Disruption in Sleep and Circadian Rhythm: A Potential Accelerator in Alzheimer's Disease Progression

Annals of Neurosciences
31(4) 246–249, 2024
© The Author(s) 2023
Article reuse guidelines:
in.sagepub.com/journals-permissions-india
DOI: 10.1177/09727531231200958
journals.sagepub.com/home/aon
Sage

Abdul Hadi Khan[1], Ali Abdullah[1], Muhammad Saqlain Mustafa[1] and Muhammad Abdul Qadeer[1]

Introduction

Alzheimer's disease (AD) is a neurodegenerative dementia that currently affects more than 40 million people worldwide and is expected to affect more than 131 million people by 2050.[1] The pathological hallmarks of AD are extracellular plaques, intracellular tangles, and neuronal loss.[2–4] To create effective treatments for preventing or delaying the onset of AD, a deeper understanding of its pathogenesis and potential risk factors is essential. Intriguingly, sleep disturbance and circadian rhythm disruption share several common molecular signaling and anatomic pathways that promote the neurodegeneration of AD. For example, the hypothalamus–pituitary–adrenal (HPA) axis is regulated by the circadian rhythm.[5] Also, both sleep duration and quality (i.e., continuity and intensity) are essential for maintaining good human performance and cognition.[6] The circadian system governs several physiologic functions, such as sleeping and waking up, activity, temperature, and cognitive function.[7] Although the therapeutic importance of circadian rhythm and sleep disruption owing to aging is well recognized, its role as an accelerator in dementia and AD is still not known. This article explores the intricate relationship between sleep, circadian rhythm, and AD, shedding light on their potential therapeutic implications.

Main Text

The circadian rhythm, often referred to as the body's internal clock, has an intricate relationship with the etiology of AD.[8] The circadian rhythm plays a vital role in coordinating various physiological processes throughout the day and night. In humans, this innate rhythm operates on a slightly longer than 24-h cycle, ensuring that essential bodily functions, including sleeping and waking, activity levels, temperature regulation, and cognitive function, occur in a rhythmic and coordinated manner.[9] At the core of the circadian rhythm's orchestration lies the suprachiasmatic nucleus (SCN), a small region within the brain's hypothalamus. As the central circadian pacemaker, the SCN serves as the master regulator, orchestrating and synchronizing the circadian rhythms of nearly all peripheral tissues in the body.[10,11] This synchronization is crucial for maintaining overall physiological harmony and promoting optimal health. Moreover, it allows the body to anticipate and adapt to regular environmental changes, such as the natural transition from day to night. Interestingly, the circadian rhythms of different bodily systems can also exhibit short-term independent oscillations, known as ultradian rhythms. These ultradian rhythms, operating on much shorter cycles than the circadian rhythm, contribute to various biological processes, including hormone secretion and cellular metabolism.[11,12] The coordination between circadian and ultradian rhythms ensures a finely tuned and dynamic internal environment, enabling the body to respond efficiently to internal and external stimuli. As individuals age, disturbances in the circadian rhythm become increasingly prevalent, affecting more than 80% of people over the age of 65.[13] Older adults often experience changes in sleep patterns, with difficulties falling asleep, staying asleep, or experiencing restorative sleep. These disruptions can lead to a host of issues, including daytime sleepiness, reduced cognitive function, and impaired memory consolidation. For individuals already grappling with AD, circadian rhythm abnormalities are even more pronounced.[14,15] Alzheimer's disease patients

[1]Department of Medicine, Jinnah Sindh Medical University, Karachi, Sindh, Pakistan

Corresponding author:
Muhammad Saqlain Mustafa, Department of Medicine, Jinnah Sindh Medical University, Karachi, Sindh 75510, Pakistan.
E-mail: msaqlain.mustafa@gmail.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-Commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

frequently encounter significant sleep disturbances, characterized by fragmented sleep patterns, nighttime restlessness, and increased confusion during the evening hours, a phenomenon known as "sundowning." These sleep disturbances not only exacerbate cognitive decline but can also intensify emotional distress for both patients and caregivers.

Numerous human investigations have demonstrated that with a dampened circadian rhythm, melatonin production decreases during aging. Melatonin levels, particularly nocturnal levels, have been found to be lower in plasma, saliva, and the pineal gland, as well as in urine melatonin and 6-hydroxy melatonin.[16,17] Melatonin is a hormone that is primarily produced by the pineal gland. It is a multifunctional, circadian-regulated chemical that performs a neuroprotective effect in the pathophysiology of AD.[18–21] It modulates the activity and levels of several key proteins, including ADAM10, BACE1, and GSK-3, resulting in decreased β-amyloid (Aβ) production and increased Aβ clearance. Melatonin's electron transport capacity also allows it to directly scavenge free radicals and repair damaged biomolecules.[22,23] Melatonin levels in cerebrospinal fluid (CSF) have been found to fall in AD patients, even during the preclinical stages,[17,22,23] and continue to decline as the disease progresses.[24–26] Therefore, disruptions in circadian rhythm could also impact melatonin levels, causing an imbalance in Aβ metabolism and resulting in Aβ-induced neurotoxicity.

Interestingly, the frequent disruption of the sleep/wake pattern observed in AD patients provides additional evidence supporting the close association between the circadian rhythm and AD pathogenesis.[8] Inadequate sleep duration, typically ranging from 0 to 6 h per night, or poor sleep quality has been consistently linked to impairments in memory and cognitive function, which are critical aspects significantly affected in AD.[27] These sleep disturbances, such as sundowning and night-time restlessness, are particularly distressing for patients,[28,29] and their impact extends far beyond mere discomfort. These disruptions in sleep not only intensify cognitive decline but also impose functional limitations on AD patients.[30–32] The combination of fragmented sleep patterns and restless nights hampers the restorative functions of sleep, preventing the brain from effectively processing and consolidating memories. As a result, patients may experience heightened confusion, a reduced attention span, and difficulty carrying out daily activities independently. Furthermore, chronic sleep disturbances may lead to increased agitation and behavioral issues, placing additional burden on caregivers and affecting the overall quality of life for both patients and their families.

Recent studies have shed light on the bidirectional relationship between sleep and the presence of Aβ, a key player closely associated with the development of AD.[33,34] Under normal circumstances, Aβ levels in the brain exhibit a diurnal variation, fluctuating in response to the body's natural sleep-wake cycle. Sleep deprivation, a common consequence of circadian rhythm disruption and sleep disturbances, has been shown to lead to an increase in Aβ levels, facilitating the formation of amyloid plaques in the brain.[35–37] These plaques, composed of aggregated Aβ proteins, are a hallmark feature of AD and are believed to contribute to neurodegeneration. Conversely, obtaining adequate and restorative sleep has been found to play a protective role in minimizing Aβ deposition in the brain. When the body experiences healthy sleep patterns and maintains a well-regulated circadian rhythm, the natural clearance mechanisms are more effective in removing Aβ, reducing the risk of plaque accumulation and subsequent neurotoxicity. This compelling finding underscores the critical importance of maintaining a healthy sleep pattern and circadian rhythm as potential protective factors against AD. By prioritizing proper sleep and striving for a well-balanced circadian system, individuals may reduce their risk of developing AD and potentially slow down disease progression. As ongoing research continues to elucidate the intricate links between sleep, circadian rhythm, and Aβ metabolism, new therapeutic avenues may emerge, offering hope for improved AD prevention and management.

Conclusion

In conclusion, the complex connection between sleep, circadian rhythm, and AD needs to be further explored. A deeper knowledge of these relationships may pave the way for therapeutic approaches targeted at postponing or lowering the severity of AD. By focusing on possible therapies that target the circadian rhythm, like melatonin, and patients' sleep health, we might be able to devise novel, effective strategies in our battle against this debilitating disease. As the scientific community continues to explore these relationships, new avenues for AD prevention and treatment may emerge, offering hope for a better future for those affected by this condition.

Abbreviations

AD, Alzheimer's disease, HPA, hypothalamus–pituitary–adrenal axis; SCN, suprachiasmatic nucleus, CSF, cerebrospinal fluid, Aβ, β-amyloid.

Authors' Contribution

AHK conceived and designed the study and did the literature search. MAQ and AA wrote the original draft. MSM edited and revised the original manuscript. All authors read and approved the final manuscript.

Availability of Data and Material

The data that supports the findings of this study are available on PubMed: https://pubmed.ncbi.nlm.nih.gov/.

Declaration of Conflicting Interests

The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

ORCID iDs

Abdul Hadi Khan https://orcid.org/0009-0004-9267-7680
Ali Abdullah https://orcid.org/0009-0007-3696-6076
Muhammad Saqlain Mustafa https://orcid.org/0000-0002-3067-3543

References

1. Prince MJ, Wimo A, Guerchet MM, et al. World Alzheimer Report 2015-the global impact of dementia: an analysis of prevalence, incidence. *Alzheimer's Disease International* 2015. http://www.alz.co.uk/research/world-report-2015
2. Masters CL, Bateman R, Blennow K, et al. Alzheimer's disease. *Nat Rev Dis Primers* 2015; 1: 15056.
3. Glenner GG and Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun* 1984; 120(3): 885–890.
4. Hardy JA and Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science* 1992; 256(5054): 184–185.
5. Girotti M, Weinberg MS and Spencer RL. Diurnal expression of functional and clock-related genes throughout the rat HPA axis: system-wide shifts in response to a restricted feeding schedule. *Am J Physiol Endocrinol Metab* 2009; 296(4): E888–E897.
6. Goel N, Basner M, Rao H, et al. Circadian rhythms, sleep deprivation, and human performance. *Prog Mol Biol Transl Sci* 2013; 119: 155–190.
7. Wyatt JK, AR-D Cecco, Czeisler CA, et al. Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a 20-h day. *Am J Physiol Regul Integr Comp Physiol* 1999; 277(4): R1152–R1163.
8. Witting W, Kwa IH, Eikelenboom P, et al. Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. *Biol Psychiatry* 1990; 27(6): 563–572.
9. Scheer FAJL, Wright KP Jr, Kronauer RE, et al. Plasticity of the intrinsic period of the human circadian timing system. *PLoS One* 2007; 2(8): e721.
10. Saper CB, Lu J, Chou TC, et al. The hypothalamic integrator for circadian rhythms. *Trends Neurosci* 2005; 28(3): 152–157.
11. Akhtar RA, Reddy AB, Maywood ES, et al. Circadian cycling of the mouse liver transcriptome, as revealed by cDNA microarray, is driven by the suprachiasmatic nucleus. *Curr Biol* 2002; 12(7): 540–550.
12. Nagoshi E, Saini C, Bauer C, et al. Circadian gene expression in individual fibroblasts: cell-autonomous and self-sustained oscillators pass time to daughter cells. *Cell* 2004; 119(5): 693–705.
13. Foley DJ, Monjan AA, Brown SL, et al. Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep* 1995; 18(6): 425–432.
14. Bliwise DL. Sleep in normal aging and dementia. *Sleep* 1993; 16(1): 40–81.
15. Van Someren EJ. Circadian and sleep disturbances in the elderly. *Exp Gerontol* 2000; 35: 1229–1237.
16. Skene DJ and Swaab DF. Effect of age and Alzheimer's disease. *Exp Gerontol* 2003; 38(1–2): 199–206.
17. Y-H Wu and Swaab DF. The human pineal gland and melatonin in aging and Alzheimer's disease. *J Pineal Res* 2005; 38(3): 145–152.
18. Hossain MF, Uddin MS, Uddin GMS, et al. Melatonin in Alzheimer's disease: a latent endogenous regulator of neurogenesis to mitigate Alzheimer's neuropathology. *Mol Neurobiol* 2019; 56(12): 8255–8276.
19. Lin L, Q-X Huang, S-S Yang, et al. Melatonin in Alzheimer's disease. *Int J Mol Sci* 2013; 14(7): 14575–14593.
20. Vincent B. Protective roles of melatonin against the amyloid-dependent development of Alzheimer's disease: a critical review. *Pharmacol Res* 2018; 134: 223–237.
21. Rosales-Corral SA, Acuña-Castroviejo D, Coto-Montes A, et al. Alzheimer's disease: pathological mechanisms and the beneficial role of melatonin: Alzheimer's disease and melatonin. *J Pineal Res* 2012; 52(2): 167–202.
22. Reiter RJ, Paredes SD, Manchester LC, et al. Reducing oxidative/nitrosative stress: a newly-discovered genre for melatonin. *Crit Rev Biochem Mol Biol* 2009; 44(4): 175–200.
23. Reiter RJ, Mayo JC, D-X Tan, et al. Melatonin as an antioxidant: under promises but over delivers. *J Pineal Res* 2016; 61(3): 253–278.
24. Urrestarazu E and Iriarte J. Clinical management of sleep disturbances in Alzheimer's disease: current and emerging strategies. *Nat Sci Sleep* 2016; 8: 21–33.
25. Mishima K, Tozawa T, Satoh K, et al. Melatonin secretion rhythm disorders in patients with senile dementia of Alzheimer's type with disturbed sleep–waking. *Biol Psychiatry* 1999; 45(4): 417–421.
26. J-N Zhou, R-Y Liu, Kamphorst W, et al. Early neuropathological Alzheimer's changes in aged individuals are accompanied by decreased cerebrospinal fluid melatonin levels. *J Pineal Res* 2003; 35(2): 125–130.
27. Gildner TE, Liebert MA, Kowal P, et al. Associations between sleep duration, sleep quality, and cognitive test performance among older adults from six middle income countries: results from the Study on Global Ageing and Adult Health (SAGE). *J Clin Sleep Med* 2014; 10(6): 613–621.
28. Rabins PV, Mace NL and Lucas MJ. The impact of dementia on the family. *JAMA* 1982; 248(3): 333–335.
29. Gallagher-Thompson D, Brooksrd JO, Bliwise D, et al. The relations among caregiver stress, sundowning symptoms, and cognitive decline in Alzheimer's disease. *J Am Geriatr Soc* 1992; 40: 807–10.
30. Bonanni E, Maestri M, Tognoni G, et al. Daytime sleepiness in mild and moderate Alzheimer's disease and its relationship with cognitive impairment. *J Sleep Res* 2005; 14(3): 311–317.

31. Briones B, Adams N, Strauss M, et al. Relationship between sleepiness and general health status. *Sleep* 1996; 19(7): 583–588.
32. Moran M, Lynch CA, Walsh C, et al. Sleep disturbance in mild to moderate Alzheimer's disease. *Sleep Med* 2005; 6(4): 347–352.
33. Song Q, Feng G, Huang Z, et al. Aberrant axonal arborization of PDF neurons induced by Abeta42-mediated JNK activation underlies sleep disturbance in an Alzheimer's model. *Mol Neurobiol* 2016; 54(8): 6317–6328.
34. Lucey YE and Holtzman BP. Sleep Alzheimer disease pathology-a bidirectional relationship. *Nat Rev Neurol* 2014; 10: 115–119.
35. Mattis J and Sehgal A. Circadian rhythms, sleep, and disorders of aging. *Trends Endocrinol Metab* 2016; 27(4): 192–203.
36. Roh JH, Huang Y and Bero AW. Disruption of the sleep-wake cycle and diurnal fluctuation of beta-amyloid in mice with Alzheimer's disease pathology. *Sci Transl Med* 2012; 4: 150–122.
37. Huang Y, Potter R and Sigurdson W. Effects of age and amyloid deposition on Abeta dynamics in the human central nervous system. *Arch Neurol* 2012; 69: 51–58.