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# Circadian Clock Regulates Inflammation and the Development of Neurodegeneration

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The circadian clock regulates numerous key physiological processes and maintains cellular, tissue, and systemic homeostasis. Disruption of circadian clock machinery influences key activities involved in immune response and brain function. Moreover, Immune activation has been closely linked to neurodegeneration. Here, we review the molecular clock machinery and the diurnal variation of immune activity. We summarize the circadian control of immunity in both central and peripheral immune cells, as well as the circadian regulation of brain cells that are implicated in neurodegeneration. We explore the important role of systemic inflammation on neurodegeneration. The circadian clock modulates cellular metabolism, which could be a mechanism underlying circadian control. We also discuss the circadian interventions implicated in inflammation and neurodegeneration. Targeting circadian clocks could be a potential strategy for the prevention and treatment of inflammation and neurodegenerative diseases.

**Keywords: circadian clock, immune response, systemic inflammation, neurodegeneration, cellular metabolism**

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## INTRODUCTION

Virtually all life has an intrinsic timing system, the so-called biological clock, which coordinates biological processes to adapt to the regular 24-hour light/dark cycles generated by the Earth's rotation (Bell-Pedersen et al., 2005). In mammals, numerous physiological and behavioral processes exhibit a daily rhythm of approximately 24-hour, such as sleep-wake cycle, locomotor activity, feeding, body temperature, metabolism, immune response, hormone secretion, and cognition (Gerstner and Yin, 2010; Mohawk et al., 2012; Scheiermann et al., 2013; Gnocchi and Bruscalupi, 2017; Mure et al., 2018). These rhythmic activities are driven by cell-autonomous circadian clocks that existed in almost every cell in organisms. However, circadian rhythm can also be affected by external cues and pathological conditions, such as light, diet, feeding pattern, temperature, exercise, oxygen, as well as cancer, cardiovascular disease, inflammation, and neurodegenerative diseases (Cavadini et al., 2007; Kohsaka et al., 2007; Pivovarova et al., 2015; Adamovich et al., 2017; Manoogian and Panda, 2017; Hood and Amir, 2017a; Hood and Amir, 2017b; Crosby et al., 2019; Gabriel and Zierath, 2019).

The circadian system regulates numerous cellular processes, which interact and affect biological activities. For example, circadian clocks modulate cellular metabolism, epigenetic modification, cell cycle, redox homeostasis, gut microbiota, immune response, and cognition. Cellular metabolism is associated with immune activity and neurodegeneration (Camandola and Mattson, 2017;

Geltink et al., 2018; Vijayan et al., 2019; Wang et al., 2019). Additionally, both central and peripheral inflammation implicate in neurodegeneration (Trager and Tabrizi, 2013; Chitnis and Weiner, 2017). Disruption of circadian rhythms leads to obesity, diabetes, cancer, immune dysfunction, and cognitive decline. Just as circadian disruption can induce biological disorders, circadian disturbances have also been regarded as the consequences of microbial infection, metabolic disorder, and neurodegenerative diseases. For example, circadian abnormality in sleep/wake cycles is one of the common and earliest signs of neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD); while the abnormality of circadian rhythms exacerbates the progression of neurodegeneration (Hood and Amir, 2017a). Here, we review the complex circadian network and summarize the circadian control of immune function and neurodegeneration. We explore the complex interplay between systemic inflammation and neurodegeneration and discuss the potential mechanism underlying circadian regulation.

## THE CIRCADIAN CLOCK IN MAMMALS

The circadian system is an internal timekeeping device, which is hierarchical and organized in multiple oscillators at the organism, cellular, and molecular level in mammals (Reppert and Weaver, 2002; Bell-Pedersen et al., 2005; Saini et al., 2019). The central pacemaker is located in the hypothalamic suprachiasmatic nucleus (SCN) and consists of multiple populations of oscillating neurons and astrocytes; these cells are integrated as a single circadian unit and output a coordinated circadian signal (Herzog et al., 2017; Hastings et al., 2018; Brancaccio et al., 2019). SCN forwards the rhythmic signal *via* the hypothalamus-pituitary-adrenal (HPA)-axis and the autonomic nervous system, which align the circadian clocks throughout the organism with the external environmental cues, such as light (Kalsbeek et al., 2012; Koronowski and Sassone-Corsi, 2021). At the molecular level, the core clock machinery exists in almost all cells and is a self-sustaining system based on transcription-translation feedback loops (TTFLs); molecular clocks can generate circadian rhythms autonomously without the need of an external signal (Reppert and Weaver, 2001; Dudek and Meng, 2014). The transcriptional factors brain and muscle ARNT-like 1 (Bmal1)/circadian locomotor output cycles Kaput (Clock) heterodimer activate the expression of genes that containing clock regulatory elements (E-box) in their promoters, including *Period circadian clock* (*Per1/2/3*), *Cryptochrome* (*Cry1/2*), RAR-related orphan receptor alpha (*Rorα*), *Rev-erbα*, and D site albumin promoter binding protein (*Dbp*) genes. Per and Cry, in turn, inhibit the activity of the Bmal1/Clock complex; while the opposing function of nuclear receptors Rorα and Rev-erbα fine-tune the transcription of *Bmal1* and nuclear factor interleukin 3 (*Nfil3*, also known as E4BP4) *via* activation and repression, respectively (Gekakis et al., 1998; Sato et al., 2004; Ripperger and Schibler, 2006; Haque et al., 2019). DBP and NFIL3 synergistically regulate the expression of *Per* (Ohno et al., 2007; Yamajuku et al., 2011; Curtis et al., 2014) (**Figure 1**).

Except for autoregulation, circadian clocks control the rhythmic expression of widespread genes and proteins throughout the body, thus affect numerous physiological processes (Duffield, 2003; Bass and Takahashi, 2010; Gerstner and Yin, 2010; Curtis et al., 2014; Zhang et al., 2014; Rahman et al., 2015; Man et al., 2016; Loizides-Mangold et al., 2017; Stenvers et al., 2019b; Barca-Mayo et al., 2019). For example, synaptic plasticity and density vary according to time-of-day and circadian clock-Bmal1 deficiency in the brain impairs neuronal function and cognitive performance (Perez-Cruz et al., 2009; Musiek et al., 2013; Jasinska et al., 2015; Krzeptowski et al., 2018; Hasegawa et al., 2019). Transcripts of inflammatory cytokines and host immune responses also show a diurnal variation, while disruption of the circadian clock leads to dysfunction of immunity (Halberg et al., 1960; Bellet et al., 2013; Fonken et al., 2015; Deng et al., 2018). Moreover, circadian clock participates in diverse metabolic processes ranging from glucose transport to gluconeogenesis, lipogenesis, and mitochondrial processes (such as morphological changes, mitochondrial biogenesis, respiration, and oxidative phosphorylation) in both peripheral tissues and the brain (Kohsaka, 2007; Bass and Takahashi, 2010; Kawai et al., 2010; Zhang et al., 2010; Schiaffino et al., 2016; Robles et al., 2017; de Goede et al., 2018). Therefore, disruption of the cell-autonomous clock network has a profound influence on immune responses, energy metabolism, and cognition in mammals (Schiaffino et al., 2016; Stenvers et al., 2019b).

To maintain daily oscillations of circadian clocks to approximately 24 h, the negative-feedback loop of clock network requires a crucial delay between activation and repression of transcription, which is achieved by post-translational modifications (PTMs). For example, transcription repressor Per2 is phosphorylated by casein kinase Iε (CKIε) and targeted for ubiquitin-mediated degradation, while Cry1 is phosphorylated and destabilized by adenosine monophosphate-activated protein kinase (AMPK) (Eide et al., 2005; Lamia et al., 2009). Transcription activator Bmal1 is phosphorylated by mitogen-activated protein kinase (MAPK) and glycogen synthase kinase-3β (GSK3β) (Sanada et al., 2002; Sahar et al., 2010); while Clock possesses intrinsic histone acetyltransferase (HAT) activity indicated a close link between clock machinery and chromatin remolding (Doi et al., 2006). The PTMs modulated by phosphorylation, ubiquitylation, sumoylation, acetylation, and epigenetic modification affect the stability and nuclear translocation of core clock proteins, thus control the time-specific transcription of clock genes (Gallego and Virshup, 2007; Bellet and Sassone-Corsi, 2010; Shi et al., 2016). Protein phosphorylation is the widely reported PTM of the core clocks and plays a key role in generation of circadian rhythms (Reischl and Kramer, 2011). It's also known that epigenetic modification uses cellular metabolites as a source, which indicates the implication of cellular metabolism in PTMs (Borrelli et al., 2008). Notably, rhythmic oscillations of peroxiredoxins, highly conserved antioxidant proteins, have been observed in both mice and cultured human red blood cells (naturally no nucleus or DNA) (O'Neill and Reddy, 2011; Edgar et al., 2012). These studies indicate the essential role of non-transcriptional dependent redox

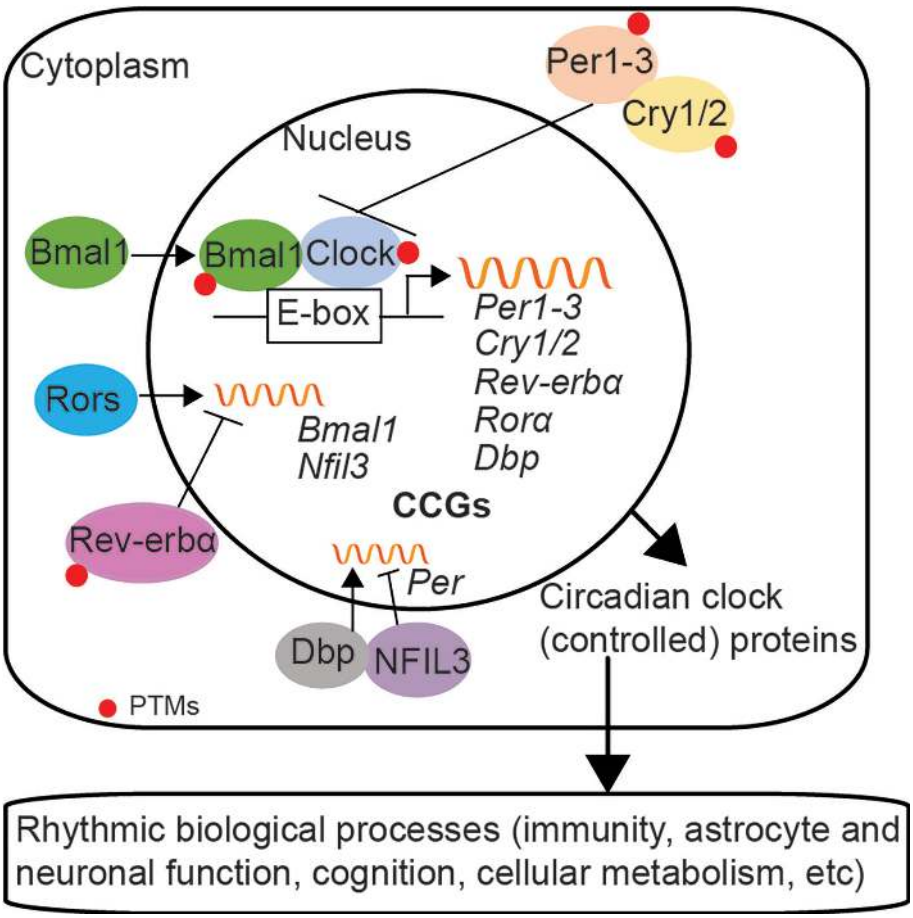


**FIGURE 1** | The circadian clock machinery in mammals. The mammalian circadian clock network at the molecular level consists of transcription-translation feedback loops (TTFLs). Bmal1/Clock heterodimer activates the transcription of genes that containing E-box elements in their promoters, such as *Per1/2/3*, *Cry1/2*, *Rorα*, *Rev-erbα*, and *Dbp*. Per and Cry proteins translocate back into the nucleus and repress the activity of the Bmal1/Clock complex, which subsequently inhibits their own expression. Rorα and Rev-erbα fine-tune the expression of *Bmal1* and *Nfil3*, *via* activation and repression, respectively. DBP and NFIL3 regulate the expression of *Per*. Besides, the stability and nuclear translocation of circadian clock proteins are modulated by post-translational modifications (PTMs). Circadian clocks also control the rhythmic expression of numerous clock-controlled genes (CCGs) and biological processes, such as immunity and brain function.

oscillations in generation of circadian rhythms (Rey and Reddy, 2015). Besides, the redox state can regulate circadian clocks and is also relevant for their functions (Rutter et al., 2001; Fleischhacker et al., 2018; Sundar et al., 2018; Uriz-Huarte et al., 2020). Moreover, the expression pattern of clock genes varies in a tissue-specific manner, which may determine the functional difference of some clock components in different tissues (Ko and Takahashi, 2006).

## EFFECT OF CIRCADIAN CLOCK ON PERIPHERAL IMMUNE RESPONSE

The immune system protects against infections and tissue injury, which has beneficial effects to the host. However, the dysregulated immune response can lead to chronic inflammation, tissue damage, and endotoxin shock (Medzhitov, 2008). While chronic inflammation also presents in tissue stress and malfunction conditions, such as type 2 diabetes, obesity, and neurodegenerative and neuropsychiatric diseases; the persistent low-grade inflammation, in turn, contributes to the further progression of these diseases (DeLegge and Smoke, 2008; Donath and Shoelson, 2011; Cox et al., 2015). Growing evidence shows that circadian clock controls multiple immune functions, such as trafficking of immune cells, pathogen recognition, phagocytic capacity, and secretion of inflammatory cytokines, chemokines, and complement factors (Keller et al., 2009; Curtis et al., 2014; Man et al., 2016; Timmons et al., 2020). Additionally, the mortality caused by lethal bacteria varies according to the time of infection (Halberg et al., 1960; Shackelford and Feigin, 1973; Marpegan et al., 2009). Here, we review the cell-specific disruption of the circadian clock-induced dysfunction of innate and adaptive immunity in peripheral immune cells (Sato et al., 2014; Nakazato et al., 2017; Deng et al., 2018) (**Table 1**).

In peritoneal macrophages, the transcript of *Bmal1* exhibits diurnal rhythm with the peak at the dark phase (Deng et al., 2018;

**TABLE 1 |** Effect of the circadian clock on peripheral innate and adaptive immunity.

| Cell type | Target | Stimulation | Phenotype | Mouse/ cell Model | Ref. |
|---|---|---|---|---|---|
| **Peritoneal macrophage** | Bmal1 | LPS | Increased IL6, CXCL1, TNFα, MCP1/CCL2, and reduced IL10 | Myeloid Bmal1$^{-/-}$ mouse | (Curtis et al., 2015) |
| **BMDM** | Bmal1 | LPS | Increased IL6, CXCL1, TNFα, MCP1/CCL2, and *Il1b* | Myeloid Bmal1$^{-/-}$ mouse | (Curtis et al., 2015; Early et al., 2018) |
| **Alveolar macrophage** | Bmal1 | *S. aureus* infection | Increased phagocytosis and reduced pro- and anti-inflammatory cytokines in the lung | Myeloid Bmal1$^{-/-}$ mouse | (Kitchen et al., 2020) |
| **Peritoneal macrophage** | Bmal1 | *S. aureus* or *S. pneumoniae* infection | Increased phagocytosis | Myeloid Bmal1$^{-/-}$ mouse | (Kitchen et al., 2020) |
| **BMDM** | Clock | LPS | Reduction of *Il-6*, *Il1b*, *Tnfα*, *Ifn-β*, and *Ccl2* and reduced secretion of IL-6 and TNFα | Clock$^{-/-}$ mouse | (Bellet et al., 2013) |
| **BMDM** | Clock | *Salmonella* infection | Decreased secretion of IL-6 and IL-1β | Clock$^{-/-}$ mouse | (Bellet et al., 2013) |
| **Peritoneal macrophage** | Per2 | TLR9 ligand | Less TNFα and IL12 production | *Per2* mutant mouse | (Silver et al., 2012) |
| **BMDM** | Cry1 and Cry2 | LPS | Increased secretion of TNFα and IL-6 | *Cry1–/–;Cry2–/–* mouse | (Narasimamurthy et al., 2012) |
| **Peritoneal macrophage** | Rev-erbα | LPS/ None | Increased *Ccl2* gene expression | *Rev-erbα*$^{-/-}$ mouse | (Sato et al., 2014) |
| **MDM, alveolar macrophage, or THP-1** | Rev-erbα | LPS | Decreased or increased IL-6 level | Rev-erbα agonist or knockdown in human cell | (Gibbs et al., 2012) |
| **Monocyte** | Bmal1 | *Listeria monocytogenes* infection | Increased inflammatory cytokines and monocyte-attracting chemokines in serum | Myeloid Bmal1$^{-/-}$ mouse | (Nguyen et al., 2013) |
| **Monocyte and macrophage** | Bmal1 | Diet-induced obesity and atherosclerosis | Exacerbation or reduction chronic inflammation | Myeloid Bmal1$^{-/-}$ mouse | (Nguyen et al., 2013; Huo et al., 2017; Yang et al., 2020) |
| **THP-1** | Rorα | LPS/ None | Increased expression of TNFα, IL-1β, and IL-6 | Deletion of Rorα in THP-1 | (Moharrami et al., 2018) |
| **NK and DC** | Nfil3 | None | Lack of NK and CD8α(+) conventional DCs | Nfil3-/- mouse | (Gascoyne et al., 2009; Kashiwada et al., 2011) |
| **CD4+ T cell** | Rorα | Inflammatory condition | Reduced IL-17 production | Rorα-/- mouse | (Yang et al., 2008) |
| **CD4+ T cell** | Rorγt | None | Reduced Th17 cells and IL17 expression | Rorγ–/– mouse | (Ivanov et al., 2006) |
| **Th17 cell** | REV-ERBα | None | Increased inflammatory response | REV-ERBα–/– mouse | (Amir et al., 2018) |
| **CD4+ T cell** | REV-ERBα | None | Decreased Th17 cell differentiation | T cell-specific REV-ERBα/β–/– mouse | (Chang et al., 2019) |
| **CD4+ T cell** | Nfil3 | None | Increased Th17 cells | Nfil3–/– mouse | (Yu et al., 2013) |
| **B cell** | Nfil3 | None | Impaired IgE production | Nfil3–/– mouse | (Kashiwada et al., 2010) |
| **Th1 and Th2 cells** | Nfil3 | Antigen stimulation | Altered cytokine production | Nfil3–/– mouse/ cell | (Kashiwada et al., 2011; Motomura et al., 2011) |
| **T and B cells** | Bmal1 | None | Abolished the diurnal oscillation of T and B cell numbers in lymph nodes | CD4$^{+}$/ CD19$^{+}$ cell Bmal1$^{-/-}$ mouse | (Druzd et al., 2017) |

*BMDM, bone marrow-derived macrophage; MDM, monocyte-derived macrophage; THP-1, myelomonocytic cell line; NK, natural killer; DC, dendritic cell; Ref., reference.*

Early et al., 2018; Lee et al., 2020). Bmal1 deficient peritoneal macrophages or bone marrow-derived macrophages (BMDMs) show increased production of IL6, CXCL1, TNFα, MCP1/CCL2, or *Il1b* expression upon bacterial endotoxin-lipopolysaccharide (LPS) stimulation; both NRF2 and microRNA miR-155 are implicated in Bmal1 control of inflammatory phenotype (Curtis et al., 2015; Early et al., 2018). Myeloid Bmal1 deficient mice show increased IL-1β levels in the serum after LPS administration and increased mortality response to experimental or LPS-induced sepsis (Curtis et al., 2015; Deng et al., 2018; Early et al., 2018). However, deletion of Bmal1 in macrophages protects mice from pneumococcal infection through increased phagocytosis of macrophages and reduced pro-inflammatory cytokines in the lungs (Kitchen et al., 2020). Additionally, *Clock* deficient BMDMs exhibit reduced expression of proinflammatory genes *Il-6*, *Il1b*, *Tnf*α, *Ifn*-β, and *Ccl2* upon LPS stimulation and decreased secretion of IL-6 and IL-1β after *Salmonella* infection (Bellet et al., 2013). Per2 mutation reduces the Toll-like receptor 9 (TLR9)-dependent TNFα and IL12 levels in peritoneal macrophages upon challenge with TLR9 ligand (Silver et al., 2012). Cry1 and Cry2 deficiency increases the secretion of TNFα and IL-6 in BMDMs upon LPS stimulation by binding to adenylyl cyclase and subsequently regulating cAMP levels and protein kinase A and NF-κB activity (Narasimamurthy et al., 2012). Moreover, Rev-erbα inhibits the expression of Chemokine (C-C motif) ligand 2 (*Ccl2*) in peritoneal macrophages and represses the production of IL-6 in human macrophages response to LPS (Gibbs et al., 2012; Sato et al., 2014).

Besides, both clock genes of blood monocytes and Ly6C$^{hi}$ inflammatory monocytes numbers in blood and spleen show a diurnal variation in mice; depletion of Bma1 in myeloid cells disrupts rhythmic trafficking of Ly6C$^{hi}$ monocytes and induces higher expression of inflammatory cytokines and monocyte-attracting chemokines in serum during *Listeria monocytogenes* infection (Nguyen et al., 2013). *Bmal1* is also involved in monocytes and macrophages-related chronic inflammation in diet-induced obesity and atherosclerosis conditions (Nguyen et al., 2013; Huo et al., 2017; Yang et al., 2020). Additionally, Bmal1 regulates the rhythmic expression of chemokine genes-*Ccl2*, *Ccl8*, and *S100a8* by binding to E-boxes in their promotors in monocytes and peritoneal macrophages (Nguyen et al., 2013). Deletion of Rorα increases the expression of TNFα, IL-1β, and IL-6 in human monocytic cell line (THP-1) (Moharrami et al., 2018). Moreover, NFIL3 is essential for the development of natural killer (NK) cells and CD8α+ conventional dendritic cells (Gascoyne et al., 2009; Kashiwada et al., 2011). It has been reported that approximately 8% of genes are under circadian control in macrophages and more complex molecular mechanisms may be underlying the circadian clock regulation of the innate immune response (Keller et al., 2009).

Furthermore, circadian clock also modulates adaptive immunity (Downton et al., 2020). Rorα and Rorγt regulate the differentiation of pro-inflammatory T helper 17 (Th17) cells and induce the expression of cytokine-interleukin-17 (IL-17) and IL-17F, whereas Rev-erbα antagonizes the function of Rorγt by binding the same DNA motif (Ivanov et al., 2006; Yang et al., 2008; Korn et al., 2009; Amir et al., 2018; Chang et al., 2019). Transcription repressor NFIL3 also suppresses Th17 cell development by directly binding the *Rorγt* promoter and repressing its activity (Yu et al., 2013). The production of IgE by activated B cells and secretion of cytokines by Th1 and Th2 cells also require the involvement of NFIL3 (Kashiwada et al., 2010; Kashiwada et al., 2011; Motomura et al., 2011; Male et al., 2012). Additionally, lymphocyte migration through lymph nodes and lymph show diurnal variation, which depends on the rhythmic expression of promigratory factors on lymphocytes and can be abolished in lymphocytes loss of Bmal1 (Druzd et al., 2017). However, a study showed that the differentiation of T and B cells and the adaptive immune response are independent of the expression of Bmal1 (Hemmers and Rudensky, 2015). Since the widespread and complex effect of circadian clocks on peripheral immune response, it is necessary to review the role of the molecular clock at the systemic level, especially in circadian disruption and immune dysfunction-related neurodegenerative diseases (**Figure 2**).

## EFFECT OF CIRCADIAN CLOCK ON NEURODEGENERATION

Neurodegeneration is mainly characterized by the progressive loss of structure or function of neurons and finally leads to neuronal death. Increasing evidence suggests multiple cell types in the brain are involved in the progression of neurodegeneration (Heneka et al., 2015; Phatnani and Maniatis, 2015; Liddelow et al., 2017; Hickman et al., 2018; Parodi-Rullan et al., 2019). Microglia provide immune surveillance and shape the neural circuits, while astrocytes regulate neuronal signal transmission. Activated microglia and astrocytes induced-chronic neuroinflammation plays a critical role in the development and progression of neurodegeneration (Hickman et al., 2018; Labzin et al., 2018). Thus, maintenance of brain homeostasis is crucial to avoid and prevent the development of neurodegenerative diseases. Compelling studies indicated that circadian clock modulates brain functions and has a direct effect on the function of brain cells, including neurons, astrocytes, microglia, and endothelial cells (Perez-Cruz et al., 2009; Musiek et al., 2013; Jasinska et al., 2015; Barca-Mayo et al., 2017; Krzeptowski et al., 2018; Hasegawa et al., 2019). Circadian clock disruption is an early symptom of neurodegeneration and also could be a risk factor for the development of neurodegenerative diseases (Hood and Amir, 2017a; Leng et al., 2019). AD and PD are the most common neurodegenerative diseases and best studied in relation to circadian rhythms (Breen et al., 2014; Lauretti et al., 2017; Musiek et al., 2018; Leng et al., 2019). Here, we review the effect of disruption of the circadian clock on the function of brain cells and neurodegeneration.

Circadian clock is associated with microglial immune activity. It has been shown that the circadian clock genes are rhythmically expressed in microglial cells isolated from rodents housed under light/dark conditions (Hayashi et al., 2013; Fonken et al., 2015; Wang et al., 2021). Transcripts of pro-inflammatory cytokines-*Il1b*, *Il6*, and *Tnfa*, also show a time-of-day difference in microglia, with elevated expression during the light phase

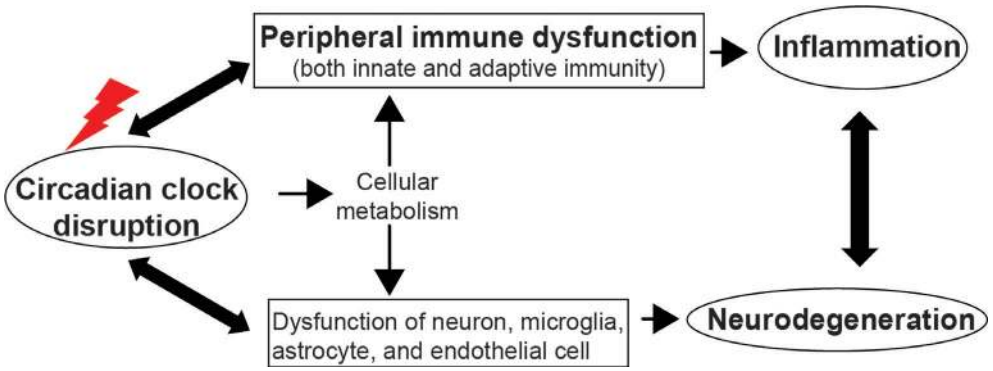


**FIGURE 2** | The circadian clock regulates immune function and neurodegeneration. Disruption of the circadian clock machinery leads to immune dysfunction and neurodegeneration, which, in turn, exacerbates the circadian abnormality. The bidirectional communication between systemic inflammation and neurodegeneration deteriorates immune dysfunction and the progression of neurodegenerative diseases. The cellular metabolism pathway could be a mechanism underlying circadian control of immunity and brain function.

(Fonken et al., 2015; Wang et al., 2020). Additionally, microglial phagocytosis exhibits time-of-day variation (Choudhury et al., 2020; Griffin et al., 2020). Disruption of the circadian function of microglia may sensitize hippocampal inflammatory response in aged rats (Fonken et al., 2016). Notably, the expression of *Bmal1* is higher during the light phase compared to the dark phase in microglia isolated from mice, which is consistent with transcripts of pro-inflammatory cytokines (Hayashi et al., 2013; Wang et al., 2020). Microglial Bmal1 deficient mice exhibit less *Il6* expression and diminished neuronal damage following middle cerebral artery occlusion than controls (Nakazato et al., 2017). In microglial BV-2 cells, Bmal1 knockdown decreases the expression of pro-inflammatory cytokines (*Il1b*, *Tnfa*, and *Il6*) and increases the expression of anti-inflammatory cytokine-*Il10* upon LPS stimulation (Nakazato et al., 2017; Wang et al., 2020). Moreover, lacking Bmal1 increases the microglial phagocytosis in mice on a high-fat diet as well as during the learning process (Wang et al., 2021). Rev-erbα deficient microglia reveal pro-inflammatory phenotypes and elevated NF-kB activation *via* binding to the promoter regions of related genes; global deletion of Rev-erbα leads to hippocampal microgliosis and neuronal damage in mice (Griffin et al., 2019a). Pharmacologic activation of Rev-erbα inhibits TNFα or LPS-induced pro-inflammatory cytokine expression (Griffin et al., 2019a; Wolff et al., 2020). Furthermore, astrocytes are also involved in innate immunity in the brain and secrete inflammatory mediators. Excessive activation of astrocytes may trigger cell death and neurodegeneration. Rorα deficiency decreases the level of IL-6 at basal conditions in astrocytes, whereas significantly increases IL-6 expression after inflammatory stimulations (Journiac et al., 2009). This study suggests that the circadian clock may exert different effects under different conditions.

In addition, both global *Bmal1* knockout and global Rev-erba knockout increase the expression of complement-related genes in the hippocampus; an enhanced transcript of *C4b* is also observed in the cerebral cortex of neuron and astrocyte *Bmal1* knockout mice (Lananna et al., 2018; Griffin et al., 2019b; Griffin et al., 2020). Elevated expression of *C4b* has also been seen in the neuron-specific *Bmal1* knockout and astrocyte-specific *Bmal1* knockout mice, but not in microglia-specific *Bmal1* knockout mice (Griffin et al., 2020). It's known that increased *C4b* and *C3* expression is critical for synaptic elimination, which leads to increased microglial phagocytosis and significant synaptic loss in the hippocampal CA3 region of the global Rev-erba mice (Griffin et al., 2020). However, inhibition of Rev-erbα reduces amyloid plaque burden and prevents synaptic loss in 5XFAD mice, an animal model of AD, which may be caused by increased microglial amyloid-β (Aβ) clearance (Lee et al., 2020). Circadian clock also regulates the rhythmic expression of cathepsin S (catS), a microglia-specific lysosomal cysteine protease in the brain, to control the diurnal variation of synaptic strength of the cortical neurons *via* extracellular proteolysis; *Clock* deficiency reduces the gene expression of CatS in microglia cells, while deletion of CatS increases spine density and alters synaptic strength, which leads to hyperlocomotor activity in mice (Hayashi et al., 2013).

Global *Bmal1* knockout mice are complete loss of locomotor circadian rhythm in constant darkness and display impaired hippocampus-dependent learning and memory (Bunger et al., 2000; Wardlaw et al., 2014). These mice also exhibit age-dependent severe astrocyte activation in the cortex and hippocampus, increased expression of pro-inflammatory cytokines-*Tnfa* and cyclooxygenase-2 (COX2, *Ptghs2*), and discrete presynaptic terminal degeneration caused by increased oxidative stress-induced neuronal damage (Musiek et al., 2013; Yang et al., 2016). The astrogliosis and neuropathology are recapitulated in neuron and astrocyte *Bmal1* knockout and *Clock*/neuronal PAS domain protein 2 (*NPAS2*) double-knockout mice, but not in *Per1*/*Per2* double-knockout mice (Musiek et al., 2013). Neuron and astrocyte *Bmal1* knockout mice also exhibit increased total activity in response to novel environment (Musiek et al., 2013). Additionally, global *Bmal1* knockout abolished the rhythmic expression of soluble Aβ peptide in hippocampal interstitial fluid and increases amyloid plaque

deposition in a mouse model of β-amyloidosis (*APPPS1-21*), which might be mediated by the increased expression of apolipoprotein E (A*poe*) (Kress et al., 2018). Specific-deletion of *Bmal1* from forebrain excitatory neurons impairs forebrain dependent spatial memory in mice (Snider et al., 2016). Moreover, in MPTP induced-PD mouse model, lacking *Bmal1* exacerbates dopaminergic neuronal loss and glial activation, decreases dopamine transmitter, and aggravates the deficit motor ability (Liu et al., 2020). A study shows that astrocyte-specific *Bmal1* deletion induces cell-autonomous astrocyte activation and inflammatory gene expression, which may be partially mediated by inhibition of glutathione signaling; primary cell co-culture experiment shows that Bmal1 deficient astrocytes promote wild-type neuronal death (Lananna et al., 2018). Deletion of *Bmal1* from astrocytes affects the vasoactive intestinal polypeptide (VIP) expression in SCN and the oscillation of neuronal clocks through GABA signaling; astrocyte-specific *Bmal1* knockout mice display altered circadian locomotor and impaired cognitive phenotypes (Barca-Mayo et al., 2017).

The blood-brain barrier (BBB) isolates the brain from the periphery and is critical for neural function and brain homeostasis. The dysfunction of BBB is implicated in the progression of neurodegeneration in both AD and PD (Kortekaas et al., 2005; Sagare et al., 2013; Parodi-Rullan et al., 2019). The function of BBB is also controlled by circadian clock. Endothelial-specific knockout Bmal1 abolishes the rhythmic efflux by BBB and reduces the efflux from the brain (Zhang et al., 2021). Additionally, *Bmal1* deletion from Nestin-positive cells decreases the pericyte coverage of blood vessels and increases the permeability of BBB (Nakazato et al., 2017). Notably, the brain also contains macrophages in perivascular, meningeal, and choroid plexus, which are distinct from microglia and regulate the function of brain barriers (Mendes-Jorge et al., 2009; Bergen et al., 2015). These macrophages may be also regulated by circadian clock and involved in neurodegeneration (Hawkes and McLaurin, 2009; Baruch et al., 2013; Maleki and Rivest, 2019; Ivan et al., 2020). These studies emphasize the importance of circadian clock in maintaining brain homeostasis. Coordinated response of brain cells promotes the progression of neurodegeneration in response to circadian disruption.

## EFFECT OF PERIPHERAL IMMUNITY ON NEURODEGENERATION

Systemic inflammation or infection has been regarded as a risk factor for neurodegeneration. Past infections may contribute to cognitive impairment and increase the odds of AD and PD development in later life (Dunn et al., 2005; Katan et al., 2013; Semmler et al., 2013; Widmann and Heneka, 2014; Meng et al., 2019). The low dose of peripheral LPS injection induces sickness behaviors and hippocampal inflammation in rats, which are more severe when the administration during the light (i.e. sleep) phase (Fonken et al., 2015). A single LPS injection induced-severe systemic inflammation leads to persistent microglial activation and inflammatory gene expression, as well as long-term cognitive deficits *via* remained elevated NOS2 expression (Weberpals et al., 2009). Besides, peripheral LPS challenge results in the persistent increase of TNFα expression in the brain through TNFα receptors, which leads to microglial proliferation and activation, as well as progressive dopamine neuronal loss (Qin et al., 2007). Importantly, numerous studies revealed that LPS administration is able to recapitulate the pathologies and symptoms of PD in animal models (Liu and Bing, 2011; Zhao et al., 2018). Accumulating evidence suggests that low-grade systemic inflammation caused by tissue stress and malfunction conditions, such as high-fat diet consumption, obesity, and diabetes, also leads to cognitive impairment in both adult humans and rodents (Dunn et al., 2005; Murray et al., 2009; Pistell et al., 2010; Edwards et al., 2011; Holloway et al., 2011; Heyward et al., 2012; Pedditzi et al., 2016). The communication between peripheral inflammatory mediators and the brain has been well studied in animal models. It's shown that the immunological mediators can activate the local afferent vagus pathway; they can also enter into circulation and directly activate macrophages in circumventricular organs where lack a functional BBB (Tracey, 2002; Perry et al., 2007). Additionally, inflammatory mediators interact with endothelial cells and perivascular macrophages, which may cause dysfunction of BBB and peripheral immune cell infiltration (Laflamme and Rivest, 1999; Bohatschek et al., 2001). The peripheral signals and infiltrated immune cells stimulate microglia and astrocyte activation, which subsequently contributes to neuroinflammation and neuronal damage (Puntener et al., 2012; Widmann and Heneka, 2014).

Moreover, systemic inflammation exacerbates the progression of the ongoing neurodegenerative diseases. A single peripheral LPS injection increases the production of IL-1β and transiently elevates the level of amyloid-β in the brain of Tg2576 and APP/PS1 mice (Sly et al., 2001; Tejera et al., 2019). Besides, LPS treatment triggers microglial activation and peripheral myeloid cell infiltration as well as impairs microglial clearance of amyloid-β in APP/PS1 mice (Tejera et al., 2019). Long-term LPS challenge significantly increases the production of IL-1β and deposition of amyloid precursor protein as well as exacerbates the tau phosphorylation in AD mouse models (Sheng et al., 2003; Kitazawa et al., 2005). Notably, neurodegeneration is a systemic disorder. Both human and animal studies reveal the increased levels of peripheral pro-inflammatory factors and immune cells in the circulation of AD and PD (Collins et al., 2012; Chen et al., 2015; Lai et al., 2017; Yang et al., 2017; King et al., 2018). The blood-borne molecules and peripheral immune cells infiltrate into the brain and exacerbate the progression of neurodegeneration (Zenaro et al., 2015; Kempuraj et al., 2017; St-Amour et al., 2019; Cipollini et al., 2019). In periphery, neutrophil migration from blood to tissue follows a diurnal rhythm, which can be abolished by neutrophil-specific Bmal1 deletion (Adrover et al., 2019). Neutrophil invasion has been seen in the brain of both human and mouse models of AD (5xFAD and 3xTg-AD), while depletion of neutrophils improves memory and reduces AD pathology (Zenaro et al., 2015). Infiltrating T lymphocytes have also been observed in post-mortem brains of patients with frontotemporal dementia and

PD (Brochard et al., 2009; Laurent et al., 2017). Depletion of the T cell prevents hippocampal T cell infiltration and reverts spatial memory deficits in a mouse model of AD (THY-Tau22) (Laurent et al., 2017). Th17 cells are also involved in the pathogenesis of AD; neutralization of IL17 cytokine produced by Th17 cells rescues cognitive deficits and ameliorates amyloid-β-induced neuroinflammation in mice (Zhang et al., 2013; Zenaro et al., 2015; Cristiano et al., 2019). Deficiency of mature T lymphocytes or lacking $CD4^+$ T cell attenuates dopaminergic neuronal death in the MPTP mouse model of PD (Brochard et al., 2009). Studies also indicated the Th17 cell infiltration in MPTP-treated mice, which exaggerates dopaminergic neuronal loss (Reynolds et al., 2010; Dutta et al., 2019). Moreover, monocytes have been seen in the brain of APP/PS1 mice, but these cells take up Aβ aggregates and transport them back to the bloodstream (Michaud et al., 2013). These infiltrated cell populations have been identified as key players in neurodegenerative diseases. The complex interplay between systemic inflammatory components and dysfunctional brain cells deteriorates the progression of neurodegeneration.

## THE CELLULAR METABOLISM - A MECHANISM UNDERLYING CIRCADIAN CONTROL OF IMMUNITY AND NEURODEGENERATION

Recent studies have shown that the metabolic pathway plays a central role in modulation of immunity and brain function (Fukuzumi et al., 1996; Kelly and O'Neill, 2015; Man et al., 2016; O'Neill and Kishton, 2016; O'Neill and Pearce, 2016; Geltink et al., 2018; Wang et al., 2019; Bernier et al., 2020). Immune activity is high energy demand and metabolic disorders are associated with immune dysfunction and neurodegeneration (Bird, 2019; Muddapu et al., 2020). Alteration of cellular metabolisms, such as glycolysis, oxidative phosphorylation, fatty acid, and amino acid metabolism, affects the immune cell response (O'Neill and Kishton, 2016). Enhanced glycolysis and fatty acid synthesis are correlated with peripheral immune cell activation, which leads to a more pro-inflammatory state (Doughty et al., 2006; Posokhova et al., 2008; Rodriguez-Prados et al., 2010; Michalek et al., 2011; Everts et al., 2014; Sharma et al., 2020); whereas, oxidative phosphorylation and fatty acid oxidation have been associated with a more anti-inflammatory phenotype (Michalek et al., 2011; Jha et al., 2015; Patsoukis et al., 2015). Besides, cellular metabolism plays a crucial role in regulating the function of brain cells, which is associated with brain homeostasis. Microglial inflammatory response depends on glycolysis for energy production (Orihuela et al., 2016). Inhibition of glucose transporter 1 reduces glucose uptake and glycolysis in microglia under LPS + IFNγ stimulation, which prevents the upregulation of pro-inflammatory cytokines (Wang et al., 2019). Specific knockdown of lipoprotein lipase (Lpl) in microglia reduces lipid uptake and shifts fuel utilization to glutamine, which attenuates microglial immune response under inflammatory stimuli (Gao et al., 2017). Suppression of glutamine synthetase decreases insulin-mediated glucose uptake and increases the expression of inflammatory mediators in activated microglia (Palmieri et al., 2017). In addition, astrocytes regulate the brain glucose metabolism and provide lactate that is converted from glycogen to supply the high energy requirement of neurons (Suzuki et al., 2011; Weber and Barros, 2015). Astrocytes also rapidly uptake glutamate and metabolize to glutamine to maintain brain homeostasis (Schousboe et al., 2014). Metabolic dysfunction of astrocytes contributes to neurodegeneration (Yan et al., 2013; Oksanen et al., 2019; Sonninen et al., 2020).

Numerous transgenic animal studies revealed that circadian clocks control metabolic processes in extensive tissues (Rudic et al., 2004; Hatanaka et al., 2010; Marcheva et al., 2010; Zhang et al., 2010; Sadacca et al., 2011; Marcheva et al., 2013; Dudek and Meng, 2014; Jha et al., 2015; Schiaffino et al., 2016; Dyar et al., 2018; Sussman et al., 2019). Rhythmic expression of metabolic-related genes optimizes the amount of energy consumption (Wang et al., 2015). It has known that the expression of genes related to microglial glucose and fatty acid uptake shows a time-of-day difference; the expression of glucose transporter member 5 (*Glut5*) and *Lpl* is increased during the dark phase when microglia are more active (Wang et al., 2020). Thus, oscillation in immunity may be driven by rhythmic changes in cellular metabolism. Circadian disruption impacts cellular metabolism and subsequently drives immune dysfunction and neurodegeneration (Carroll et al., 2019; Bernier et al., 2020; Wang et al., 2020). For example, deletion of *Bmal1* in macrophages increases pyruvate kinase M2 expression (PKM2) and lactate production, which is required for expression of the immune checkpoint protein-programmed cell death 1 ligand 1 (PD-L1); mice lacking Bmal1 in myeloid cells are more vulnerable to septic death response to severe infection (Deng et al., 2018). However, knockdown of Bmal1 in microglia decreases expression of *Glu5* and *Lpl*, as well as reduces *Il1b* (Wang et al., 2020). A study also showed that the protein expression of Clock and Bmal1 in astrocytes is elevated in the human cortex with AD; Overexpression of Clock and Bmal1 in human astrocytes significantly inhibits aerobic glycolysis and lactate production but promotes cytotoxicity and functional impairment (Yoo et al., 2020). Thus, maintenance of the homeostasis of the molecular clock network and cellular metabolism is crucial to proper immune function and prevents neurodegeneration.

## MOLECULE INTERVENTION OF CIRCADIAN CLOCK IN INFLAMMATION AND NEURODEGENERATION

It's reported that 82.2% of protein-coding genes identified as druggable targets by the U.S. Food and Drug Administration show rhythmic transcription in at least one human tissue (Mure et al., 2018). Therapeutic targeting circadian core clocks could be a potential strategy to prevent or alleviate inflammation and neurodegenerative diseases (Griffett and Burris, 2013; Ruan et al., 2021) (**Table 2**). Drug molecules that modulate REV-ERBα have been widely studied in different disease models (Uriz-Huarte et al., 2020; Wang et al., 2020). GSK4112-a agonist of

**TABLE 2 |** Molecule intervention of circadian clock under different stimulation.

| Target | Molecule intervention | Stimulation | Phenotype | Ref. |
|---|---|---|---|---|
| **REV-ERBα** | Agonist-GSK4112 | LPS | Decreased IL-6 in human MDMs, primary alveolar macrophages, and THP-1 cells; Reduced *Cxcl11*, *Cxcl6*, *Il19*, and *Il10* in human MDMs | (Gibbs et al., 2012) |
| **REV-ERB** | Agonist-GSK4112/ Hemin | LPS | Reduced Il6 in THP-1 | (Raghuram et al., 2007; Gibbs et al., 2012) |
| **REV-ERBα** | Antagonist-SR8278 | viral-induced encephalitis | Reduced survival rate in mice; Increased *CCL2* expression | (Gagnidze et al., 2016) |
| **REV-ERBα** | Antagonist-GSK1362 | LPS | Reduced *Il6*, *Ccl2*, and *G-csf* in alveolar macrophages and decreased *Il6* expression in BMDMs | (Pariollaud et al., 2018) |
| **RORα and RORγ** | Agonists-SR100, ursolic acid, SR2211, SR1555, or ML209 | / | Inhibited development of Th17 cells and reduced inflammatory gene expression | (Kojetin and Burris, 2014) |
| **REV-ERBα** | Agonist-GSK4112/ SR9011 | LPS | Inhibited microglial activation and reduced iNOS and COX-2 secretion and *Il6* and *Tnfα* expression | (Nakazato et al., 2017; Guo et al., 2019) |
| **REV-ERBα** | Agonist-SR9011 | / | Reduced phagocytosis, mitochondrial respiration, energy production, and metabolic-related gene expression in primary microglia | (Wolff et al., 2020) |
| **REV-ERBα** | Agonist-SR9011 | TNFα | Decreased *Tnfα*, *Il6*, *Ccl2*, and *Il1β*, and increased Il10 in primary microglia | (Wolff et al., 2020) |
| **REV-ERBα** | Agonist-SR9009 | LPS+ATP | Suppressed IL-1β and Il6 expression in primary microglia | (Griffin et al., 2019a) |
| **REV-ERBα** | Agonist-SR9009 | LPS | Reduced *Il6*, *Tnfa*, and *Il1b* in primary astrocyte | (Griffin et al., 2019a) |
| **REV-ERBα** | Agonist-SR9009 | LPS | Reduced *Il6* and *Ccl2* in hippocampus | (Griffin et al., 2019a) |
| **REV-ERBα** | Agonist-SR9011, SR9009, and SR10067 | / | Increased wakefulness and reduced sleep and anxiety-like behavior in mice | (Banerjee et al., 2014) |
| **REV-ERBα** | Antagonist-SR8278 | / | Induced Mania-like behavior | (Chung et al., 2014) |
| **REV-ERBα** | Antagonist-SR8278 | fAβ1-42 | Enhanced microglial phagocytosis and increased fAβ1-42 uptake by BV-2 cells | (Lee et al., 2020) |

REV-ERBα, suppresses IL-6 protein secretion in human MDMs, primary alveolar macrophages, and THP-1 cells in response to LPS; GSK4112 also represses the gene expression of chemokine (*Cxcl11* and *Cxcl6*), and cytokine (*Il19* and *Il10*) in human primary MDMs (Gibbs et al., 2012). Both Hemin-the endogenous activator of REV-ERB and GSK4112 reduce the transcript of *Il6* in THP-1 cells after LPS administration (Raghuram et al., 2007; Gibbs et al., 2012). In contrast, during viral-induced encephalitis, pretreatment of REV-ERBα antagonist-SR8278 significantly reduces the survival rate in mice when infection at the start of the active phase, *via* an increased transcript of pro-inflammatory chemokine-CCL2 (Gagnidze et al., 2016). Surprisingly, REV-ERBα antagonist-GSK1362 also represses the transcript of LPS-induced inflammatory genes-*Il6*, *Ccl2*, and *G-csf* in alveolar macrophages and inhibits the *Il6* gene expression in BMDMs, which may be mediated by stabilizing REV-ERBα protein (Pariollaud et al., 2018). Moreover, inverse agonists of RORα and RORγ, including SR100, ursolic acid, SR2211, SR1555, and ML209, inhibit the development of Th17 cells and reduce associated inflammatory gene expression (Kojetin and Burris, 2014).

Besides, REV-ERBα agonists-GSK4112 and SR9011 suppress microglial activation, reduce iNOS and COX-2 secretion, and transcription of *Il6* and *Tnfα*, which may be mediated by repression of nuclear factor kappa B (NF-κB) pathway in LPS-treated microglial cells (Nakazato et al., 2017; Guo et al., 2019). Moreover, SR9011 reduces phagocytosis, mitochondrial respiration, energy production, and metabolic-related gene expression in primary microglial cells; while under TNFα stimulation, SR9011 decreases the transcripts of *Tnfα*, *Il6*, *Ccl2*, and *Il1β*, and increases the expression of *Il10* in primary microglia (Wolff et al., 2020). Activation of Rev-erbα with agonist-SR9009 suppresses IL-1β secretion and *Il6* mRNA expression in primary microglial cells under LPS combined with ATP stimulation, and also significantly reduces the gene expression of *Il6*, *Tnfa*, and *Il1b* in LPS-induced primary astrocytes (Griffin et al., 2019a). SR9009 diminishes LPS-induced transcripts of *Il6* and *Ccl2* in mice hippocampus (Griffin et al., 2019a). REV-ERB agonists (SR9011, SR9009, and SR10067) increase wakefulness and reduce sleep and anxiety-like behavior in mice; notably, the anxiolytic activity of SR10067 is significantly superior than SR9011 (Banerjee et al., 2014; Chung et al., 2014). Whereas, microinfusion of REV-ERBα antagonist-SR8278 into the ventral midbrain induces Mania-like behavior related to the central hyperdopaminergic state (Chung et al., 2014). Additionally, SR8278 promotes microglial phagocytic capacity and increases fAβ1-42 uptake by BV-2 cells (Lee et al., 2020).

## CONCLUSION

There is clear evidence for the involvement of circadian clock machinery in immune homeostasis and the function of brain cells. Circadian clocks regulate the rhythmic activity of immune cells and govern immune response throughout the body. The function of neuron, astrocyte, and endothelia cells is also

regulated by circadian clocks. Circadian disruption leads to immune dysfunction and neurodegeneration. Systemic inflammation is a risk factor and also an accelerator of neurodegenerative diseases, such as AD and PD. Cellular metabolism pathways could be involved in the circadian control of immunity and brain function. Thus, modulation of circadian clocks and cellular metabolism could be a promising therapeutic avenue for inflammatory and neurodegenerative diseases. According to the rhythmic expression of numerous druggable target genes, the time of day for treatment should also be considered to optimize the efficiency. Changing the environment and lifestyle, such as light exposure, exercise, and food intake pattern can entrain the circadian system, which may have a therapeutic effect on inflammation and neurodegeneration (Riemersma-van Der Lek et al., 2008; Figueiro, 2017; Videnovic et al., 2017; Ruan et al., 2021). Moreover, microbial infection, inflammation, and neurodegeneration, in turn, disrupt the clock machinery and subsequently exacerbate the progression of neurodegeneration. Neurodegenerative diseases have a long induction period and no effective therapy. A greater mechanistic understanding of the complex circadian system and the interplay between clock network, inflammation, and neurodegeneration could be critical to identify and manage neurodegenerative diseases in their earliest form. How to pharmacologically target the circadian clock in a cell-type-specific manner from a systemic level needs to be further investigated.

## AUTHOR CONTRIBUTIONS

X-LW and LL conceived the work and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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