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The rhythm of decline: Circadian disruption in neurodegeneration

REVIEW ARTICLE

The rhythm of decline: Circadian disruption in neurodegeneration

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with a multifactorial etiology involving genetic, environmental, and metabolic factors. Among these, circadian rhythm disruption has emerged as a crucial but underexplored contributor to disease progression. The circadian system, regulated by the suprachiasmatic nucleus (SCN), controls essential physiological functions such as the sleep-wake cycle, metabolism, and neuroendocrine signaling. Disruption of this system has been increasingly linked to key pathological features of AD, including amyloid-beta accumulation, tau hyperphosphorylation, and neuroinflammation. This review critically examines the mechanistic role of circadian misalignment in AD by analyzing studies on sleep disturbances, SCN degeneration, metabolic dysregulation, clock gene polymorphisms (BMAL1, CLOCK, PER, CRY), and gut-brain axis interactions. Evidence indicates that circadian abnormalities manifest as reduced melatonin secretion, impaired glymphatic clearance, and altered SCN signaling, all of which contribute to neuronal dysfunction and cognitive decline. Additionally, sleep deprivation has been shown to exacerbate amyloid-beta accumulation, while tau pathology can further disrupt circadian control, creating a vicious cycle. Dysregulated gut microbiota rhythms and associated metabolic changes further enhance neuroinflammatory responses, increasing AD risk. Diagnostic advances such as actigraphy, melatonin assays, and plasma biomarkers provide non-invasive methods for early detection of circadian misalignment. Therapeutic strategies targeting the circadian system—including light therapy, melatonin supplementation, and gene-based interventions—show promise in restoring circadian homeostasis and improving cognitive outcomes. Understanding and addressing circadian disruptions may offer novel and personalized approaches for delaying or mitigating Alzheimer's disease progression, highlighting the need for further research in this direction.

Keywords: Alzheimer's disease, Amyloid-beta, Brain-gut axis, Circadian rhythms, Suprachiasmatic nucleus, Tau pathology

1. Introduction

In the suprachiasmatic nucleus, the body's internal biological clock controls circadian rhythms, which are metabolic and behavioural cycles with a periodicity of roughly 24 h. Aligned with solar time, the circadian system orchestrates daily rhythms in rest-activity patterns, feeding, body temperature, hormone levels, and various other biological functions. Disruption of this system can negatively impact sleep quality, cognitive performance, alertness, motor skills, mental health, and metabolism [1]. Nearly all human physiological and behavioral processes follow rhythmic patterns, leading to noticeable diurnal fluctuations in performance. Whether caused by voluntary factors like shift work or involuntary factors such as illness, circadian rhythm disturbances can lead to mental and physical health disorders, impairing safety, productivity, and overall performance. These disruptions are often accompanied by sleep disturbances, which complicate their role in disease

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development. A deeper understanding of the SCN's circadian signaling is vital for addressing health challenges related to rhythm disorders [2].

Alzheimer is the foremost reason of dementia, increasingly recognized for its significant impact. Recent advancements include understanding pathology, genetic factors, and emerging biomarkers. Case studies illustrate diverse clinical presentations. Current estimates project dementia prevalence will triple by 2050, particularly affecting low-income regions, despite declining incidence in wealthier countries [3]. The median survival time after an Alzheimer's dementia diagnosis is 6 years. For a 70-year-old, the total estimated duration of stages is 20 years: 10 years preclinical, 4 prodromal, and 6 dementias. Major risk factors include age, APOE ϵ4 allele, and gender, with lifestyle affecting dementia risk but not Alzheimer's pathology [4]. The widespread occurrence of clinically diagnosed AD dementia is high and projected to increase with an aging population, affecting approximately 3–4% of adults in late working or retirement years. According to studies, the prevalence increases with age; in China, estimates range from 0.2% for those aged 55 to 59 to 48.2% for people aged 95 to 99. According to a meta-analysis, the prevalence is higher in women (7.13%) than in men (3.31%) [5].

Biomarkers play essential roles in Alzheimer's disease clinical practice, aiding in early patient identification, therapeutic monitoring, and differential diagnosis. Three important biomarkers for AD in cerebrospinal fluid are phosphorylated tau (P-tau), total tau (T-tau), and Ab1-42 [6]. While research has established correlations between these biomarkers and AD pathology, variability in measurement methods and a lack of standardization hinder widespread clinical application. Recent advances in biomarker development show promise for early AD diagnosis. The primary amyloid imaging agent is [11C]-PIB, effective in distinguishing AD from normal cognition [7]. CSF phosphorylated tau indicates tau pathology, while total tau reflects neuronal injury and disease progression, with high P-tau levels unique to AD. Tau deposition correlates with cognitive decline. MRI and fluorodeoxyglucose positron emission tomography (FDG-PET) are key diagnostic tools, while blood biomarkers, including plasma Ab and tau, are emerging for accessible AD screening and evaluation.

Recent studies indicate the potential of plasma biomarkers, such as the Ab1-42/1-40 ratio, plasma tau, and neurofilament light chain (NFL) levels, in detecting Alzheimer's disease [8]. The decline in memory and hippocampal volume (HV) correlates with high Aβ levels, exacerbated by the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism in preclinical Alzheimer [9]. Studies indicate that BDNFMet carriers face greater memory decline, while KIBRA protein involvement in memory processes is disrupted by tau acetylation, linking synaptic dysfunction to cognitive decline in AD [10]. Mild Cognitive Impairment (MCI) presents cognitive functioning deficits that do not meet dementia criteria. Distinguishing MCI from Cognitive Impairment, No Dementia (CIND) relies on the severity of cognitive decline. The Mayo and Winblad Criteria serve as diagnostic standards for MCI, focusing on preserved daily activities despite cognitive decline, with MRI metrics aiding in assessing Alzheimer's Disease progression. Elevated tau and reduced Aβ1-42 levels show high specificity and sensitivity. Various biomarkers, including brain-related proteins and neurogranin, are under investigation for MCI and AD diagnosis and differentiation [11].

The intricate interactions between genetic variables and processes such as amyloid beta (Aβ) peptide buildup make it difficult to detect and treat Alzheimer's disease early. Key mutations in APP and apolipoprotein E (APOE) ϵ4 significantly impact symptomatic onset and progression [12]. Understanding these relationships is crucial for developing effective interventions against AD. APOE exhibits a protective role against oxidative stress, with its impact varying by allele type; APOE ϵ2 is notably protective, while APOE ϵ4 increases cell death risk under oxidative conditions [13]. Additionally, the Amyloid Cascade Hypothesis (ACH) has faced scrutiny despite attempts to develop therapies targeting Aβ peptides, which have largely failed in trials [14].

2. The central clock and SCN

The mammalian biological clock, which regulates the circadian rhythm cycle, is made up of a peripheral clock and a central master clock. Located in the hypothalamic suprachiasmatic nucleus is the central master clock. The intrinsically photosensitive retinal ganglion cells (ipRGCs) provide external light signals to the SCN via the retinohypothalamic tract, and the SCN simultaneously communicates with other parts of the brain [15] as shown in Fig. 1. Hormones, body temperature, and sleep-wake cycles are all regulated by the SCN, which functions as a pacemaker [16]. Through bodily fluids and the neurological system, the SCN regulates the peripheral clock, which is widely dispersed throughout many organs and tissues (e.g., cortisol rhythm and melatonin rhythm [17]).

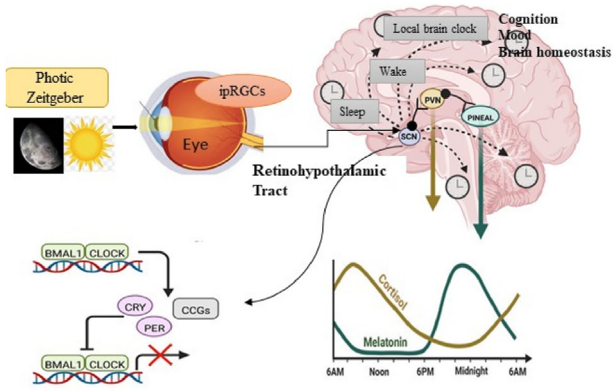

Fig. 1. Central clock: suprachiasmatic nucleus.

A transcriptional-translational feedback loop (TTFL), comprising positive, negative, and auxiliary components, controls the production of intracellular circadian rhythms [18]. CLOCK and BMAL1, two key clock proteins with a basic helix-loop-helix domain, are involved in the positive component. These proteins combine to produce heterodimers that bind to the Per1-2 and Cry1-2 genes' E-box enhancer regions, increasing the transcription of those genes. The PER and CRY proteins, which make up the negative component, go back to the nucleus after translation and work with the CLOCK/BMAL1 complex to inhibit transcription [19]. This inhibition reduces PER and CRY transcription, and the proteins are subsequently degraded, allowing CLOCK/BMAL1-mediated transcription to resume. An accessory loop further modulates this system through CLOCK/BMAL1-driven transcription of the REV-ERBα gene. In Fig. 2, the nuclear receptor REV-ERBα that results interact with the retinoic acid receptor-related orphan receptor (ROR) response element in the Bmal1 promoter to suppress its transcription. When CLOCK/BMAL1 activity is inhibited by PER and CRY, REV-ERB α expression falls, releasing Bmal1's repression and allowing its levels to increase [20]. The transcription of many other genes with E-box enhancer elements in their promoters is also regulated by CLOCK/BMAL1 heterodimers; these genes are collectively referred to as clock-controlled genes (CCGs), which extend circadian regulation to a variety of physiological functions [21]. The elucidation of this molecular mechanism highlights how genetic regulation underpins complex behaviors, demonstrating how mutations in a single gene can alter circadian periods or even disrupt rhythmicity altogether [22].

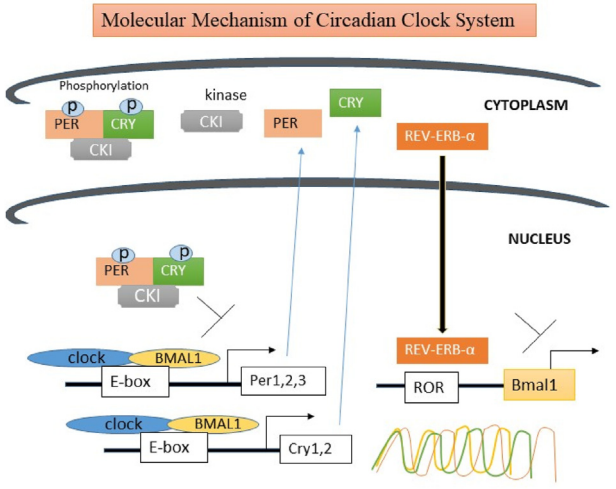

Fig. 2. Molecular mechanism of circadian rhythm regulation.

During the subjective night, decreasing levels of PER result in heightened signaling from intrinsically photosensitive retinal ganglion cells (ipRGCs), causing a phase delay in *Per* expression. Later in the subjective night, as *Per* expression increases, ipRGC signaling facilitates a phase advance. The suprachiasmatic nucleus also responds to non-photic cues, often influenced by behavioral arousal [23]. The SCN is a heterogeneous network predominantly composed of GABAergic neurons that release regionally distinct peptide neurotransmitters, reflecting diverse functional roles [24]. Keeping synchronised neural rhythms requires the SCN's intrinsic network. The main neuron types in the SCN include arginine vasopressin (AVP)-secreting neurons in the shell area, and neurons in the core that secrete vasoactive intestinal peptide (VIP) and gastrin-releasing peptide (GRP) [25]. Neuropeptides such as VIP and AVP play critical roles in sustaining and modulating circadian rhythms. Previously, VIP neurons were thought to be the primary cell type receiving direct input from ipRGCs [26]. However, recent findings indicate that AVP and GRP secreting neurons are also linked to ipRGCs synaptically [27]. This implies that a range of chemicals might be needed to create appropriate ipRGC synaptic connections with the heterogeneous population of retino-recipient cells engaged in visual processes other than picture formation, like pupil constriction and circadian photoentrainment [28]. The SCN integrates inputs from ipRGCs and other brain regions to maintain circadian rhythms. It projects to multiple hypothalamic and extrahypothalamic areas, potentially influencing arousal and mood regulation [29].

3. Changes in SCN associated with AD

The primary circadian pacemaker in mammals, including humans, is the SCN in the hypothalamus. Clinical evidence indicates that lesions in this area

result in disrupted circadian rhythms and decreased vasopressin expression [30–32]. Notably, a patient with a bilateral SCN destruction experienced a reversal of the sleep-wake pattern. SCN neurons exhibit heterogeneity based on neuropeptide content, notably vasoactive intestinal peptide (VIP) in the entrainment area and vasopressin (AVP) elsewhere, with AVP being crucial for rhythmicity across brain regions [33,34]. Aging reduces AVP-expressing neurons after age 50, while VIP numbers in females remain stable, though males show a decrease with age. GABA is also a key neurotransmitter in the SCN [35].

Aging may disrupt the suprachiasmatic nucleus, particularly in Alzheimer, where there is a notable decline in vasopressin (AVP)-expressing neurons in the SCN, especially in those under 65 with presenile AD. VIP-expressing neuron numbers also diminish in these patients. Increased astrocytes (GFAP-stained) signify reduced SCN activity, alongside observed neuro-pathological changes like pre-tangles and tangles [36]. In patients with AD, AVP mRNA levels were considerably lower, and their diurnal cycles were disturbed. Notably, even cognitively intact individuals in early AD stages show reduced AVP gene expression, hinting at early SCN dysfunction affecting circadian rhythms in AD, meriting further investigation [37]. In aging, the molecular mechanisms regulating circadian rhythms within SCN cells exhibit notable changes. Research indicates a decrease in Bmal1 and Clock expression in the SCN with age, while Per1 and Per2 levels remain stable in hamsters and rats [38]. Additionally, light-induced expression of Per1 and Per2 declines in aged rodents. Studies on heterozygous Clock mutant mice suggest that Clock mutations do not heighten age-related circadian disruptions. However, evidence shows accelerated decay of the clock in certain mutant mice. Age-related declines in clock gene expression also occur in peripheral organs. Recent findings indicate severely impaired circadian gene expression in senescent human vascular smooth muscle cells, highlighting potential therapeutic avenues [39].

4. Role of clock genes in pathogenisis of AD

Recently, there has been an increase in interest in chronogenetics, the study of circadian genetics [40], especially regarding its relationship with Alzheimer's disease. AD may be associated with changes in clock gene expression and polymorphisms in these genes [41,42]. Studies reveal that sleep behavior changes in AD patients correlate with reduced expression of various clock genes, particularly after sleep deprivation. In transgenic mouse models, chronic sleep deprivation lowered levels of BMAL1, CLOCK, and CRY1, leading to increased tau phosphorylation in the cortex [43]. BMAL1 deficiency in knockout mice resulted in cognitive decline and reduced hippocampal long-term potentiation. Moreover, the severity of AD is correlated with higher BMAL1 gene methylation. Finally, genes like BMAL1 and CLOCK regulate astrocyte dysfunction in AD, influencing energy metabolism and lactate production [44]. CLOCK and BMAL1 overexpression activate caspase-3-dependent apoptosis in human astrocytes, highlighting the need to explore strategies to reduce their levels for neuroprotection [45]. Clock gene polymorphisms, particularly CLOCK T3111C, increase the likelihood of developing Alzheimer's disease by 47% [41]. Additionally, these polymorphisms interact with cardiovascular factors that may further impact AD progression. Nobiletin, a flavonoid from tangerines, has been shown to counteract BMAL1 reduction in female AD mouse models while activating metabolic genes linked to insulin signaling and mitochondrial function [46]. Modulating clock genes could offer a promising approach for preventing and treating neurodegenerative diseases like AD, with a focus on further studies targeting astrocyte dysfunction and gene expression.

5. Brain cognitive functions and circadian rhythm: a connection

5.1. Attention

The distribution of our finite cognitive processing resources to our surroundings is known as attention. Vigilance, tonic attention, phasic alertness, and selective alertness are its subcategories. Selective attention filters environmental stimuli, allowing us to focus on relevant information. Phasic alertness prepares us for specific upcoming events, while tonic alertness reflects our overall activation level. Vigilance refers to the capacity to maintain focus on a single object for extended periods. Although results on sustained attention are conflicting, research suggests that circadian rhythms and sleep deprivation may affect tonic and phasic alertness as well as selective attention [47]. The cerebral cortices play a crucial role in attention activation, with tonic alertness regulated by the reticular activating system and phasic alertness linked to the frontal and parietal cortices [48,49]. Studies show that selective attention peaks around midday, with varying peak times in the morning for tonic alertness [50]. Additionally, cognitive functions are associated with the

temperature of body, as this is an essential measure of these functions. The interplay between circadian rhythms and cognitive processes remains an area of ongoing research [51].

The metabolic rhythm of the body is particularly evident in temperature variations, which typically rise during the day and drop in the evening [52]. Research indicates a strong link between core body temperature and cognitive performance, with factors like chronotype and task difficulty further influencing attention changes associated with circadian rhythm [53]. Manipulations of circadian rhythm desynchronization reveal that sustained attention diminishes, correlating with reduced activation in related cortical and neural networks, particularly due to sleep deprivation. Tasks like the Stroop test, which engage the prefrontal cortex, demonstrate sensitivity to lack of sleep, impacting tonic alertness, selective attention, and vigilance [54]. Neuroimaging studies, especially using functional magnetic resonance imaging (fMRI), illustrate that sleep deprivation significantly hinders activity in the prefrontal and parietal cortices, crucial for cognitive functions [55]. Additionally, attention networks are compromised post-sleep deprivation, evidenced by decreased accuracy in tasks and altered connectivity in the default mode network. Long-term studies on sustained attention reveal how circadian rhythms influence neural responses across different phases [56].

5.2. Working memory

A key component of the cognitive system, working memory is divided into long-term and short-term memory according to the length of time it may be retained [57]. Long-term memory lasts over a day, whereas short-term memory spans seconds to hours and plays a vital role in advanced cognitive functions like reasoning and problem-solving [58]. Neuroimaging studies link working memory tasks to prefrontal cortex activation, indicating that damage to this area can impair performance [59]. Additionally, circadian rhythms significantly influence memory formation, with studies indicating that blue light exposure impacts working memory efficiency [60]. Research shows that working memory capacity peaks around noon, corresponding with brain metabolic activity. This relationship suggests that temperature fluctuations and hormonal indicators like salivary cortisol are also linked to circadian effects on working memory performance [61].

Working memory capacity varies throughout the day and is influenced by individual differences among participants, task types, and circadian rhythms categorized into “mornings” and “evenings.” Children typically excel in cognitive functions in the morning, while adults perform better at night [62]. Age also contributes to these variations, as noted by Rowe et al., [63] indicating that visual working memory capacity is affected by testing times and external factors. The relationship between working memory load and daily fluctuations has been noted, with Folkard linking easier tasks to temperature changes, which is less evident under heavier loads. Additionally, metabolic activity underpins circadian rhythms, while neuroimaging studies have shown diverse outcomes in cognitive function based on sleep deprivation, revealing activation patterns in different brain areas. Future research may benefit from advanced technologies to better assess these dynamics [64].

Lack of sleep causes the left anterior cingulate cortex to become less active during memory tasks, whereas the left and right middle occipital gyrus become more active. This results in a severe exhaustion of working memory. When sleep deprivation is present, a noteworthy interaction effect demonstrates deactivation in the right insula, right middle frontal gyrus, and left inferior frontal [65]. The superior parietal and left thalamus were among the brain regions that showed decreased activation in both the deprivation of sleep and resting groups when compared to baseline. Additionally, studies on circadian disorders and bipolar disorder indicate that disruptions in sleep patterns may impair working memory due to decreased function in the prefrontal cortex [66]. As task demands rise in patients with primary insomnia, task related memory areas are also deactivated, especially in the right dorsolateral prefrontal cortex [56].

5.3. Executive tasks

The capacity to start, program, and regulate behaviour is a component of executive functions, which are essential for resolving issues controlled behaviour, and making decisions. The frontal lobe integrates several essential elements, such as initiative, inhibition, adaptability, arranging, prevision, self-management, verification, and correction [67]. Initiative establishes goals while cognitive inhibition restrains irrelevant behaviors. Flexibility adapts response strategies, and planning organizes actions toward goals [68]. Prevision assesses potential outcomes, self-monitoring adjusts actions based on environmental requirements, verification examines results, and correction modifies actions to meet goals. Assessment of these functions in laboratories can be challenging due to the need for novel tests that avoid practiced strategies [69,70].

To assess circadian rhythms in executive functions, tests need to be repeated throughout the day, impacting novelty. Components like planning rely on novelty, while others, such as inhibition, flexibility, and self-monitoring, can utilize repeated tasks (e.g., Stroop and go/no-go tasks). Studies showed cognitive inhibition worsens at low body temperatures, especially overnight and early mornings (03:00–06:00) [71]. Similar patterns of decreased cognitive flexibility and self-monitoring were noted, particularly from 05:00 to 09:00, affecting decision-making and problem-solving tasks [51].

6. Circadian rhythm disruption linked to Alzheimer's disease

6.1. Sleep-wake activity and sleep deprivation

Sleep-wake activity is governed by the circadian clock, with disruptions occurring in Parkinson's disease (PD) and AD models. Genetic mutations, such as those in pink1, parkin, and GBA1, influence sleep patterns [72]. Also, sleep disturbances, prevalent in 14%–69% of AD patients, may exacerbate neurodegenerative processes by hindering protein clearance in the brain. Research indicates a 24% decrease in insulin sensitivity after just five nights of restricted sleep. Changes in endocrine profiles, such as heightened nocturnal cortisol and impaired TSH secretion, have been noted [73]. Mechanisms include insulin resistance linked to changes in adipose tissue signaling and DNA methylation alterations in key molecular clock genes [74].

Sleep disturbances in Alzheimer's Disease are often bidirectional, influencing disease progression [75]. Studies suggest sleep deprivation may exacerbate amyloid accumulation, while circadian rhythm disruptions contribute to sundowning syndrome. Sundowning occurs in 2.5%–66% of Alzheimer's disease patients, linked to phase delays in body temperature and hormone secretion. Restless legs syndrome (RLS) is found in 4%–6% of AD cases and more frequently in Parkinson's disease [76,77]. Sleep-disordered breathing affects 15%–54% of AD patients and may worsen cognitive decline, whereas roughly 10% of AD individuals have a sudden eye movement sleep behaviour problem. Circadian rhythm disruptions are linked to AD progression, affecting sleep, neuroinflammation, and Aβ production [78] as shown in Fig. 3. Irregular Sleep-Wake Rhythm Disorder is common among AD patients, linked to hypothalamic changes and senile plaque deposition. Alzheimer's disease patients exhibit disrupted circadian rhythms due to neuron loss in the suprachiasmatic nucleus. Sleep

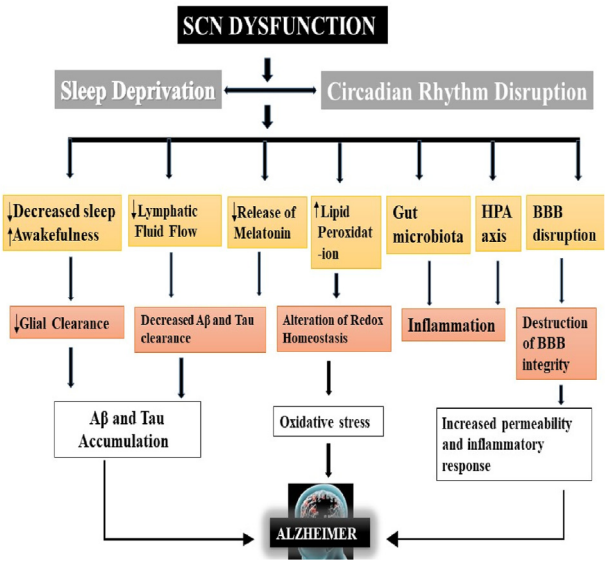

Fig. 3. - Bidirectional relationship between microbiota rhythmicity, systemic inflammation, and Alzheimer's pathology.

disturbances hinder Aβ clearance, potentially exacerbating AD pathology. Treatments targeting circadian alignment might aid in managing symptoms and delaying institutionalization, emphasizing the intertwined roles of sleep and AD progression [79].

6.2. Melatonin

Melatonin, or N-acetyl-5-methoxytryptamine, is a crucial timing signal produced by the suprachiasmatic nucleus and synthesized mainly in the pineal gland from serotonin [80]. Its production occurs during the dark phase of the circadian cycle and is regulated by light exposure, with melatonin secretion starting 2 h before bedtime [81]. This rhythmicity involves various transcription factors known as CLOCK genes. Melatonin influences numerous physiological processes, notably regulating body temperature, mood, immune function, and sleep. Interactions with the MT1 and MT2 melatonin receptors in the SCN mediate its sleep-promoting effects, contributing to both direct sleep induction and the advancement of circadian rhythms [82]. However, melatonin's effects vary based on the timing of administration, with differing influences on the circadian clock during different phases of the night.

The pineal gland's function is disrupted in Alzheimer's disease, although it itself remains unaffected by pathology. CLOCK gene expression, regulated by the pineal gland, is impaired in both clinical and preclinical AD, resulting in the loss of diurnal patterns [83]. This disruption may stem from decreased output from the suprachiasmatic nucleus, which influences the pineal gland's activity. Studies

indicate that serotonin, a melatonin precursor, is depleted in early AD stages, and overall melatonin levels decline significantly with aging, particularly in AD patients [84]. Studies reveal that AD patients have significantly reduced amounts of melatonin in their cerebrospinal fluid. As the disease progresses, melatonin secretion becomes irregular, suggesting that SCN control over the pineal gland is compromised, leading to a loss of melatonin's circadian rhythm [85].

6.3. Cortisol

Cortisol, a crucial hormone in human physiology, impacts nearly all body cells, transmitting circadian signals from the SCN to peripheral tissues. During stress, adrenal glands release cortisol to manage the stress response, following a rhythm controlled by the SCN [86]. After waking, cortisol peaks synchronize the body with the retinoic acid receptor (RAR) and light-dark cycle. Age-related changes include an earlier peak and decreased amplitude, potentially linked to neurodegeneration in older individuals. While some studies show elevated morning cortisol in mild cognitive impairment (MCI) patients, meta-analyses indicate no significant differences in blood or salivary cortisol levels between MCI patients and healthy controls [87]. Cortisol levels, measured in CSF, exhibit minimal heterogeneity and are linked to cognitive function. A cross-sectional study indicated that lower morning-evening cortisol ratios correlate with cognitive impairment in men, while findings for women are less clear. Increased salivary cortisol responses were observed in mild cognitive impairment patients versus healthy controls. High evening salivary cortisol in healthy individuals is associated with visual recognition memory deficits. Moreover, higher cortisol levels correlate with worse cognitive changes in aging but not brain atrophy. Exercise suggests potential cognitive benefits through diurnal cortisol patterns [88].

6.4. The axis of gut-brain microbiota

Neurodegenerative diseases, including Alzheimer's disease, may arise as a result of disruptions in circadian control of peripheral processes, such as oscillations in the gut microbiota. Loss of gut microbiota can compromise gut barrier integrity, triggering immune activation and systemic inflammation. This, in turn, impairs BBB, leading to neuroinflammation, neuronal damage, and eventual neurodegeneration [89–91]. There is growing evidence that the human's circadian clock controls the rhythmic patterns of gut bacteria [92]. On the other hand, the functional gene profile of the gut microbiome is negatively impacted by disturbances in the host's circadian rhythm, which lowers the expression of genes essential for fostering advantageous immune responses [93]. This changed microbial profile is comparable to what is seen in AD patients [94].

7. Pathogenic mechanisms of circadian rhythm disruption and Alzheimer

7.1. Amyloid-β pathology

The Aβ plaque is made up of Aβ peptides that are produced by secretases (α, β, and γ) enzymatically cleaving the amyloid precursor protein. The cleavage of APP by β-secretase, which results in C-terminal membrane-bound fragments of 89 or 99 amino acids, is the first step in the development of the Aβ plaque [11]. Aβ accumulation occurs 15–20 years prior to cognitive dysfunction in AD, with sleep disturbances often emerging during the preclinical stage, serving as a predictive factor for neurodegeneration [95]. Research indicates that Aβ buildup is closely correlated with an insufficient amount of sleep, which is characterised by shorter sleep duration, lower efficiency, and increased latency. This is especially true in brain regions like the prefrontal cortex and angular gyrus, as seen in PET imaging [96]. Sleep deprivation studies indicate that even one night without sleep can elevate Aβ42 levels in the CSF, while chronic deprivation increases Aβ production significantly [97]. ISF Aβ levels in transgenic mice were found to rise during active periods and decrease during sleep, reflecting similar diurnal fluctuations observed in human CSF [98].

Both Tg2576 and APP/PS1 amyloid-developing model mice exhibited significant increases in amyloid plaque pathology due to chronic sleep deprivation [79]. On the other hand, giving APP/PS1 animals an orexin receptor antagonist every day for eight weeks decreased amyloid pathology [99]. While Kang et al. suggested that wakefulness correlates with increased Aβ production and Xie et al. found that sleep aids in Aβ clearance through the glymphatic system, which enhances cerebrospinal fluid influx during sleep compared to wakefulness [100]. Experiments demonstrated that APP/PS1 mice lacking orexin had less Aβ pathology and more sleep. Orexin modulation influenced the sleep-wake cycle but didn't directly impact Aβ levels. Ultimately, sleep's role is crucial in regulating Aβ dynamics and amyloid pathology in various amyloid precursor protein mice models [101].

Aβ pathology likely drives early sleep changes in AD, although mechanisms remain unclear and may involve specific neuronal circuits. While amyloid pathology in subcortical and brainstem areas occurs later, it may contribute to worsening sleep deficits as the disease progresses [102]. Regions like the hypothalamus, where sleep regulation occurs, show significant amyloid deposition, potentially explaining sleep loss [103]. Research indicated that amyloid accumulation disrupts the sleep-wake cycle and diurnal fluctuations of interstitial fluid Aβ. Vaccination against Aβ deposits restored normal sleep patterns and interstitial fluid (ISF) Aβ fluctuations in affected mice [104]. The periaqueductal grey matter (PAG), a dopaminergic wake-active region, also exhibits amyloid pathology in 81% of AD cases. While these findings highlight Aβ′s significant role in sleep disturbances linked to AD, they do not encompass other pathological aspects like tau aggregation. The mechanisms by which Aβ induces sleep changes likely involve various factors, including its impact on neuronal circuits in regions governing sleep, indicating a bidirectional link between sleep disturbance and Aβ deposition [105].

7.2. Tau (τ) pathology

In AD patients, tau proteins are misfolded and altered in shape, leading to debates about their role in disrupting the biological clock [106]. Research on aged tau transgenic or Tg4510 mice shows their prolonged free-running durations suggest a disruption in the equilibrium of the circadian clock. The disturbed cyclic regulation of the clock proteins PER2 and BMAL1 in the hippocampal and hypothalamic regions of Tg4510 animals supports this [107]. These findings suggest that tauopathy impairs internal clock functions and offers a model for studying the link between tau pathology and circadian dysfunction. Further studies in Drosophila reveal tau deficiency disrupts circadian functions and sleep patterns [94]. Recent studies have shifted focus to the relationship between sleep and tau protein in the brain, an important factor in Alzheimer's disease. CSF tau and P-tau serve as markers for neuronal injury and neurofibrillary tangles, respectively [108]. Although there is strong evidence that Aβ aggregation causes Alzheimer's disease, including promoting the aggregation and distribution of tau proteins, tau aggregation appears to worsen neurological damage [109]. The researchers examined whether sleep deprivation and the sleep-wake cycle affected tau levels by measuring tau protein levels in the cerebrospinal fluid and interstitial fluid. According to the results, mice's ISF tau levels increased by roughly 90% when they were awake normally and by 100% when they were not sleeping. Similarly, when humans were sleep deprived, their CSF tau levels rose by over 50%. These findings imply that tau levels in the ISF are regulated by the sleep-wake cycle, and that lack of sleep raises tau levels in the ISF and CSF and increases pathological diffusion [110].

According to recent studies, tau pathology is among the first observable alterations in the human brain that resemble AD. Early adulthood is when irregular tau phosphorylation and agglomeration in the locus coeruleus start [111], subsequently expanding to further interconnected areas before amyloid deposits are noticeable [112]. Additional research has also shown that the norepinephrine metabolite DOPEGAL can covalently alter tau's K353 site in the locus coeruleus, which encourages tau aggregation and lesion propagation [113]. Despite these discoveries, little is known about how tau disease affects sleep in preclinical and clinical AD. These findings highlight the crucial part tau plays in AD-related sleep problems [114].

7.3. Vascular dysfunction

The vascular hypothesis was initially put forth in 1993 and is supported by experimental and clinical data that show that chronic brain hypoperfusion is a major contributing factor to the negative consequences of all known risk factors for Alzheimer's disease. It is believed that this ongoing hypoperfusion is the primary cause of neurodegeneration [115]. The pathological changes linked to the vascular hypothesis are best studied in rat models of long-term brain hypoperfusion, which show changes more similar to the pathology of AD than vascular dementia. The posterior parietal cortices and the hippocampus CA1 area are especially susceptible to alterations brought on by hypoperfusion [116]. After a decrease in hippocampal blood flow, these models show neuronal energy metabolism, astrocyte activation (astrocytosis), reduced protein synthesis, increased protein abnormalities, oxidative stress, loss of spatial memory, damage to endothelial cells, upregulation of amyloid-beta 1-42, brain atrophy, and finally, neuronal death [115].

The vascular hypothesis is further supported by research on humans. Vascular risk factors are important in the development of AD, according to epidemiological studies [117,118]. Cerebral hypoperfusion and hypometabolism are frequently indicated by single-photon emission computed tomography (SPECT) and positron emission tomography (PET) scans in people with moderate cognitive

impairment who are at high risk of developing AD [119,120]. Antihypertensive treatments have been shown to lower AD risk. Additionally, microvascular changes in the brain are recognized as critical contributors to AD pathogenesis, both clinically and pathologically [121,122]. Circadian rhythms affect cerebral vascular perfusion. The daily regularity of cerebral blood flow rate in humans throughout a 30-h period of prolonged awake was examined in a study by Conroy et al. The purpose of this study was to ascertain whether sleep-independent intrinsic circadian rhythms or behavioural and metabolic alterations alone were responsible for time-of-day differences in perfusion [123]. The results showed that blood flow rate has an endogenous circadian rhythm, which calls for more research when it comes to deteriorating cognitive function and cardiovascular or cerebrovascular incidents. Using laser-Doppler flowmetry, similar findings were seen in rats, suggesting a diurnal periodicity in cerebral blood flow that is unaffected by variations in blood pressure or locomotor activity [124]. Future studies investigating the role of vascular function in the etiopathogenesis of AD should take into account the effect of circadian rhythms on cerebral perfusion and brain metabolism [125].

7.4. α-Synuclein aggregation

Vesicle release and trafficking are believed to be significantly influenced by α-Synuclein. This 140-amino acid protein is primarily expressed in neurons' pre-synaptic terminals [126]. Lewy neurites and Lewy bodies, which are intracytoplasmic aggregates of α-synuclein, are pathological features of multiple system atrophy, Parkinson's disease, and dementia with Lewy bodies (DLB), among other neurodegenerative diseases [127]. It is noteworthy that up to 60% of patients with sporadic Alzheimer's disease have Lewy body pathology in their brains. While the substantia nigra and brainstem may also be partially involved, the amygdala exhibits consistent pathology in AD cases with Lewy bodies. The pathology may also spread to the neocortex [128]. In cases of AD that are dominantly inherited, Lewy bodies are highly prevalent and are primarily found in the amygdala, brainstem, limbic regions, and neocortical areas [129]. Interestingly, patients with inherited AD and Lewy bodies outside the amygdala often exhibit a longer disease progression [130]. Furthermore, the pathophysiology and clinical symptoms of AD and DLB significantly overlap, underscoring the significance of examining their interaction, especially in respect to sleep disruptions [131]. According to Harper et al., compared to AD patients and non-demented controls, individuals with DLB had more noticeable disturbances in their circadian rhythms of locomotor activity [94].

7.5. Metabolic dysfunction

Research on Alzheimer's disease has recently focused a lot of attention on metabolic dysfunction because of its correlation with neurodegenerative alterations seen in both clinical and experimental trials [132]. Early onset of metabolic problems suggests that changes in energy systems may be a key factor in the pathophysiology of AD. This has clinical significance because fluorodeoxyglucose positron-emission tomography (FDG-PET) can identify problems in glucose metabolism *in vivo*. There is growing evidence that FDG-PET is useful for detecting AD in its early stages [133,134]. The theory that impaired insulin signalling may play a significant role in the development of AD has emerged as a result of the increasing understanding of insulin as a crucial regulator of brain metabolism [135]. The brain was formerly thought to be insulin-insensitive, but studies conducted in the last few decades have shown that insulin has pleiotropic effects in controlling vital functions for maintaining brain homeostasis, such as metabolism of glucose, synaptic plasticity, and growth of neurons or survival [136].

Circadian fluctuations in metabolic processes are regulated by both internal and environmental factors. The behavioural patterns that alternate between times of activity and feeding and rest and fasting are consistent with these differences [137]. The significance of circadian control of metabolism is shown by research, which reveals that disturbances, whether exogenous [138] or endogenous [139] can induce metabolic syndrome-related changes in both humans and animals. Circadian-related metabolic abnormalities should be regarded as a potential factor in the development of age-related neuropathology, given epidemiological evidence that links metabolic dysfunction to an increased risk of AD and animal studies that implicate metabolic disruption as a causative mechanism in neurodegeneration [140,141].

8. Additional factors associated with AD and sleep

8.1. Apolipoprotein E (APOE)

The brain's astrocytes produce the majority of apolipoprotein E, which is an essential cholesterol carrier that makes lipid transport between cells easier [142]. The most important genetic risk factor

for late-onset Alzheimer's disease, which accounts for more than 99% of cases, is the APOE genotype. By altering Aβ clearance and aggregation, APOE affects AD aetiology [143]. Among the three polymorphic alleles (ϵ2, ϵ3, ϵ4), ϵ3 is the most prevalent (77%) and ϵ2 is the least prevalent (8%). Nearly 50% of AD patients have the ϵ4 allele, which is significantly associated with an elevated risk of AD and has a 15% prevalence in the general population [144]. Compared to non-carriers, those with one ϵ4 allele are three to four times more likely to acquire AD early. Additionally, Aβ deposition is more common in ϵ4 carriers, suggesting that ϵ4 encourages Aβ aggregation while ϵ2 seems to be protective [145]. Additionally, recent research suggests that tau-dependent neurodegeneration is made worse by ϵ4. Additionally, there is a reported link between sleep apnoea and APOE ϵ4, albeit this link is debatable [146]. Research indicates that ϵ4 carriers have lower-quality sleep, which could raise their risk of dementia. To fully understand how APOE genotypes affect sleep problems in AD patients and animal models, more research is required [147].

8.2. Microglia

Microglia are central nervous system immune cells derived from myeloid progenitor cells. In healthy brains, they are active, constantly monitoring the environment and rapidly adjusting their processes [148]. According to research, both people and transgenic mice with amyloid deposition exhibit active microglia in close proximity of amyloid plaques [149,150]. Alzheimer's disease risk is greatly increased by genetic variations in the TREM2 gene, indicating the involvement of microglia in the pathophysiology of AD [151]. Loss of TREM2 function exacerbates toxicity associated with Aβ plaques, such as P-tau accumulation and neuritic dystrophy. Interestingly, TREM2 deficiency may reduce neuroinflammation and protect against neurodegeneration in tauopathy models, suggesting a complex role for TREM2 [152]. Sleep disturbances negatively impact microglial morphology and Aβ clearance, with chronic sleep deprivation increasing phagocytosis of synaptic structures. Poor sleep correlates with adverse CSF biomarker profiles in AD, underscoring the need for further investigation into sleep's effects on microglial function in this context [105].

8.3. Potential diagnostic tools for monitoring circadian rhythm

The correlation between Alzheimer's disease and sleep problems emphasises how important it is to accurately diagnose sleep disorders and circadian rhythm abnormalities. While variations in sleep patterns may act as early diagnostic markers for at-risk populations, sleep problems in AD patients might exacerbate cognitive impairment. In dementia patients, abnormal rest-activity timing is linked to increased institutionalization and reduced survival rates [153]. Circadian rhythms can be monitored through methods like plasma melatonin measurement and rectal thermometry, although the latter is limited by confounding factors [154]. Behavioral outputs like sleep-wake cycles are practical for clinical use, though not perfectly indicative of circadian rhythms. Sleep-wake disturbances may present various manifestations, making their diagnosis complex. Analyzing these disturbances can yield insights into disease progression, as shown by a study linking decreased sleep efficacy to amyloid deposition in cognitively healthy individuals [155].

8.4. History and questionnaires

The first step in evaluating sleep-wake abnormalities in people with Alzheimer's disease is gathering a thorough medical history, frequently from carers. This should include information on comorbidities, medications, sleep hygiene habits, and ideally a sleep journal tracking sleep timing, quality, nighttime awakenings, behavioral symptoms, and daytime naps [156]. Traditional questionnaires like the Pittsburgh Sleep Quality Index have limitations, as AD patients may underestimate their issues, and caregivers may bias the responses [157]. The Sleep Disorders Inventory (SDI), which evaluates frequent sleep symptoms in AD, and the Neuropsychiatric Inventory are two tools that can be used to measure sleep abnormalities. Furthermore, the assessment needs to look for primary sleep disturbances because diseases like restless legs syndrome, which can affect up to 24% of dementia patients, and obstructive sleep apnoea, which affects 40–70% of AD patients, are prevalent and curable [158,159].

8.5. Actigraphy

Actigraphy offers objective information on each patient's unique sleep-wake patterns in their natural settings, making it a useful tool for the diagnosis and treatment of insomnia, circadian cycle disorders, and excessive daytime sleepiness [160]. It makes use of an actigraph, a portable accelerometer worn on the wrist or ankle that continually records patterns of rest and activity over long periods of time (days to months). For accurate analysis, data gathering should take at least seven days [161].

While basic actigraphs require certain technical standards, additional features like waterproof cases and light sensors enhance functionality. To improve analysis accuracy, supplementary sleep logs can be used, noting habitual behaviors and awakenings [162]. Actigraphy may, however, exaggerate sleep and underestimate wake time; accuracy will decline as sleep quality declines. Compared to polysomnography, validation studies demonstrate excellent sensitivity and specificity; nevertheless, it is crucial to remember that polysomnography usually records only one night's sleep, which limits its use in the diagnosis of circadian rhythm sleep-wake disorders [163].

8.6. DLMO as a biomarker for SCN phase

The Dim Light Melatonin Onset is an important biomarker for identifying the SCN circadian rhythm phase [164]. Although melatonin secretion is influenced by light, its relationship with the sleep-wake cycle demonstrates minimal masking effects, indicating robustness as a marker for central circadian phase, even under altered conditions. Despite being regarded as the gold standard for assessment, DLMO has potential errors, including measurement inaccuracies and variability in the phase relationship between melatonin and SCN rhythms [165]. Kronauer et al. (2002) evaluated melatonin's effectiveness against other methods, finding its superior reliability with standard deviations ranging from 14 to 21 min, allowing for reliable phase assessments above 30 min. The DLMO's limitations include the need for dim lighting and prolonged sampling periods, which can vary based on prior phase knowledge [166]. In certain scenarios, like shift work or jet lag, a 24-h observation may be necessary. While primarily utilized in laboratory settings, protocols exist for DLMO assessment in home environments, enhancing its practical application in various populations [167,168].

8.7. Timing and effect of light

The circadian system has a cycle length close to 24 h, with healthy sighted humans averaging about 24.2 h, varying between 23.5 and 24.5 h [169,170]. To stay aligned with the 24-h environmental clock, the endogenous circadian clock requires regular resetting through a process known as entrainment, heavily influenced by light. Various characteristics of light exposure, such as spectral composition, intensity, and timing, are crucial for this resetting [171]. The circadian response to light is particularly phase dependent; exposure to light in the early biological day causes phase advances, whereas exposure to light in the late afternoon/early evening (4–7 p.m.) causes phase delays [172]. Generally, a small average phase advance of about 0.2 h results from ideal daily light exposure. People need to be exposed to more light in the morning than in the evening for entrainment to work. The success of light treatment depends on the precise timing of light exposure because misalignment might exacerbate symptoms of hypersomnia or insomnia [173].

9. Future perspectives

The growing recognition that circadian rhythm disruption is a key factor in the aetiology of Alzheimer's disease opens up new avenues for research and therapeutic strategies. Utilising cutting-edge omics technologies like transcriptomics and epigenomics may help us gain a deeper understanding of the connection between circadian gene expression and neurodegenerative processes. Additionally, the involvement of clock gene polymorphisms and epigenetic modifications (CLOCK, BMAL1, PER, and CRY) in AD vulnerability and development should be examined. CRISPR-Cas9 and other advanced genome-editing methods could be used to model these genetic changes both *in vitro* and *in vivo*. The impact of re-establishing microbiome rhythmicity through probiotics, diet, or microbiota transplantation on the pathogenesis of AD should be investigated in future research. AI and machine learning can be used to examine vast amounts of genetic data, clinical results, and circadian patterns. It might be feasible to develop predictive models that would identify people who are susceptible to AD due to abnormalities in their circadian cycles and recommend specialised treatment methods. All things considered, interdisciplinary research that combines chronobiology, neurodegeneration, and precision medicine could revolutionise our understanding of AD and how we treat it. By addressing the complex link between circadian rhythms and AD pathogenesis, future research may pave the way for innovative therapeutics that significantly enhance patient outcomes and quality of life.

10. Conclusion

This review highlights the pathogenic effects of circadian rhythm disturbance in Alzheimer's disease and clarifies the basic role these rhythms play in preserving physiological and behavioural balance. As the primary pacemaker, the suprachiasmatic nucleus coordinates central and peripheral clocks that control important biological functions such as

body temperature, hormone secretion, sleep-wake cycles, and oscillations of the gut microbiome. Whether brought on by ageing, genetic mutations, or environmental causes, disturbances in these rhythms have a series of negative consequences that worsen AD's neurodegenerative processes.

One important mechanism in the pathophysiology of AD is the circadian modulation of peripheral systems, including the gut-brain axis. Amyloid-beta deposition, tau hyperphosphorylation, and neuronal damage are accelerated when the gut microbiota loses its rhythmicity, compromising the integrity of the gut barrier and causing systemic and neuroinflammation. Additionally, changes in important circadian genes, including as BMAL1 and CLOCK, as well as their downstream targets, affect vascular health, immunological regulation, metabolic processes, and cellular rhythmicity—all of which are linked to the development of AD. There is evidence that sleep deprivation increases amyloid-beta buildup and impairs its clearance through the glymphatic system, making sleep abnormalities a hallmark of circadian dysregulation in AD.

Additionally, there is a reciprocal link between tau disease and sleep, whereby disturbed sleep-wake cycles worsen tau aggregation and diffusion, hence compromising cognitive abilities. Likewise, circadian misalignment-driven metabolic dysfunctions underscore the complex interplay of insulin signalling, energy management, and brain health in AD patients. Modern diagnostic techniques like actigraphy and the Dim Light Melatonin Onset (DLMO) assay offer non-invasive ways to evaluate circadian misalignment and how it affects the course of AD. These technologies highlight the significance of circadian indicators as therapeutic targets and provide insightful information on early detection and illness monitoring. There is potential for reducing AD-related pathology through therapeutic approaches that target circadian realignment. Techniques including light treatment, melatonin supplementation, and pharmacological circadian gene modification may help to improve cognitive outcomes, decrease neuroinflammation, and restore rhythmicity.

However, further research is required due to the intricacy of circadian systems and how they interact with AD pathology. Future studies should concentrate on how epigenetic changes and genetic variations in circadian genes interact to affect neurodegenerative processes. Gaining insight into these complex networks could help create individualised treatment plans that use circadian biology to slow or stop the progression of AD. The management of AD could be completely transformed by the incorporation of circadian-based diagnostics and treatments into clinical practice, which would also improve patient quality of life and lessen the disease's severe worldwide impact.

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