleep deprivation is a widespread problem in today's society, along with the prevalence of Alzheimer's disease. This work will help us further understand the mechanisms contributing to Alzheimer's disease and highlight circadian mechanisms as a possible target for investigation.

Sleep and its Relationship with Circadian Rhythms and Alzheimer's Disease

Sleep is a fundamental physiological function in the human body, a period for rest, energy restoration, learning, and memory consolidation. During sleep, the brain and other systems undergo restorative processes, and sleep is irreplaceable for promoting cognitive focus and optimal brain function. The circadian rhythm, a biological clock that controls the sleep-wake cycle within a human body, also regulates the levels of hormones, metabolism, body temperature, and other physiological functions throughout the day. Chronic sleep deprivation can lead to the dysregulation of the circadian rhythm, and emerging studies have found that patients and animal models with dysregulated circadian rhythms show abnormal increased accumulation of proteins in Alzheimer's disease [1,2].

Alzheimer's disease is a neurodegenerative disease affecting millions worldwide. Its prevalence is particularly pronounced among the older population, especially in individuals over 65 years of age. At the core of Alzheimer's disease lies the involvement of two essential proteins: Amyloid beta (Aβ) and tau. Those two proteins are responsible for the formation of tangles and plaques within the brain, which leads to severe disruptions in neurological functions. Despite extensive research spanning over a century, a cure for this condition remains elusive. Recent scientific investigations have found a potential link between Alzheimer's disease and disruptions in the circadian rhythm [1,2].

Sleep deprivation, a phenomenon affecting millions of individuals, has also been observed to affect many individuals with Alzheimer's disease. Sleep deprivation, being awake for a prolonged period during the standard sleep-designated time, includes not being able to fall asleep, waking up in the middle of the night, intentional sleep disruption, etc. Sleep disturbances can also be related to dysregulation of the circadian rhythm, and around 25-66% of Alzheimer's disease patients have some form of sleep disturbance [3,4]. This review discusses the potential relationship between dysregulated circadian rhythms and the accumulation of tangles and plaques in the brain.

Another part of investigation in this review is the dysregulation of circadian genes in Alzheimer's disease. Exploring how these genes are affected and whether a connection exists between genes dysregulated in Alzheimer's disease and those involved in circadian rhythm dysregulation may provide evidence for this neurological disorder.

By understanding the connections between these disorders, this review seeks to reveal potentially groundbreaking treatment strategies for Alzheimer's disease. Studying the dysregulation of the circadian rhythm may lead to a deeper understanding of the cause of Alzheimer's disease. Aligning treatment methods with circadian rhythm regulation might help to advance Alzheimer's disease research.

Circadian rhythms and sleep deprivation

The circadian rhythm is the fundamental 24-hour biological clock that controls many critical processes in the human body. Its functions are primarily affected by the surroundings, including the alternation between light and darkness in the environment. The circadian rhythm is essential — it extends across an extensive array of physiological domains, encompassing the regulation of bodily functions, the orchestration of sleep-wake patterns, hormone secretion, the optimization of cognitive performance, and the balance of core body temperature. Because of its profound influence, any disruption in circadian rhythms might have significant consequences on the overall health of a human [5].

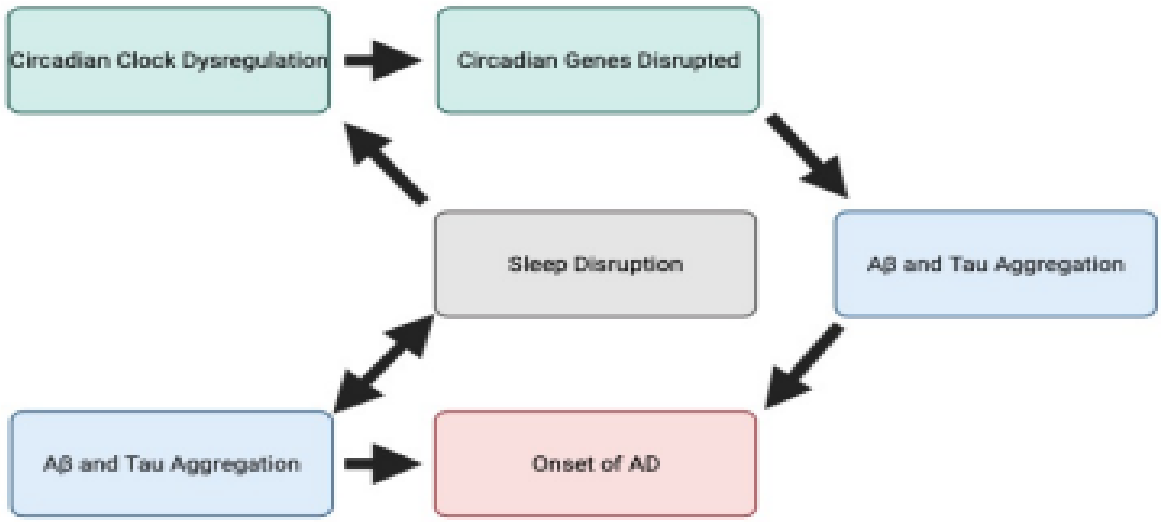
The delicate relationship between the circadian rhythm and sleep disruption is not to be overlooked. Disturbances in the circadian rhythm can also lead to disruptions in the sleep-wake cycle, making it challenging to maintain quality sleep. If this continues, the overall well-being of a human can be affected due to the irregular sleep-wake cycle. This includes possible metabolic dysregulation, heightened mood disorders, and impaired cognitive function [5]. Maintaining a balanced sleep-wake cycle is essential towards a healthy lifestyle.

Extensive research has yielded compelling evidence linking sleep deprivation to an increased accumulation of amyloid-beta (Aβ) and tau proteins, pivotal components towards the onset of Alzheimer's disease [6]. These proteins have modulating effects on the circadian rhythm, and if the circadian rhythm were to be dysregulated, the abnormal accumulation of these proteins would occur. The prevalence of sleep deprivation's impact is widespread, as evidenced by scientific investigations. For example, a comprehensive study in the Netherlands discovered that 27.3% of a sizable cohort comprising 20,000 individuals manifested signs of sleep-related disturbances [9]. Similarly, another research study conducted in the Netherlands found that 23.5% of

subjects observed had sleep-related issues [10]. These research findings collectively highlight the prevalence of sleep deprivation.

Chronic sleep deprivation has profound negative consequences on the brain, especially linked to Alzheimer's disease. Research indicates that ongoing sleep restriction amplifies the buildup of amyloid-beta and tau proteins, both related to neurodegeneration. Interestingly, wakefulness duration correlates with intensified Aβ and tau accumulation, while subsequent sleep reduces Aβ [1,7]. Both Aβ and tau follow a cyclic pattern, with high levels during wake and low levels during rest. Disrupted sleep disrupts this rhythm, leading to persistent Aβ and tau accumulation. This highlights the critical role of sleep in regulating Aβ and tau dynamics. Therefore, the dysregulation of the circadian rhythm significantly impacts Aβ regulation, and maintaining proper sleep patterns is vital for cognitive health and preventing the onset of neurodegeneration.

Disruptions in the circadian rhythm have emerged as significant contributors to various health issues in addition to Alzheimer's disease. Understanding the correlation



between these

Figure1. Relationship Between Sleep Disruption, Circadian Rhythm Deregulation, and the Onset of AD

factors may help to find a more effective treatment or even cure for Alzheimer's disease. Sleep disturbance is quite common in Alzheimer's disease patients, as studies show fluctuations in Aβ and tau accumulation due to sleep disturbances (Figure 1). Studies in animal models have also demonstrated a correlation between the sleep-wake cycle and the accumulation of Aβ [8]. For example, a study done on mice shows a 25-30% increase in Aβ accumulation overnight [1,2]. A different study showed an increase of tau protein in the cerebral spinal fluid (CSF) in humans with sleep disruption, which suggests its possible role in Alzheimer's disease development. Therefore, change and

dysregulation in the circadian rhythm might have impacted the development of Alzheimer's disease [8].

Dysregulation of Circadian Genes in Alzheimer's Disease

Chronic sleep deprivation has been shown to affect circadian genes within the human body. Animal models with severe sleep deprivation also have disrupted circadian genes like Clock, Bmal1, and Cry1. This study also found that with the disruption of the circadian gene Bmal1, there was an increase in tau accumulation [11]. The disruption of Bmal1 leads to the accumulation of tau tangles, which in turn leads to an increased risk of developing Alzheimer's. The disruption of these genes has been shown to increase the risk of developing Alzheimer's disease. Increased wakefulness, along with the disruption of the circadian rhythm, has shown increased tau accumulation [7]. These data highlight a significant role that circadian gene disruption may play in the onset of Alzheimer's disease.

Although circadian gene disruptions can influence the onset of Alzheimer's disease, other genetic factors can also contribute to this risk. The APOE4 and APOE2 genes are of particular interest, as they are known to play prominent roles in Alzheimer's disease pathology. APOE4 amplifies Alzheimer's disease risk and accelerates onset, while APOE2 demonstrates protective effects. Both genes influence Aβ metabolism and clearance, with APOE4 promoting Aβ aggregation and APOE2 facilitating clearance. APOE4's negative impact on Aβ metabolism contributes to plaque formation, a hallmark of Alzheimer's disease. APOE2, on the other hand, mitigates plaque accumulation [12]. Even though the onset of Alzheimer's disease is unpredictable, the connection between circadian disruption, APOE status, and inflammation may serve as an early indicator.

Table1. Correlation Between Alzheimer's and Sleep Disruption

Authors	Year	Model	Conclusions	Citation
Holtzman	2019	Animal - APP Transgenic mice	Increased wakefulness leads to the acceleration of and Aβ and Tau pathology.	Wang, C., & Holtzman, D. M. (2020). Bidirectional relationship between sleep and Alzheimer's disease: Role of amyloid, tau, and other factors. Neuropsychopharmacology, 45, 104–120.https://doi.org/10.1038/s41386-019-0478-5

Holth	2019	Animal - *APPswe/PS1δE9*transgenic mice	The sleep-wake cycle influences the accumulation of Aβ. Tau accumulation is increased with wakefulness and sleep deprivation.	Holth, J. K., Fritschi, S. K., Wang, C., Pedersen, N. P., Cirrito, J. R., Mahan, T. E., Finn, M. B., Manis, M., Geerling, J. C., Fuller, P. M., Lucey, B. P., & Holtzman, D. M. (2019). The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science (New York, N.Y.)*, *363*(6429), 880–884. https://doi.org/10.1126/science.aav2546
Derex	2014	Human	Sleep disturbances have a profound impact on Alzheimer's patients.	Peter-Derex, L., Yammine, P., Bastuji, H., & Croisile, B. (2015). Sleep and Alzheimer's disease. *Sleep medicine reviews*, *19*, 29–38. https://doi.org/10.1016/j.smrv.2014.03.007
Borges	2019	Human	Sleep disruption correlates with Alzheimer's disease, which can increase the likelihood of developing Alzheimer's disease in those with mild cognitive impairment (MCI).	Borges, C. R., Poyares, D., Piovezan, R., Nitrini, R., & Brucki, S. (2019). Alzheimer's disease and sleep disturbances: a review. *Arquivos de neuro-psiquiatria*, *77*(11), 815–824. https://doi.org/10.1590/0004-282X20190149

Conclusion

In summation, the balance between the circadian rhythm, which maintains numerous physiological functions, and the sleep-wake cycle, which regulates restorative processes within the human body, are fundamental towards human well-being. The ever-increasing problem of worldwide sleep disruption is not to be overlooked. Sleep and circadian rhythm disruptions lead to the abnormal accumulation of tau and Aβ proteins, which can lead to the development of Alzheimer's (Table 1). New techniques

are emerging to study sleep disruptions, circadian rhythm deregulations, and the onset of neurodegenerative diseases such as Alzheimer's disease, however, a cure is yet to be found. One of the most feasible and efficient solutions might lie in the improvement of sleep quality, allowing for mechanisms within the body to regulate those proteins that are implicated in Alzheimer's disease. This may be important towards curing this neurodegenerative disease that has been plaguing humans for centuries: Alzheimer's disease.

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