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Review

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Influence of sleep disruption on protein accumulation in neurodegenerative diseases

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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 (Aβ) 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 Aβ clearance, which is mediated by the aquaporin (AQP-4) water channel on astrocytes. The rate of the clearance of Aβ by the glymphatic pathway is different during the sleep/wake cycle. Most importantly, circadian rhythms facilitate glymphatic clearance of solutes and Aβ 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.

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 (Aβ) 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 Aβ 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. Aβ: 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 grand, 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 Aβ 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 Aβ, tau or α-syn can form oligomers, protofibrils and fibrils, which accumulate and deposit in diseased brains (Soto and Pritzkow[48], 2018) [Figure 1].

Aβ

The homeostasis of Aβ, either accumulation or clearance, is important for AD pathology. Aβ 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 Aβ peptides[51,52]. The deposition of Aβ in AD brains and in APP transgenic mice is a typical pathological feature.

It has been reported that Aβ has daily oscillations[53]. The levels of soluble Aβ 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 Aβ also occurs in the cerebral spinal fluid (CSF) in humans[53]. In sleep-deprived mice, Aβ is increased in the ISF in the hippocampus in both wild-type and APP transgenic mice; however, Aβ is decreased in the ISF in the hippocampus in animals with more sleep[53]. In *APPswe/PS1δE9* mice, diurnal fluctuation of Aβ in the ISF and the hippocampus but not in the striatum was attenuated at 6 months of age. Diurnal fluctuation of Aβ in ISF in the striatum is decreased at 9 months of age when Aβ 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 Aβ in the ISF occurs earlier in the hippocampus than in the striatum, and Aβ plaques appear earlier in the hippocampus than in the striatum, suggesting a link between Aβ pathological progression and daily oscillations. In addition, active immunolization with Aβ, which decreases Aβ deposition in *APPswe/PS1δE9* mice, restores the diurnal fluctuation of Aβ in the ISF and normal sleep-wake cycle[54], suggesting that Aβ deposition disrupts Aβ oscillations and the sleep-wake cycle.

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

In animal models, *APPswe/PS1δE9* 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 Aβ 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 Aβ plaques in the hippocampus in APP transgenic mice[53,57]. Sleep deprivation increases Aβ 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 Aβ accumulation. However, Aβ has a role in circadian rhythms in multiple transgenic mouse models with Aβ pathology. In *5×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 Aβ accumulation and sleep disorders[59].

The association of the accumulation of Aβ 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 Aβ levels in blood[60] and the Aβ 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 Aβ42/40 ratio in patients who are complete recovered from sleep disturbance[62]. Interestingly, there are no changes in blood Aβ42/40 ratio in those patients who have no improvement in sleep[62], suggesting an involvement of sleep in the regulation of Aβ 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 Aβ deposition in APP/PS1 mouse brains[64].

Tau

Tau is another important protein in association with AD. In the AD brain, tau is hyperphosphrylated and forms intracellular neurofibrillary tangles, a pathological hallmark of Aβ 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 Aβ. 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 Aβ 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 locomoter output cycles kaput (CLOCK) and brain and muscle arnt-like 1 (BMAL1) form heterodimers that bind to E-boxes and drive the expression of peroid (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 Aβ 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 Aβ 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×FAD* mice, the amplitude of BMAL1 and PER2 in a 24 h oscillation is greatly decreased[58]. Moreover, Aβ 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 Aβ 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-erbα 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 Aβ deposits in AD. In *APP/PS1* mice, long-term melatonin treatment at ages starting from 2-2.5 months decreases Aβ 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 Aβ accumulation[94]. It has also been reported that melatonin can induce lymphatic clearance of Aβ 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

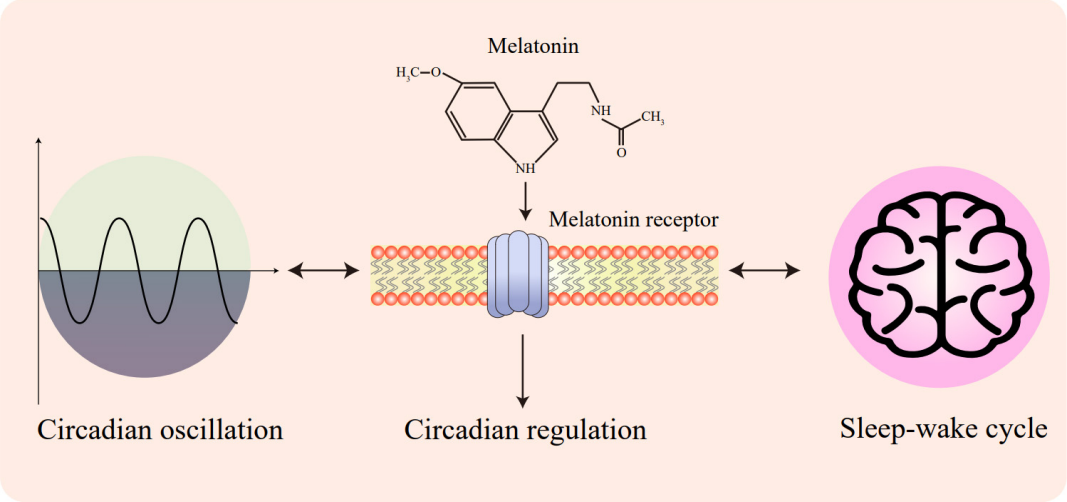

Figure 2. Impact of circadian genes and hormones on neurodegeneration and the glymphatic system. The secretion of the circadian hormone melatonin is controlled by circadian rhythm. In addition to functioning in circadian rhythm, melatonin has protective effects on neurons. In neurodegenerative diseases,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

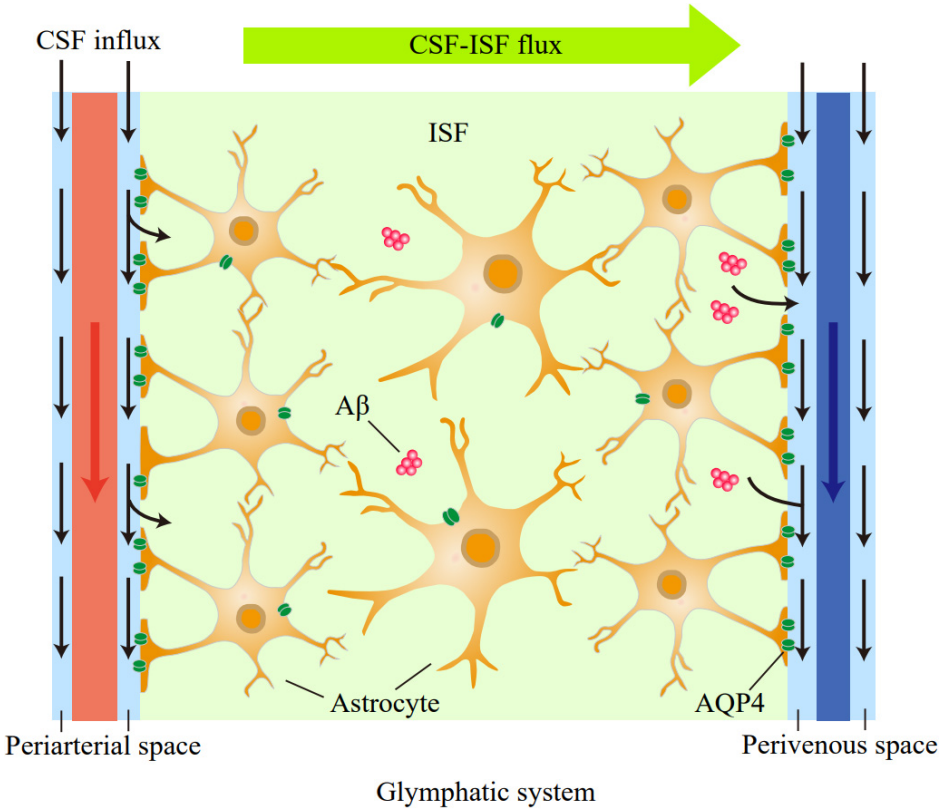

Figure 3. The glymphatic system in association with the clearance of neurodegenerative disease proteins. The glymphatic system is a perivascular network that has lymphatic functions. Driven by arterial pulsation, the CSF flows into the brain along periarterial spaces surrounding cerebral arteries and 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 Aβ[119] [Figure 3]. In *APP/PS1* mice, Aβ also shows an impact on the glymphatic pathway, leading to dysfunction of the glymphatic pathway[120]. The inflow of Aβ40 into the brain and the clearance of Aβ40 by the glymphatic pathway in the brain are decreased in *APP/PS1* mice (Peng *et al.*[120], 2016). Disruption of meningeal lymphatic vessels in *5×FAD* mice also aggravates Aβ deposition in the meninges and Aβ 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 Aβ 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.

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Conflicts of interest
All authors declared that there are no conflicts of interest.

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