ACCSCIENCE PUBLISHING

Gene & Protein in Disease

EDITORIAL

Circadian rhythms in Alzheimer's disease: A molecular clock worth watching

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Alzheimer's disease was first described in 1906 by Dr. Alois Alzheimer.[1] Since then, there has been a compelling shift in our understanding of this and other neurodegenerative disorders. While amyloid-β plaques and tau tangles remain pathological hallmarks of Alzheimer's disease, they do not fully account for the variability in disease onset, progression, or therapeutic response.[2] Among several emerging factors under investigation, circadian rhythm has gained recognition as a critical modulator of brain health, aging, and neurodegeneration.

Circadian rhythm involves a central clock within the suprachiasmatic nucleus (SCN) of the hypothalamus and peripheral clocks distributed across nearly all body tissues. These clocks operate through transcriptional–translational feedback loops, comprising core clock genes, such as *BMAL1*, *CLOCK*, *PER*, and *CRY*, which regulate essential cellular processes including inflammation, redox balance, proteostasis, and mitochondrial function.[3] This pathway does not operate in isolation; it is tightly interconnected with hormonal, immune, and metabolic systems, forming a unified temporal network that maintains neurobiological homeostasis across the lifespan.

Disruptions in circadian rhythms have been implicated in a wide range of systemic disorders, including cardiovascular, metabolic, neurodegenerative, endocrine, and immune-related conditions.[4] These disturbances may arise from intrinsic factors, such as aging and genetic vulnerability, or extrinsic influences, such as shift work, jet lag, irregular light exposure, and environmental misalignment. In individuals with Alzheimer's disease, signs of circadian misalignment – such as altered sleep-wake cycles, sundowning behaviors, and dysregulated hormonal patterns (e.g., cortisol and melatonin) – often emerge before the onset of cognitive decline, reflecting core disruptions in molecular timing systems.[5]

At the mechanistic level, circadian misalignment impairs proteostasis, reduces the fidelity of DNA repair, and weakens glymphatic clearance of neurotoxic proteins, such as amyloid-β and tau.[6] Moreover, astrocytes and microglia exhibit circadian oscillations, and dysfunction in these glial clocks can alter neuroinflammatory tone, impair synaptic pruning, and disrupt mitochondrial function.[7] These desynchronized processes contribute to accelerated neurodegeneration and impaired synaptic plasticity, particularly in vulnerable regions, such as the hippocampus.

The relationship between circadian disruption and Alzheimer's disease is bidirectional: not only does circadian misalignment accelerate neuropathological processes, but the progression of Alzheimer's disease also disrupts circadian output – particularly through degeneration of the SCN.[8] This feed-forward loop underscores the role of circadian rhythms not merely as biomarkers of the disease, but also as active drivers of its progression.

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Chronotherapy – the alignment of medical treatment with biological rhythms – is a promising avenue for Alzheimer's disease care. Drug metabolism follows circadian patterns, influencing efficacy and toxicity. Melatonin, traditionally used to regulate sleep, also influences autophagy, oxidative stress, and synaptic signaling – making it a promising chronotherapeutic agent. In addition, dual orexin receptor antagonists have shown early success in regulating sleep-wake cycles and promoting tau clearance.[9]

Restoring circadian synchrony through lifestyle interventions – such as time-restricted feeding, structured light exposure, and regular physical activity – has shown benefits in sleep quality, systemic inflammation, and cognitive resilience, particularly in the early stages of Alzheimer's disease.[10]

A growing field of interest is chronoepigenetics, where epigenetic regulators – such as sirtuin-1, an NAD^+-dependent deacetylase, and poly(ADP-ribose) polymerase 1 – intersect with circadian clock gene expression, modulating neuroprotective and synaptic pathways.[11,12] Targeting these molecular intersections may lead to precision therapies that simultaneously stabilize circadian rhythms and mitigate neurodegeneration.

These insights also transform our approach to biomarkers. Circadian-informed markers – such as rhythmic fluctuations in melatonin, cortisol, body temperature, retinal responses, and microglial activation – may offer early diagnostic signals and optimize therapeutic timing. Technologies such as actigraphy, metabolomic profiling, and neuroimaging of circadian structures are advancing the field of time-based phenotyping and risk stratification.

Despite these advances, challenges remain. Clinical adoption of chronotherapy is hindered by the absence of standardized chronotyping protocols, limited longitudinal data, and the lack of circadian integration into trial design. Regulatory frameworks must evolve to incorporate time-of-day considerations in drug labeling and approval. Public health initiatives should also promote circadian hygiene – including consistent sleep schedules, timed meals, and light exposure – as a core component of brain health.

As Alzheimer's disease cases continue to rise globally, particularly among aging and urbanized populations, there is an urgent need to expand our clinical and research frameworks. The circadian system, once considered peripheral, now emerges as a central regulatory axis linking genes, proteins, metabolism, and behavior within a unified pathophysiological model.

The phrase "time is brain," often cited in stroke care, is equally profound in the context of Alzheimer's disease. It is time for temporal regulation to emerge as a therapeutic target.

Conflict of interest

The author declares no conflict of interest.

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