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Review article

Circadian regulation of microglia function: Potential targets for treatment of Parkinson's Disease

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ABSTRACT

Circadian rhythms are involved in the regulation of many aspects of the body, including cell function, physical activity and disease. Circadian disturbance often predates the typical symptoms of neurodegenerative diseases and is not only a non-motor symptom, but also one of the causes of their occurrence and progression. Glial cells possess circadian clocks that regulate their function to maintain brain development and homeostasis. Emerging evidence suggests that the microglial circadian clock is involved in the regulation of many physiological processes, such as cytokine release, phagocytosis, and nutritional and metabolic support, and that disruption of the microglia clock may affect multiple aspects of Parkinson's disease, especially neuroinflammation and α-synuclein processes. Herein, we review recent advances in the circadian control of microglia function in health and disease, and discuss novel pharmacological interventions for microglial clocks in neurodegenerative disorders.

1. Introduction

The circadian clock is an approximately 24-hour internal cycle that keeps the body in sync with its external environment, most typically represented as the sleep-wake cycle. The center of the mammalian circadian system is located in the suprachiasmatic nucleus (SCN), which consists of approximately 20,000 specialized neurons that receive optical signals from the retina and transmit integrated rhythm information to other areas of the brain and peripheral tissues to maintain the body in sync with the external light-dark cycle (Logan and McClung, 2019). In addition to light signals, other exogenous factors such as the timing of food intake, physical activity, and temperature can affect the synchronization of the circadian system (Murayama et al., 2017; Gabriel and Zierath, 2019; Queiroz et al., 2021). At the molecular level, the circadian system is regulated by the transcription-translation feedback loop (TTFL), which includes the core and complementary loops. The core loop is activated by heterodimers of the BMAL1 and CLOCK proteins, which bind to the E-BOX of their target genes to drive transcription, including PERIOD, CRYTOCHROME, and REV-ERB proteins (Menet et al., 2014). After translation, PERIOD and CRYTOCHROME proteins are transferred from the cytoplasm to the nucleus, inhibiting the transcriptional activity of the BMAL1-CLOCK heterodimer and ultimately reducing its transcription (Cao et al., 2021). When PERIOD and CRYTOCHROME proteins are gradually degraded by E3 ligase, the TTFL can be restarted. The complementary loop includes REV-ERBs and RORs, which are also transcribed by BMAL1-CLOCK heterodimers and are integral to the stability of the circadian loop by inhibiting and promoting the transcription of *Bmal1*, respectively.

The most intuitive manifestation of the circadian rhythms is the sleep-wake cycle. Sleep accounts for one-third of the mammalian lifespan and plays a central role in memory formation, brain development, metabolism, immune function, cognitive performance, and mental and behavioral health (Mason et al., 2021). Sleep consists of two alternating phases: a slow-wave phase, also known as the non-rapid eye movement

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta; ALS, amyotrophic lateral sclerosis; AMD, age-related macular degeneration; Apoe, apolipoprotein E; APP-KI, amyloid precursor protein knock-in; ATP, adenosine triphosphate; BMAL1, brain and muscle Arnt-like protein-1; CCRs, chemokine receptors; CLOCK, circadian locomotor output cycles kaput; CNS, central nervous system; CSF, cerebrospinal fluid; DA, dopamine; DAMPs, damp-associated molecular patterns; EDS, excessive daytime sleep; EEG, electroencephalographic; ENS, enteric nervous system; Gsr, gunshot residue; Hmox1, heme oxygenase-1; HO-1, heme oxygenase-1..

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(REM) sleep, and an anomalous phase, also known as the REM sleep, which is characterized by electroencephalographic (EEG) activity (Senzai and Scanziani, 2022). Isolated REM sleep behavior disorder (iRBD), a parasomnia characterized by dream enactment, is closed associated with synucleinopathies (Ye et al., 2022). In addition, sleep deprivation, fragmentation and other forms of sleep disruption have been shown to contribute to various systemic diseases ranging from cancer to neurodegenerative diseases (Morawska et al., 2021; Qian et al., 2022).

In complex organisms, the clock function originates from molecular oscillators within each cell, including neurons, astrocytes, and microglia, in the central nervous system (CNS) (McCauley et al., 2020). Neurons located in the SCN act as pacemakers to drive circadian rhythms, especially those expressing neuromedin S, arginine vasopressin, vasoactive intestinal peptide (VIP) and D1 dopamine receptors (Stowie et al., 2023). In addition, neuronal clocks play a key role in the generation and synchronization of circadian clock, and influence the interaction of the clock network with the sleep center of the brain (Scammell et al., 2017; Schlichting et al., 2022). Astrocytes have also been shown to play an indispensable role in regulating SCN timing and the sleep-wake cycle via glutamatergic signaling (Brancaccio et al., 2019). Moreover, the circadian rhythms of astrocytes are involved in the regulation of the glymphatic and lymphatic system, which may significantly influence waste clearance that helps maintain brain homeostasis (Hablitz et al., 2020). Recently, increasing attention has been paid to the connection between microglia and circadian rhythms. Microglial are involved in hippocampal synaptic transmission and sleep duration during the light/dark cycle (Corsi et al., 2022). Microglia depletion can disrupt of sleep-wake cycles and circadian rhythms (Picard et al., 2023). Moreover, regulation of the circadian rhythms in microglia can deeply affect the immune response, phagocytic function, metabolism, and other aspects of microglia, which play a key role in neurodegenerative diseases (Brecier et al., 2023). Research on circadian rhythms, microglia and neurodegenerative diseases is expanding rapidly; however, many questions remain unanswered. Therefore, we conducted a systematic review of the literature on the circadian regulation of microglia in neurodegenerative diseases and suggested possible therapeutic strategies in this area.

2. The interplay between circadian disruption and neurodegeneration

The circadian system exists in almost all cells of the body and regulates a wide range of physiological processes, including transcriptomic, proteomic and epigenetic activities (Oh et al., 2018; Ruben et al., 2018; Kaushik et al., 2022). The circadian clock is involved in a variety of processes, including the sleep-wake cycle, cellular metabolism, immune function, autophagy, and redox homeostasis, and circadian dysfunction has been linked to many disease states, ranging from cancer to neurodegeneration (Masri and Sassone-Corsi, 2018).

Parkinson's disease(PD) is a common late-onset neurodegenerative disease characterized by a range of motor and non-motor symptoms (Leite et al., 2023). Circadian dysfunction is one of the most common non-motor symptoms of PD, affecting more than 60% of patients with PD, manifested as disturbed sleep-wake cycle, unstable dopaminergic efficacy, fluctuating motor symptoms, abnormal diurnal blood pressure, neuroendocrine dysrhythmias, etc (Breen et al., 2014; Breen et al., 2016; Videnovic et al., 2016). The disturbed sleep-wake cycle usually manifests as multiple types of sleep disorders, including excessive daytime sleep (EDS) (Xu et al., 2021), restless leg syndrome (RLS) (Trenkwalder et al., 2016), REM sleep behavior disorders (RBD) (Almeida et al., 2021) and insomnia (Shafazand et al., 2017), which have a widely negative influence on the patient's quality of life (Maggi et al., 2023). Interestingly, pathological α-synuclein (α-Syn) deposition has been found in nerve nuclei that regulate sleep and rhythm, such as SCN and pineal gland (De Pablo-Fernandez et al., 2018). Moreover, sleep-controlling neurons in the laterodorsal and pedunculopontine tegmental nuclei are sensitive and vulnerable to various forms of α-Syn, which seemed to explain the cause of circadian disturbance and sleep disorders in α-synucleinopathies (Dos et al., 2022). However, emerging studies suggest that circadian disturbances and sleep disorders often appear before motor symptoms in PD, which may not only be the causes of the disease but may also be potential risk factors for the occurrence and development of PD (Fereshtehnejad et al., 2019; Hunt et al., 2022; Roland and Avidan, 2023). iRBD often appears decades before typical motor symptoms, and more than 90% of iRBD cases eventually develop into synucleinopathies (Iranzo et al., 2014). Moreover, RBD is associated with faster motor progression and cognitive decline in patients with PD (Pagano et al., 2018). In an 8-year cohort study involving 100,882 patients without PD, RLS was associated with a higher risk of incident PD, suggesting that RLS may also be an early clinical feature of PD (Szatmari et al., 2017).

Alzheimer's disease(AD) is the most common form of dementia, and also the highest incidence in older individuals (Ding et al., 2023). Similar to patients with PD, patients with AD also suffer from circadian disturbances, and there is a bidirectional relationship between the two. Circadian disturbances usually present as a fragmentation of the rest-activity rhythm, with increased arousal at night and decreased activity during the day (Targa et al., 2021). They are also manifested by autonomic nervous system dysfunction and dysrhythmic hormone secretion, such as orthostatic hypotension and abnormal melatonin secretion, respectively (Manni et al., 2019; de Heus et al., 2020). Sleep disorders are very common in AD, often manifesting as insomnia, EDS, RLS, and sleep-disordered breathing. Postmortem studies have found neuronal loss in the SCN of patients with AD, especially in neurons expressing vasopressin, melatonin receptor type 1 and VIP (Wang et al., 2015). In addition, AD patients with circadian dysrhythmia have shown that ipRGC loss is associated with extracellular amyloid beta (Aβ) deposition (La Morgia et al., 2016), which may be the reasons of sleep and circadian disturbance in AD. In turn, sleep deprivation or disruption can significantly increase the levels of Aβ in the cerebrospinal fluid (CSF) of patients with AD (Lucey et al., 2018), as well as Aβ accumulation in the hippocampus and thalamus of healthy controls (Shokri-Kojori et al., 2018). Furthermore, tau protein level in the interstitial fluid is regulated by the sleep-wake cycle and increases during sleep deprivation in human CSF (Holth et al., 2019).

Taken together, circadian disturbance may not just be the result of neurodegeneration, but may also be the cause of disease onset or progression. However, the mechanisms underlying the interactions between circadian rhythms and PD are not well characterized. Given that the circadian regulation of microglia has received increasing attention (Carvalhas-Almeida et al., 2023), understanding the role of microglia in the CNS may help clarify and resolve these questions.

3. Microglial functions in health and neurodegeneration

Microglia, the most abundant mononuclear phagocytes, account for approximately 10% of the total cells in the CNS and are the first line of defense of the innate immune system, which is crucial for both the development and maintenance of homeostasis of the brain (Colonna et al., 2017). During development, microglia are essential for pruning synapses and supporting neurons, oligodendrocytes and other cells (Bohlen et al., 2019; Hammond et al., 2021; Li et al., 2022). Whereas in homeostasis, microglia are mainly responsible for injury repair, phagocytosis and clearance of pathogens, protein aggregates, dead cells, and other waste products in the CNS, as well as the secretion of inflammatory cytokines and chemokines (Wright-Jin and Gutmann, 2019). However, when microglia are aging or overburdened, they may even exacerbate inflammatory responses and promote the spread of pathological proteins, which are common pathological mechanisms in neurodegenerative diseases (Iba et al., 2022).

Different types of receptors on the microglial surface form the basis

for microglia to perform physiological functions. The first receptor type is pattern recognition receptors, such as toll-like receptors and nod-like receptors that detect pathogen-associated molecular patterns or damp-associated molecular patterns (DAMPs) to facilitate the clearance of pathogens, pathological proteins or other harmful substances (Li et al., 2021). The second is chemokine receptors (CCRs), such as CCR2 and CX3CR1, which promote the migration of microglia to the damaged site when injury occurs (Cherry et al., 2020; Subbarayan et al., 2022). The third type of receptors function by receiving neurotransmitters and neuropeptides released by neurons, thereby maintaining neural-glia communication, such as P2Y12, a purinergic receptor for adenosine triphosphate(ATP) (Cserep et al., 2020).

In the mature brain, microglia are usually in a resting state; however, when activated, they are usually divided into M1 and M2 phenotypes. M1-type microglia are generally considered harmful to the body and have both proinflammatory and neurotoxic effects (Spiteri et al., 2022). They secrete pro-inflammatory cytokines and chemokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)−6, IL-1β, and CCL2, which mediate neuroinflammation. They also synthesize Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which produces superoxide and reactive oxygen species (ROS) that mediate oxidative stress responses (Dos Santos Pereira et al., 2020). In addition, they generate inducible nitric oxide oxidase, which contributes to glutamate-mediated neurotoxicity. In contrast to the M1 type, the M2 type is thought to be beneficial to the body. They express cytokines, such as IL-10, arginase-1, and transforming growth factor beta (TGF-β), which play an anti-inflammatory role (Kwon and Koh, 2020). They also secrete neurotrophic factors, such as brain-derived neurotrophic factor and glial cell-derived neurotrophic factor, which have supportive functions (Prowse and Hayley, 2021). In addition, they can perform repair functions in the brain (Kobashi et al., 2020). However, very few activated microglia are of the M1 or M2 type alone, usually having some characteristics of both types, with their complex roles depending on the specific situation (Ransohoff, 2016).

Microglia play a central role in physiological conditions and disease. Lewy bodies (LB) formed by aggregated α-Syn, neuroinflammation, and loss of dopaminergic neurons in the substantia nigra are the main pathological features of PD (Strohaker et al., 2019; Lopes et al., 2022; Garrido et al., 2023). In addition to neurons, oligomeric α-Syn can be recognized and uptaken by microglia (Kim et al., 2013). A small amount of α-Syn can be degraded and cleared by microglia, but excessive α-Syn can activate microglia and trigger inflammatory responses, thereby accelerating disease progression (Park et al., 2016). Moreover, pathologic α-Syn can reach neurons via microglia-derived exosomes, further promoting its propagation and inflammatory responses (Xia et al., 2019; Xia et al., 2021). Prominent features in AD are Aβ plaques and intracellular tau bundles (Wang et al., 2023). Similar to the processing of α-Syn, microglia also play a double-edged role in waste clearance and prion-like seeding of fibrillar Aβ and hyperphosphorylated tau (Chen et al., 2023; Wang et al., 2023). In addition, microglia are responsible for complement-mediated synaptic loss and dysfunction, which are strongly associated with cognitive impairment in AD (De Schepper et al., 2023). Taken together, these studies suggest that microglia mediate the pathological progression of neurodegenerative diseases.

Considering their various states and functions, it is clear that microglia are integral to brain health. Therefore, it is essential to understand the factors that affect the activation and function of microglia, which are closely related to the maintenance of brain homeostasis. Therefore, the effects of circadian rhythms and sleep on microglial function are the focus of our review.

4. Microglia circadian clocks

Nakazato et al. demonstrated for the first time, the existence of clock genes in primary microglia and BV2 cell line using PCR, including *Bmal1*, *Clock*, *Per1–3*, *Cry1–2*, *Dec1–2*, and *Npas2* (Nakazato et al., 2011). Hayashi et al. subsequently confirmed that microglia have clock genes, and the expression pattern of clock genes exhibits a significant circadian rhythm, such as *Per1* and *Per2* peak at zeitgeber time (ZT)14, *Rev-erbα* peak at ZT18, *Bmal1* peak at ZT2 (Hayashi et al., 2013). Recent studies have shown that circadian oscillations in microglial clock genes can provide the basis for diurnal fluctuations in microglial physiological functions (Fonken et al., 2015).

4.1. Microglial circadian clocks modulate inflammatory cytokines

The secretion of inflammatory cytokines is an important pathway for the immune function of microglia. Multiple studies have shown that the inflammatory cytokines secreted by microglia have a spontaneous circadian rhythm, even in the absence of external stimuli. For example, the expression of *TNF-α*, *IL-1β*, and *IL-6* mRNA in microglia displayed robust rhythms, with peak expression during the middle of the light phase (Fonken et al., 2015). Clock gene manipulation in microglia explains circadian regulation of cytokine expression. *Bmal1* knockout effectively inhibited the LPS-induced elevated expression of *IL-6* in microglia (Nakazato et al., 2017). Chromatin immunoprecipitation confirmed that BMAL1 directly binds to the promoter region of *IL-6* gene to regulate its transactivation. Moreover, *Bmal1* deletion could decrease the expressions of pro-inflammatory genes, such as *IL-1β*, *TNF-α*, and NADPH oxidases 2 (*Nox2*), and increase the expressions of anti-oxidative genes, such as gunshot residue (*Gsr*) and heme oxygenase-1 (*Hmox1*), in LPS-stimulated microglia (Wang et al., 2020). On the contrary, *Rev-erbα* in microglia decreased the expression of pro-inflammatory cytokines, such as *IL-1β*, *IL-6*, *CCL2*, and *TNF-α*, and promoted the expression of anti-inflammatory cytokines, such as *IL-10* (Griffin et al., 2019; Guo et al., 2019). In addition, REV-ERBα has been shown to bind directly to TNF receptor associated factor 2 and NFKBIB promoters, which are related to NF-κB signaling pathway (Griffin et al., 2019). Activation of Rev-erbα may inhibit the phosphorylation of IκBα kinase inhibitor (IκK) and IκBα itself, thus blocking the nuclear transport of NF-κB subunit p65, thereby suppressing the NF-κB signaling pathway (Guo et al., 2019). Furthermore, primary microglia isolated during the light phase showed a more intense inflammatory response after LPS stimulation than those isolated during the dark phase, with a significant diurnal difference (Fonken et al., 2015). Together, these results suggest that the secretion of inflammataory cytokines by microglia is regulated by the circadian rhythms.

4.2. Microglial circadian clocks modulate morphology and phagocytosis

The circadian regulation of microglia can also be observed visually through morphological changes (Nakanishi et al., 2021). Ionized calcium-binding adapter molecule 1, the most commonly used molecule for labeling microglia, varies according to the time of the day, with significantly higher expression during the resting period (Griffin et al., 2019). As revealed by fluorescence microscopy and flow cytometry, microglia are weakly activated and show larger granular bodies in the light phase than in the dark phase (Griffin et al., 2019; Choudhury et al., 2020). It has been found that the morphology of microglia also varies with circadian rhythms and has longer processes and increased branching points during wakefulness, which is dependent on the lysosomal cysteine protease cathepsin S and adenosine diphosphate P2Y12 receptors (Hayashi et al., 2013; Nakanishi et al., 2021). In addition, Rev-erbα knockout leads to loss of diurnal variation and decreased microglial branching morphology (Griffin et al., 2019). The pharmacological inhibition of Rev-erbα also promotes microglial polarization toward phagocytic M2-like phenotypes with increased microglial process length (Lee et al., 2020).

Consistent with circadian control of morphology, many studies have shown that clocks are involved in the regulation of microglial phagocytosis. CD11b, a marker of microglial phagocytosis, peaks during the day in the hippocampus (Choudhury et al., 2020). CD68, another

microglial phagocytosis marker, peaks during the day and decreases to a minimum at night, showing a stable rhythm (Choudhury et al., 2020). Loss of Bmal1 or Rev-erbα can lead to the disappearance of the diurnal fluctuations, with constantly high CD68 levels, and induce microglia to exhibit a phagocytotic phenotype (Griffin et al., 2019; Wang et al., 2021). Interestingly, complement-dependent synaptic pruning also follows a circadian rhythm, and microglial phagocytosis appears to play a central role in this process (Bodea et al., 2014; Rocha et al., 2015; Hong et al., 2016; Gregersen et al., 2021). It has been shown that plasma C3 and C4 concentrations drop at night and recover during the day, and plasma C3a levels rise during night sleep, while sleep deprivation prevents this phenomenon (Reis et al., 2011). Moreover, C3 levels are upregulated by microglial phagocytosis in the brain following chronic sleep restriction (Bellesi et al., 2017). In addition, a recent study found that deletion of Rev-erbα and Bmal1 increased microglial phagocytosis and synaptic loss in the hippocampus, which was mediated by increased C4b and C3 expression (Griffin et al., 2020). Another recent study has shown that Bmal1 plays a role in synaptic pruning during aging by regulating C1q and C3 expression (Iweka et al., 2023). Bmal1 knockout also increased microglial phagocytosis, thereby promoting the formation of mature spines in the hippocampus during the learning process and improving memory performance in mice subjected to a high-fat diet (Wang et al., 2021).

4.3. Microglial circadian clocks modulate metabolism

Microglial metabolism is also regulated by circadian clocks, including immune metabolism, glucose metabolism, lipid metabolism or other energy metabolism. As mentioned earlier, circadian clocks are involved in regulating the immune metabolism, affecting the phagocytic activity, glycolysis, expression of inflammatory factors and oxidative stress factors in microglia (Wang et al., 2020; Wolff et al., 2020). In addition, circadian rhythms are also involved in the regulation of glucose metabolism and lipid metabolism in microglia. Bmal1 deficiency reduces nutrient utilization in microglia, with decreased expression of glucose transporter member 5 and lipoprotein lipase, and increased pyruvate carboxylase expression (Wang et al., 2020). Microglia-specific knock-down of Bmal1 protects mice from high fat diet-induced obesity (Wang et al., 2021). Rev-erbaα regulates lipid metabolism and lipid droplet expression in microglia, and abnormal expression of Rev-erbaα causes lipid accumulation, which leads to impaired uptake and deposition of tau protein (Lee et al., 2023). Rev-erbα has also been shown to be involved in energy metabolism of microglia, including ATP production and mitochondrial respiration (Wolff et al., 2020).

5. Potential role of microglial circadian rhythms in PD and other neurodegenerative diseases

As mentioned above, microglia clocks are central to the maintenance of sleep and circadian rhythms under physiological conditions. Recently, the effects of circadian rhythms on neurodegenerative diseases have attracted increasing attention. Investigating the effects of circadian rhythms on microglial biology and their involvement in neurodegenerative diseases through microglia may provide new insights for PD research and treatment (Fig. 1).

5.1. Neuroinflammation

Microglia-secreted inflammatory cytokines are regulated by clocks and may, in turn, modulate circadian rhythms and sleep (Shen et al., 2017; Griffin et al., 2019; Wolff et al., 2020). Microglia-mediated neuroinflammation, particularly the NF-kB and NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome pathways and their downstream inflammatory cascades, play a central role in brain health

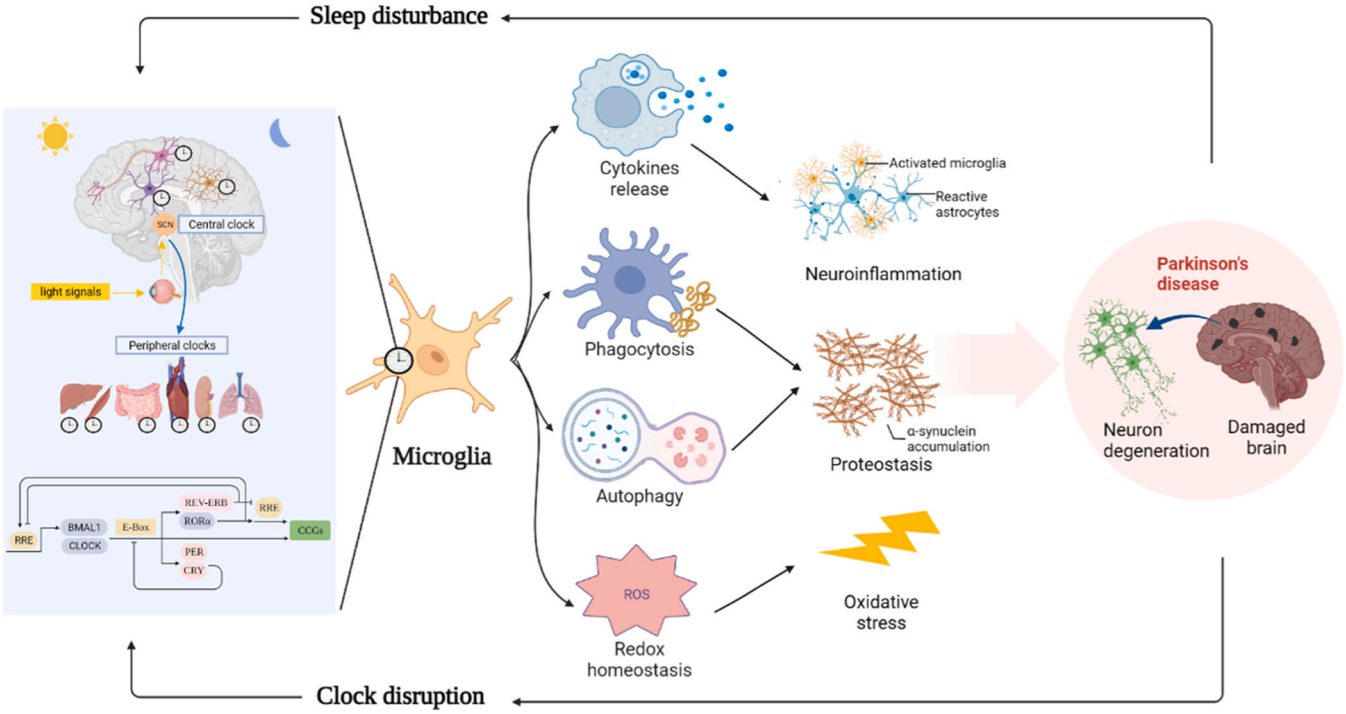

Fig. 1. Proposed bidirectional relationship between circadian disruption of microglia and Parkinson' disease. The circadian clock is an internal cycle of about 24 hours that keeps the body in sync with the external environment, most typically represented as the sleep-wake cycle (Cao et al., 2021). The circadian system is present in almost all cells of the body, including microglia (Hayashi et al., 2013). Numerous studies have shown that circadian clocks in microglia may influence inflammatory cytokines release, autophagy, phagocytosis, and REDOX homeostasis under physiological conditions (Fonken et al., 2015; Choudhury et al., 2020), though some theories are still need to be further studied. Consistently, circadian or sleep disturbances may exacerbate PD progression through microglia-mediated neuroinflammation, oxidative stress, and protein homeostasis (Morawska et al., 2021; Kou et al., 2022). Most importantly, neurodegeneration and abnormal protein aggregation caused by various causes will in turn disrupt sleep and circadian rhythms, forming a vicious circle.

(Leng and Edison, 2021). The effects of circadian disturbances on neuroinflammation have become a new focus in the study of neurodegenerative diseases (Fonken et al., 2018). In older adults, greater sleep fragmentation is associated with more severe microglia activation (Kaneshwaran et al., 2019). In microglia isolated from the hippocampus of 25-month-old mice, the expression pattern of clock genes *Per1* and *Per2* as well as inflammatory cytokines TNF-α and IL-1β was disturbed and flattened, and the diurnal differences in response to inflammatory stimuli also disappeared (Fonken et al., 2016). In 2-month-old APP-KI mice, CLOCK/BMAL1-driven transcriptional negative feedback loops in microglia were impaired, which was associated with the activation of NF-κB and abnormal expression of pro-inflammatory genes (Ni et al., 2019). In addition, chronic sleep deprivation exacerbated synaptic loss and memory impairment by modulating neuroinflammation in a mouse model of AD induced by Aβ oligomers (Kincheski et al., 2017). Similar results were obtained in the PD model. Bmal1 knockout exacerbated MPTP-induced glial activation and dopaminergic neuron loss (Liu et al., 2020), as did Rev-erbα deficiency in the 6-OHDA-induced mouse model of PD (Kim et al., 2018). Moreover, Rev-erbα was involved in the regulation of microglial NLRP3 inflammasome in the MPTP mouse model (Kou et al., 2022), which is similar to the anti-inflammatory effects of *Rev-erbα* in the epilepsy model (Yue et al., 2020). Furthermore, the clock gene RORα, an activator of *Bmal1* transcription, is involved in STAT-dependent microglial polarization in the substantia nigra in PD (Li et al., 2022). These findings suggest that circadian rhythms and sleep are involved in the regulation of microglia-mediated neuroinflammation in neurodegenerative diseases.

5.2. Oxidative stress

Microglia-mediated oxidative stress plays an important role in neurodegenerative diseases (Sharma et al., 2018; Trist et al., 2019). The regulation of oxidative stress by circadian rhythms has been extensively studied and involves many different cell types in the body. In macrophages, BMAL1 directly binds to the *Nrf2* promoter and regulates its transcription through E-box elements (Early et al., 2018). *Bmal1* is also involved in the regulation of mitochondrial metabolism, redox homeostasis, and effector function by affecting hypoxic reactive protein HIF-1α expression (Alexander et al., 2020). Knockout of *Bmal1* mitigates the response of NRF2 to LPS challenge, resulting in decreased antioxidant reactions and glutathione synthesis, and increased accumulation of ROS and HIF-1α in macrophages (Early et al., 2018). Moreover, loss of *Bmal1* was reported to cause oxidative damage to neurons and decrease the expression of redox defense genes, such as *Nqo1* and *Aldh2*, thus exacerbating neurodegeneration (Musiek et al., 2013). In human aortic endothelial cells, downregulation of Bmal1 can lead to CLOCK release and phosphorylation of p65, further enhancing NF-κB signaling pathway, increasing oxidative stress and inflammatory response, and exacerbating atherosclerosis induced by porphyry monas gingivalis (Xie et al., 2020). Besides *Bmal1*, the lack of *Per1* could lead to impaired mitochondrial dynamics and an imbalance in GPX1-related ROS fluctuations in the liver and intestinal tissues (Sun et al., 2020). In addition, the inhibition of REV-ERBα degradation can increase mitochondrial volume and oxidative phosphorylation, as well as the expression levels of antioxidant genes, such as heme oxygenase-1 (HO-1), manganese superoxide dismutase and catalase in fibroblasts (Sengupta et al., 2016). Furthermore, sleep deprivation leads to decreased expression of the transcription factor *Nrf-2* and the antioxidant enzyme HO-1 in the hippocampus of mice (Xue et al., 2019). Although direct evidence is limited, it can be inferred from the above study that oxidative stress in microglia may be regulated by circadian rhythms, similar to other cell types.

5.3. Protein aggregation and clearance in PD

LB is the core pathological feature of PD, and its main component, pathological α-Syn, is considered to be the initiating factor of PD pathology (George et al., 2019; Mahul-Mellier et al., 2020). Numerous studies have found that sleep and circadian rhythms are involved in the aggregation and propagation of pathological proteins in the brain, including Aβ, tau, as well as α-Syn (Holth et al., 2019; Barthelemy et al., 2020; Guisle et al., 2020; Niu et al., 2022). In older adults without PD, sleep fragmentation was positively associated with LB pathology and neuronal loss in the substantia nigra (Sohail et al., 2017). A clinical study has found an 80% increase in total α-Syn levels in human CSF after 36 hours of sleep deprivation, but no significant effect on phosphorylated α-Syn levels (Barthelemy et al., 2020). In animal studies, α-Syn levels in the CSF of mice were regulated by the sleep-wake cycle, and increased during normal wakefulness compared with that during sleep (Beesley et al., 2020), and after sleep deprivation (Holth et al., 2019). Furthermore, sleep deprivation significantly aggravated the pathological α-Syn load in VMAT2-deficient mice, while an enhanced slow-wave sleep reduced pathological α-Syn accumulation in both VMAT2-deficient and A53T mouse models of PD, which was related to proteostatic processes according to mass spectrometry data (Morawska et al., 2021). Sleep deprivation promoted the pathological deposition of α-Syn in LRRK2 G2019S knock-in mice, thus exacerbating dopaminergic neuron loss and motor deficits (Liu et al., 2022). The involvement of sleep and circadian rhythms in the regulation of α-Syn homeostasis has been well established, and the role of microglia in this process is increasingly being appreciated.

5.3.1. The uptake of α-Syn

Recent studies have shown that circadian rhythms are involved in the uptake of pathological proteins by microglia. Lee et al. demonstrated that microglia expressed higher levels of BMAL1 protein at CT4 than at CT12, with more phagocytotic fibrillary Aβ1–42. *Rev-erb* deletion accelerates microglial uptake of Aβ and ultimately reduces amyloid plaque deposition in 5XFAD mouse model, mainly by increasing P2Y12 receptors on the microglial surface (Lee et al., 2020). Lananna, Brian V et al. found that multiple clock genes are involved in the regulation of Chi3l1 expression in astrocytes, and the latter could promote the phagocytosis of microglia, thus decreasing the amyloid plaque burden in the APP/PS1 mouse model of AD (Lananna et al., 2020).

Pathological α-Syn is recognized and internalized by various receptors on the surface of microglia in a DAMP manner. Integrin CD11b, a subunit of the CR3 protein, has been shown to interact with various forms of α-Syn, including monomers, oligomers, and fibrinogen, to mediate microglial phagocytosis of α-Syn (Wang et al., 2015; Hou et al., 2018). Flow cytometry revealed that CD11b expression in microglia was increased at CT0 compared with that at CT12, with a stable diurnal rhythm (Choudhury et al., 2020), indicating that circadian rhythms may regulate microglial α-Syn internalization by CD11b expression. The triggering receptor expressed on myeloid cells 2 (TREM2), a receptor responsible for pathological protein internalization (Kleinberger et al., 2014; Benitez et al., 2021), has reports of its CSF levels being associated with poor sleep quality in patients with PD (Mo et al., 2021), even in healthy older adults without cognitive impairment (Hu et al., 2021). Although direct evidence is limited, it is speculated that circadian rhythms and sleep are involved in microglial uptake of α-Syn by regulating TREM2.

5.3.2. The degradation of α-Syn

The autophagy-lysosome system is controlled by circadian clocks and sleep, thus affecting the deposition of pathological proteins (Choi et al., 2019; Choi et al., 2022; Li et al., 2022). Xie, Y., et al. found that, chronic sleep fragmentation led to increased expression of endosomal markers Rab5 and Rab7, lysosome marker LAMP1, autophagy markers LC3B, UVRAG, and Beclin1, as well as increased lysosome volume, resulting in dysfunction of the endosome-autophagosome-lysosome pathway, which aggravated Aβ deposition and cognitive impairment in wild-type mice (Xie et al., 2020). ATG5, a key macroautophagy initiation protein, is involved in the degradation, induction of

inflammation, and exosomal secretion of α-Syn (Fussi et al., 2018; Han et al., 2019; Tu et al., 2021). Interestingly, ATG5 has been shown to be a direct downstream target of clock gene NR1D1, mediating the anti-cancer effect in small cell lung cancer (Shen et al., 2020) and follicular atresia in the ovarian development cycle (Zhang et al., 2022). Furthermore, the CLOCK gene is found to be involved in the process of mitochondrial autophagy, which is closely related to the α-Syn process (Rabinovich-Nikitin et al., 2021). These data suggest that sleep and circadian rhythms are critical for the clearance of pathological intracellular proteins via the autophagy-lysosome pathway (Ma et al., 2012).

Notably, not only can circadian rhythms regulate the autophagy-lysosome system, but the autophagy-lysosome system can also, in turn, modulate circadian rhythms. Juste, Y.R., et al. demonstrated that chaperone-mediated autophagy mediates the degradation of the circadian molecules BMAL1 and CLOCK, whereas disruption of the autophagy pathway leads to time-shifting and amplitude changes in clock-dependent transcriptional activity and fragmented circadian patterns, similar to sleep disorders and aging (Juste et al., 2021). Toledo, M., et al. also found that macroautophagy is involved in the degradation process of CRY1, and the loss of autophagy affects the nuclear levels of core circadian proteins (Toledo et al., 2018). Therefore, the interaction between the autophagy pathway and circadian system and their specific mechanism of action in microglia requires further study.

5.4. Mitochondria dysfunction

Mitochondria are one of the most important organelles in the cell, and their division, fusion, bioenergetics, including oxidative phosphorylation and ATP production are under the strong control of circadian clock (Schmitt et al., 2018). Mutiple studies have shown that microglia-mediated mitochondrial dysfunction plays a key role in the imbalance of protein homeostasis in neurodegenerative diseases, including abnormal mitophagy and mitochondria-linked inflammatory responses (Sarkar et al., 2017; Ahmed et al., 2021; Hinkle et al., 2022). Besides, studies have shown that time-limited feeding can improve mitophagy and mitochondrial quality control, thereby slowing the progression of PD (Austad et al., 2022). And melatonin supplements improved cognitive function and alleviated Aβ pathology by improving mitophagy and mitochondrial function (Chen et al., 2021). All these suggest that circadian rhythms may be involved in the progression of neurodegenerative diseases by regulating the mitochondrial function in microglia.

5.5. Microglia ablation disrupts sleep

It has been widely recognized that sleep and circadian rhythms regulate the morphology, phenotype, and function of microglia. However, microglia can also regulate sleep and circadian rhythms, and even play an integral role. In Cx3cr1-Dtr transgenic Wistar rat models, activation of diphtheria toxin receptors leads to the ablation of microglia, resulting in abnormal rhythms of body temperature, metabolism, and daily activities, as well as disrupted expression of core clock genes in the SCN and hippocampal tissues (Sominsky et al., 2021). Additionally, microglial depletion induced by PLX-5622 treatment increases the duration of non-rapid eye movement (NREM) sleep and disrupts phase-dependent synaptic activity in the hippocampus (Corsi et al., 2022). Microglial ablation increases the transition between wakefulness and NREM sleep in mice, thereby reducing stable wakefulness at night, suggesting that microglia regulate the sleep-wake cycle through ceramide signaling via neurons located in the thalamic reticular nucleus (Liu et al., 2021). Besides, it is worth noting that NF-κB mediated transcriptional repression is involved in the circadian feedback regulation of transcriptional-translational circuits (Hong et al., 2018). Furthermore, inflammatory cytokines secreted by microglia, such as IL-1β and TNF-α, promote sleep (Picard et al., 2023; Pinto et al., 2023).

6. Circadian rhythm as a therapeutic target

Recently, studies on the effects of clock gene manipulation on neurodegenerative diseases have been emerging, especially for *Bmal1* (Kress et al., 2018; Yoo et al., 2020; McKee et al., 2022) and *Rev-erbα* (Roby et al., 2019; Huang et al., 2022; Killoy et al., 2022; Kim et al., 2022; Nam et al., 2022), which are potential directions for exploring therapeutic strategies and need further research (Table 1). Medication is a relatively safe and routine method of regulating sleep and circadian rhythms. Melatonin, an important sleep regulator and circadian synchronizer, is commonly deficient during aging and in neurodegenerative diseases. Therefore, melatonin replacement therapy and melatonin agonists have been widely studied as pharmacological approaches to insomnia and neurodegenerative disease (Sumsuzzman et al., 2021; Choi et al., 2022; Moon et al., 2022). Orexin, also known as hypocretin, primarily promotes arousal and wakefulness. Dual orexin receptor antagonists have been used clinically to enhance sleep maintenance and initiation (Coleman et al., 2017). Natural compounds, such as nobiletin, can directly activate RORs, thereby effectively enhancing circadian rhythms, which require further clinical research (He et al., 2016). In addition to medication, environmental or lifestyle modifications, such as light therapy (Videnovic et al., 2017), time-restricted feeding (Mattson et al., 2017), and exercise (Wang et al., 2022), can also improve circadian rhythms and sleep quality and, alleviate movement symptoms or cognitive impairments in neurodegenerative diseases. In addition, chronotherapy, which considers circadian rhythms, usually refers to the timed dosing of drugs to maximize the therapeutic index, which can improve treatment outcomes. For example, drugs, such as anti-hypertensive drugs, glucocorticoid receptor agonists, and anti-cancer drugs, usually show much higher efficacy at a certain time than at other times (Smolensky et al., 2007; Gumz et al., 2023; Petkovic et al., 2023). Therefore, the timing of neurodegenerative disease treatment must be precise (Hogl, 2017).

7. Conclusions

Microglia play a central role in PD because of their complex and diverse functions. Circadian disturbances and sleep disorders are precursor symptoms of PD and, as well as important risk factors for PD. Microglial circadian rhythms have received increasing attention as they mediate diverse physiological processes in the CNS, including microglial interactions, cytokine release, phagocytosis, metabolism, sleep, and circadian behavior. Disruption of the microglial circadian rhythms may cause neuroinflammation, oxidative stress, and abnormal uptake and degradation of misfolded proteins, ultimately leading to pathological protein aggregation and propagation and, neuronal death. Remarkably, whether the microglial clock genes are beneficial or detrimental depends on the context. For example, Rev-erbα can inhibit microglia-mediated neuroinflammation (Griffin et al., 2019), and loss of Rev-erbα aggravated neuroinflammation, disrupted lipid metabolism, and promoted tau protein aggregation, leading to anxiety-like behavior and cognitive deficits in mice (Chen et al., 2023; Lee et al., 2023). However, another study has also shown that inhibition of Rev-erbα enhances microglial phagocytosis, promotes Aβ clearance, and reduces the deposition of amyloid plaque in the 5XFAD mouse model (Lee et al., 2020). Besides, several studies have found that Bmal1 deficiency disrupts immune function and synaptic pruning, accelerating brain aging and cognitive decline (Wang et al., 2020; Iweka et al., 2023). However, a study also confirmed that microglia-specific knockdown of Bmal1 enhanced its phagocytic activity, promoted significant retention of pro-opiomelanocortin immune reactivity and formation of mature spines, improved memory and protected mice from obesity caused by a high-fat diet (Wang et al., 2021). Therefore, further research is needed to explore the detailed function and impact of the microglial circadian rhythms, while considering specific conditions, such as disease stage, brain region, and sex.

Table 1
Effects of manipulating clock genes on models of neurodegenerative disease.

First author, year	Clock genes	Disease	Research object	Cell type	Effects
(McKee et al., 2022)	Bmal1	AD	APP/PS1 mice	Astrocyte	Bmal1 deficient in astrocytes enhances activation responses to amyloid-beta pathology without changing plaque burden
(Kress et al., 2018)	Bmal1	AD	APPPS1–21 transgenic mice	-	Global Bmal1 deletion leads to disruption of daily hippocampal interstitial fluid Aβ oscillations and markedly accelerates amyloid plaque accumulation, whereas loss of peripheral Bmal1 in the brain parenchyma increases expression of Apoe and modestly promotes fibrillar plaque deposition.
(Yoo et al., 2020)	Bmal1 and CLOCK	AD	Astrocytes of cerebral cortex from AD patients	Astrocyte	Over-expression of CLOCK and Bmal1 contribute to the aerobic glycolysis and cytotoxicity in astrocytes
(Liu et al., 2020)	Bmal1	PD	MPTP-treated mice	Microglia	Absence of Bmal1 exacerbates neuroinflammation, dopaminergic neurons loss and motor function
(Lee et al., 2020)	Rev-erbα	AD	5XFAD mice	Microglia	Pharmacological inhibition of REV-ERBs with SR8278 or genetic knockdown of REV-ERBs stimulates microglial amyloid-beta clearance and reduces amyloid plaque deposition
(Nam et al., 2022)	Rev-erbα	AD	$Psen2^{N141I/+}$ mice	Microglia	Chlorpromazine prevents microglia-mediated hyperimmune response and cognitive decline in Psen2N141I/+ mice by restores the REV-ERBα level
(Roby et al., 2019)	Rev-erbα	AD	SAMP8 mice	-	REV-ERB agonist SR9009 reversed cognitive dysfunction, reduced amyloid-β burden and improved synaptic function.
(Ni et al., 2019)	Rev-erbα	AD	APP-KI mice	Microglia	REV-ERB agonist SR9009 induced microglia activation, increased proinflammatory gene expression and decreased cognitive function.
(Kou et al., 2022)	Rev-erbα	PD	MPTP-treated mice	Microglia	REV-ERBα agonist SR9009 partially reversed MPTP induced microglial polarization, NLRP3 inflammasome activation and dopaminergic neurons loss in the nigrostriatal system.
(Kim et al., 2022)	Rev-erbα	PD	6-OHDA-injected mice	-	REV-ERBα antagonist SR8278 exerted antidepressant and anxiolytic effects in a circadian time-dependent manner
(Kim et al., 2018)	Rev-erbα	PD	6-OHDA-injected mice	-	NR1D1 deficiency significantly exacerbated 6-OHDA-induced motor deficits as well as DAergic neuronal loss in the vertebral midbrain
(Killoy et al., 2022)	Rev-erbα	ALS	Mutant hSOD1 linked mice	Astrocyte	NR1D1 downregulation in primary astrocyte cultures induces a pro-inflammatory phenotype and decreases the survival of cocultured motor neurons
(Huang et al., 2022)	Rev-erbα	AMD	Aging mice	Retinal pigment epithelium	Loss of NR1D1 exacerbates chemical-induced RPE damage, pharmacological activation of REV-ERBα protects RPE from oxidative damage both in vivo and in vitro

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CRediT authorship contribution statement

Liang Kou and Xiaosa Chi wrote the manuscript and constructed the figure. Yadi Sun and Sijia Yin contributed to the literature search. Jiawei Wu, Wenkai Zou, Yiming Wang and Zongjie Jin reviewed the manuscript. Jinsha Huang and Nian Xiong contributed to the review and editing of the manuscript prior to the submission. Yun Xia and Tao Wang conceived the structure of the manuscript and participated in the entire writing process.

Declaration of Competing Interest

The authors declare that they have no competing financial interests.

Data availability

No data was used for the research described in the article.

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