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Review

Clock and the Cleaner: Circadian Rhythms and Autophagy Coupling in Alzheimer's Disease

Liyun Ma[1,3], Zhenxiang Gong[1,3], Rong Gao[1,3], Lina Zhu[1,3], Liru Wu[1,3], Min Zhang[2,3*], Li Ba[1,3*]

[1]Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430000, China. [2]Department of Neurology, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University, Tongji Shanxi Hospital, Taiyuan, 030032, China. [3]Hubei Key Laboratory of Neural Injury and Functional Reconstruction, Huazhong University of Science and Technology, Wuhan 430000, China

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ABSTRACT: Alzheimer's disease (AD) continues to progress despite decades of research on protein aggregation, highlighting the need to understand upstream homeostatic failures. Among the earliest alterations in AD are disruptions of circadian rhythms and autophagy, which are mechanistically intertwined. Although circadian dysfunction and autophagic failure have been studied separately, the stage-dependent, region-specific, and cell-type-specific interplay between these systems remains poorly integrated, limiting the development of targeted interventions. In a healthy brain, the circadian clock and autophagy mutually interact, maintaining proteostasis, neuronal function, and rhythmic metabolic and immune processes. In early-stage AD, circadian rhythms show mild disruption and autophagy initiation remains active, but downstream autophagosome-lysosome fusion and lysosomal degradation are impaired, leading to the accumulation of AD pathological proteins. Dysregulation is cell-type-specific: neuronal clocks remain relatively intact, whereas astrocytic and microglial clocks exhibit altered metabolic and immune rhythms, contributing to early pathogenic events. In late-stage AD, severe circadian disruption likely uncouples circadian control from autophagy, and these dysfunctions mutually exacerbate each other, driving neuroinflammation, neuronal dysfunction, and further accumulation of pathological proteins. This review synthesizes current evidence on the circadian-autophagy axis, highlighting mechanistic insights and therapeutic opportunities, and emphasizes the importance of integrating stage-, region-, and cell-type-specific dynamics for the development of precise interventions in AD.

Keywords: Circadian rhythms, Autophagy, Circadian Rhythms-Autophagy Coupling, Alzheimer's Disease

1. Introduction

Alzheimer's disease (AD) stands as the leading cause of dementia [1, 2], and represents a major public health challenge [3]. Its pathological hallmarks include extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau [4, 5]. Despite the recent introduction of Aβ-targeted therapies, halting disease progression remains elusive, highlighting the need to identify upstream mechanisms that drive AD pathogenesis. Notably, profound disruptions in two fundamental biological processes—circadian rhythms and autophagy—are increasingly implicated not only as consequences but also as active participants in disease initiation and progression.

Circadian rhythms, orchestrated by the suprachiasmatic nucleus (SCN) as the central pacemaker, generate near-24-hour cycles that regulate physiology and behavior [6]. In AD, circadian disruption exceeds that observed in normal aging [7-10]. These changes emerge

***Correspondence should be addressed to:** Dr. Li Ba, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. Email: Li Ba: bali2015@126.com, Dr. Min Zhang, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University, Tongji Shanxi Hospital, Taiyuan, China. Email: Min Zhang: zhang_min_3464@126.com.

early, prior to significant cognitive decline, and experimental deletion of clock genes directly impairs memory and learning in animal models [11-14], suggesting a causal role. Concurrently, autophagy, the essential cellular clearance pathway, is critically impaired in AD [15, 16]. This impairment is evidenced by the accumulation of autophagic vesicles [17] and reduced levels of autophagy-related proteins [18], leading to Aβ and tau accumulation and subsequent neurodegeneration [19]. Importantly, circadian disruption and autophagic failure are mechanistically intertwined rather than occurring in isolation [20]. Recent work has uncovered a direct molecular link, in which *Nr1d1* (also known as *Rev-erbα*), a nuclear receptor and core circadian transcriptional repressor, suppresses autophagy [21]. Depletion of *Nr1d1* enhances autophagic flux across models, from human cells to AD C. elegans and 5xFAD mice [21]. This reflects a broader principle in which circadian clock genes transcriptionally regulate autophagy, while autophagy contributes to the stability of clock proteins via degradation [22].

A central question remains: does disruption of the circadian-autophagy axis play a causal role in AD pathogenesis, or is it merely a consequence of the disease? Addressing this question requires moving beyond simple associations to examine the bidirectional interplay between circadian rhythms, autophagy, and AD pathology. Previous studies have largely investigated circadian rhythms and autophagy separately in AD, without systematically summarizing evidence for their coupling. Therefore, our review first integrates findings on circadian and autophagic dysregulation across different AD stages, brain regions, and cell types in both human and animal studies, providing a perspective for understanding circadian-autophagy interactions in AD. We then focus on early-stage AD, where circadian-autophagy coupling is already disrupted. Although direct evidence in advanced stages is limited, these alterations are likely to worsen in late-stage AD and may accelerate disease progression. We further discuss potential therapeutic strategies targeting this axis, including chronotherapy and time-restricted feeding (TRF) in AD, as well as challenges associated with autophagy modulators, such as limited blood-brain barrier (BBB) penetration and mixed clinical outcomes. Finally, we highlight methodological strengths and limitations of key studies (Table 1), identifying gaps that constrain causal inference. Together, this synthesis offers a foundation for understanding how circadian-autophagy dysregulation may drive AD progression and for guiding stage-, region- and cell-type-specific therapeutic strategies, including interventions to restore circadian rhythms, enhance autophagic flux, or combine both approaches.

Table 1. A summary of the key studies.

References	Study subjects	Stage	Brain Region	Cell Type	Methods / Measures	Key findings	Typical Methodological Strengths	Limitations
Circadian rhythms in AD								
Sheehan PW et al. [72]	APP/PS1mice	Early-to-mid AD (mouse)	Cerebral cortex	Astrocytes; Microglia	-TRAP to profile astrocyte, microglial, and bulk cortical translatomes; -Analysis of circadian oscillations in gene expression	-Glial circadian rhythms were altered. -AD-risk genes exhibited abnormal oscillations. -Microglial functional rhythms were disrupted. -Astrocytic autophagy and phagocytosis partially compensated for these changes.	-Astrocytes were profiled using TRAP, and microglia were profiled using RiboTag. -High-resolution circadian RNA sequencing was performed. -Samples were collected every 2 hours over a 24-hour period. -Rhythmicity was analyzed using the RAIN algorithm. -Functional assays assessed microglial phagocytosis and oxidative stress rhythms.	-Mouse model may not fully replicate human disease. -TRAP measures translational activity, not full transcription. -Analysis limited to cortex. -Temporal resolution depends on sampling frequency.
Hollis HC et al. [73]	AD patients;	Late	Cerebral cortex	Astrocytes;Microglia	-snRNA-seq; -Computational phase	-The core circadian clock was preserved.	-Human cell-type resolution was achieved.	-Circadian phases in

	APP/PS1 mice				reconstruction of circadian rhythms across cell types; - Pathway/rhythms analysis; -Comparative analyses in APP/PS1 mice under circadian stress;	-Cell-type-specific output rhythms were disrupted. -Rhythms of ribosomal function and oxidative phosphorylation were dampened. -Translation deficits were linked to circadian stress.	-Circadian patterns were reconstructed using computational methods. -Findings were validated across species, integrating experimental data with modeling.	humans are inferred. -Post-mortem variability may affect results. -Mouse model does not fully replicate AD pathology.
Yang H et al. [43]	APP/PS1 mice	Early; Late	SCN; Hippocampus;Cortex	Neurons; Astrocytes;Microglia	-Wheel-running activity; -Actigraphy; -EEG/EMG; -Molecular clock gene expression (*Per2, Bmal1*); - Immunohistochemistry for amyloid plaques	-In plaque-free subjects, activity onset was altered, and mild changes in clock gene expression were observed. -In plaque-burdened subjects, circadian activity was significantly fragmented. -The amplitude of rhythms was dampened, and *Per2* and *Bmal1* oscillations were disrupted.	-The study was conducted across pre- and post-plaque stages. -A combination of behavioral and molecular assays was used.	-Mouse model may not fully recapitulate human AD circadian pathology. -Sample size per stage is limited. -Analysis focuses mainly on hippocampus and cortex.
Autophagy in AD								
Veverová et al. [104]	CU, MCI patients, AD patients	Early; Late	NA	NA	-CSF & serum biomarkers (PINK1, BNIP3L, TFEB); -Cognitive tests; -Brain imaging	-PINK1 levels were increased in both CSF and serum. -BNIP3L levels were elevated in serum. -Serum TFEB levels were decreased in AD. -Mitophagy impairment correlated with cognitive decline and with tau, NEFL, and NRGN levels.	-Human samples spanning the full AD continuum were analyzed. -Measurements were performed in parallel in both CSF and serum. -Multi-modal assessments included biomarkers, cognitive testing, and brain imaging.	-Cross-sectional design prevents causal inference. -Biomarker changes may be affected by peripheral factors. -No direct cellular resolution.
Kim S et al. [16]	Human astrocytes; Mouse astrocytes; APP/PS1 mice; Human AD brain tissue	Late	Hippocampus; cortex	Astrocytes	-RNA-seq, -AAV-mediated astrocyte-specific LC3B/SQSTM1 manipulation, - Immunofluorescence /Western blot/TEM, behavioral assays	-Aβ induces astrocytic autophagy. -Knockdown of astrocyte *LC3B* or SQSTM1 increased Aβ levels, reduced neuronal survival, and led to cognitive deficits. -*LC3B* overexpression decreased Aβ accumulation. -Human AD astrocytes exhibited increased LC3B and SQSTM1 levels.	-A multi-model approach was employed. -Astrocyte-specific manipulations were performed. -Functional outcomes were validated through behavioral assays. -Findings were confirmed using imaging and ultrastructural analyses.	-APP/PS1 model is limited to Aβ pathology. -Cell cultures may not reflect full brain microenvironment. -Genetic manipulations may have off-target effects.
Lucin KM et al. [108]	BV2 and primary microglia;	Pre-pathology	Cortex; Hippocampus	Microglia	-Beclin 1 knockdown/over expression;	-Beclin 1 is essential for	-A combination of in vitro, in vivo, and human tissue	-Mouse models may not fully

	Becn1$^{+/-}$ mice; Human AD and control brain microglia	(mouse); Late (human AD)			-Phagocytosis assays; -Retromer trafficking analysis; -Western blot, immunofluorescence	microglial phagocytosis. -Beclin 1 deficiency impairs retromer recruitment and reduces recycling of phagocytic receptors CD36 and TREM2. -Human AD microglia show reduced Beclin 1 and retromer levels, supporting the relevance of these findings to disease.	experiments was used for validation. -The study provided mechanistic insight into the link between microglial autophagy and phagocytosis.	recapitulate human disease. - Observations in human tissue are correlative, not causal. -Temporal changes cannot be precisely tracked.
Circadian rhythms and Autophagy in AD								
Zhou et al.[155]	APP/PS1 mice	Early-to-mid AD (mouse)	Hippocampus	Neurons	- *Bmal1* overexpression in HT22 hippocampal neuronal cells by transient transfection of *Bmal1* plasmid; - Immunofluorescence; -Co-IP; RT-PCR; luciferase assay; -TEM for autophagosome-lysosome fusion	- *Bmal1* promotes STX17 transcription and facilitates the formation of the STX17-SNAP29-VAMP8 complex, which enhances autophagosome–lysosome fusion and reduces Aβ deposition.	-Molecular and cellular assays were performed at multiple levels. -Autophagy was directly visualized using microscopy. -STX17 and *Bmal1* expression were altered to assess their functional roles.	-Focus on hippocampal neurons limits generalization to other brain regions. -APP/PS1 overexpression may exaggerate pathology. -In vitro assays may lack in vivo complexity.
Chen et al. [128]	APP/PS1 mice	Early-to-mid AD (mouse)	Cortex; Hippocampus	Neurons	- Stereotaxic injection of lentiviral EGFP-Lc3 into mouse cortex and cerebellum for neuronal autophagy labeling; -Two-photon microscopy; -Time-lapse imaging; - Immunohistochemistry; -Fluorescently labeled Aβ to track intracellular degradation	-Fasting increased autophagosome number, size, and intensity. -Basal autophagy was higher in AD mice. -Fasting-induced autophagy was insufficient to degrade intracellular Aβ. -Basal autophagy in hippocampal neurons exhibited a circadian rhythms.	-Autophagosomes were imaged in real time in vivo. -Autophagy dynamics were quantitatively assessed.	-Fasting cannot fully mimic therapeutic autophagy induction. -Aβ degradation was measured mainly in acute settings. - Extrapolation to humans is limited.
Zhang SQ et al. [21]	human SH-SY5Y neuroblastoma cells; AD C. elegans; 5xFAD mice	Early-to-mid AD (mouse)	Cortex; Hippocampus	Neurons	-*NR1D1* knockdown; -Measurement of autophagy markers (LC3, p62, CTSB); SIRT1 and Cathepsin B activation; -Mitophagy assessment;	-*NR1D1* depletion significantly enhanced autophagic flux and mitophagy, increased autophagy markers, and activated SIRT1 and Cathepsin B. -In C. elegans AD models, depletion of the worm *NR1D1*	-A multi-model approach was employed, combining molecular, cellular, and behavioral readouts.	-No direct human in vivo validation. -NR1D1 function may differ between species, limiting extrapolation to humans.

					-Behavioral assays in C. elegans	ortholog improved neuronal mitophagy and memory. -In 5xFAD mouse models, *Nr1d1* knockdown restored autophagy marker expression.		
McKee CA et al. [187]	Astrocyte-specific *Bmal1* knockout mice; Cultured astrocytes	Early-to-mid AD (mouse)	Cortex	Astrocytes	- Astrocyte-specific *Bmal1* deletion - Electron microscopy (autophagosome detection) - Immunofluorescence for *Lamp1* and *Rab7* - Transcriptional profiling of isolated astrocytes	- *Bmal1* deletion disrupts astrocyte circadian function. -Endocytosis and lysosome-dependent protein cleavage are increased. -*Lamp1*- and *Rab7*-positive organelles accumulate in vitro. -Autophagosome-like structures accumulate in vivo. -Lysosome-related pathways are dysregulated independently of *Tfeb*.	-The study combined in vivo and in vitro approaches. -Cell-type-specific genetic manipulations were performed. -Multi-level measurements were conducted, including electron microscopy, immunofluorescence, and transcriptomics.	-Mouse model may not fully represent human AD. -Neuronal and cognitive effects were not directly tested.

Abbreviations: AD, Alzheimer's Disease; TRAP, Translating Ribosome Affinity Purification; RiboTag, Translating Ribosome Affinity Purification; RAIN, Rhythmicity Analysis Incorporating Nonparametric methods; snRNA-seq, Single-nucleus RNA sequencing; SCN, Suprachiasmatic nucleus; NEFL, Neurofilament Light Chain; NRGN, Neurogranin; Co-IP, Co-Immunoprecipitation; RT-PCR, Reverse Transcription Polymerase Chain Reaction; TEM, Transmission Electron Microscopy.

2. Molecular Mechanisms of Circadian Rhythms and Disruptions in AD

2.1. The Fundamental Mechanism of Circadian Rhythms

In mammals, the circadian system generates near-24-hour physiological rhythms at the molecular, cellular, and circuit levels. Organized hierarchically—from a central pacemaker to distributed local oscillators—it maintains precise temporal coordination of brain functions [23].

Within cells, circadian clocks depend on a set of clock genes and the proteins they encode [24]. At the heart of this mechanism is the transcriptional-translational feedback loop (TTFL). The CLOCK-BMAL1 heterodimer binds E-box sequences and drives expression of clock-controlled genes (CCGs) [25, 26], including period (*PER1/2/3*) and cryptochrome (*CRY1/2*) genes [27]. PER and CRY proteins build up in the cytoplasm, and once they reach a critical level, they move into the nucleus. There, they suppress CLOCK-BMAL1 activity, closing the feedback loop [25, 28, 29]. A secondary network adds another layer of control. REV-ERB α/β and ROR α/β/γ fine-tune the system, helping to stabilize and sharpen circadian rhythms (Fig. 1A) [30].

Moving to the circuit level, the circadian network is organized hierarchically. The SCN serves as the master pacemaker [8], receiving photic input from intrinsically photosensitive retinal ganglion cells (ipRGCs) to align with the external world and disseminating timing signals to coordinate neuroendocrine rhythms, autonomic functions, and sleep-wake cycles(Fig. 1B) [26, 31]. Circadian clocks also operate in other brain regions—the hippocampus, cortex, and hypothalamus, for example—where they fine-tune local functions like memory, cognition, and emotional regulation [32, 33]. These local clocks do more than keep time within their own regions—they also contribute to coordinating wider physiological processes across the brain [33]. Circadian regulation in the central nervous system (CNS) extends beyond neurons. Astrocytes and microglia also keep their own time and contribute to the brain's rhythmicity. Astrocytes shape the extracellular environment and influence neurotransmitter handling. Microglia, meanwhile, regulate immune responses that follow a circadian pattern [33-35]. Neurotransmitters—dopamine, serotonin, and γ-aminobutyric acid (GABA)—help spread circadian signals between cells and, in turn, modulate clock machinery in both neurons and glia. The result is a multi-layered network—finely tuned, with the SCN at its center—that ensures precise timing across the brain and body [36].

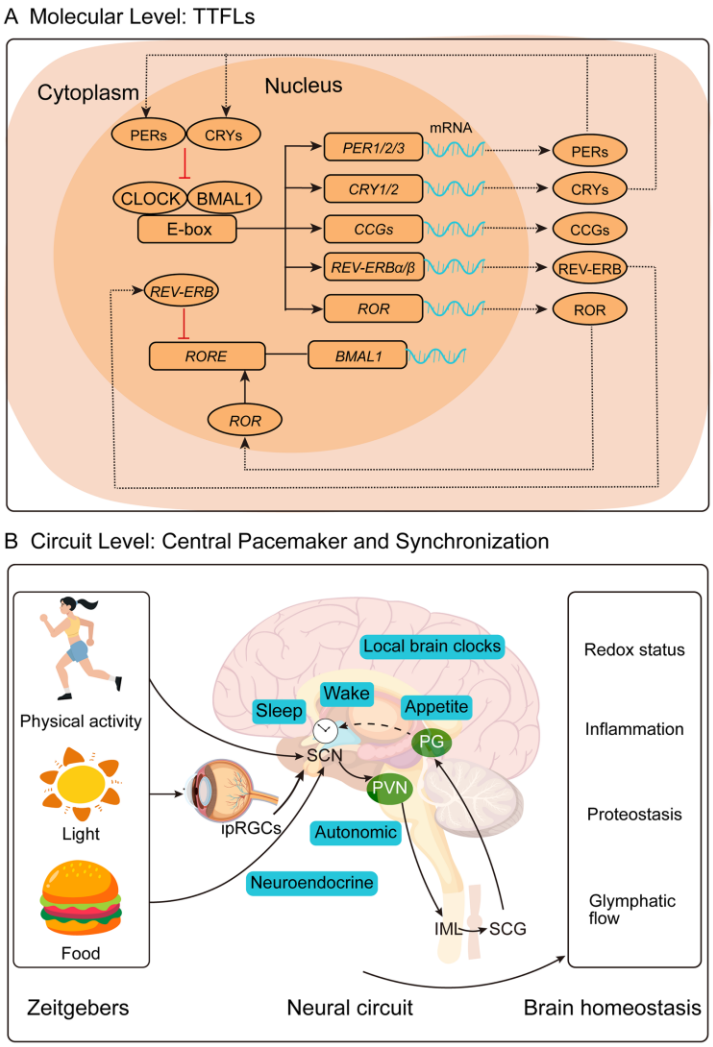

Figure 1. Organization of the mammalian circadian system. (A) The molecular clock mechanism is primarily governed by TTFLs. The CLOCK/BMAL1 heterodimer binds to enhancer box (E-box) elements, thereby initiating the transcription of CCGs, such as *PER*, *CRY*, *REV-ERB*, and *ROR*. The PER and CRY proteins serve as repressors of CLOCK/BMAL1 activity, whereas REV-ERB and ROR exert competitive regulation over *BMAL1* transcription through ROREs. **(B)** Neural circuitry of the central circadian pacemaker. The SCN is entrained by light signals (the most potent zeitgeber) via ipRGCs through the retinohypothalamic tract. The SCN synchronizes peripheral oscillators via autonomic and neuroendocrine pathways. A key output pathway regulating melatonin release comprises sequential connections from the SCN to the PVN, then to the IML of the spinal cord, next to the SCG, and finally to the PG. Abbreviation: TTFLs, transcriptional feedback loops; CLOCK, circadian locomotor output cycles kaput; BMAL1, brain and muscle Arnt-like protein-1; *CCGs*, clock-controlled genes; ROREs, retinoic acid-related orphan receptor response elements; ipRGCs, intrinsically photoreceptive retinal ganglion cells; SCN, suprachiasmatic nucleus; PG, pineal gland; PVN, paraventricular nucleus; IML, intermediolateral; SCG, superior cervical ganglion.

2.2. Alterations in Circadian Rhythms in AD: Insights from Human Studies

2.2.1. Alterations in Circadian Rhythms Across Stages of AD

Circadian rhythms disruptions appear early in AD—well before diagnosis—and worsen as the disease advances [23, 37]. Changes in rest-activity patterns and core body temperature are two widely used markers of this disruption [6]. Neuroendocrine rhythms, too, are affected. Notably, the breakdown of these rhythms varies with disease stage, suggesting that circadian timing may influence the progression of AD.

Early Stage (e.g., Mild Cognitive Impairment -MCI)

Circadian disturbances emerge early in AD, already detectable in MCI stages. In one study, individuals with MCI showed altered sleep architecture—more

wakefulness after sleep onset and delayed rapid eye movement (REM) sleep—pointing to circadian disruption at an early disease phase [38]. In individuals with early-stage AD, actigraphy monitoring showed a fragmented rest-activity cycle without distinct phase shifts when compared to controls [13]. In contrast, MCI patients exhibited a significant phase advance in their circadian rest-activity cycles compared to age-matched controls [38-40]. This was paralleled by a phase advance in core body temperature rhythms in MCI patients, further supporting the phase shifts in circadian rhythms observed in early AD [40]. Studies on melatonin rhythms, a critical neuroendocrine marker of circadian function, have yielded inconsistent results in AD. One study found no significant difference in the amplitude of melatonin rhythms (measured in saliva) between early-stage AD patients and age-matched controls [41]. Similarly, research on individuals with MCI showed no significant alterations in melatonin levels associated with the disease [38]. However, other evidence suggests that MCI patients experience a phase advance in melatonin secretion [38, 42].

The inconsistency observed in the phase shifts of the rest-activity cycle and melatonin rhythms in early-stage AD may be due to the fact that many studies included relatively small cohorts, with participants exhibiting a wide range of demographics. Collectively, these findings suggest that the multi-system phase advance observed may reflect early dysfunction of the SCN, implicating it in the pathophysiology of AD rather than merely suggesting a sleep disorder [43].

Transition to Late Stage

As AD progresses, disturbances in circadian rhythms become increasingly evident, affecting both behavioral and physiological systems.

Sleep onset tends to occur later in AD than in healthy aging [10, 39, 44], but this pattern varies with disease stage. In moderate-to-severe AD, however, sleep times move earlier, suggesting a phase advance [45]. Beyond phase shifts, actigraphy data in AD patients reveal increased fragmentation and overnight activity, although the evidence for reduced circadian amplitude remains mixed [9, 46-49]. Core body temperature also exhibits disturbances in AD, with early-stage AD typically showing a phase advance in temperature rhythms, while more advanced AD is associated with a phase delay [39, 50, 51]. These disruptions extend beyond sleep and temperature regulation. Studies have found a general decrease in melatonin levels in cerebrospinal fluid (CSF), serum, and post-mortem pineal glands of AD patients compared to cognitively healthy controls [52-55]. Additionally, AD individuals tend to display more dampened or atypical melatonin profiles [41]. Disruptions in the diurnal rhythms of other hormones, proteins, and neurotransmitters have also been observed [56]. For instance, histamine synthesis is impaired in AD, as evidenced by reduced mRNA levels of histidine decarboxylase in the tuberomammillary nucleus [56, 57]. Moreover, elevated CSF levels of 5-hydroxyindoleacetic acid (5-HIAA), the primary metabolite of serotonin, have been reported in AD [58]. In the case of Aβ, while diurnal fluctuations are present, the amplitude of these fluctuations is significantly reduced in AD patients compared to controls [59-61]. As the disease progresses, these disturbances in rest-activity cycles, circadian melatonin rhythms and other circadian-regulated processes become more irregular [62]. In summary, while differences in disease severity and progression can explain some of the circadian phase variations, the current body of evidence is based on studies involving relatively small and diverse cohorts. Longitudinal studies with highly standardized protocols are crucial to fully understand how these changes evolve throughout the AD continuum.

2.2.2. Circadian Rhythms Disruptions in AD Across Brain Regions

SCN: The Core Circadian Pacemaker

Circadian rhythms disturbances in AD are prominently observed in the SCN, the brain's central circadian pacemaker. Neurofibrillary tangles, but not Aβ plaques, have been found specifically in the SCN of individuals with AD [63]. In AD patients, the SCN exhibits neuronal loss, dendritic abnormalities, and receptor deficits, reflecting both structural and functional impairments. Post-mortem studies of AD patients and age-matched controls using immunocytochemistry, Golgi/Nissl staining, and silver impregnation techniques have revealed decreased SCN neuronal number and volume, as well as dendritic and receptor (melatonin receptor type 1 [MT1], arginine vasopressin [AVP], vasoactive intestinal peptide [VIP]) abnormalities, especially in late-stage AD [44, 64-68]. Behavioral monitoring of rest-activity rhythms in these patients demonstrates that SCN neuron loss is associated with reduced circadian amplitude and delayed phase [44]. These findings in humans provide a neurobiological basis for the circadian disruptions observed in AD.

Local Brain Clocks Exhibit Region-Specific Vulnerability in AD

Circadian dysregulation in AD is not uniform across the brain but exhibits region-specific vulnerability, which

aligns with areas most susceptible to AD pathology. Human studies reveal that in the cortex, altered *BMAL1* DNA methylation flattens its rhythmic expression and correlates with tau pathology, sleep fragmentation, cognitive decline, and mood disturbances, suggesting that epigenetic disruption of cortical clocks contributes to early disease processes [69, 70]. In postmortem pineal glands from AD patients, rhythmic *BMAL1* and *PER1* expression is completely lost, *CRY1* is elevated, and normal coupling with SCN output is abolished, reflecting an early functional disconnection of this endocrine clock from the central pacemaker [71]. Collectively, this evidence underscores the importance of local brain clocks in AD and supports the development of region-specific strategies to restore circadian homeostasis and mitigate early disease processes.

2.2.3. Cell-Type-Specific Circadian Clocks in AD

Human studies provide critical insights into how circadian clocks function in specific brain cell types during AD. Post-mortem single-nucleus RNA sequencing of the dorsolateral prefrontal cortex has shown that core clock gene oscillations are largely preserved, but many downstream circadian outputs, particularly in microglia, are disrupted. Genes regulating ribosomal biogenesis and oxidative phosphorylation exhibit dampened rhythms, suggesting that cell-type-specific circadian dysfunction contributes to early AD pathology [72, 73]. Together, these studies suggest that circadian clocks operate in a cell-type-specific manner, with astrocytic clocks primarily regulating neuronal and metabolic rhythms, and microglial clocks coordinating immune oscillations; their dysregulation may drive early pathogenic events in AD.

2.3. Circadian Rhythms and AD: Insights from Animal Studies

Circadian disruption driving AD pathology

Experimental studies in animals provide evidence that disruption of circadian rhythms can exacerbate AD pathology. Global or SCN-specific deletion of *Bmal1* acceleratesAβ plaque accumulation and alters hippocampal Aβ oscillations in mice, demonstrating a forward causal pathway from circadian dysregulation to impaired Aβ clearance [74]. Similarly, pharmacological or genetic inhibition of the circadian repressor *Rev-erbα* enhances *Bmal1* expression, promotes microglial uptake of fibrillary Aβ42, and reduces amyloid burden in models [75]. Beyond molecular manipulations, modeling studies suggest that circadian regulation of the sleep-wake cycle critically influences Aβ fibrillization, with disrupted sleep accelerating plaque formation and disease onset [76]. Functionally, in C57BL/6 mice with experimentally induced circadian disruption, hippocampal Brain-Derived Neurotrophic Factor (BDNF) levels decline, Aβ deposition increases, and learning and memory are impaired, highlighting the behavioral and cognitive consequences of circadian dysregulation [77]. Collectively, these studies provide converging evidence that circadian disruption is not merely a consequence but a potential driver of AD pathology, acting through impaired amyloid clearance, neurotrophic deficits, and synaptic dysfunction. These findings underscore the importance of preserving circadian homeostasis as a potential therapeutic avenue in AD.

AD pathology impairing circadian rhythms

Accumulating evidence from animal models demonstrates that AD pathology disrupts circadian rhythms in a region- and cell-type-specific manner. Region-specific effects are evident in APPxPS1 knock-in mice, where circadian Aβ rhythms are abolished in the olfactory bulb—an early-affected region—while the cerebellum maintains rhythmicity until late stages [78]. At the cellular level, Aβ pathology impairs circadian regulation in both astrocytes and microglia. In APP/PS1 mice, Aβ plaques reprogram glial circadian translatomes, dampening rhythmic expression of genes controlling glial reactivity, immunometabolism, and proteostasis, and disrupting time-of-day–dependent microglial functions such as oxidative stress regulation and Aβ clearance [72]. Complementary studies further show that disruption of microglial CLOCK/BMAL1 feedback loops increases pro-inflammatory gene expression, impairs Aβ clearance, and induces cognitive deficits, highlighting a mechanistic role for glial circadian dysfunction in early neuroinflammation and cognitive impairment [79]. Tau pathology similarly perturbs circadian function. In Tg4510 mice, tau accumulation in the SCN disrupts core clock proteins (Per2 and Bmal1) and prolongs the free-running period [80]. Collectively, these findings indicate that AD pathology actively remodels circadian rhythms in a cell-type- and region-specific manner, contributing to early neuroinflammatory processes, synaptic dysfunction, and cognitive decline. This mechanistic understanding provides a rationale for considering circadian stabilization as a potential therapeutic strategy in AD.

3. Molecular Mechanisms of Autophagy and Disruptions in AD

3.1. The Molecular Core of Autophagy

Autophagy is a highly conserved catabolic process within eukaryotic cells [81, 82], wherein cytoplasmic

components, such as defective proteins or organelles, are transported to lysosomes for degradation [83]. Autophagy can be broadly classified into three distinct types based on the mechanisms by which autophagic cargo is delivered to lysosomes: macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy [84]. In this review, we mainly discuss macroautophagy. Macroautophagy represents the most extensively studied and predominant form of autophagy. Under physiological conditions, the basal level of autophagy is typically low; however, it can be rapidly activated by various stimuli, including energy deprivation [85], damaged organelles [86], misfolded proteins [87], inflammation [88], and other stress-inducing factors [89]. The entire autophagic process, known as autophagic flux, is composed of four distinct stages based on the status of the autophagosome: the initiation phase, the autophagosome formation stage, the maturation phase, and the degradation phase (Fig. 2) [90]. Each step of the autophagy process is meticulously regulated by multiple molecules.

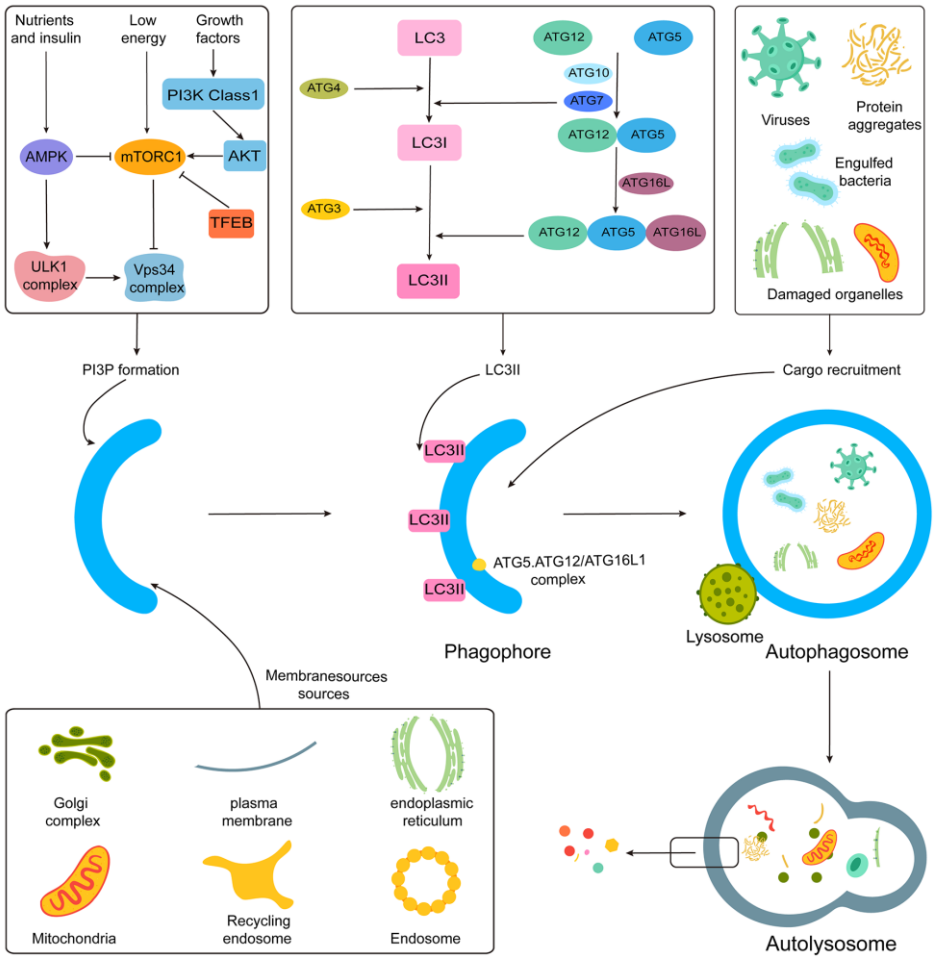

Figure 2. Schematic illustration of the macroautophagy (autophagy) machinery. The phagophore membrane becomes covalently linked to LC3-II, which in turn recruited proteins that contain an LC3-interacting region. Subsequently, the phagophore elongates and seals, forming a vesicle structure known as the autophagosome. Eventually, the autophagosome fused with a lysosome, resulting in the formation of an autolysosome. The cargos, such as damaged organelles and protein aggregates, in the autolysosome are degraded by lysosomal enzymes, resulting in the recycling of nutrients and metabolites.

Autophagy initiation is regulated by the unc-51-like kinase (ULK) complex [3], which activates the downstream VPS34 complex [91] to catalyze the production of phosphatidylinositol 3-phosphate (PI3P) [92], thereby initiating phagophore formation [93-95]. Autophagosome formation relies on two ubiquitin-like conjugation systems [3]: the assembly of the autophagy-related 5–autophagy-related 12–autophagy-related 16 like 1 (ATG5–ATG12–ATG16L1) complex [96] and the lipidation of microtubule-associated protein 1 light chain 3 (LC3) (conversion from LC3-I to LC3-II). LC3-II serves as a marker of the autophagosomal membrane [97-99]. Subsequently, the autophagosome fuses with the lysosome to form an autolysosome, within which the

engulfed contents are degraded by hydrolases, and the resulting products are recycled [100-102].

3.2. Autophagic Dysfunction in AD: Insights from Human Studies

Autophagy, as a core mechanism for maintaining cellular homeostasis, is dysregulated in AD in a dynamic manner. This dysregulation evolves across disease stages and exhibits brain region- and cell type-specific complexities. These multi-level disturbances collectively drive the accumulation of core AD pathologies and the decline in neural function.

3.2.1. Stage-Dependent Evolution of Autophagic Dysfunction in AD

Autophagic dysfunction in AD follows a distinct, evolving trajectory, with significant changes occurring as the disease progresses through different stages. The dysfunction manifests differently in the early and late stages of the disease, which is important for understanding potential therapeutic strategies.

Early Stage

Early-stage alterations of autophagy in AD follow a stage-specific pattern across brain regions and biofluids. In preclinical AD, autophagy markers in the inferior parietal lobule (IPL), including Beclin-1 and LC3, are already decreased, indicating an initial impairment of the autophagic machinery [103]. As AD progresses to MCI, neurons in the IPL show hyperactivation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway and its downstream targets (p70S6K, 4EBP1), accompanied by elevated tau phosphorylation, suggesting that autophagy inhibition coincides with emerging AD pathology [103]. At the same stage, serum Transcription Factor EB (TFEB), an autophagy-related transcription factor, is slightly reduced, reflecting the onset of impaired autophagic-lysosomal function [104]. In early-stage AD hippocampal CA1 neurons, LC3-positive puncta and p62/SQSTM1 accumulation, both colocalizing with hyperphosphorylated tau, along with elevated lysosomal marker LAMP1, indicate impaired autophagy-lysosome function that may contribute to tau pathology [105]. Together, these studies provide converging evidence that autophagy and lysosomal function are already compromised in early-stage AD. These alterations reflect an early imbalance between compensatory autophagosome formation and impaired substrate clearance, linking neuronal stress and tau pathology to autophagy-lysosome dysfunction in the initial stages of the disease.

Transition to Late Stage

In late-stage AD, widespread autophagy-lysosome dysfunction is observed across multiple brain regions and biofluids, reflecting severe impairment of neuronal clearance mechanisms. Post-mortem brain analysis of AD patients shows persistent autophagosome formation, LC3-positive vesicle accumulation colocalizing with phospho-tau [106], and dysregulated lysosomal proteins (e.g., reduced Beclin-1 and LC3) [107, 108], collectively indicating impaired autophagy flux and lysosomal dysfunction that contribute to tau pathology and neuronal degeneration. In the human IPL, autophagy markers Beclin-1 and LC3 are markedly reduced, while PI3K/Akt/mTOR signaling is strongly hyperactivated with substantially elevated downstream targets (p70S6K, 4EBP1) and pronounced tau phosphorylation, collectively indicating persistent and severe autophagy impairment and sustained mTOR overactivation, which likely accelerates disease progression [103]. Consistently, serum and CSF TFEB levels are reduced, reflecting systemic autophagic-lysosomal impairment, and correlate with CSF p-tau181, total tau, neurofilament light chain (NEFL), neurogranin, and cognitive decline [109, 104]. Genetic evidence further supports a role for autophagy in AD susceptibility. A case-control study found that the NDP52^GE variant, a functional variant of the autophagy receptor, is associated with reduced risk of AD [110], whereas genome-wide association studies (GWAS) studies identified BIN1 variants, involved in endosomal trafficking and autophagy, as risk factors for late-onset AD [111].

Together, these findings demonstrate that persistent autophagic stress, lysosomal dysfunction, and mTOR overactivation converge in late-stage AD to exacerbate tau pathology, neuronal degeneration, and cognitive decline.

3.2.2 Brain-Region Specificity of Autophagy in AD

Autophagy alterations in AD exhibit pronounced brain region specificity. Postmortem human hippocampal CA1 neurons, autophagosomes progressively accumulate due to impaired autophagic flux, as evidenced by elevated LC3-II and p62/SQSTM1 within enlarged autolysosomes, indicating a decline in autophagic degradation specifically in this region [105]. Consistent with this, cortical regions from Boston University AD Center samples show significantly elevated LC3B and SQSTM1/p62 protein levels compared to controls, suggesting that autophagosome accumulation also occurs in cortical

neurons [16]. In familial AD (FAD) brains, analysis of the frontal cortex revealed both an accumulation of LC3-positive autophagic vesicles and elevated levels of the lysosomal marker LAMP1, further demonstrating disruption of the autophagosome-lysosome pathway in cortical regions [106]. In the human IPL, total levels of Beclin-1 and LC3 are markedly reduced, accompanied by strong hyperactivation of PI3K/AKT/mTOR signaling and increased tau phosphorylation, indicating that autophagy initiation is impaired and the overall autophagic machinery is dysfunctional, which may accelerate AD progression [103]. Finally, RNA sequencing of postmortem AD brains identified the parahippocampal gyrus as exhibiting the most pronounced alterations in autophagy pathways, including downregulation of multiple genes encoding components of autophagy kinase complexes such as BECN1-PIK3C3 and ULK1/2-FIP200, suggesting that gene expression is regionally dysregulated [112]. Collectively, these findings indicate that autophagic dysfunction in AD is both region-specific and multifaceted, involving impaired flux, lysosomal disruption, and transcriptional dysregulation, which may underlie differential vulnerability across brain regions.

3.2.3 Cell-Specific Autophagy Programs in AD

Autophagy is selectively altered in reactive astrocytes in AD. Post-mortem analysis of hippocampal tissue from AD patients revealed that LC3B and SQSTM1/p62 protein levels were significantly elevated, and LC3B immunoreactivity correlated positively with GFAP intensity, indicating preferential accumulation of autophagy components in reactive astrocytes [16]. Mechanistic in vitro studies further showed that Aβ exposure upregulates LC3B and SQSTM1 expression and affects autophagy-related processes in human astrocytes, supporting the involvement of astrocytic autophagy in AD [16]. Together, these findings suggest that astrocytic autophagy is selectively upregulated in reactive astrocytes in AD. However, direct assessment of astrocytic or microglial autophagic activity in living AD patients remains very limited due to the lack of non-invasive indicators; for example, autophagy markers such as LC3 and p62 are difficult to quantify via PET, blood, or CSF. Moreover, much of the research on cell-specific autophagy mechanisms still relies primarily on animal models and in vitro experiments.

3.3. Autophagic Dysfunction in AD: Insights from Animal Studies

Autophagic dysfunction drives AD pathology

Genetic mouse models demonstrate that autophagic disruption is sufficient to trigger AD-related phenotypes, whereas enhancing autophagy can ameliorate established pathology. Adult forebrain neuron-specific *Atg7* knockout (Atg7iKO) mice show synaptic protein accumulation and cognitive deficits, indicating that autophagy disruption alone impairs synaptic function and cognition [113]. Postnatal forebrain-specific *Atg7* knockout mice exhibit neurodegeneration and accumulation of phosphorylated tau, highlighting a mechanism by which autophagy deficiency drives structural neuronal damage [114]. *Bin1* deficiency in mouse hippocampal neurons (via RNAi in vitro and adeno-associated virus (AAV)-mediated knockdown in vivo) induces dendritic atrophy, localized hippocampal volume loss, and spatial memory impairment by activating ULK3-dependent autophagy, all of which are rescued by pharmacological or genetic inhibition of autophagy/ULK3 [115]. Conversely, enhancing autophagic function can protect against tau pathology. AAV-mediated overexpression of *Tfeb* in the hippocampus of rTg4510 tauopathy mice selectively clears hyperphosphorylated and misfolded tau, restores dendritic spine density, rescues cognitive deficits, and prevents neuronal loss, providing evidence that boosting autophagy can counteract AD pathology [116]. *Tfeb* knockout in PS19 tauopathy mice exacerbates intraneuronal tau accumulation and accelerates pathological spreading, indicating that *Tfeb*-mediated autophagy protects against tau pathology [117].

Autophagy also regulates Aβ pathology. In 5xFAD mice, adiponectin deficiency accelerates Aβ deposition and cognitive impairment, while AdipoRon treatment activates AMPK-mTOR-mediated autophagy and reduces Aβ pathology [118]. HDAC6 inhibition via valproic acid restores vacuolar-type H^+-ATPase (V-ATPase) assembly and lysosomal acidification, enhancing autophagic clearance of Aβ aggregates and ameliorating cognitive deficits in AD mice [119]. GSK-3 inhibition in 5xFAD mice restores lysosomal acidification, reduces Aβ deposition, and improves cognition, linking kinase dysregulation to autophagic failure [120]. In TgCRND8 mice, genetic deletion of *Cystatin B* restores lysosomal proteolysis, clears Aβ and ubiquitinated proteins, reduces amyloid deposition, and rescues cognitive deficits—demonstrating that remediating lysosomal function directly ameliorates Aβ pathology [121].

Collectively, these findings establish that autophagic integrity is crucial for clearing both tau and Aβ, and that enhancing autophagy can reverse established pathology.

AD pathology impairs autophagic function

Conversely, AD-associated protein aggregation can disrupt autophagy. Mouse models reveal that Aβ and tau

pathology interfere with multiple nodes of the autophagy-lysosome pathway. Lysosomal acidification is a primary target: in 5×FAD mice, *Acly* deficiency impairs V-ATPase assembly, blocking autophagic flux and exacerbating Aβ deposition and neuritic dystrophy [122]. Despite age-related increases in autophagy-related proteins, 5×FAD mice exhibit impaired clearance of autophagic substrates, resulting in toxic protein accumulation and neuronal death [123]. Sex- and region-specific vulnerabilities are also evident. In 3xTg-AD mice, females exhibit impaired autophagic degradation and enhanced mitophagy in the cortex, correlating with cognitive deficits [124]. In early-stage AppNL−G−F×MAPT mice, sleep–wake neurons exhibit autophagic impairment prior to significant Aβ deposition, leading to sleep deficits that precede cognitive decline, and activation of autophagy improves sleep recovery [125]. Calcium dysregulation constitutes an additional mechanism: overactivation of neuronal RyanR2 receptors suppresses autophagy via Calcineurin–Ampk–Ulk1 signaling, promoting amyloid accumulation, while reducing RyanR2 activity restores autophagic flux and rescues Aβ pathology [126]. Collectively, these findings establish that AD pathology actively disrupts autophagic function through converging pathways—acidification failure, substrate accumulation, cell-type vulnerability, and calcium signaling—contributing to impaired proteostasis and neurodegeneration.

4. Bidirectional Crosstalk between Circadian Rhythms and Autophagy and Dysregulation in AD

4.1. Coupling between Circadian Rhythms and Autophagy

4.1.1. Circadian Rhythms Regulate Autophagy in Physiological States

Circadian inputs (light/feeding) synchronize autophagic oscillations

External zeitgebers, such as light/dark cycles and feeding/fasting rhythms, synchronize autophagic oscillations. The basal autophagy levels in the outer retina, for instance, exhibit dynamic fluctuations across the day-night cycle, regulated by circadian light input [127]. During fasting, autophagic vesicle number and intensity increase, supporting processes like mitophagy and protein degradation. This enhanced autophagy, particularly in neurons, is crucial for maintaining synaptic health and clearing dysfunctional components, thereby safeguarding long-term cellular integrity [128].

Circadian clock genes regulate autophagy through a multi-staged network

Core circadian clock genes play a pivotal role in regulating autophagy [129, 130] (Fig. 3). These genes not only control autophagy initiation but also regulate the rhythmic of key components necessary for autophagosome formation and degradation. Autophagy is tightly regulated by circadian clock genes, with *Per2* playing a crucial role in the initiation stage. At this stage, *Per2* activates the PI3K/Akt pathway, leading to the downregulation of mTORC1, which promotes autophagy [130]. Knockdown of *Per2* results in reduced autophagy levels and decreased cellular levels of the *Ulk1* protein, an essential initiator of autophagy [131]. Additionally, mice with cardiomyocyte-specific knockout of *Bmal1* or mutations in *Clock* show increased activation of the PI3K/Akt/mTOR pathway, leading to decreased autophagic activity [132]. Conversely, transient overexpression of *Per2* downregulates this pathway and enhances autophagic flux [131, 133]. The BMAL1/CLOCK complex directly activates the transcription of ULK1, further promoting autophagy initiation [134]. At the nucleation stage, Bmal1/Clock also regulates the expression of Atg14, a key protein in autophagosome nucleation [135]. For autophagosome elongation, the rhythmic expression of *Atg5* and *Atg7*—regulated by *Per1*—plays an essential role [136]. Mutations in *Per1* disrupt this rhythmic expression, impairing the elongation and maturation stages of autophagy. This disruption leads to a lack of coordinated expression of genes such as *Ulk1* (initiation), *Becn1* (nucleation), *Lc3b* (elongation and cargo recognition), and *Atg4* (LC3 processing and recycling), ultimately reducing the efficiency and quality of the autophagic process [137, 138]. Finally, Bmal1 enhances autophagic flux by activating AMPK, which supports efficient degradation processes [139]. Together, these circadian clock genes, including *Per2*, *Bmal1*, *Clock*, and *Per1*, form a precise, multi-layered system that regulates autophagy across different stages, ensuring its efficiency and proper coordination.

Rhythmic metabolic products regulate autophagic flux through deacetylation-dependent pathways

Some rhythmic metabolic products, for example, the silent mating type information regulation 2 homolog 1 (Sirt1), an NAD^+-dependent histone deacetylase that deacetylates proteins [140], have been shown crucial importance for circadian clock rhythms pathways [141-143] (Fig. 3). Sirt1 regulates autophagy primarily through the deacetylation of core components, including Atg proteins, Lc3, and Foxo transcription factors. During

starvation, SIRT1 directly activates the autophagic machinery by deacetylating essential Atg proteins, such as Atg5, Atg7, and Atg12 [144, 145]. This modification promotes the assembly of the Atg5–Atg12–Atg16 complex, thereby facilitating autophagosome elongation and maturation [146, 147]. Similarly, Sirt1-mediated deacetylation activates Lc3 in the nucleus under nutrient stress [148], enhancing its role in autophagosome formation and cargo recruitment [149]. Beyond these direct effects, Sirt1 also modulates autophagy at the transcriptional level [150]. Sirt1 deacetylates Foxo1 [151, 152], increasing its activity, and promotes the nuclear translocation of Foxo3 [153] via deacetylation. Once in the nucleus, Foxo3 upregulates a broad set of autophagy-related genes, systemically enhancing autophagic capacity [153]. In summary, Sirt1 integrates both post-translational modifications and transcriptional regulation to finely tune the autophagic process, linking metabolic states with circadian rhythms to maintain cellular homeostasis.

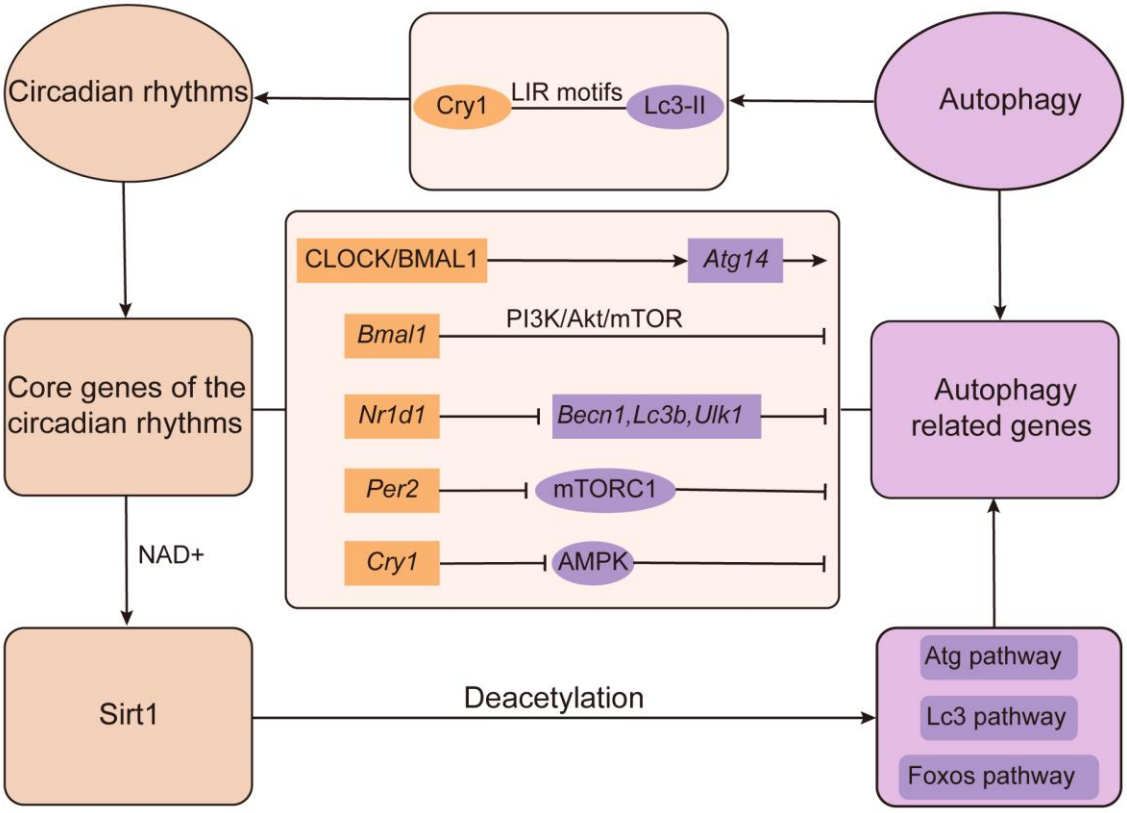

Figure 3. The interplay between circadian rhythms and autophagy is characterized by a bidirectional regulatory relationship. The circadian clock exerts control over autophagy through transcriptional and post-translational metabolic pathways. Conversely, autophagy influences circadian clock function by degrading core clock proteins. Abbreviations: CLOCK, circadian locomotor output cycles aput; Bmal1, brain and muscle arnt-like 1; Nr1d1, nuclear receptor subfamily 1 group d member 1 (also called Rev-erbα); Per2, period circadian regulator 2; Cry1, cryptochrome circadian regulator 1; NAD+, nicotinamide adenine dinucleotide (oxidized form); SIRT1, sirtuin 1; Atg14, autophagy-related gene 14; Becn1, beclin-1; Ulk1, unc-51 like autophagy activating kinase 1; mTORC1, mechanistic target of rapamycin complex 1; AMPK, AMP-activated protein kinase; Atg pathway, autophagy-related pathway; Lc3 pathway, Lc3-dependent autophagy pathway; Foxos pathway: forkhead box o transcription factor pathway; LIR motifs, Lc3-interacting region motifs

4.1.2 Molecular Mechanisms of Autophagy in Regulating Circadian Rhythms

Autophagy regulates the circadian rhythms primarily through the selective degradation of core clock proteins (Fig. 3). For instance, structural studies have revealed that the clock protein Cry1 contains multiple Lc3-interacting region (LIR) motifs, which target it for autophagic recognition and clearance [22]. Similarly, mitophagy, a specialized form of autophagy, can degrade another core clock component (e.g. Nr1d1) via an analogous LIR-mediated mechanism [154]. Furthermore, the suppression of *Target of Rapamycin (Tor)* gene expression specifically results in a significant reduction in the period length of the locomotor activity rhythms in Drosophila melanogaster [136], while AMPK activation promotes Cry protein degradation, thereby altering circadian rhythmicity [129]. Several other core circadian proteins,

including Bmal1 and Clock, have also been shown to be degraded via the autophagy-lysosomal pathway [22]. In summary, the autophagy pathway constitutes a critical post-transcriptional regulatory network, which directly shapes and maintains the precision of the circadian clock by periodically clearing core clock components.

The physiological role of autophagy in circadian regulation has been validated in multiple experiments. Urolithin A (UA), a pharmacological activator of mitophagy, can restore diminished circadian rhythms amplitudes in SCN tissues by promoting Nr1d1 degradation [154]. In *Atg7*-deficient mice, impaired autophagy leads to Cry1 accumulation, reduced Bmal1, and suppressed Nr1d1 expression, ultimately attenuating circadian oscillations [22]. Similarly, in NIH3T3 cells, knockdown of *Atg5* or treatment with the lysosomal inhibitor chloroquine (CQ) both result in increased Nr1d1 expression and decreased Bmal1 protein levels [154]. These findings collectively demonstrate that autophagy deficiency disrupts circadian rhythmicity by impairing the normal degradation of core clock proteins, leading to their abnormal accumulation or depletion, which in turn disturbs the expression and oscillation of downstream clock components.

4.2. Decoupling Between Circadian Rhythms and Autophagy in AD

4.2.1. Circadian Regulation of Autophagy in AD

Circadian rhythms regulate autophagy in a stage-dependent manner in AD. In early stages, autophagy initiation may remain active while downstream processing is impaired. Most studies to date have been conducted in animal models, focusing primarily on overall neuronal mechanisms rather than individual cell types. Evidence in later-stage AD is sparse, and human data are very limited. Nevertheless, it is likely that neuronal loss and circadian disruption exacerbate autophagic deficits. Although direct evidence for cell-specific regulation is scarce, circadian-related stressors—such as chronic sleep deprivation in mice—can impair microglial autophagy, underscoring the need to explore cell-type-specific mechanisms.

Stage-Dependent Effects of Circadian Rhythms on Autophagy in AD

Disruption of circadian rhythms exerts stage-dependent effects on autophagy in AD, with most research focusing on early pathological stages, whereas knowledge regarding late-stage disease remains limited (Fig. 4).

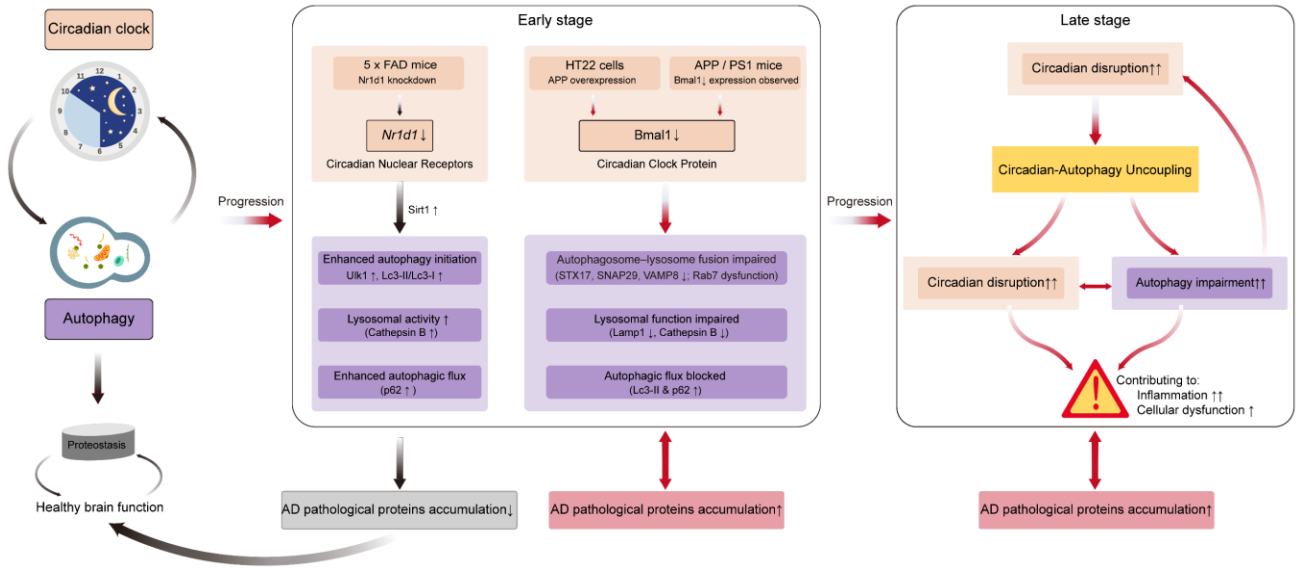

Figure 4. Stage-dependent effects of circadian rhythms and autophagy in AD. In a healthy brain, the circadian clock and autophagy mutually interact, maintaining proteostasis and neuronal function. In early-stage AD, circadian rhythms show mild disruption, while autophagy initiation remains active; however, defects in autophagosome–lysosome fusion and lysosomal degradation block autophagic flux, leading to accumulation of AD pathological proteins. In late-stage AD, although direct evidence remains limited, severe circadian disruption likely uncouples circadian control from autophagy. We hypothesize that circadian disruption and autophagy impairment mutually exacerbate each other, driving neuroinflammation, neuronal dysfunction, and further accumulation of AD pathological proteins. Abbreviation: AD, Alzheimer's Disease; Bmal1, brain and muscle arnt-like 1; Lamp1, lysosomal-associated membrane protein 1.

During early AD, a paradox arises in which autophagy initiation remains active while downstream autophagosome–lysosome fusion and lysosomal degradation are selectively impaired. Physiological interventions provide insight into these mechanisms. For example, in 3-month-old 5xFAD mice, intermittent fasting, which engages circadian outputs via behavioral pathways, enhanced autophagy initiation, as evidenced by upregulated Ulk1/Beclin-1, increased Lc3-II/Lc3-I ratio, and elevated autophagosome numbers. However, this upstream activation was insufficient to reduce intracellular Aβ accumulation, indicating that downstream fusion and degradation steps remain rate-limiting. Further mechanistic assessment in these neurons revealed that autophagosome–lysosome fusion and lysosomal degradation remained inadequate, demonstrated by reduced Lc3/Lamp1 co-localization, increased yellow puncta in mRFP-GFP-Lc3 reporter assays, and sustained Lc3-II and p62 levels [128].

Building on these physiological insights, direct modulation of circadian regulators was then investigated in a cellular model. In APP-overexpressing HT22 cells, Bmal1 knockdown decreased STX17, SNAP29, and VAMP8 expression and caused Rab7 dysfunction, limiting autophagosome–lysosome fusion, while Lamp1 downregulation and reduced cathepsin activity compromised lysosomal degradation, leading to Lc3-II and p62 accumulation and intracellular Aβ buildup. These cellular findings demonstrate that Bmal1 directly regulates autophagic processing in neurons. To determine whether these cellular mechanisms operate in vivo, the same molecular features were examined in APP/PS1 mice. In 4–8-month-old APP/PS1 mice, reduced STX17, SNAP29, and VAMP8 expression, Rab7 dysfunction, lowered Lamp1, and decreased cathepsin activity similarly impaired autophagosome–lysosome fusion and lysosomal degradation, resulting in blocked autophagic flux and persistent neuronal Aβ accumulation [155]. Extending these findings to circadian nuclear receptors, Nr1d1, which negatively regulates autophagy, was also investigated. In 3–6-month-old 5xFAD mice, Nr1d1 inhibition restored autophagy markers such as Lc3-II and p62 to near-normal levels, indicating improved autophagic flux and enhanced macroautophagy. This intervention also increased Sirt1 activity, promoting autophagy initiation and mitochondrial homeostasis, and elevated Cathepsin B activity, enhancing lysosomal degradation capacity and facilitating the clearance of intracellular cargo, including Aβ [21].

In contrast, in late-stage AD, evidence is sparse. Advanced disease features widespread neuronal loss, severe circadian disruption, and profound autophagic impairment, likely limiting the effectiveness of interventions targeting circadian-autophagy pathways alone. This highlights the need for research addressing stage-specific circadian-autophagy interactions, particularly in advanced pathology, to identify potential therapeutic windows and mechanistic targets.

Cell-Specific Dysregulation of Circadian Control of Autophagy in AD

Circadian regulation of autophagy may vary among different brain cell types, yet current evidence largely focuses on neurons, where Bmal1/STX17 and Nr1d1/Sirt1 constitute the core molecular framework. Whether this framework applies to glial cells remains unclear.

Given the limited evidence regarding glial cells, recent studies have focused on microglia under circadian-related stress. Using chronic sleep deprivation (CSD) mouse models, researchers observed that S100A8 was upregulated, autophagic flux was impaired (altered Lc3-II, Beclin-1, and p62), and cognitive deficits were present. To test whether S100A8 mediates these effects, in vivo knockdown was performed via hippocampal AAV-si-S100A8 injection. This intervention reduced S100A8 expression, activated the PI3K/Akt pathway (increased phosphorylated PI3K and Akt), restored microglial autophagic flux, decreased apoptosis, and significantly improved cognitive performance. Consistently, complementary experiments in BV2 microglial cells confirmed that S100A8 knockdown similarly activated PI3K/Akt, normalized autophagy, and reduced cell death [156]. These findings reveal the unique sensitivity of microglia to circadian-related stress. However, it remains unclear whether this mechanism operates under AD pathology. Regarding astrocytes, research on circadian regulation of autophagy is sparse; given their critical roles in Aβ clearance, metabolic support, and inflammatory modulation, this represents a notable knowledge gap.

4.3. Bidirectional Causal Interactions Between Circadian Rhythms and Autophagy in AD

Current research integrating central and peripheral systems has revealed a clear bidirectional regulatory relationship between the circadian clock and autophagy. Core clock genes (e.g., *Bmal1* and *Clock*) drive rhythmic expression of key autophagy components, such as *Ulk1* and *Atg* family genes, generating diurnal oscillations of autophagic activity [157]. Conversely, autophagy contributes to circadian homeostasis by selectively degrading core clock proteins such as Cry1 [22]. In the context of AD, evidence already supports circadian regulation of autophagy [155], whereas whether autophagy can in turn modulate circadian rhythms remains unclear. Based on these findings, we hypothesize

that the relationship between circadian rhythms and autophagy in AD is bidirectional.

4.4. Unresolved Causal Hierarchy

Animal studies show that circadian disruption [74-77] and impaired autophagy [113-121] can drive Aβ and tau pathology, synaptic dysfunction, and neurodegeneration, while accumulating Aβ/tau further disrupt circadian rhythms [72, 78, 80] and multiple nodes of the autophagy-lysosome pathway [122-126], forming reciprocal feedback loops. Complementary human evidence indicates strong associations of both circadian [13, 71, 73, 158, 159] and autophagic dysfunction [107, 108] with AD, yet longitudinal causality remains unresolved, underscoring the need to clarify temporal hierarchies to inform targeted interventions.

Most mechanistic evidence is derived from transgenic mouse models, while causal relationships in humans have not been firmly established, leaving open the possibility of reverse effects—whether Aβ/tau accumulation disrupts circadian or autophagic processes — or bidirectional interactions. Several challenges further complicate the causal hierarchy. First, the relative contribution and temporal order of circadian versus autophagic dysregulation in initiating or exacerbating pathology remain unclear. Second, different brain regions and cell types may respond heterogeneously, but human data at such resolution are limited. Third, potential modifiers—such as age, sex, genetic background, and lifestyle factors—have not been systematically integrated. Finally, although interventions targeting circadian rhythms or autophagy show promise in animal models, their translational efficacy in humans has yet to be established. Addressing these gaps requires well-powered longitudinal studies, high-resolution biomarker analyses, and integrative approaches that combine mechanistic insights from animal models with human data, in order to clarify which processes initiate AD pathology, which drive its progression, and how they may be targeted therapeutically.

5. Targeting Circadian Rhythms and Autophagy: Clinical and Translational Insights

5.1. Circadian Rhythms Intervention Strategies

Circadian rhythms disruption is common in AD, contributing to sleep disturbances, behavioral symptoms, and possibly faster disease progression. Both pharmacological and non-pharmacological strategies — such as light therapy, melatonin supplementation, and orexin antagonists — have been explored to stabilize circadian rhythms. While these interventions show promise, their efficacy is variable and influenced by patient characteristics, disease stage, adherence, and environmental factors. The following sections provide an overview of clinical trial outcomes, highlight translational failures and limitations, and address practical challenges for each intervention in AD.

Light therapy

Light therapy has been widely studied as a non-pharmacological intervention to stabilize circadian rhythms, improve sleep, and modulate behavioral in patients with AD. Evidence indicates that morning bright light exposure (>2500 lux for 1 hour daily, five days per week for 10 weeks) can improve rest‑activity rhythms stability in institutionalized patients with severe AD, particularly in those with misaligned activity patterns, although overall sleep improvements remain modest [160]. Subsequent randomized studies further demonstrate that several weeks of scheduled morning or afternoon bright light can stabilize rest‑activity rhythms and prevent phase delays in institutionalized severe AD patients, even when improvements in sleep or daytime alertness are limited (e.g., comparing different timing schedules) [161]. Moreover, combined morning and evening exposure has been shown to enhance nighttime sleep consolidation and improve circadian rhythms quality in institutionalized severe AD patients [162]. Together, these findings indicate that bright light interventions can reliably stabilize circadian rhythms in severely impaired AD patients, although effects on sleep quality and daytime alertness are generally modest.

To evaluate the effectiveness of light therapy outside institutional settings, community-based programs combining bright light and walking have shown increases in total wake time, although results are moderated by adherence, and sleep quality may not improve [163]. Thus, while light therapy is feasible in less controlled environments, its effectiveness depends on patient compliance and environmental factors. Extending these approaches, longer and more comprehensive interventions, such as a 14-week, all-day tailored lighting program in patients with AD, have demonstrated benefits for sleep and circadian stability [164]. Following these findings, individualized light therapy protocols, adjusted according to patients' circadian profiles, have demonstrated reductions in fragmentation of daily activity patterns in mild-to-moderate AD, irrespective of blue-light supplementation [165]. These results emphasize the importance of individualized, time-based interventions to stabilize circadian rhythms in home or outpatient settings. Furthermore, targeted interventions for specific patient

subgroups, such as patients with agitation, can increase nocturnal sleep but may have limited effects on behavior or mood [166], highlighting that symptom-specific responsiveness can vary. Finally, evidence from systematic reviews and meta-analyses supports a general trend toward positive effects of light therapy on sleep, circadian rhythms, mood, and cognition, with good safety and tolerability [167, 168]. Taken together, across institutional, community-based, and personalized interventions, light therapy shows promise for modulating circadian outputs and certain behavioral outcomes in AD. However, several challenges limit the effectiveness of light therapy in AD. First, patient adherence represents a significant barrier, particularly in outpatient or home settings, where environmental control is often suboptimal and patients may not reliably adhere to prescribed light schedules. Second, interindividual differences in disease severity, circadian baseline, and patterns of circadian misalignment contribute to variability in treatment response; severely impaired patients may achieve circadian stabilization without experiencing measurable improvements in sleep, cognition, or behavior. Third, protocol heterogeneity—including variations in timing, intensity, duration, and spectral composition of light—complicates cross-study comparisons and undermines reproducibility. Collectively, these limitations suggest that although light therapy can modulate circadian rhythms, it is insufficient as a stand-alone intervention and is best implemented as part of a tailored, multimodal treatment approach.

Melatonin supplementation

Several clinical trials have evaluated the effects of melatonin supplementation on sleep, cognition, and circadian rhythms in patients with MCI and AD, with results varying depending on dose, treatment duration, and patient population. Short-term, high-dose melatonin interventions in AD have generally shown limited efficacy. In a 10-day trial, 24 institutionalized AD patients received 8.5 mg immediate-release plus 1.5 mg sustained-release melatonin nightly, which revealed no significant improvement in circadian rhythms [169]. Similarly, in a 4-week study of 20 AD patients, 3 mg nightly melatonin increased nighttime sleep and reduced nighttime activity, suggesting modest benefits for cognitive and behavioral function [170]. Intermediate-term studies (1 – 3 months) have yielded mixed results. In a 12-week feasibility trial of 40 adults with MCI, 25 mg nightly melatonin was safe but had no effect on brain oxidative stress or cognition [171]. In a 2-month multicenter trial of 157 AD patients with sleep disturbances, 2.5 – 10 mg slow-release melatonin did not significantly improve objective sleep measures, highlighting the variability of effects depending on dose, formulation, and outcome measures [172]. Longer-term or strategically combined interventions appear more promising. In a 24-week multicenter trial of 80 patients with mild to moderate AD, 2 mg nightly prolonged-release melatonin improved cognitive function, suggesting longer treatment duration may confer greater benefit [173]. Furthermore, in a 10-week trial of 50 institutionalized AD patients, nightly melatonin combined with 1 hour of morning bright-light therapy reduced daytime sleep, increased activity, improved day:night sleep ratio, and strengthened rest-activity rhythms amplitude, whereas light therapy alone was insufficient [174]. A planned trial (NCT06756828) will evaluate 3-month melatonin treatment in AD spectrum patients with insomnia, aiming to clarify optimal dose, duration, and responsive subgroups.

Overall, melatonin is generally safe; however, short-term or high-dose single interventions have shown inconsistent effects, and responsiveness is influenced by patient characteristics, disease stage, and sleep disturbance severity. Effects on cognition and behavioral symptoms are generally modest. Moreover, most trials are limited by small sample sizes, short durations, and protocol heterogeneity, reducing generalizability. Therefore, while melatonin can be a valuable adjunct for symptom management, it is insufficient as a standalone therapy for AD. Its clinical utility should be considered within a multimodal treatment framework, and larger, well-controlled trials are needed to clarify optimal dose, duration, and patient subgroups most likely to benefit.

Orexin antagonists

Orexin (hypocretin) is a neuropeptide produced in the lateral hypothalamus that regulates the sleep-wake cycle [175, 176]. Dysregulation of the orexin system contributes to the sleep disturbances commonly observed in AD. Evidence suggests that orexin activity evolves across the AD continuum: early-stage patients show subtle circadian dysregulation [177], while moderate-stage AD is characterized by hyperactive orexin signaling associated with tau pathology and impaired sleep [45, 178, 179]. This hyperactive phase provides a rational target for therapeutic intervention with orexin receptor antagonists.

Emerging clinical evidence supports the efficacy of orexin receptor antagonists in AD-related sleep disturbances. For instance, suvorexant has been shown to improve sleep in patients with AD and insomnia [180, 181], while lemborexant demonstrated efficacy in individuals with AD and irregular sleep-wake rhythms disorder [182]. These promising findings are now being tested in several ongoing clinical trials, including those

investigating suvorexant (SToP-AD; NCT04629547) in healthy older adults, lemborexant (NCT06274528) in cognitively normal individuals with amyloid deposition, lemborexant (NCT06093126) in early-onset dementia with insomnia, daridorexant (DARIDOR-ALZ; NCT05924425) in MCI or mild AD patients, and seltorexant (NCT05307692) in AD patients with significant anxiety. Collectively, these trials highlight the potential of targeting the orexin system not only to alleviate sleep disturbances but also to potentially slow or modify the progression of AD.

Currently, orexin receptor antagonists face multiple challenges in the treatment of AD. Clinical evidence indicates that agents such as suvorexant and lemborexant can improve sleep disturbances and circadian rhythms abnormalities in AD patients, but their efficacy is largely limited to sleep, with no conclusive evidence for benefits on cognitive function or disease progression. The activity of the orexin system varies across different stages of AD, making precise stage-specific targeting necessary; otherwise, treatment may lead to safety risks such as daytime sleepiness, impaired attention, or falls. Existing clinical trials are limited by small sample sizes and short intervention durations, leaving long-term efficacy and safety uncertain. Moreover, whether sleep improvement can indirectly slow AD pathology or cognitive decline remains to be determined in large, long-term trials with cognitive and pathological endpoints.

5.2. Autophagy-Targeted Therapy for AD Treatment

Rapamycin has been evaluated in a single-site, open-label Phase 1 trial (NCT04200911) in 10 participants with MCI. While no significant cognitive changes were observed over eight weeks of 1 mg/day treatment, rapamycin modulated AD-related biomarkers—including CSF phosphorylated tau-181, GFAP, and neurofilament light (NfL)—as well as inflammatory markers such as plasma interferon-γ, IL-5, Vascular Endothelial Growth Factor D (VEGF-D), soluble Flt-1, and placental growth factor, highlighting its potential biological effects despite limited CNS penetration [183].

Beyond rapamycin, multiple autophagy- and proteostasis-targeting strategies are under investigation in AD and MCI. mTOR inhibitors include Rapamune (Sirolimus, NCT04200911) and rapamycin (NCT04 629495, NCT06022068); AMPK activators, such as metformin (NCT00620191, NCT01965756, NCT0409 8666) and trehalose (NCT04663854), alone or combined with lifestyle interventions (NCT05109169); ABL tyrosine kinase inhibitors, including nilotinib (NCT029 47893, NCT05143528); IMPase and GSK-3β inhibitors, particularly lithium and derivatives (NCT00088387, NCT01055392, NCT02129348, NCT02204969, NCT03185208, NCT05363293, NCT05423522); and a monoclonal antibody targeting sortilin (AL101, GSK-4527226, 282 participants, 18 months). Collectively, these trials address multiple autophagy- and proteostasis-related pathways underscoring the translational potential of autophagy modulation in AD therapy.

Despite these efforts, clinical trial evidence remains limited. Most studies are early-phase, with modest biomarker effects but minimal or inconsistent cognitive improvements. Challenges include difficulties in directly measuring autophagy in humans, limited BBB penetration of candidate drugs, and the involvement of targets such as mTOR in fundamental metabolic processes, which increases the risk of adverse effects. These limitations underscore the need for further trials with optimized CNS delivery, validated biomarkers, and clinically meaningful endpoints.

5.3. TRF May Alleviate the Pathology of the AD by Enhancing Autophagy and Restoring Circadian Rhythms

TRF represents a practical intervention to realign circadian rhythms with nutrient intake, enhancing autophagic flux, restoring metabolic homeostasis, and potentially reducing AD pathology [128, 184-186]. Ongoing clinical trials (e.g., ChiCTR2400092653) are evaluating the 16:8 TRF regimen in mild-to-moderate AD patients, stratified by *ApoE* genotype, with primary outcomes including cognitive scores and secondary endpoints assessing AD biomarkers, ketone metabolism, lipid profiles, and circadian-associated markers.

TRF shows promise as a non-pharmacological intervention in AD by potentially enhancing autophagy, restoring circadian rhythms, and improving metabolic homeostasis. However, its clinical translation faces several challenges. First, most mechanistic evidence comes from animal studies, and robust human data demonstrating cognitive or disease-modifying effects are still limited. Second, adherence to TRF regimens, particularly in older adults with cognitive impairment, may be difficult to maintain over the long term, raising concerns about feasibility and consistency. Third, the optimal timing, duration, and frequency of TRF for maximal therapeutic benefit in AD remain unclear, and effects may vary according to disease stage, metabolic status, or genetic factors such as *ApoE* genotype. Additionally, standardized outcome measures, including cognitive endpoints, AD biomarkers, and circadian-related markers, need to be validated across larger, diverse populations. To enable successful clinical translation, well-designed, large-scale, long-term randomized trials are required to establish efficacy, safety, optimal regimen

parameters, and patient subgroups most likely to benefit from TRF interventions.

6. Integrated Translation Challenges and Future Research Directions

Animal studies indicate that circadian rhythms and autophagy are mechanistically interconnected, with clock genes regulating autophagic oscillations and autophagy maintaining circadian stability by degrading clock proteins. This interplay suggests that simultaneous modulation of both systems could potentially yield synergistic effects in slowing AD progression. Key regulators, such as Sirt1, AMPK, and mTOR, integrate metabolic signals with circadian timing and autophagy activity, highlighting potential nodes for dual modulation. However, translation to humans remains limited. Clinical trials have yet to test combined circadian interventions (e.g., light therapy, TRF) and autophagy-targeted strategies, and interindividual variability — including disease stage, *ApoE* genotype, and metabolic status — complicates generalization. In addition, dynamic biomarkers for autophagy and circadian phase are still under development, and the cell-type-specific dynamics of neurons, astrocytes, and microglia add further complexity to effectively targeting these pathways.

Future research should focus on several key areas to overcome these challenges. First, elucidating molecular interactions at core regulatory nodes is essential. Studies should investigate how core clock genes, such as BMAL1 and PER2, transcriptionally regulate autophagy-related pathways (e.g., ULK1, STX17), and how autophagy reciprocally affects the stability and activity of clock proteins (e.g., CRY1, NR1D1), using cell-type-specific models and advanced tools such as time-resolved proteomics, chromatin conformation mapping, and dynamic imaging. Second, the development of stage- and cell-specific dynamic monitoring tools is needed. Novel approaches, including PET tracers for autophagy or clock proteins, blood-based rhythmic biomarkers, and wearable devices for tracking activity-rest cycles, could enable patient stratification, optimize intervention timing, and facilitate assessment of treatment efficacy. Third, constructing spatiotemporal precision intervention paradigms is critical. Preclinical studies should determine dose-response and time-of-day effects for pharmacological agents (e.g., rapamycin, SIRT1 activators) and lifestyle interventions (e.g., TRF, light therapy), while advanced delivery systems responsive to local cues (e.g., low pH or Aβ oligomers) may improve targeting to specific brain cells. In clinical settings, individualized protocols that align light exposure, feeding windows, and drug administration with patients' circadian rhythms and metabolic profiles could enhance efficacy and reduce adverse effects. Finally, biomarker-based stratification and innovative clinical trial designs are essential. Systematic characterization of peripheral and central biomarkers reflecting circadian and autophagy status (e.g., melatonin rhythms, LC3-II/p62 levels, activity patterns) can guide trial design, stratify patients most likely to respond, compare single-target versus combination strategies, and optimize intervention timing according to individual chronotypes.

Overall, while preclinical evidence supports integrated modulation of circadian rhythms and autophagy as a promising strategy, well-designed, large-scale, and long-term clinical studies are needed to validate mechanisms, establish clinically meaningful endpoints, and identify patient subgroups most likely to benefit, moving beyond single-pathway interventions toward restoring network-level homeostasis in AD.

7. Conclusion

Both circadian rhythms dysfunction and impaired autophagy are hallmarks of AD. Their interaction, when dysregulated, appears to drive disease progression. This raises the possibility that restoring circadian-autophagy coupling could offer a new approach to treatment.

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Author Contributions

MLY: Methodology, Data curation, Formal analysis, Visualization, Writing - Original Draft; GZX: Conceptualization, Methodology, Data curation, Project administration; GR: Data curation, Visualization
WLR: Visualization; ZM: Conceptualization, Supervision, Funding acquisition, Writing - review & editing; BL: Conceptualization, Supervision, Funding acquisition, Writing - review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

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