

Review

Open Access



Influence of sleep disruption on protein accumulation in neurodegenerative diseases

Xiying Wang^{1,2}, Rui Wang³, Jiada Li^{1,4}

¹Center for Medical Genetics, School of Life Sciences, Central South University, Changsha 410078, Hunan, China.

²Xiangya School of Medicine, Central South University, Changsha 410078, Hunan, China.

³School of Life Science and Technology, Key Laboratory of Developmental Genes and Human Disease, Southeast University, Nanjing 210096, Jiangsu, China.

⁴Hunan Key Laboratory of Animal Models for Human Diseases, and Hunan Key Laboratory of Medical Genetics, Changsha 410078, Hunan, China.

Correspondence to: Prof. Jiada Li, Center for Medical Genetics, School of Life Sciences, Central South University, 172 Tong-Zi-Po Road, Changsha 410078, Hunan, China. E-mail: lijada@sklmg.edu.cn

How to cite this article: Wang X, Wang R, Li J. Influence of sleep disruption on protein accumulation in neurodegenerative diseases. *Ageing Neur Dis* 2022;2:4. <https://dx.doi.org/10.20517/and.2021.10>

Received: 29 Dec 2021 **First Decision:** 1 Mar 2022 **Revised:** 10 Mar 2022 **Accepted:** 23 Mar 2022 **Published:** 31 Mar 2022

Academic Editor: Weidong Le **Copy Editor:** Xi-Jun Chen **Production Editor:** Xi-Jun Chen

Abstract

Abnormal accumulation of disease proteins in the central nervous system is a neuropathological feature in neurodegenerative disorders. Recently, a growing body of evidence has supported a role of disruption of the sleep-wake cycle in disease development, pathological changes and abnormal protein accumulation in neurodegenerative diseases, especially in Alzheimer's disease and Parkinson's disease. Sleep deprivation promotes abnormal accumulation of disease proteins. Interestingly, amyloid- β ($A\beta$) has daily oscillations in human cerebral spinal fluid (CSF) and is cleared more in sleep. Both circadian genes and circadian hormones are associated with disease protein deposition. Recently, the glymphatic pathway and meningeal lymphatics have been shown to play a critical role in $A\beta$ clearance, which is mediated by the aquaporin (AQP-4) water channel on astrocytes. The rate of the clearance of $A\beta$ by the glymphatic pathway is different during the sleep/wake cycle. Most importantly, circadian rhythms facilitate glymphatic clearance of solutes and $A\beta$ in the CSF and interstitial fluid in an AQP-4-dependent manner, which further provides evidence for the involvement of circadian rhythms in disease protein clearance.



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



Keywords: Neurodegenerative diseases, protein accumulation, glymphatic clearance, Alzheimer's disease, Parkinson's disease, circadian disruption

INTRODUCTION

The sleep-wake cycle is controlled by circadian rhythms. Circadian rhythms are biological processes that follow a daily cycle and respond to light and darkness in an organism's environment. Circadian rhythms are endogenously synchronized to the day/night cycle to form oscillations of 24 h^[1]. The central pacemaker in mammals is the suprachiasmatic nucleus (SCN), which receives light signals from the retina through the retinohypothalamic pathway^[2]. Ablation of the SCN in animals, aneurysms near the SCN, or pituitary tumors in patients disrupts daily rhythms^[3-5]. Moreover, intrahypothalamic grafts of neonatal SCN tissue to SCN-ablated animals restore rest-activity rhythms^[3]. Thus, the SCN plays a principal role in circadian rhythms.

The SCN clock entrains the peripheral clock, nearly all of the cells in the body, through autonomic innervation, body temperature, humoral signals, and feeding-related cues^[6]. The rhythms of the cells from different organs are affected not only by the oscillation of hormones, the nervous system and temperature but also by local circadian oscillators^[1]. Increasing lines of evidence demonstrate that dysfunction of circadian rhythms is associated with diseases in many systems and organs, including neurodegenerative diseases^[7,8], cancer^[9], hypertension^[10], diabetes^[11], and autoimmune diseases^[12]. The circadian rhythms in mammals are generated internally but synchronized to the external environment (light and dark cycles by the Earth's 24 h rotation^[13]). Sleep/wake cycles have a typical 24 h pattern, which is linked to circadian rhythms^[13]. Sleep loss is a representative symptom of circadian rhythm disruption.

Aberrant accumulation of abnormal disease proteins is a common pathological feature of neurodegenerative diseases. The aggregation of proteins associated with neurodegenerative disease is present in patient brains in both familial and sporadic cases, such as the formation of extracellular plaques by β -amyloid ($A\beta$) and intracellular neurofibrillary tangles by tau in Alzheimer's disease (AD), intracellular Lewy bodies by α -synuclein (α -syn) in Parkinson's disease (PD), TDP-43 inclusions in amyotrophic lateral sclerosis and nuclear inclusions in Huntington disease^[14-16]. Circadian rhythm abnormalities are frequently present in patients with neurodegenerative diseases, in which patients obviously show abnormalities in the sleep-wake cycle. Patients, especially with AD or PD, often decrease activities during the daytime and increase activities at night, showing changes in rest-activity patterns^[7,8]. Increasing evidence suggests that circadian rhythms are associated with protein homeostasis, which functions in the clearance of abnormal proteins^[17,18]. Disruption of circadian rhythms increases the accumulation of disease proteins, which promotes pathological changes in neurodegenerative diseases.

In this review, we discuss the associations of circadian rhythm disruption and protein homeostasis dysfunction in neurodegenerative diseases. We focused on the influence of protein aggregation and pathological changes by circadian rhythm abnormalities. We summarized the studies on circadian rhythm disruption in AD and PD and the protein homeostasis regulated by circadian rhythms. We also described the pathological significance of circadian rhythm disruption and the underlying mechanisms in neurodegenerative diseases.

CLINICAL ASSOCIATIONS BETWEEN SLEEP DISRUPTION AND NEURODEGENERATIVE DISEASES

Alterations in circadian rhythms can be presented by behavioral and physiological changes, including sleep-wake rhythms, body temperature, blood pressure and hormone levels. The sleep-wake cycle is often disrupted in patients with neurodegenerative diseases. The degeneration of neurons in neurodegenerative diseases is associated with or leads to circadian dysfunction and sleep disturbance, and it was previously believed that the disruption of circadian rhythms is a consequence of neurodegeneration. However, increasing evidence suggests that circadian dysfunction contributes to the formation of pathological changes, such as the accumulation of abnormal proteins and the progression of neurodegenerative diseases [Figure 1]. Importantly, sleep disorders are presented in many neurodegenerative diseases, including early AD, PD, dementia with Lewy bodies, frontotemporal dementia (FTD) and multiple system atrophy (MSA) patients^[8,19-23], further suggesting that they play a role in disease development.

Alzheimer's disease

Sleep disturbance can occur at all stages in AD patients. AD patients lose a normal resting-activity pattern, showing an increase in daytime sleepiness. It has been reported that sleep fragmentation can increase the risk of AD and the rate of cognitive decline^[24]. In a Swedish cohort, 214 Swedish adults aged 75 and over participated in a longitudinal study with 9 years of follow-up. All participants were dementia-free at baseline and the first follow-up (3 years later). After a total of 9 years of follow-up, participants with moderate or severe sleep problems showed an increased risk for developing dementia, particularly AD^[25]. After adjusting for age, education and gender, moderate/severe sleep disruption causes a 2.5 times greater risk of all-cause dementia and a more than 3 times greater risk of AD^[25]. In a prospective study, women without dementia were subjected to overnight polysomnography measurements to determine sleep status. After a 5-year follow-up, their cognitive status was evaluated. Women with sleep-disordered breathing have a high incidence of developing mild cognitive impairment or dementia, suggesting that sleep problems are associated with the development of dementia^[26]. Shift workers are subjected to sleep deprivation, which causes circadian disruption. By analysis of a Danish nurse cohort (28,731 female nurses), shift work increased AD risk^[27]. Moreover, sleep disorder is believed to occur at the preclinical stage of AD^[28]. Using a tailored light treatment that maximally regulates the circadian system, AD patients show significant improvements in sleep, mood and behavior, further suggesting that there is an association between circadian system disruption and the symptoms in AD patients and that an entrainment of circadian rhythms benefits AD patients^[29].

Parkinson's disease

It is estimated that nearly half of dopamine neurons in the substantia nigra are lost when patients start motor symptoms. Before motor symptoms, PD patients often demonstrate nonmotor symptoms, including mood disorders, pain, gastrointestinal dysfunction and sleep disorders. Sleep disturbance, including insomnia, excessive daytime somnolence (EDS), fragmented sleep and rapid eye movement sleep behavior disorder (RBD), is the most common nonmotor symptom, which appears in up to 90% of PD patients^[30-32]. The changes in temporal sleep patterns, including insomnia, EDS and fragmented sleep, that are controlled by circadian rhythms suggest a disruption of the circadian system in PD. Characterized by polysomnography signals, sleep is divided into two states: rapid eye movement (REM) and nonrapid eye movement. Patients with PD at an early stage show increased sleep latency and decreased REM sleep as well as sleep efficiency^[7]. In a study involving 3078 men free of PD and dementia, the risk of developing PD within 10 years was threefold higher in men with EDS than in those without EDS^[33], suggesting that EDS increases the risk of PD and is a prodromal stage of PD. In a population-based prevalence study, RBD was identified as a symptom in the early phase of PD, which occurs in nearly 30% of newly diagnosed PD patients^[34]. The prevalence of RBD in PD patients is estimated to be near 40%, showing that the risk for the



Figure 1. Interactions between sleep disturbance and neurodegenerative diseases. Sleep disturbance plays roles in neurodegenerative disease. It promotes the pathogenesis of Alzheimer's disease (AD) and Parkinson's disease (PD). Sleep disturbance is tightly associated with A β and tau deposition in AD and α -syn accumulation in PD. It also promotes the transmission of disease proteins, such as tau in AD and α -syn in PD. Furthermore, sleep disturbance is positively related to dementia in AD and excessive daytime somnolence (EDS) and rapid eye movement sleep behavior disorder (RBD) in PD. However, there are bidirectional relationships between sleep disturbance and neurodegenerative diseases. Neurodegeneration and pathogenesis in neurodegenerative diseases induce sleep disturbance, further leading to deterioration of the disease. A β : Amyloid- β ; α -syn: α -synuclein.

conversion from idiopathic RBD to PD is extremely high. RBD is associated not only with the development of PD but also with a risk for dementia^[20]. Importantly, among the sleep disorders in PD, RBD is mostly associated with the development of PD pathology. In an observational cohort study, patients with idiopathic RBD were followed up for 7 years and examined with dopamine transport imaging, transcranial sonography and olfactory testing^[35]. With this cohort, 82% of patients with idiopathic RBD show neurodegenerative syndrome with an increased risk for developing PD and Lewy body dementia. In three patients with antemortem diagnosis of PD and Lewy body dementia, there were widespread Lewy bodies in the brains and α -syn aggregates in the peripheral autonomic nervous system, suggesting an association between RBD and synucleinopathy^[35]. Interestingly, these three patients show Lewy pathology as well as a loss of neurons in the brainstem nuclei that regulate REM sleep atonia^[35], which may also reflect a connection between synucleinopathy and REM sleep without atonia in PD.

Frontotemporal dementia

FTD includes a group of heterogeneous dementias with the frontal and temporal lobe atrophy in patients. Behavioral variant FTD (bvFTD) is a common form of FTD syndromes. In comparison to AD patients, FTD patients have more severe daytime somnolence and sleep disturbance^[36]. The sleep disturbance appears earlier in FTD than in AD patients. Moreover, FTD patients have longer sleep onset and less total sleep time than AD patients^[37]. In the prodromal symptoms, sleep disturbance occurs more frequent in bvFTD patients (40%) than in AD patients (12%)^[38].

The hexanucleotide (G4C2) repeat expansion in the chromosome 9 open reading frame 72 (*C9orf72*) gene causes both FTD and amyotrophic lateral sclerosis (ALS)^[39,40]. In a screen for *C9orf72* repeat expansion in 344 RBD patients, two of them have G4C2 expansion, suggesting a possible linkage between RBD and *C9orf72* mutation^[41]. It is well known that dipeptide repeat proteins (DPRs) that are encoded by the expansion of *C9orf72* by non-ATG translation form inclusions in c9FTD/ALS. Interestingly, the abundant DPR inclusions are presented in pineal gland, as well as the supraoptic nucleus and paraventricular nucleus (PVN) that are related to the SCN, implying an association of sleep disruption and c9FTD/ALS^[42].

Multiple system atrophy

The sleep disturbance occurs highly in MSA patients. RBD is a very common symptom in MSA patients. In a meta-analysis, the prevalence of RBD in MSA ranks from 25% to 100%^[43]. In a cross-sectional study in which 165 MSA patients are engaged, sleep disorders are observed in most patients^[44]. RBD occurs in 49.7% of patients, and the frequency of EDS is 27.3%^[44]. Importantly, there is a positive correlation between sleep

disturbances and the severity of MSA^[44]. Another study also shows that there is an association of RBD and MSA, with a frequency of RBD as high as 70.4% in MSA patients^[45]. A cross-sectional study shows that the MSA patients with EDS have a higher score of Non-Motor Symptoms Scale and a higher apnea-hypopnea index as compared the MSA patients without EDS, suggesting that EDS in MSA patients is more associated with sleep-related breathing disorder and other the non-motor symptoms^[46].

PATHOLOGICAL ACCUMULATION OF DISEASE PROTEINS IN ASSOCIATION WITH SLEEP DISRUPTION

The pathological hallmark is the presence of abnormal protein deposition in diseased brains in patients with neurodegenerative diseases. The formation of amyloid plaques by A β and intracellular neurofibrillary tangles by tau in AD or the formation of Lewy bodies by α -syn is a typical pathological process in AD or PD brains^[47]. Soluble A β , tau or α -syn can form oligomers, protofibrils and fibrils, which accumulate and deposit in diseased brains (Soto and Pritzkow^[48], 2018) [Figure 1].

A β

The homeostasis of A β , either accumulation or clearance, is important for AD pathology. A β is a small peptide that is released from amyloid precursor protein (APP) after APP is cleaved by β -secretase and subsequently cleaved by γ -secretase^[49,50]. Mutations in APP or presenilin (catalytic subunit of γ -secretase) that cause early-onset familial AD increase the processing of APP, which promotes the generation of A β peptides^[51,52]. The deposition of A β in AD brains and in APP transgenic mice is a typical pathological feature.

It has been reported that A β has daily oscillations^[53]. The levels of soluble A β in brain interstitial fluid (ISF) in the hippocampus in wild-type or human APP transgenic mice have a pronounced diurnal rhythm^[53]. Moreover, the fluctuation of A β also occurs in the cerebral spinal fluid (CSF) in humans^[53]. In sleep-deprived mice, A β is increased in the ISF in the hippocampus in both wild-type and APP transgenic mice; however, A β is decreased in the ISF in the hippocampus in animals with more sleep^[53]. In *APP^{Swe}/PS1 δ E9* mice, diurnal fluctuation of A β in the ISF and the hippocampus but not in the striatum was attenuated at 6 months of age. Diurnal fluctuation of A β in ISF in the striatum is decreased at 9 months of age when A β plaques appear in the striatum and more often in the hippocampus^[54]. Animals also have significant disturbances in the sleep-wake cycle at 6 months of age^[54]. Thus, the decrease in diurnal fluctuation of A β in the ISF occurs earlier in the hippocampus than in the striatum, and A β plaques appear earlier in the hippocampus than in the striatum, suggesting a link between A β pathological progression and daily oscillations. In addition, active immunization with A β , which decreases A β deposition in *APP^{Swe}/PS1 δ E9* mice, restores the diurnal fluctuation of A β in the ISF and normal sleep-wake cycle^[54], suggesting that A β deposition disrupts A β oscillations and the sleep-wake cycle.

In humans, the daily oscillation of A β in the CSF shows that A β increases during the day, reaches a peak in the evening, and then decreases overnight^[53]. Loss of diurnal fluctuation of the CSF A β occurs in patients with presenilin mutation when A β deposition is detected by amyloid imaging with Pittsburgh Compound B^[54]. An attenuation of diurnal fluctuation of the CSF A β also occurs in patients with presenilin mutation^[54]. Most interestingly, using a radiotracer 18F-florbetaben that binds to A β , images from healthy individuals scanned by positron emission tomography show that even one night of sleep deprivation can increase A β in the hippocampus and thalamus, the regions vulnerable to damage in AD^[55]. This study demonstrates the first evidence, in living humans, that sleep disturbance is directly associated with A β accumulation^[55].

In animal models, *APP^{swe}/PS1^{ΔE9}* transgenic mice show changed sleep architecture compared with control mice. Moreover, sleep disturbance occurs at 4 months of age, but plaque deposition and tau phosphorylation typically occur at 6 months of age^[56], suggesting that sleep changes occur earlier than AD pathology. APP transgenic mice also develop more A β plaques in the hippocampus after exposure to sleep deprivation^[53,57]. Chronic sleep deprivation of 8 h per day for 2 months or chronic sleep deprivation of 20 h per day for 21 days increases A β plaques in the hippocampus in APP transgenic mice^[53,57]. Sleep deprivation increases A β levels in the CSF in humans^[53] and amyloid plaques in the hippocampus in APP transgenic mice^[53,57], suggesting an impact of sleep disorders on A β accumulation. However, A β has a role in circadian rhythms in multiple transgenic mouse models with A β pathology. In *5 \times FAD* mice that model AD, the circadian rhythms are changed, evidenced by alterations in home cage activity and body temperature^[58]. Thus, there is a bidirectional relationship between A β accumulation and sleep disorders^[59].

The association of the accumulation of A β with sleep disturbance has been further verified in patients who accept sleep intervention or in animal models that are treated with drugs to improve sleep. In patients with obstructive sleep apnea, the A β levels in blood^[60] and the A β deposition in brain^[61] are increased. In AD patients with sleep-disordered breathing, a 6-month sleep intervention with a constitutive positive airway pressure ventilation decreases blood A β _{42/40} ratio in patients who are completely recovered from sleep disturbance^[62]. Interestingly, there are no changes in blood A β _{42/40} ratio in those patients who have no improvement in sleep^[62], suggesting an involvement of sleep in the regulation of A β levels. In animal, an administration of nobiletin, a natural compound that is able to enhance the amplitude of clock gene oscillation^[63], improves clock gene expressions and decreases A β deposition in APP/PS1 mouse brains^[64].

Tau

Tau is another important protein in association with AD. In the AD brain, tau is hyperphosphorylated and forms intracellular neurofibrillary tangles, a pathological hallmark of A β plaques. Tau pathology occurs in the early AD. Aggregates of tau first appear in the brainstem locus coeruleus (LC) and then spread to the transentorhinal and entorhinal regions and subsequently to the hippocampus^[65]. The LC is strongly linked to wakefulness and sends norepinephrine-containing projections to the cortex, amygdala, hippocampus, cerebellum and spinal cord. In tau *P301S* transgenic mice expressing the human P301S tau mutation that is associated with parkinsonism linked to chromosome 17, chronic short sleep at the age of 2-3 months induces deterioration in behaviors and increases in tau oligomers with sustained increases in phosphorylated tau and neuronal loss in the LC and the amygdala^[66]. The brain ISF tau in mice and the CSF tau in humans are also regulated by the sleep-wake cycle, although tau is known as an intracellular protein^[18]. Tau in brain ISF in the hippocampus has diurnal oscillations similar to A β . In sleep-deprived mice, tau levels are 2-fold increased in brain ISF^[18]. Interestingly, the increase in tau in brain ISF induced by sleep deprivation can be blocked by terodotoxin, a toxin that blocks voltage-dependent sodium channels, suggesting that neuronal activity is related to tau levels in brain ISF. In addition, sleep deprivation in humans increases CSF A β by 30%, while it increases CSF tau by over 50% in the same participants^[18]. With chronic sleep deprivation, the administration of recombinant P301S human tau fibrils does not change tau seeding in the hippocampus; however, it increases tau spreading to the LC, a nucleus associated with wakefulness^[18], suggesting that sleep disorders may induce tau spreading to other brain regions that are associated with the wake-sleep cycle, producing feedback effects on sleep.

α -syn

It has been reported that the severity of hypothalamic Lewy pathology is correlated with Braak stages^[67]. Moreover, Lewy pathology is presented in the SCN with mild or moderate severity in most cases of PD, much fewer in pineal gland^[67]. In multiple system atrophy, no Lewy pathology is present in the SCN or pineal gland^[68], suggesting a tight association between circadian dysfunction and PD pathology. According

to the Braak hypothesis, α -syn pathology can spread from the peripheral autonomic nerve endings of the gastrointestinal tract to the brain^[69]. In a study involving 602 patients with clinical assessment for RBD and neuropathological examination for Lewy-type α -synucleinopathy, Lewy-type α -synucleinopathy occurred in 79.2% of patients with RBD but only 39.5% of those without RBD^[70]. In addition to the brain, α -syn pathology occurs in many organs, including the vagus nerve, gastrointestinal tract, adrenal gland and heart, in PD patients^[71]. The presence of pathological α -syn in the gastrointestinal tract is identified in prodromal PD patients up to 20 years prior to diagnosis^[72]. Moreover, the transmission of α -syn inclusions has been well identified in recent studies that show the development of α -syn pathology in the brain after injecting α -syn preformed fibrils into the duodenum^[73,74]. Thus, peripheral tissues with α -syn pathology may reflect, at least partially, central pathology. In a study using biopsy samples of labial minor salivary glands, α -syn pathology occurred in labial minor salivary glands in 50% of patients with idiopathic RBD and 54% of patients with PD but only 3% of controls^[75]. Moreover, the deposits of α -syn in the parotid gland in idiopathic RBD patients occur at the prodromal stage of PD^[76]. Thus, studies suggest an association of α -syn deposition and RBD.

TDP-43

TDP-43 that is encoded by *TARDBP* is a major pathogenic protein in FTD and ALS^[77]. Although the mutations in *TARDBP* only cover about 5% familial ALS cases and even less in FTD patients^[78]. The TDP-43 pathology is presented in about 97% of ALS patients and 45% FTD patients^[79]. In ALS patients, the volume of the hypothalamus is decreased^[80]. Moreover, the volume of the PVN in the hypothalamus is also decreased. Furthermore, TDP-43-positive inclusions are observed in the PVN, lateral hypothalamus and fornix^[80]. TDP-43 inclusions are also presented in the reticular formation in the brainstem, which has an important role in the rhythmical cycle of sleep and wakefulness^[81]. The presence of TDP-43 pathology in sleep-related brain regions and nuclei suggests a linkage between the abnormal accumulation of TDP-43 and the symptoms of sleep disorders in ALS and FTD patients.

FACTORS INVOLVED IN CIRCADIAN RHYTHM DISRUPTION IN NEURODEGENERATIVE DISEASES

Clock gene

The molecular basis of circadian rhythms is the oscillation of 24 h clock gene expression in the SCN^[1]. The core clock gene products circadian locomotor output cycles kaput (CLOCK) and brain and muscle arnt-like 1 (BMAL1) form heterodimers that bind to E-boxes and drive the expression of period (PERs) and cryptochrome (CRYs). The expression of PERs and CRYs in turn represses CLOCK-BMAL1 activity, thus inhibiting their own expression, which forms a feedback loop that takes 24 h^[1]. Thus, the molecules involved in the molecular clock are important for the maintenance of circadian rhythms.

It has been reported that the alteration of DNA methylation of BMAL1 in early AD patients causes changes in BMAL1 expression patterns in both amplitude and phase^[82]. Knockout of *Bmal1* disrupts A β oscillation in brain ISF in the hippocampus. Moreover, in tamoxifen-inducible global *Bmal1* knockout mice with an APP transgenic background, *Bmal1* knockout significantly increases hippocampal A β plaques 4 months after tamoxifen induction^[17]. In AD patients, there is a disruption of circadian rhythms, typically showing sleep problems. Sleep deprivation also affects clock gene expression and the DNA binding patterns of BMAL1 and CLOCK heterodimers, which disturbs clock function. Three different polymorphisms of the CLOCK gene are associated with AD in the Chinese population^[83,84]. Moreover, changes in expression patterns and decreases in expression levels of *Bmal1* and *Clock* in senescent cells and aged rodent brains suggest a role of circadian genes in aging^[84]. In 5 \times FAD mice, the amplitude of BMAL1 and PER2 in a 24 h oscillation is greatly decreased^[58]. Moreover, A β is able to induce BMAL1 degradation *in vitro*^[58]. In

APP/PS1 mice, there is also a modest alteration of PER2 in the SCN, which is consistent with the findings in *5×FAD* mice^[58,85]. In addition, at circadian time 4 (CT4, 4 h after the onset of activity of diurnal organisms, based on the free-running period of a rhythm), when microglia express higher levels of BMAL1 than at CT12, the clearance ability for fibrillary A β by microglia at CT4 is also higher than that at CT12 in *5×FAD* mice^[86]. Pharmacological inhibition of REV-ERBs that is transactivated by BMAL1 and negative feedback on BMAL1 activity promote a microglial M2-like phenotype. Moreover, a constitutive deletion of *Rev-erba* in *5×FAD* mice can repress amyloid plaque formation^[86], further suggesting a role of the clock gene in protein homeostasis.

It has been reported that BMAL1 oscillation amplitude is decreased in PD patients and that BMAL1 mRNA levels are decreased in leukocytes in PD patients, suggesting that dysfunction of the clock gene *Bmal1* may be associated with PD.

Melatonin

In the brain, circadian information in the SCN can be sent to different areas. Through multisynaptic projections, the SCN circadian information is integrated and sent to the superior cervical ganglia (SCG). The noradrenergic neurons in the SCG send projections to the pineal gland^[87]. The pineal gland produces melatonin, the hormone that synchronizes and stabilizes circadian rhythms, which is important for the maintenance of the biological clock of the brain in the SCN. Melatonin is synthesized in the dark and shows oscillation at its level, which is controlled by the SCN [Figure 2]. The secretion of melatonin starts at early night and usually reaches a peak level at 3:00 to 4:00 am. With aging or neurodegenerative diseases, the circadian amplitude is decreased with desynchronization of physiological rhythms, leading to a decrease in melatonin levels^[88]. Melatonin binds to melatonin receptor 1 (MT1) and MT2, which are G-protein coupled receptors and are highly expressed in neurons in the SCN, hippocampus, thalamus, vestibular nuclei and cerebral and cerebellar cortex^[89]. In addition to the maintenance of circadian rhythms, melatonin has multiple functions, including antioxidative stress and regulating metabolism^[88].

AD patients have lower melatonin levels than normal controls. The melatonin level is decreased in the CSF in early AD patients before clinical symptoms^[90]. Meanwhile, the loss of neurons in the SCN further shows a correlation between AD and circadian rhythm dysfunction^[91]. In patients with AD at the early stage, the initial evening secretion of melatonin is delayed and mildly decreased, suggesting that a circadian phase shift occurs in early AD patients^[92]. Moreover, the risk variant rs12506228, which is located downstream of *MTNR1A* (MT1A-encoding gene), is associated with AD^[93]. The rs12506228 variant leads to a decrease in MT1A expression and is associated with both clinical and pathological changes in AD patients^[93], further suggesting a role of melatonin in AD.

It has been reported that melatonin has effects on A β deposits in AD. In *APP/PS1* mice, long-term melatonin treatment at ages starting from 2-2.5 months decreases A β deposits in the hippocampus and the entorhinal cortex when the animals are examined at the age of 7.5 months^[94]. Meanwhile, there was a decrease in inflammatory cytokines in the hippocampus in *APP/PS1* mice treated with melatonin, suggesting a role of melatonin in anti-inflammation and decreasing A β accumulation^[94]. It has also been reported that melatonin can induce lymphatic clearance of A β in *Tg2576* mice^[95].

Using real-time PCR analysis, it has been identified that MT1 and MT2 are decreased in both the substantia nigra and the amygdala in PD patients compared to controls^[96]. In PD patients, circulating melatonin is decreased in early PD patients compared with controls^[7]. Moreover, plasma melatonin, both the amplitude of daily oscillation and the levels, is lower in PD patients than in controls^[97]. In PD patients who accept

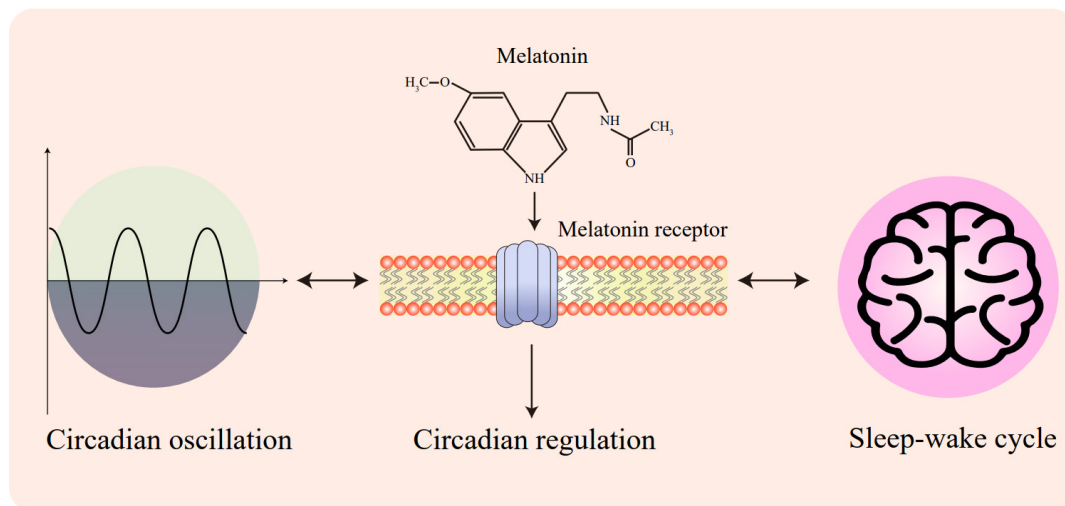


Figure 2. Impact of circadian genes and hormones on neurodegeneration and the glymphatic system. The secretion of the circadian hormone melatonin is controlled by circadian rhythm. In addition to functioning in circadian rhythm, melatonin has protective effects on neurons. In neurodegenerative diseases, the levels of melatonin are decreased.

melatonin treatment at a dose of 5 mg or a high dose of 50 mg 30 min before bedtime over 14 days, the nocturnal sleep that is evaluated with actigraphy is significantly improved in PD patients during melatonin treatment at both doses^[98]. Interestingly, the treatment of PD patients with levodopa increases melatonin levels^[99].

In a rotenone PD animal model^[100] or in a 6-hydroxydopamine with or without pinealectomy animal model^[101], melatonin protects DA neurons. Melatonin also improves rotenone-induced defects in behaviors, including grip strength and performance on rotarods^[102]. In *MPTP* mice, melatonin protects DA neurons against MPTP-induced neurotoxicity, which may be mediated by antioxidant effects and neuroprotective effects of melatonin^[103-105]. In *MPTP* mice that receive both melatonin and levodopa treatments, melatonin increases the therapeutic effects of levodopa in the improvement of MPTP-induced akinesia and catalepsy^[105]. In a lentivirus-infected animal model that expresses A30P pathogenic α -syn, melatonin administration protects DA neurons against A30P elsyn-induced TH neuronal loss^[106]. In amphetamine-treated 4-day-old postnatal rats, melatonin decreases amphetamine-induced α -syn accumulation in the substantia nigra, dorsal striatum, nucleus accumbens, and prefrontal cortex^[107]. Thus, melatonin has multiple effects on circadian rhythm regulation, neuroprotection and protein clearance, which can be associated with the pathogenesis of neurodegenerative diseases [Figure 2]

GLYMPHATIC PATHWAY

Although the central nervous system is thought to anatomically lack lymphatic vessels for the removal of interstitial metabolic waste products, it has been recently discovered that glymphatic (glial-lymphatic)^[108] and meningeal lymphatic vessels^[109,110] execute functions to transport and drain brain wastes, such as the peripheral lymphatic system. The glymphatic system is a glial-dependent perivascular network that has lymphatic functions^[111]. The CSF produced by the choroid plexuses flows into the brain along periarterial spaces surrounding cerebral arteries and arterioles, running in the same direction as blood flow, which is driven by arterial pulsation^[112]. The CSF enters the brain parenchyma and mixes with ISF, which is facilitated by the aquaporin (AQP-4) water channel on the perivascular end-foot processes of astrocytes^[113]. Mixtures of CSF and ISF with interstitial solutes outflow along the perivenous space and drain out of the brain via meningeal lymphatic vessels or along cranial and spinal nerves^[113] [Figure 3]. The meningeal

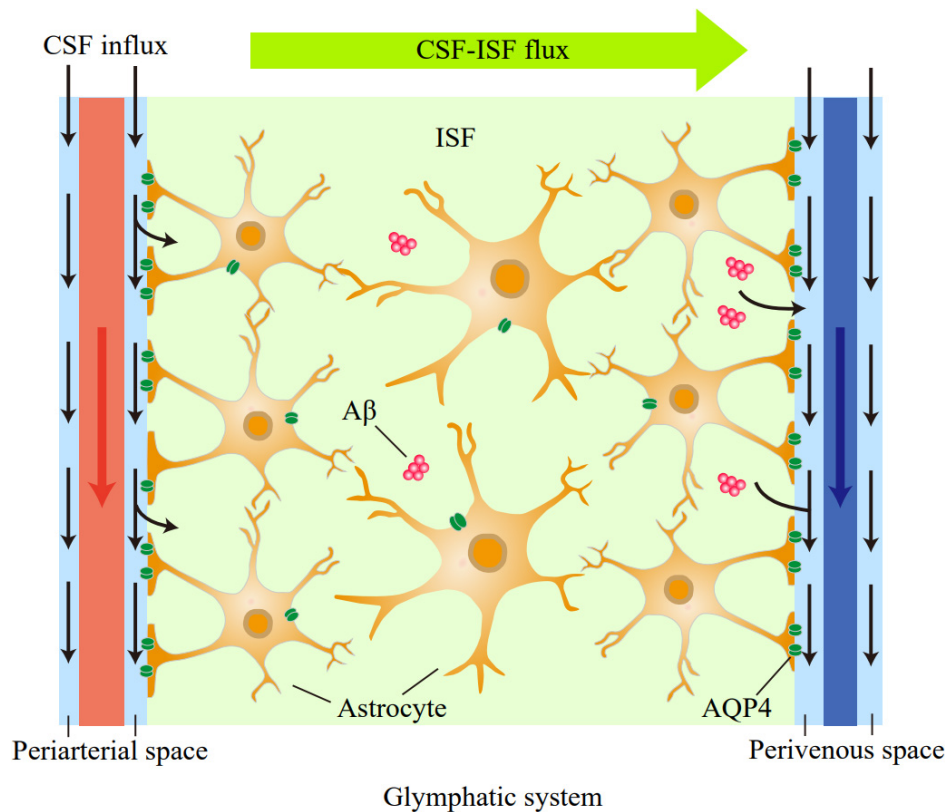


Figure 3. The glymphatic system in association with the clearance of neurodegenerative disease proteins. The glymphatic system is a perivascular network that has lymphatic functions. Driven by arterial pulsation, the CSF flows into the brain along periarterial spaces surrounding cerebral arteries and arterioles, running in the same direction as blood flow. The CSF enters the brain parenchyma mediated by the aquaporin (AQP-4) water channel on the perivascular end-foot processes of astrocytes. Mixtures of CSF and ISF with interstitial solutes outflow along the perivenous space and drain out of the brain, which can clear Aβ in the ISF. The glymphatic system depends on AQP-4 on astrocytes. Sleep enhances glymphatic system function to promote the clearance of Aβ and other disease proteins in the brain. CSF: Cerebral spinal fluid; ISF: interstitial fluid; Aβ: amyloid-β.

lymphatic vessels are located in the dura matter^[109,110]. The metabolites in the CSF are cleared from the brain by fluid flow and finally drained to extracranial deep cervical lymph nodes^[114]. Dysfunction of the glymphatic system may be a final common pathway to dementia^[115]. Using gadobutrol as the CSF tracer with intrathecal administration, the glymphatic system assessed with magnetic resonance imaging demonstrates delayed glymphatic clearance of gadobutrol from the subarachnoid space, with an enhancement of the signal in the brain parenchyma, in idiopathic normal hydrocephalus, which is the first study in humans showing glymphatic clearance of a CSF tracer (solute)^[116].

The glymphatic system is tightly associated with the clearance of neurodegenerative disease proteins, such as Aβ^[108,113]. In PD patients, the glymphatic system is impaired, and in animals, blockage of meningeal lymphatic vessels increases α -syn preformed fibril-induced α -syn pathology^[117]. Interestingly, the activity of the brain glymphatic system is controlled by circadian rhythms^[118], which are related to the clearance of neurodegenerative disease proteins^[119]. Glymphatic clearance is facilitated by AQP-4, which influences CSF influx into the brain parenchyma where it mixes with ISF^[108]. In *Aqp4* (AQP-4 encoding gene) knockout mice, CSF tracer influx into the brain parenchyma is markedly reduced; however, the periarterial movement of the tracer is not significantly decreased^[108]. Moreover, in *Aqp4* knockout mice, a 55% reduction in the clearance of Aβ occurs compared with wild-type mice when ¹²⁵I-Aβ₄₂ is infused into the striatum^[108]. The interstitial space in sleeping mice is larger than that in awake mice^[119], which increases the convective ISF

bulk flow in the brain parenchyma to increase glymphatic clearance of A β ^[119] [Figure 3]. In *APP/PS1* mice, A β also shows an impact on the glymphatic pathway, leading to dysfunction of the glymphatic pathway^[120]. The inflow of A β 40 into the brain and the clearance of A β by the glymphatic pathway in the brain are decreased in *APP/PS1* mice (Peng *et al.*^[120], 2016). Disruption of meningeal lymphatic vessels in *5xFAD* mice also aggravates A β deposition in the meninges and A β accumulation in the brain parenchyma^[121]. Most recently, it has been reported that there is a circadian rhythm in glymphatic influx, and loss of AQP-4 eliminates circadian CSF distribution, further suggesting a linkage between circadian rhythms and glymphatic clearance^[118]. Interestingly, the localization of AQP-4 to the endfeet of astrocytes surrounding the vasculature has diurnal variation, showing an increase in AQP-4 polarization surrounding the vasculature during the day^[118]. Correspondingly, glymphatic influx and the clearance of solutes are increased during the day. In addition, the influx that is indicated by a CSF tracer shows an increase during the rest phase compared with the active phase of animal behavior, further suggesting a role of circadian rhythms in glymphatic influx^[118]. There are also some controversial studies. In *Aqp4* knockout mice and rats, no significant difference in tracer (Alexa 647-labeled ovalbumin) penetration into the striatal parenchyma from the paravascular space was observed^[122]. The mechanisms for the clearance of waste by the glymphatic pathway are still largely unknown. Furthermore, the linkage between circadian rhythms and the glymphatic pathway is still being identified.

CONCLUSION

It is clear that there is a link between circadian disruption and neurodegenerative diseases. Sleep problems often start at the early stage in patients with neurodegenerative diseases. Clinical studies and animal models have revealed an association between the pathological progression of neurodegenerative diseases and circadian disruption. It has been well documented that sleep deprivation aggravates the deposition of neurodegenerative disease proteins in animal models. It is also known that sleep increases the glymphatic clearance of A β and tau in the CSF. However, our understanding of the role of circadian rhythms in protein homeostasis and disease development is very limited. There are still some key questions that need to be addressed: (1) whether circadian rhythms influence protein quality control systems, such as the ubiquitin-proteasomal pathway or autophagic pathway, facilitating disease protein degradation; (2) why RBD, within different sleep disturbances, is the highest risk factor associated with synucleinopathy, PD and dementia; (3) how the phenotypes of AQP-4 deficiency can be linked to the phenotypes of neurodegenerative diseases in animal models; and (4) whether there are different or the same mechanisms accounting for the interactions between abnormal accumulation of disease proteins and the dysfunction of circadian rhythms in patients with different neurodegenerative diseases. Further studies should address how circadian rhythm affects the clearance or accumulation of disease proteins and by which mechanism the abnormal proteins lead to dysfunction of circadian, which may guide the development of novel strategies for clinical treatment and drug targets for neurodegenerative diseases.

DECLARATIONS

Authors' contributions

Conceived the idea of this review article: Li J

Drafted the manuscript: Wang X

Revised the manuscript: Li J

Designed pictures: Wang R, Wang X

Completed the pictures: Wang R

Available of data and materials

Not applicable.

Financial support and sponsorship

This work was supported by the National Natural Science Foundation of China (31972913), Key Research and Development Programs from Hunan Province (2018DK2010 and 2018DK2013), Guangdong Key Project in Development of new tools for diagnosis and treatment of Autism (2018B030335001) and National Undergraduate Training Program for Innovation (No. 201910533108).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2022.

REFERENCES

1. Patke A, Young MW, Axelrod S. Molecular mechanisms and physiological importance of circadian rhythms. *Nat Rev Mol Cell Biol* 2020;21:67-84. [DOI](#) [PubMed](#)
2. Hastings MH, Maywood ES, Brancaccio M. Generation of circadian rhythms in the suprachiasmatic nucleus. *Nat Rev Neurosci* 2018;19:453-69. [DOI](#) [PubMed](#)
3. Ralph MR, Foster RG, Davis FC, Menaker M. Transplanted suprachiasmatic nucleus determines circadian period. *Science* 1990;247:975-8. [DOI](#) [PubMed](#)
4. Bloch KE, Brack T, Wirz-Justice A. Transient short free running circadian rhythm in a case of aneurysm near the suprachiasmatic nuclei. *J Neurol Neurosurg Psychiatry* 2005;76:1178-80. [DOI](#) [PubMed](#) [PMC](#)
5. Borgers AJ, Romeijn N, van Someren E, Fliers E, Alkemade A, Bisschop PH. Compression of the optic chiasm is associated with permanent shorter sleep duration in patients with pituitary insufficiency. *Clin Endocrinol (Oxf)* 2011;75:347-53. [DOI](#) [PubMed](#)
6. Mohawk JA, Green CB, Takahashi JS. Central and peripheral circadian clocks in mammals. *Annu Rev Neurosci* 2012;35:445-62. [DOI](#) [PubMed](#) [PMC](#)
7. Breen DP, Vuono R, Nawarathna U, et al. Sleep and circadian rhythm regulation in early Parkinson disease. *JAMA Neurol* 2014;71:589-95. [DOI](#) [PubMed](#) [PMC](#)
8. Musiek ES, Bhimasani M, Zangrilli MA, Morris JC, Holtzman DM, Ju YS. Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. *JAMA Neurol* 2018;75:582-90. [DOI](#) [PubMed](#) [PMC](#)
9. Masri S, Sassone-Corsi P. The emerging link between cancer, metabolism, and circadian rhythms. *Nat Med* 2018;24:1795-803. [DOI](#) [PubMed](#) [PMC](#)
10. Douma LG, Gumz ML. Circadian clock-mediated regulation of blood pressure. *Free Radic Biol Med* 2018;119:108-14. [DOI](#) [PubMed](#) [PMC](#)
11. Mason IC, Qian J, Adler GK, Scheer FAJL. Impact of circadian disruption on glucose metabolism: implications for type 2 diabetes. *Diabetologia* 2020;63:462-72. [DOI](#) [PubMed](#) [PMC](#)
12. Man K, Loudon A, Chawla A. Immunity around the clock. *Science* 2016;354:999-1003. [DOI](#) [PubMed](#) [PMC](#)
13. Foster RG. Sleep, circadian rhythms and health. *Interface Focus* 2020;10:20190098. [DOI](#) [PubMed](#) [PMC](#)
14. Taylor JP, Hardy J, Fischbeck KH. Toxic proteins in neurodegenerative disease. *Science* 2002;296:1991-5. [DOI](#) [PubMed](#)
15. Zhang S, Wang R, Wang G. Impact of dopamine oxidation on dopaminergic neurodegeneration. *ACS Chem Neurosci* 2019;10:945-53. [DOI](#) [PubMed](#)
16. Wang R, Sun H, Ren H, Wang G. α -Synuclein aggregation and transmission in Parkinson's disease: a link to mitochondria and lysosome. *Sci China Life Sci* 2020;63:1850-9. [DOI](#) [PubMed](#)
17. Kress GJ, Liao F, Dimitry J, et al. Regulation of amyloid- β dynamics and pathology by the circadian clock. *J Exp Med* 2018;215:1059-68. [DOI](#) [PubMed](#) [PMC](#)
18. Holth JK, Fritschl SK, Wang C, et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans.

- Science* 2019;363:880-4. DOI PubMed PMC
19. Sinforiani E, Terzaghi M, Pasotti C, Zucchella C, Zambrelli E, Manni R. Hallucinations and sleep-wake cycle in Alzheimer's disease: a questionnaire-based study in 218 patients. *Neurol Sci* 2007;28:96-9. DOI PubMed
 20. Li S, Wang Y, Wang F, Hu LF, Liu CF. A new perspective for Parkinson's disease: circadian rhythm. *Neurosci Bull* 2017;33:62-72. DOI PubMed PMC
 21. He C, Hu Z, Jiang C. Sleep disturbance: an early sign of Alzheimer's disease. *Neurosci Bull* 2020;36:449-51. DOI PubMed PMC
 22. McCarter SJ, St Louis EK, Boeve BF. Sleep disturbances in frontotemporal dementia. *Curr Neurol Neurosci Rep* 2016;16:85. DOI PubMed
 23. Fifel K, De Boer T. The circadian system in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Handb Clin Neurol* 2021;179:301-13. DOI PubMed
 24. Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep* 2013;36:1027-32. DOI PubMed PMC
 25. Hahn EA, Wang HX, Ansel R, Fratiglioni L. A change in sleep pattern may predict Alzheimer disease. *Am J Geriatr Psychiatry* 2014;22:1262-71. DOI PubMed
 26. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* 2011;306:613-9. DOI PubMed PMC
 27. Jørgensen JT, Karlsen S, Stayner L, Hansen J, Andersen ZJ. Shift work and overall and cause-specific mortality in the Danish nurse cohort. *Scand J Work Environ Health* 2017;43:117-26. DOI PubMed
 28. Liguori C, Mercuri NB, Izzi F, et al. Obstructive sleep apnea is associated with early but possibly modifiable Alzheimer's disease biomarkers changes. *Sleep* 2017. DOI PubMed
 29. Figueiro MG, Plitnick B, Roohan C, Sahin L, Kalsher M, Rea MS. Effects of a tailored lighting intervention on sleep quality, rest-activity, mood, and behavior in older adults with Alzheimer disease and related dementias: a randomized clinical trial. *J Clin Sleep Med* 2019;15:1757-67. DOI PubMed PMC
 30. Shen Y, Huang JY, Li J, Liu CF. Excessive daytime sleepiness in Parkinson's disease: clinical implications and management. *Chin Med J (Engl)* 2018;131:974-81. DOI PubMed PMC
 31. Li T, Le W. Biomarkers for Parkinson's disease: how good are they? *Neurosci Bull* 2020;36:183-94. DOI PubMed PMC
 32. Zhang F, Niu L, Liu X, et al. Rapid eye movement sleep behavior disorder and neurodegenerative diseases: an update. *Ageing Dis* 2020;11:315-26. DOI PubMed PMC
 33. Abbott RD, Ross GW, White LR, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. *Neurology* 2005;65:1442-6. DOI PubMed
 34. Gjerstad MD, Boeve B, Wentzel-Larsen T, Aarsland D, Larsen JP. Occurrence and clinical correlates of REM sleep behaviour disorder in patients with Parkinson's disease over time. *J Neurol Neurosurg Psychiatry* 2008;79:387-91. DOI PubMed
 35. Iranzo A, Tolosa E, Gelpi E, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol* 2013;12:443-53. DOI PubMed
 36. Sani TP, Bond RL, Marshall CR, et al. Sleep symptoms in syndromes of frontotemporal dementia and Alzheimer's disease: a proof-of-principle behavioural study. *eNeurologicalSci* 2019;17:100212. DOI PubMed PMC
 37. Bonakis A, Economou NT, Paparrigopoulos T, et al. Sleep in frontotemporal dementia is equally or possibly more disrupted, and at an earlier stage, when compared to sleep in Alzheimer's disease. *J Alzheimers Dis* 2014;38:85-91. DOI PubMed
 38. Korhonen T, Katisko K, Cajanus A, et al. Comparison of prodromal symptoms of patients with behavioral variant frontotemporal dementia and Alzheimer disease. *Dement Geriatr Cogn Disord* 2020;49:98-106. DOI PubMed
 39. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron* 2011;72:245-56. DOI PubMed PMC
 40. Renton AE, Majounie E, Waite A, et al; ITALSGEN Consortium. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* 2011;72:257-68. DOI PubMed PMC
 41. Daoud H, Postuma RB, Bourassa CV, et al. C9orf72 repeat expansions in rapid eye movement sleep behaviour disorder. *Can J Neurol Sci* 2014;41:759-62. DOI PubMed
 42. Dedeene L, Van Schoor E, Vandenberghe R, Van Damme P, Poesen K, Thal DR. Circadian sleep/wake-associated cells show dipeptide repeat protein aggregates in C9orf72-related ALS and FTLD cases. *Acta Neuropathol Commun* 2019;7:189. DOI PubMed PMC
 43. Palma JA, Fernandez-Cordon C, Coon EA, et al. Prevalence of REM sleep behavior disorder in multiple system atrophy: a multicenter study and meta-analysis. *Clin Auton Res* 2015;25:69-75. DOI PubMed PMC
 44. Lin JY, Zhang LY, Cao B, et al. Sleep-related symptoms in multiple system atrophy: determinants and impact on disease severity. *Chin Med J (Engl)* 2020;134:690-8. DOI PubMed PMC
 45. Wu DD, Su W, Li SH, et al. A questionnaire-based study on clinical REM sleep behavior disorder and subtypes in multiple system atrophy. *Eur Neurol* 2021;84:368-74. DOI PubMed
 46. Wang H, Tang X, Zhou J, Xu Y. Excessive daytime sleepiness is associated with non-motor symptoms of multiple system atrophy: a cross-sectional study in China. *Front Neurol* 2021;12:798771. DOI PubMed PMC
 47. Soto C. Unfolding the role of protein misfolding in neurodegenerative diseases. *Nat Rev Neurosci* 2003;4:49-60. DOI PubMed
 48. Soto C, Pritzkow S. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. *Nat Neurosci*

- 2018;21:1332-40. [DOI PubMed PMC](#)
49. Zhao J, Liu X, Xia W, Zhang Y, Wang C. Targeting amyloidogenic processing of APP in Alzheimer's disease. *Front Mol Neurosci* 2020;13:137. [DOI PubMed PMC](#)
50. Wang X. A bridge between the innate immunity system and amyloid- β production in Alzheimer's disease. *Neurosci Bull* 2021;37:898-901. [DOI PubMed PMC](#)
51. De Jonghe C, Esselens C, Kumar-Singh S, et al. Pathogenic APP mutations near the gamma-secretase cleavage site differentially affect Abeta secretion and APP C-terminal fragment stability. *Hum Mol Genet* 2001;10:1665-71. [DOI PubMed](#)
52. Selkoe DJ, Wolfe MS. Presenilin: running with scissors in the membrane. *Cell* 2007;131:215-21. [DOI PubMed](#)
53. Kang JE, Lim MM, Bateman RJ, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science* 2009;326:1005-7. [DOI PubMed PMC](#)
54. Roh JH, Huang Y, Bero AW, et al. Disruption of the sleep-wake cycle and diurnal fluctuation of β -amyloid in mice with Alzheimer's disease pathology. *Sci Transl Med* 2012;4:150ra122. [DOI PubMed PMC](#)
55. Shokri-Kojori E, Wang GJ, Wiers CE, et al. β -Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci U S A* 2018;115:4483-8. [DOI PubMed PMC](#)
56. Zhang F, Zhong R, Li S, et al. Alteration in sleep architecture and electroencephalogram as an early sign of Alzheimer's disease preceding the disease pathology and cognitive decline. *Alzheimers Dement* 2019;15:590-7. [DOI PubMed](#)
57. Qiu H, Zhong R, Liu H, Zhang F, Li S, Le W. Chronic sleep deprivation exacerbates learning-memory disability and Alzheimer's disease-like pathologies in A β PP(swe)/PS1(Δ E9) mice. *J Alzheimers Dis* 2016;50:669-85. [DOI PubMed](#)
58. Song H, Moon M, Choe HK, et al. A β -induced degradation of BMAL1 and CBP leads to circadian rhythm disruption in Alzheimer's disease. *Mol Neurodegener* 2015;10:13. [DOI PubMed PMC](#)
59. Dufort-Gervais J, Mongrain V, Brouillette J. Bidirectional relationships between sleep and amyloid-beta in the hippocampus. *Neurobiol Learn Mem* 2019;160:108-17. [DOI PubMed](#)
60. Bhuniya S, Goyal M, Chowdhury N, Mishra P. Intermittent hypoxia and sleep disruption in obstructive sleep apnea increase serum tau and amyloid-beta levels. *J Sleep Res* 2022. [DOI PubMed](#)
61. Yun CH, Lee HY, Lee SK, et al. Amyloid burden in obstructive sleep apnea. *J Alzheimers Dis* 2017;59:21-9. [DOI PubMed](#)
62. Huang H, Li M, Zhang M, et al. Sleep quality improvement enhances neuropsychological recovery and reduces blood A $\beta_{42/40}$ ratio in patients with mild-moderate cognitive impairment. *Medicina (Kaunas)* 2021;57:1366. [DOI PubMed PMC](#)
63. He B, Nohara K, Park N, et al. The small molecule nobiletin targets the molecular oscillator to enhance circadian rhythms and protect against metabolic syndrome. *Cell Metab* 2016;23:610-21. [DOI PubMed PMC](#)
64. Kim E, Nohara K, Wirianto M, et al. Effects of the clock modulator nobiletin on circadian rhythms and pathophysiology in female mice of an Alzheimer's disease model. *Biomolecules* 2021;11:1004. [DOI PubMed PMC](#)
65. Brettschneider J, Del Tredici K, Lee VM, Trojanowski JQ. Spreading of pathology in neurodegenerative diseases: a focus on human studies. *Nat Rev Neurosci* 2015;16:109-20. [DOI PubMed PMC](#)
66. Zhu Y, Zhan G, Fenik P, et al. Chronic sleep disruption advances the temporal progression of tauopathy in P301S mutant mice. *J Neurosci* 2018;38:10255-70. [DOI PubMed PMC](#)
67. Pablo-Fernandez E, Courtney R, Holton JL, Warner TT. Hypothalamic α -synuclein and its relation to weight loss and autonomic symptoms in Parkinson's disease. *Mov Disord* 2017;32:296-8. [DOI PubMed](#)
68. Pablo-Fernández E, Courtney R, Warner TT, Holton JL. A histologic study of the circadian system in Parkinson disease, multiple system atrophy, and progressive supranuclear palsy. *JAMA Neurol* 2018;75:1008-12. [DOI PubMed PMC](#)
69. Braak H, Rüb U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J Neural Transm (Vienna)* 2003;110:517-36. [DOI PubMed](#)
70. Shprecher DR, Adler CH, Zhang N, et al. Predicting alpha-synuclein pathology by REM sleep behavior disorder diagnosis. *Parkinsonism Relat Disord* 2018;55:92-6. [DOI PubMed PMC](#)
71. Gelpi E, Navarro-Otano J, Tolosa E, et al. Multiple organ involvement by alpha-synuclein pathology in Lewy body disorders. *Mov Disord* 2014;29:1010-8. [DOI PubMed](#)
72. Stokholm MG, Danielsen EH, Hamilton-Dutoit SJ, Borghammer P. Pathological α -synuclein in gastrointestinal tissues from prodromal Parkinson disease patients. *Ann Neurol* 2016;79:940-9. [DOI PubMed](#)
73. Kim S, Kwon SH, Kam TI, et al. Transneuronal propagation of pathologic α -synuclein from the gut to the brain models Parkinson's disease. *Neuron* 2019;103:627-41.e7. [DOI PubMed PMC](#)
74. Van Den Berge N, Ferreira N, Gram H, et al. Evidence for bidirectional and trans-synaptic parasympathetic and sympathetic propagation of alpha-synuclein in rats. *Acta Neuropathol* 2019;138:535-50. [DOI PubMed PMC](#)
75. Iranzo A, Borrego S, Vilaseca I, et al. α -Synuclein aggregates in labial salivary glands of idiopathic rapid eye movement sleep behavior disorder. *Sleep* 2018. [DOI PubMed](#)
76. Fernández-Arcos A, Vilaseca I, Aldecoa I, et al. Alpha-synuclein aggregates in the parotid gland of idiopathic REM sleep behavior disorder. *Sleep Med* 2018;52:14-7. [DOI PubMed](#)
77. Forman MS, Trojanowski JQ, Lee VM. TDP-43: a novel neurodegenerative proteinopathy. *Curr Opin Neurobiol* 2007;17:548-55. [DOI PubMed PMC](#)
78. Kabashi E, Valdmanis PN, Dion P, et al. TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis. *Nat Genet* 2008;40:572-4. [DOI PubMed](#)

79. Ling SC, Polymenidou M, Cleveland DW. Converging mechanisms in ALS and FTD: disrupted RNA and protein homeostasis. *Neuron* 2013;79:416-38. DOI PubMed PMC
80. Gabery S, Ahmed RM, Caga J, Kiernan MC, Halliday GM, Petersén Å. Loss of the metabolism and sleep regulating neuronal populations expressing orexin and oxytocin in the hypothalamus in amyotrophic lateral sclerosis. *Neuropathol Appl Neurobiol* 2021;47:979-89. DOI PubMed
81. Calderón-Garcidueñas L, Rajkumar RP, Stommel EW, et al. Brainstem quadruple aberrant hyperphosphorylated tau, beta-amyloid, alpha-synuclein and TDP-43 pathology, stress and sleep behavior disorders. *Int J Environ Res Public Health* 2021;18:6689. DOI PubMed PMC
82. Cronin P, McCarthy MJ, Lim ASP, et al. Circadian alterations during early stages of Alzheimer's disease are associated with aberrant cycles of DNA methylation in BMAL1. *Alzheimers Dement* 2017;13:689-700. DOI PubMed PMC
83. Chen HF, Huang CQ, You C, Wang ZR, Si-qing H. Polymorphism of CLOCK gene rs 4580704 C > G is associated with susceptibility of Alzheimer's disease in a Chinese population. *Arch Med Res* 2013;44:203-7. DOI PubMed
84. Musiek ES, Xiong DD, Holtzman DM. Sleep, circadian rhythms, and the pathogenesis of Alzheimer disease. *Exp Mol Med* 2015;47:e148. DOI PubMed PMC
85. Duncan MJ, Smith JT, Franklin KM, et al. Effects of aging and genotype on circadian rhythms, sleep, and clock gene expression in APPxPS1 knock-in mice, a model for Alzheimer's disease. *Exp Neurol* 2012;236:249-58. DOI PubMed
86. Lee J, Kim DE, Griffin P, et al. Inhibition of REV-ERBs stimulates microglial amyloid-beta clearance and reduces amyloid plaque deposition in the 5XFAD mouse model of Alzheimer's disease. *Ageing Cell* 2020;19:e13078. DOI PubMed PMC
87. Bodinat C, Guardiola-Lemaitre B, Mocaër E, Renard P, Muñoz C, Millan MJ. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. *Nat Rev Drug Discov* 2010;9:628-42. DOI PubMed
88. Gunata M, Parlakpinar H, Acet HA. Melatonin: a review of its potential functions and effects on neurological diseases. *Rev Neurol (Paris)* 2020;176:148-65. DOI PubMed
89. Cardinali DP. Melatonin: clinical perspectives in neurodegeneration. *Front Endocrinol (Lausanne)* 2019;10:480. DOI PubMed PMC
90. Zhou JN, Liu RY, Kamphorst W, Hofman MA, Swaab DF. Early neuropathological Alzheimer's changes in aged individuals are accompanied by decreased cerebrospinal fluid melatonin levels. *J Pineal Res* 2003;35:125-30. DOI PubMed
91. Stopa EG, Volicer L, Kuo-Leblanc V, et al. Pathologic evaluation of the human suprachiasmatic nucleus in severe dementia. *J Neuropathol Exp Neurol* 1999;58:29-39. DOI PubMed
92. Manni R, Cremascoli R, Perretti C, et al. Evening melatonin timing secretion in real life conditions in patients with Alzheimer disease of mild to moderate severity. *Sleep Med* 2019;63:122-6. DOI PubMed
93. Sulkava S, Muggalla P, Sulkava R, et al. Melatonin receptor type 1A gene linked to Alzheimer's disease in old age. *Sleep* 2018;41:zsy103. DOI PubMed PMC
94. Olcese JM, Cao C, Mori T, et al. Protection against cognitive deficits and markers of neurodegeneration by long-term oral administration of melatonin in a transgenic model of Alzheimer disease. *J Pineal Res* 2009;47:82-96. DOI PubMed
95. Pappolla MA, Matsubara E, Vidal R, et al. Melatonin treatment enhances Aβ lymphatic clearance in a transgenic mouse model of amyloidosis. *Curr Alzheimer Res* 2018;15:637-42. DOI PubMed PMC
96. Adi N, Mash DC, Ali Y, Singer C, Shehadeh L, Papapetropoulos S. Melatonin MT1 and MT2 receptor expression in Parkinson's disease. *Med Sci Monit* 2010;16:BR61-7. PubMed
97. Videnovic A, Noble C, Reid KJ, et al. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. *JAMA Neurol* 2014;71:463-9. DOI PubMed PMC
98. Dowling GA, Mastick J, Colling E, Carter JH, Singer CM, Aminoff MJ. Melatonin for sleep disturbances in Parkinson's disease. *Sleep Med* 2005;6:459-66. DOI PubMed
99. Bordet R, Devos D, Brique S, et al. Study of circadian melatonin secretion pattern at different stages of Parkinson's disease. *Clin Neuropharmacol* 2003;26:65-72. DOI PubMed
100. Carriere CH, Kang NH, Niles LP. Chronic low-dose melatonin treatment maintains nigrostriatal integrity in an intrastriatal rotenone model of Parkinson's disease. *Brain Res* 2016;1633:115-25. DOI PubMed
101. Li Y, Wang SM, Guo L, et al. Effects of melatonin levels on neurotoxicity of the medial prefrontal cortex in a rat model of Parkinson's disease. *Chin Med J (Engl)* 2017;130:2726-31. DOI PubMed PMC
102. Rasheed MZ, Andrabi SS, Salman M, et al. Melatonin improves behavioral and biochemical outcomes in a rotenone-induced rat model of Parkinson's disease. *J Environ Pathol Toxicol Oncol* 2018;37:139-50. DOI PubMed
103. Acuña-Castroviejo D, Coto-Montes A, Monti M, Ortiz GG, Reiter RJ. Melatonin is protective against MPTP-induced striatal and hippocampal lesions. *Life Sci* 1996;60:PL23-9. DOI PubMed
104. Jin BK, Shin DY, Jeong MY, et al. Melatonin protects nigral dopaminergic neurons from 1-methyl-4-phenylpyridinium (MPP+) neurotoxicity in rats. *Neurosci Lett* 1998;245:61-4. DOI PubMed
105. Naskar A, Prabhakar V, Singh R, Dutta D, Mohanakumar KP. Melatonin enhances L-DOPA therapeutic effects, helps to reduce its dose, and protects dopaminergic neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonism in mice. *J Pineal Res* 2015;58:262-74. DOI PubMed
106. Brito-Armas JM, Baekelandt V, Castro-Hernández JR, González-Hernández T, Rodríguez M, Castro R. Melatonin prevents dopaminergic cell loss induced by lentiviral vectors expressing A30P mutant alpha-synuclein. *Histol Histopathol* 2013;28:999-1006.

[DOI PubMed](#)

107. Sae-Ung K, Uéda K, Govitrapong P, Phansuwan-Pujito P. Melatonin reduces the expression of alpha-synuclein in the dopamine containing neuronal regions of amphetamine-treated postnatal rats. *J Pineal Res* 2012;52:128-37. [DOI PubMed](#)
108. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Sci Transl Med* 2012;4:147ra111. [DOI PubMed PMC](#)
109. Aspelund A, Antila S, Proulx ST, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med* 2015;212:991-9. [DOI PubMed PMC](#)
110. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015;523:337-41. [DOI PubMed PMC](#)
111. Plog BA, Nedergaard M. The glymphatic system in central nervous system health and disease: past, present, and future. *Annu Rev Pathol* 2018;13:379-94. [DOI PubMed PMC](#)
112. Iliff JJ, Wang M, Zeppenfeld DM, et al. Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. *J Neurosci* 2013;33:18190-9. [DOI PubMed PMC](#)
113. Louveau A, Plog BA, Antila S, Alitalo K, Nedergaard M, Kipnis J. Understanding the functions and relationships of the glymphatic system and meningeal lymphatics. *J Clin Invest* 2017;127:3210-9. [DOI PubMed PMC](#)
114. Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. *Lancet Neurol* 2018;17:1016-24. [DOI PubMed PMC](#)
115. Nedergaard M, Goldman SA. Glymphatic failure as a final common pathway to dementia. *Science* 2020;370:50-6. [DOI PubMed PMC](#)
116. Ringstad G, Vatnehol SAS, Eide PK. Glymphatic MRI in idiopathic normal pressure hydrocephalus. *Brain* 2017;140:2691-705. [DOI PubMed PMC](#)
117. Ding XB, Wang XX, Xia DH, et al. Impaired meningeal lymphatic drainage in patients with idiopathic Parkinson's disease. *Nat Med* 2021;27:411-8. [DOI PubMed](#)
118. Hablitz LM, Plá V, Giannetto M, et al. Circadian control of brain glymphatic and lymphatic fluid flow. *Nat Commun* 2020;11:4411. [DOI PubMed PMC](#)
119. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science* 2013;342:373-7. [DOI PubMed PMC](#)
120. Peng W, Achariyar TM, Li B, et al. Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. *Neurobiol Dis* 2016;93:215-25. [DOI PubMed PMC](#)
121. Da Mesquita S, Louveau A, Vaccari A, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. *Nature* 2018;560:185-91. [DOI PubMed PMC](#)
122. Smith AJ, Yao X, Dix JA, Jin BJ, Verkman AS. Test of the 'glymphatic' hypothesis demonstrates diffusive and aquaporin-4-independent solute transport in rodent brain parenchyma. *Elife* 2017;6:e27679. [DOI PubMed PMC](#)