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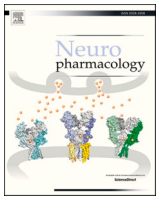

Microglia, circadian rhythm and lifestyle factors

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ABSTRACT

Microglia, a vital homeostasis-keeper of the central nervous system, perform critical functions such as synaptic pruning, clearance of cellular debris, and participation in neuroinflammatory processes. Recent research has shown that microglia exhibit strong circadian rhythms that not only actively regulate their own immune activity, but also affect neuronal function. Disruptions of the circadian clock have been linked to a higher risk of developing a variety of diseases. In this article we will provide an overview of how lifestyle factors impact microglial function, with a focus on disruptions caused by irregular sleep-wake patterns, reduced physical activity, and eating at the wrong time-of-day. We will also discuss the potential connection between these lifestyle factors, disrupted circadian rhythms, and the role of microglia in keeping brain health.

1. Introduction

Microglia are the resident immune cells in the central nervous system (CNS) and play a pivotal role in orchestrating the complex symphony of CNS activity, but also hold a critical position in the regulation of essential mechanisms governing neuronal information transmission and processing (Kettenmann et al., 2013; Salter and Stevens, 2017). These include their involvement in modulating neuro-circuitry plasticity, synapse formation, and axonal conductivity (Kettenmann et al., 2013). Beyond these functions, microglia play a crucial role in preserving neuronal homeostasis by rapidly detecting and responding to immune challenges, thereby serving as an important component of the defence system of the CNS (Borst et al., 2021). Unlike other immune cells in the CNS, such as astrocytes or oligodendrocytes, microglia are the primary responders to immune challenges and play a pivotal role in maintaining CNS homeostasis (Casali and Reed-Geaghan, 2021). Previous studies have shown that microglial ablation in animal disrupts the circadian rhythm (Sominsky et al., 2021) and microglial inflammatory responses are controlled by an intrinsic circadian clock (Fonken et al., 2015). Nevertheless, the potential contribution of microglial cells in the generation and maintenance of circadian rhythms has only been recently highlighted.

Circadian rhythms are rhythms with a period of approximately 24 h, i.e. a circadian period of about (=circa) one day (=dies) (Vitaterna et al., 2001). The endogenously generated circadian rhythms are aligned with the exact 24 h rhythm of the outside world by relying on external timing cues, of which light and food are the two most important Zeitgebers (=time givers), with light being the more powerful Zeitgeber than food (Roenneberg et al., 2013). The circadian timing system enables organisms to adapt their behaviour and physiology to the Earth's alternating light-dark cycle (Bollinger and Schibler, 2014). Circadian misalignment or circadian desynchrony is a state in which not all external and internal daily rhythms are completely aligned anymore. Circadian misalignment is particularly evident in shift workers, i.e. when the behavioural sleep/wake rhythm is not aligned with the environmental light-dark cycle, and is thought to be partly responsible for their significant health problems, including obesity, diabetes, cardiovascular disease, and cancers (Fischer et al., 2016; Knutsson and Kempe, 2014). Dysregulation of microglial circadian rhythms can have detrimental consequences on their immune response (Fonken et al., 2016; Liu et al., 2021). However, the impact of lifestyle factors on microglial rhythm and its significance in microglia-mediated CNS dysfunction remains unclear.

In this review, we will describe the complex relationship between microglial circadian rhythms and lifestyle factors, explore the possible cues that regulate them and discuss the physiological implications of this circadian control.

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Abbreviations

ALAN	artificial light at night
AUD	alcohol use disorder
Aβ	amyloid β
BBB	blood-brain barrier
Bmal1	brain and muscle ARNT-Like 1
BMDM	bone marrow-derived macrophage
C1Q	complement component 1q
CCGs	clock-controlled genes
CD68	cluster of Differentiation 68
CLOCK	circadian locomotor output cycles kaput
CNDP2	cytosolic nonspecific dipeptidase 2 positive
CNS	central nervous system
CRY1	cryptochrome 1
CRY2	cryptochrome 2
CSF1R	colony-stimulating factor-1 receptor
DBP	D-box binding protein
DEC1	basic helix-loop-helix proteins differentiated embryo chondrocyte 1
DEC2	basic helix-loop-helix proteins differentiated embryo chondrocyte 2
HFD	high-fat diet
HPA axis	hypothalamic-pituitary-adrenal axis
IBA1	Ionized calcium-binding adapter molecule1
IL-1β	interleukin-1 beta
IL-6	interleukin 6
IL10	interleukin 10
Lac-phe	N-acylphenylalanine
LPS	lipopolysaccharide
MHC	major histocompatibility complex
NFIL3	nuclear factor interleukin-3
NPAS2	neuronal PAS domain protein 2
NREM	non-rapid eye movement
PBMCs	peripheral blood mononuclear cells
PER1	period circadian regulator 1
PER2	period circadian regulator 2
PER3	period circadian regulator 3
PSEN2	presenilin 2
REM	rapid eye movement
REV-ERBα/NR1D1	nuclear receptor subfamily 1 group D member 1
REV-ERBβ/NR1D2	nuclear receptor subfamily 1 group D member 2
RORα	retinoic acid-related orphan receptor 1
RORβ	retinoic acid-related orphan receptor 2
RORγ	retinoic acid-related orphan receptor 3
SCN	suprachiasmatic nucleus
SWS	slow-wave sleep
TLR2	toll-like receptor 2
TNF-α	tumor necrosis factor-α
TRE	time-restricted eating
TRF	time-restricted feeding
TTFL	transcription-translation feedback loop
ZT	Zeitgeber time

2. Circadian rhythms

The mammalian circadian timing system consists of two parts: 1) A master clock located in the hypothalamic suprachiasmatic nucleus (SCN) and 2) Peripheral clocks distributed across various other tissues in our body, including different brain regions outside of SCN, and most peripheral tissues and organs (Stenvers et al., 2019). Briefly, the SCN receives direct light input from the retina, allowing it to keep its endogenously generated circadian rhythms relatively consistent with the precise 24-h environmental light-dark cycle. Synchronized timing signals from the SCN are then conveyed to the peripheral clocks through neural, hormonal, and temperature-related mechanisms (Buijs et al., 2019). Peripheral tissues then integrate these timing signals from the SCN with their own intrinsic rhythm and behavioural cues (e.g., sleep, physical activity, feeding), thereby rhythmically governing whole-body homeostasis (McGinnis and Young, 2016; Poggiogalle et al., 2018).

2.1. Circadian rhythms glossary

The circadian system organizes metabolism, physiology, and endocrinology to be aligned with the daily sleep/wake cycle. Mammalian species exhibit unique temporal activity patterns, classified as diurnal or nocturnal based on their preferred time of activity. Intrinsic circadian clock rhythms are periodic patterns that repeat themselves approximately every 24 h. Unlike diurnal rhythms, circadian rhythms are generated endogenously within an organism and perpetuate themselves even in the absence of external time cues (Poggiogalle et al., 2018). Mathematical techniques can be used to extract circadian rhythm components. When considering a hypothetical example (e.g., mRNA levels of a circadian clock component, whose 24-h fluctuation fits a simple cosine curve) (Fig. 1A), circadian dysregulation can manifest at the level of altered mesor (i.e., middle line or mean of a rhythm), trough or nadir (i.e., the lowest value of a rhythm), peak or acrophase (i.e., highest value of a rhythm), amplitude (i.e., mesor-to-peak or trough difference), and phase (i.e., timing of the trough/peak) or a complete disappearance of a particular rhythm (Poggiogalle et al., 2018; Rana et al., 2020).

2.2. The molecular clock

The first clock gene, *Period (Per)*, was discovered through studies of Drosophila mutants with abnormal behavioral cycles (Konopka and Benzer, 1971; Smith and Konopka, 1981; Zehring et al., 1984). It was subsequently discovered that in mammals the core of the molecular clock is a transcriptional-translational negative feedback loop (TTFL) that regulates circadian oscillations (Fig. 1B), the entire cycle of TTFL occurs around 24 h. Within this TTFL mechanism, the dominant feedback loop is the collaboration of transcriptional activators brain and muscle Arnt-like protein-1 (BMAL1) and circadian locomotor output cycles kaput CLOCK (or neuronal PAS domain protein 2, NPAS2) with repressor complexes period (PER1, PER2 and PER3) and cryptochrome (CRY1 and CRY2). The rhythmic signal produced by this molecular clock has a period of approximately 24 h, which is a circadian period.

Briefly, the BMAL1/CLOCK complex triggers the expression of *Per* and *Cry* genes, whereas the PER/CRY complex cyclically suppresses BMAL1/CLOCK, thereby regulating its own transcription (Dudek and Meng, 2014). Since the initial discovery of these four core mammalian clock genes, a number of additional genes and feedback loops have been discovered, adding to the complexity of the mammalian circadian clock gene network. In a secondary transcriptional loop, CLOCK/BMAL1 activates nuclear receptor subfamily 1 group D member 1 and 2 (REV-ERBα/NR1D1 and REV-ERBβ/NR1D2) (Preitner et al., 2002). Introducing a competitive interplay with retinoic acid-related orphan receptors RORα, RORβ, and RORγ for binding sites (ROR-binding elements) on the BMAL1. This interplay results in both positive (ROR) and negative (REV-ERB) transcriptional regulation (Sato et al., 2004). A third feedback loop revolves around the D-box binding protein (DBP) and the nuclear factor interleukin-3 regulated protein (NFIL3 or E4BP4), which are regulated by CLOCK/BMAL1 (Ripperger and Schibler, 2006) and CRY1 (Stratmann et al., 2010). These proteins bind to D-box

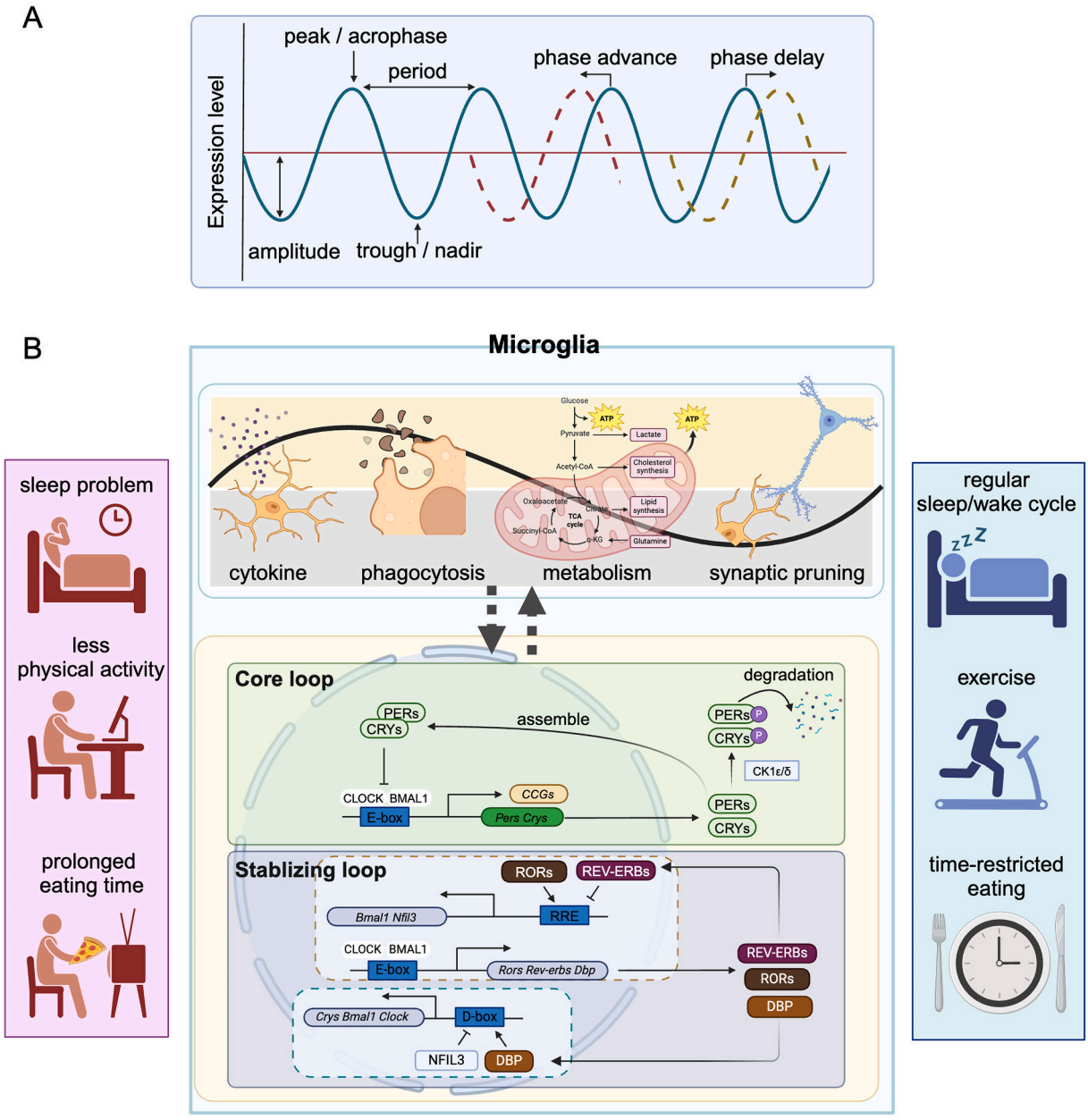

Fig. 1. Lifestyle factors interfere with microglial circadian system regulation. A: Circadian rhythm curves and terminology, including nadir or trough, peak or acrophase, period, amplitude, and phase shift. B: The core loop of circadian clock function involves the heterodimerization of BMAL1 and CLOCK, which bind to E-box elements to activate the transcription of clock-controlled genes (CCGs), including other parts of the core clock that form the negative arm of the feedback loop. The accumulation of these genes leads to their heterodimerization and inhibition of their own transcription. CRY and PER are later targeted for proteasomal degradation. The stabilizing loop involves the activation of REV-ERBs by CLOCK/BMAL1, which compete with ROR elements for binding sites, resulting in both positive and negative transcriptional regulation. Additionally, the D-Box and NFIL3 Loop is regulated by CLOCK/BMAL1 and CRY1, involving DBP and NFIL3 binding to D-box elements in circadian promoters. A disruption in circadian rhythm in microglia can result from sleep problems, reduced physical activity, prolonged eating time (i.e. lacking a clear fasting period). Whereas a consistent sleep/wake cycle, regular exercise, and a well-regulated diet, such as time-restricted eating, can help restore proper functioning. Created with BioRender.com.

elements in circadian promoters, including RORα and RORβ (Ueda et al., 2005). Together, these feedback loops form an intricate 'molecular clock' system, meticulously regulated through transcriptional, post-transcriptional (Kojima and Green, 2015), and post-translational (Gallego and Virshup, 2007) mechanisms, including phosphorylation, ubiquitination, acetylation and *O*-GlcNAcylation, and their robustness ensuring stable circadian rhythms (Okamoto-Uchida et al., 2019; Stojkovic et al., 2014). Nevertheless, as mentioned above, synchronization of these cellular rhythms within various tissues still relies on endogenous cues from the central brain clock in the SCN and external environmental cues (e.g., light, sleep, physical activity, feeding) (Cox and Takahashi, 2019; Golombek and Rosenstein, 2010; Poggiogalle et al., 2018), and a mismatch between any of these cues may cause circadian misalignment.

Among all clock genes, BMAL1 is the most studied clock gene in circadian rhythm research for two main reasons. Firstly, it is one of the two co-core components of the central transcription factor complex. Secondly, BMAL1 is the only single-gene knock-out that abrogates all circadian clock functions, since it lacks a compensatory mechanism (Lananna et al., 2018). For instance, NPAS2 serves as a secondary

protein in the molecular clock, effectively replacing CLOCK and preserving circadian rhythms even when *Clock* is deleted (Dardente, 2008; Landgraf et al., 2016; Mazzoccoli et al., 2012), whereas the PER and CRY each have several paralogs (van der Horst et al., 1999; von Schantz et al., 2006). REV-ERBα, another clock gene, has also attracted increasing attention. This is because REV-ERBα is involved in the control of multiple processes including metabolism, immune cell function, and inflammation (Griffin et al., 2019). Moreover, REV-ERBα is a nuclear receptor, so it is an attractive therapeutic target that can be modulated with existing small-molecule agonists and antagonists (Kojetin et al., 2011; Solt et al., 2012), making it a common choice for many cell culture and *in vivo* intervention studies.

3. Microglia

Microglia, which are responsible for monitoring and clearing neurological debris, originate from primitive myeloid progenitors during early fetal development and disperse throughout the CNS parenchyma (Ginhoux et al., 2010). After the establishment of the blood-brain barrier (BBB), microglia typically remain isolated from the periphery under physiological conditions (Mildner et al., 2007). These cells can self-renew and in homeostatic conditions have a low turnover rate throughout an individual's lifespan (Fuger et al., 2017). Additionally, the morphology of microglia, including the size and complexity of their processes, can change and is closely linked to their function (Ayata et al., 2018; Ayoub and Salm, 2003; Fernandez-Arjona et al., 2017; Streit et al., 1999). The relationship between circadian clock genes and immune function also shows a bidirectional relationship. In addition to driving circadian rhythms, clock genes are also involved in regulating microglial immune activity (Wang et al., 2021; Wang et al., 2020a; Wolff et al., 2020). Microglia, as the primary responders to immune challenges in the CNS, play a key role in maintaining CNS homeostasis. Given their central role in the CNS and their close connection with circadian clock genes and immune function, microglia represent a key link in understanding the interplay between circadian rhythms and brain homeostasis.

3.1. Circadian control of the microglial immune response

Microglia exhibit heightened expression of pro-inflammatory cytokines, particularly during the light phase (i.e. the resting phase of rodents) when they encounter immune challenges (Fonken et al., 2015; Fonken et al., 2016; Takayama et al., 2016). The major pro-inflammatory cytokines secreted by microglia include tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and interleukin-1 beta (IL-1β). TNFα receptors are widely expressed, and their activation plays an important role in promoting neuronal death and apoptosis. IL-1β activates numerous enzyme cascades that induce sphingomyelin hydrolysis, leading to activation of apoptotic pathways. Finally, IL-6 secretion activates the other innate immune cells, for instance astrocytes, mediates cell survival and promotes cell division (Rodgers et al., 2020; Smith et al., 2012).

3.1.1. Clock genes control microglial cytokine release

In recent years, with the advent of novel technologies and methodologies in imaging, genetics, and single-cell omics, researchers have gained deeper insights into the intricate relationship between the biological clock machinery and microglial function (Prinz et al., 2019). The first study demonstrating the presence of clock genes in microglia was published over a decade ago (Nakazato et al., 2011), they found that microglia isolated from neonatal mouse brains as well as a microglial cell line expressed canonical clock genes like *Per1-3*, *Cry1-2*, *Bmal1*, *Clock*, *Dec1-2* (basic helix-loop-helix proteins differentiated embryo chondrocyte 1 and 2) and *Npas2*. A study in microglia isolated from Bmal1-null mice showed increased expression of antioxidant and anti-inflammatory factors in microglia. In addition, after Bmal1 knockdown BV-2 cells were less responsive to lipopolysaccharide (LPS), highlighting the critical role of various components of the molecular clock in controlling microglial immune activity (Wang et al., 2020a).

Several inflammatory signaling molecules closely related to microglial activity exhibit circadian expression patterns. For instance, TNF-α shows higher expression at night in the mediobasal hypothalamus of mice, whereas expression levels of IL-1β and IL-6 do not display daily patterns (Yi et al., 2017). Manipulating clock genes in microglia has confirmed the circadian regulation of cytokine expression. Studies have shown that cultured microglia lacking the *Bmal1* gene exhibit decreased inflammatory cytokine expression compared to wild-type mice (Wang et al., 2020a). Similarly, reducing *Bmal1* expression via siRNA transfection in microglial cell cultures leads to decreased production of IL-6 and other inflammatory cytokines during immune activation (Nakazato et al., 2017). Conversely, the expression of the anti-inflammatory cytokine IL-10 increases under these conditions (Wang et al., 2020b). Additionally, activation of REV-ERBα, which lowers the expression of clock genes such as *Bmal1*, *Clock*, *Per2*, and *Cry1*, reduces cytokine expression in microglia upon immune activation, whereas IL-10 increases (Wolff et al., 2020). These findings were corroborated *in vivo*, where REV-ERBα agonists suppressed the proinflammatory response of microglia in the brain (Guo et al., 2019). Moreover, knockout of *Nr1d1* increases the levels of proinflammatory cytokines in hippocampal microglia *in vivo* (Griffin et al., 2019, 2020). Overall, enhancing *Rev-erbα* signaling or *Bmal1* deficiency reduces the secretion of inflammatory cytokines in microglia, promoting a shift towards a neuroprotective phenotype.

3.1.2. Clock genes control microglial phagocytosis

In addition to cytokine release, the phagocytic activity of microglia also shows circadian alternations, with maximum activity in the mouse hippocampus occurring during the dark phase (Griffin et al., 2020). This rhythmic phagocytic activity aligns with the circadian rhythm observed in learning and memory performance, suggesting a key role of microglial phagocytic activity in cognitive processes (Chaudhury and Colwell, 2002; Wang et al., 2021). Furthermore, microglial knockdown of *Bmal1* upregulates CD68, a lysosomal protein expressed. Microglia-specific knockdown of *Bmal1* increases microglial synaptic engulfment in the mouse hippocampus during a spatial memory task (Wang et al., 2021). *In vitro*, knockdown of *Bmal1* via siRNA transfection increases phagocytosis in microglial cell cultures from the mouse brain, indicating a cell-autonomous regulation mechanism (Wang et al., 2020a; Wang et al., 2020b). On the other hand, the REV-ERBα agonist, SR9011, while also reducing *Bmal1* expression, diminished phagocytic activity in a primary microglia culture from rat brain (Wolff et al., 2020). *In vivo* studies in mice similarly revealed that KO of the gene encoding *Rev-erbα/Nr1d1*, increases microglial phagocytosis in the cortex and thalamus (Lee et al., 2020), as well as in the hippocampus (Griffin et al., 2020). An in-depth analysis of the hippocampus revealed that *Nr1d1* KO in mice abolished the diurnal variation of microglial phagocytosis, leading to an overall increase in microglial phagocytosis (Griffin et al., 2019, 2020). In summary, these findings highlight the important role of the circadian clock in regulating microglial inflammatory responses.

3.2. Circadian control of microglia-neuron interactions

Microglia continuously survey surrounding synapses by extending and retracting their highly branched processes, contributing significantly to the shaping and maintenance of an optimal synaptic network (Colonna and Butovsky, 2017; Gao et al., 2018; Ji et al., 2013; Paolicelli et al., 2011; Wake et al., 2009; Wu et al., 2015). The pruning of inappropriate or weak synapses is essential for establishing appropriate brain connectivity and reinforcing more efficient neural networks (Caroni et al., 2014; Jiang and Nardelli, 2016). This process is closely related to the dynamic process of neural circuits, which includes the formation of new synapses, synaptic strengthening, and selective synaptic elimination (Caroni et al., 2014; Hua and Smith, 2004).

Studies found that during the dark phase, when mice are awake and active, microglial processes become longer, and the interactions between microglia and synapses are more prominent both *in vitro* (Hayashi et al., 2013) and *in vivo* (Takayama et al., 2016; Yi et al., 2017). During the dark phase also a significant decrease in the mean spine density has been found in the cerebral cortex of adult mice compared to the inactive sleep phase (Hayashi et al., 2013; Maret et al., 2011; Yang and Gan, 2012). It is believed that the reduction in spine density helps enhance the signal-to-noise ratio, thereby promoting memory consolidation and enabling new learning during subsequent periods of wakefulness (Sun et al., 2020). During the dynamic process of synapse refinement, functional synapses are preserved while non-functional synapses are eliminated (Diekelmann and Born, 2010; Tononi and Cirelli, 2006).

The average spine density in the cerebral cortex of adult mice is significantly lower during sleep than during wakefulness (Hayashi et al., 2013). There are at least two possibilities for the reduction in spine density. One is that cortical microglial phagocytose dendritic spines during wakefulness (Choudhury et al., 2020). The other possibility is that proteases secreted from cortical microglia may contribute to a reduction in spine density (Hayashi et al., 2013). The latter study showed that microglia-specific lysosomal cysteine protease, cathepsin S, exhibits a daily variation in expression, reaching a peak when the mice wake up. Additionally, disrupting cathepsin S prevented the decrease in synaptic activity and spine density observed during sleep. Given that cathepsin S functions as an extracellular matrix protease and that the extracellular matrix governs synaptic maturation and structural adaptability (Reichelt et al., 2019), it is probable that microglia eliminate synapses during sleep through a mechanism distinct from phagocytosis. These findings suggest that cathepsin S released by microglia plays a role in the regulation of synaptic function and structural adaptation.

3.3. Circadian control of microglial metabolism

In microglia, immune function and intracellular metabolism interact mutually, this so-called immunometabolism is essential for regulating inflammatory responses, maintaining neuronal homeostasis, and supporting brain function (Hotamisligil, 2017; Mathis and Shoelson, 2011; Wang et al., 2020a). Although the role of microglia in the immune response has been extensively examined (Hotamisligil, 2017; Lee et al., 2018; Mathis and Shoelson, 2011), the relationship between the circadian control and microglial metabolism is still unclear. One study showed that the function of microglia depends largely on their metabolic adaptations, such as rapid changes in energy utilization to facilitate transitions between resting and activated states (Norata et al., 2015). Alterations in microglial metabolism, including glycolysis, oxidative phosphorylation, lipid and amino acid metabolism, have implications for immune responses (Bernier et al., 2020). It was found that high-fat diet (HFD) induced obesity disrupted the rhythmic expression of core clock genes in isolated microglia compared with a regular diet, and microglia substrate utilization differs between lean versus HFD-induced obese animals, especially during the morning transition phase from dark to light (Milanova et al., 2019). Furthermore, mouse microglial Bmal1 KO significantly reduced the expression of metabolism-related genes in microglia (Wang et al., 2020a). Recent studies have also highlighted the importance of Rev-erb nuclear receptors in the molecular clock and cellular metabolism. Specifically, a study of primary cultured microglia using the REV-ERBα agonist SR9011 found that this compound reduced ATP production and cellular respiration in primary microglia (Wolff et al., 2020). Another study found that, in both *in vivo* and *in vitro* conditions, deletion of *Rev-erbα* in microglia triggered amplified inflammatory signaling, disrupted lipid metabolism, and resulted in accumulation of lipid droplets in cells, predominantly in microglia from male but not female mice (Lee et al., 2023). This brings us to a less explored area: the relationship between sex differences, circadian rhythms, and microglial function.

3.4. Circadian rhythm, microglia, and sex differences

Recent transcriptomic investigations have revealed notable disparities in microglial gene expression and functions (Guneykaya et al., 2018; Villa et al., 2018). Specifically, microglia from males exhibited heightened activation levels compared to their female counterparts under baseline conditions and mounted more potent pro-inflammatory responses in response to stressors and pathogenic challenges (Guneykaya et al., 2018; Villa et al., 2018). Additionally, a number of studies have revealed differences in circadian rhythm disruption in neural injury models. For instance, in a focal cortical ischemic model, female mice exhibited significantly smaller infarct core sizes than male *Bmal1* KO mice compared to their WT counterparts (Lembach et al., 2018). This finding suggests that immune responses to ischemic injury not only depend on circadian rhythms but also operate in a sex-specific manner. Additionally, ischemic damage in male mice can be mitigated by transplanting female microglia (Villa et al., 2018).

In a study on spinal cord injury in mice, male and female mice displayed different patterns of expression for inflammatory cytokines. IL-1β expression was rhythmic in female mice, whereas TNF-α and IL-6 expression showed rhythmicity only in male mice (Gaudet et al., 2018). Furthermore, microglial depletion demonstrated sex-specific effects on neuro-inflammation, anxiety-like behaviour, and cognitive deficits in global *Rev-erbα* KO mice (Chen et al., 2023). Specifically, microglial depletion using a CSF1R inhibitor (PLX5622) in 8-month-old mice with a global deletion of the circadian clock gene *Rev-erbα* ameliorated hyperactivity, memory impairments, and anxiety/risk-like behaviours. Interestingly, these improvements were fully observed following microglial depletion in the hippocampus of the male *Rev-erbα* KO mice, but not after *Rev-erbα* KO in the female hippocampus. Besides, male *Rev-erbα* KO mice exhibited more pronounced alterations in microglial morphology and phagocytic activity than their female counterparts (Chen et al., 2023). These findings highlight the need for further studies of sex-based immune responses.

4. Lifestyle alternations in modern society

Chronobiology has gained more attention in our society because of the negative impacts of our modern way of living on natural biological rhythms. Research indicates that 24/7 work schedules, shift work, and social jet lag can disrupt circadian rhythms, leading to decreased immune function and increased risk of metabolic disease (Li et al., 2019; Liu et al., 2018). Chronobiological interventions involving lifestyle factors such as regular sleep/wake times, time-restricted eating, and timed exercise have proven to be effective in reversing these negative impacts (Madore et al., 2020) (Fig. 1B). However, little is known about the potential effects of these lifestyle interventions on microglial functions. In the following sections, we will discuss the evidence regarding the effects of sleep quality, diets, and physical activity on microglial biology. Additionally, we explore how lifestyle choices impact microglial immune activity and brain health.

4.1. Artificial light at night

Shift work represents frequent circadian challenges associated with a modern lifestyle that lead to desynchronization of the SCN and downstream oscillators with the external environment (Vosko et al., 2010). Shift work refers to any work schedule other than regular daytime working hours (typical 9 to 5 job) that is available on multiple shifts for 24 h a week (Beers, 2000). Working in rotating shifts, especially when night shifts are included, increases the risk of chronic diseases such as obesity, type 2 diabetes and other metabolic disorders (Gan et al., 2015; Hulsegge et al., 2021; Proper et al., 2016) and cardiovascular diseases (Vyas et al., 2012). The prevalence of night shift has led to increased artificial light at night (ALAN) at the individual level (Svechkina et al., 2020). Home living rooms typically have light intensities of 100–300

lux, while work environments range from 400 to 600 lux, which is much higher compared to the 0.3 lux in a full moon night sky (Falchi et al., 2016, 2019; Zhong et al., 2023). Besides night shifts, smartphones, tablets, computers, TVs, and other electronic devices also contribute to ALAN exposure (Bhat et al., 2018; Leigh et al., 2022; Oh et al., 2015). ALAN alters the production PER1 and PER2 in dark phase in the SCN (Bedrosian et al., 2013; Fonken et al., 2013a; Shuboni and Yan, 2010), *Clock* and *Cry1* in the hippocampus (Cailotto et al., 2009), and *Per1/2/3* in the pineal gland (Cailotto et al., 2009) of rodents. ALAN also perturbs clock gene loops outside of CNS, including those in the liver, heart, adrenal glands (Cailotto et al., 2009), and fat tissue (Fonken et al., 2013a,b). These effects are also observed in other species, including mosquitos (Honnen et al., 2019) and zebra finches (Batra et al., 2019).

ALAN exposure altered the innate immune response in the CNS. Male Swiss Webster mice housed in 5 lux ALAN for 4 weeks showed elevated microglial pro-inflammatory cytokine expression (TNF and IL-6) following LPS administration (Fonken et al., 2013a–c). Similar effects were observed in female C57BL/6 mice with exposure to ALAN during development and subsequent challenge with LPS in adulthood (Chen et al., 2021). Additionally, male Swiss Webster mice exposed to 5 lux ALAN for seven days post-cardiac arrest exhibited increased CNS pro-inflammatory cytokine expression, elevated Iba1 immunoreactivity (a marker of microglial activation), and reduced survival (Fonken et al., 2019). Furthermore, one night of ALAN exposure can worsen stroke injury and increase mortality in mice. ALAN causes microglia to become pro-inflammatory, impairing stroke recovery. However, depleting microglia mitigates these adverse effects (Liu et al., 2024). Taken together, accumulating evidence demonstrates the complexity of circadian immune crosstalk, highlighting the distinct immunomodulatory roles of different clock components.

4.2. Chronic stress

The major circadian pacemaker in the hypothalamic SCN is at the center of many neuroendocrine systems, one of which is the hypothalamic-pituitary-adrenal (HPA) axis (Van Drunen and Eckel-Mahan, 2021). Persistent stimulation of the HPA axis by external stressors may lead to compromised mental health in shift workers (Kinlein and Karatsoreos, 2020). Stimulation of the (asynchronous) HPA axis activates the fear system and impairs the reward system, leading to abnormal responses to stress (Herman and Cullinan, 1997). Therefore, shift workers who are exposed to stressors at night may have difficulty managing physiological and psychological responses to these stressors. The HPA axis hormone cortisol is central to the body's response to stressors [93] and has been used in many studies as an index of response to stressors. Cortisol levels typically exhibit a distinct circadian rhythm, peaking in the morning (LEGLER et al., 1982). Night shift work has been found to alter the timing of cortisol rhythms (Harris et al., 2010), and rotating shift work has been reported to dampen the rhythms' amplitude (Touitou et al., 1990). It is widely believed that shift work can lead to heightened stress responses and, for those who are particularly susceptible, can lead to insomnia and shift work disorder (Kalmbach et al., 2015).

In humans, under constant routine conditions, exogenous glucocorticoids administered 10 h after awakening can alter peripheral blood mononuclear cells (PBMCs) circadian rhythms without altering plasma melatonin and cortisol rhythms (Dumbell et al., 2016), thereby linking HPA axis regulation to immune cell function. Consistent with this, oral administration of synthetic hydrocortisone altered *BMAL1* and *PER2/3* expression in PBMCs by 9.5–11.5 h (Cuesta et al., 2015). Initiation of stress-induced microglial inflammation in rats is affected by time of day. Animals stressed during the resting phase exhibit an enhanced neuroinflammatory response to LPS challenge compared with animals experiencing stress during the active phase (Fonken et al., 2016). HPA axis desynchrony due to circadian misalignment, increased stressors during nighttime work, and reduced access to protective psychosocial factors leads to increased long-term adverse health outcomes. For example, law enforcement professionals are at significantly higher risk for suicide, stress-related and mood disorders than the general public [104]. More research is needed to understand the mechanisms of interactions between long-term exposure to circadian misalignment and workplace stressors and mental health disorders, and perhaps microglia can be one of the directions for future research.

4.3. Sleep problem

Sleep consists of cycles of two alternating stages: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Carskadon and Dement, 2005). REM sleep, also known as paradoxical sleep, is characterized by active brain waves, loss of muscle tone, and rapid eye movements (supposedly while dreaming) (Jouvet, 1999). Sleep episodes begin with brief NREM phases, including stages 1, 2, 3, and 4, and finally enter REM, with cycles between NREM and REM phases throughout the night (Carskadon and Dement, 2005). When NREM begins, the heart rate, blood pressure, respiratory rate, and muscle tone gradually decrease (Morgan et al., 1996; Rama et al., 2005). Stages 3 and 4 of NREM sleep, also known as slow-wave sleep (SWS), are associated with adequate rest and are characterized by the release of growth hormone for physiological repair and regeneration (Dijk, 2009; Léger et al., 2018). REM sleep is important for emotional processing and memory consolidation (Le Bon, 2020). Importantly sleep disruption disturbs circadian rhythms and affects the immune response (Nadjar et al., 2017).

Recent evidence suggests that the loss of REM sleep activates microglia, which release inflammatory cytokines and exhibit a weakened ability to eliminate amyloid β (Aβ) plaques (Liu et al., 2023). Older adults (over 60 years) often report sleep disorders and insomnia (Stepnowsky and Ancoli-Israel, 2008). The reason for this may be that typical changes in sleep structure occur with age, causing lighter sleep quality and shorter sleep duration (approximately 6.5–7 h per night less than 7–8 h in young adults) (Chaput et al., 2020; Hirshkowitz et al., 2015). In addition, the activity of the SCN decreases (Swaab et al., 1985) and the expression of biological clock genes gradually declines with aging, especially PER (Long and Giebultowicz, 2017). In an aged (24 months old) $Per1^{-/-}$ mice model, people found significant alterations of microglial morphology in the hippocampus with enlarged cell bodies and shorter, thicker processes (Borner et al., 2021). Furthermore, ageing mice with myeloid deficiency of BMAL1 demonstrate accelerated cognitive decline and deficits in the sleep–wake cycle with increased wakefulness across light and dark phase (Iweka et al., 2023). Complement component 1q (C1q) deposition at synapses and synaptic phagocytosis are significantly reduced in aging Bmal1-deficient microglia, suggesting that BMAL1 plays a role in regulating synaptic pruning during aging (Iweka et al., 2023).

4.4. Alcohol use

Studies have demonstrated that the evening chronotype is associated with increased alcohol consumption in adults (Adan, 1994; Wittmann et al., 2006). In Addiction, shift workers, especially night shift workers have increased susceptibility to alcohol use disorder (AUD) (Gulick and Gamsby, 2018). This can be explained by circadian misalignment are associated with altered reward function, which may influence the use of alcohol and other drugs (Hasler et al., 2015). Specifically, circadian disruption has been observed during acute and chronic alcohol use (Meyrel et al., 2020). In human, *Clock* gene expression was significantly lower in PBMCs isolated from AUD compared to healthy volunteers (Huang et al., 2010). Moreover, fibroblasts isolated from patients with AUD display irregular PER2 cycles, with the duration of the cycles being inversely proportional to the severity of the disease (McCarthy et al., 2013). Addictingly, the same authors described that a shorter circadian expression of PER2 is correlated with greater illness severity (McCarthy

et al., 2013). Drug abuse can interact with the circadian system by altering the phase, frequency, or amplitude of endogenous rhythms, leading to maladaptive manifestations such as craving and drug-seeking behavior (Lindberg et al., 2018). Alcohol induces oscillations in GABAergic, dopaminergic, glutamatergic, and purinergic neurotransmission, which may contribute to the intermittent desires, anticipation, and impulsivity of AUD (Lindberg et al., 2018). Several studies have indicated that alcohol's modulation of purinergic and glutamatergic signaling is mediated by actions in neurons and also in microglia (Delpech et al., 2015; Gipson et al., 2021; Köles et al., 2016; Lindberg et al., 2018; Melbourne et al., 2019). Notably, microglia are involved in the regulation of circadian molecular rhythms both in SCN (Honzlova et al., 2023) and in other CNS regions more directly involved in reward system (Sominsky et al., 2021). Microglial cells regulate rhythmic synaptic transmission and purinergic signaling, indicating they may play a key role in the development and effects of dependence and abstinence (Illes et al., 2020). Therefore, microglial neuromodulation could provide a more comprehensive understanding of the synaptic and extra-synaptic events that contribute to chrono disruption and neuropsychiatric disorders, such as AUD.

5. Lifestyle interventions

5.1. Time-restricted eating

Nutrients and metabolites are known to modulate the immune system (Calder et al., 2017). However, the mechanisms underlying these diet-induced effects remain unclear. Time-restricted eating (TRE in humans, or Time-restricted feeding (TRF) in experimental animals), a dietary approach that limits eating to specific time-restricted windows during the day, has shown promise for optimizing metabolic health and weight management. Aligning mealtimes with the body's natural circadian rhythms is believed to enhance the synchronization of internal processes and promote better health (Soliman, 2022). However, the connection between time-restricted eating and microglia is a topic that is largely unknown.

One study found that dietary restriction affects the expression of major histocompatibility complex (MHC) molecules in microglia (Estrada et al., 2019). Specifically, female animals under dietary restriction showed a significant increase in MHC-I expression in microglia, whereas male animals showed no significant difference between the groups. Increased microglial MHC-I expression in dietary-restriction may play a role in maintaining tolerance in the absence of antigenic stimulation (Estrada et al., 2019). This study also further emphasizes the importance of sex differences in microglial research. The disruption of circadian rhythms has also been associated with the development of chronic health issues, including mood disorders. In a rat model that was subjected to circadian rhythm disruption, TRF intervention was effective in reducing depressive- and anxiety-like behaviors (Guerrero-Vargas et al., 2021). Additionally, TRF demonstrated its effectiveness by preventing morphological changes observed in the CA3 region of rats showing circadian disruption. This suggests that TRF could be a valuable intervention in counteracting the negative impact of circadian rhythm disruption on emotional regulation (Guerrero-Vargas et al., 2021).

It has been observed that alterations in circadian rhythm are commonly present in individuals with Alzheimer's disease (AD). A recent study found that these disruptions occur in the early stages of AD pathology in mouse models. The implementation of a time-restricted feeding strategy demonstrated good results in reversing impaired brain function, slowing down the accumulation of amyloid plaques, and improving memory deficits in AD mice (Whittaker et al., 2023). This strategy not only altered the expression of genes and pathways linked to AD and inflammation, but also improved the sleep-wake cycle and cognitive function (Whittaker et al., 2023). Additionally, the TRF strategy significantly reduced toll-like receptor 2 (Tlr2) expression, which is constitutively expressed by microglia and mediates the activation of the NF-kB pro-inflammatory pathway. This reduction in microglial inflammatory responses may contribute to the beneficial effects of TRF on treating AD (Whittaker et al., 2023).

5.2. Exercise

A sedentary lifestyle can disrupt circadian rhythms, leading to elevated levels of pro-inflammatory factors and chronic low-grade inflammation (Kolbe and Oster, 2019; Mundula et al., 2022). An earlier study in mice found that exposure to a HFD led to severe microglial activation in the hypothalamus, but running on a treadmill significantly decreased the inflammatory changes in microglia in these mice. This finding may have implications for the treatment and prevention of obesity (Yi et al., 2012). This comes on the heels of other rodent studies demonstrating that endurance exercise can significantly impact microglial proliferation, activation, and function. In young mice, wheel running increased microglial number in the cortex or hippocampus (Ehninger and Kempermann, 2003; Olah et al., 2009; Vukovic et al., 2012). In contrast, microglial proliferation is reduced in the hippocampus of aged mice (Kohman et al., 2012), suggesting that exercise may differentially affect microglial subpopulations, reflecting age-related expression.

The circadian clock plays a crucial role in maintaining physiological functions, including the immune system (de Souza Teixeira et al., 2020). Recently, it was reported that late-life physical activity levels in humans, assessed through actigraphy monitoring, correlate with cognitive resilience during one's lifetime. Additionally, a negative correlation between the physical activity and the microglial activation was observed in the postmortem brain tissue when these subjects were deceased (Casaletto et al., 2022). Another study in humans has demonstrated that circulating levels of N-acylphenylalanine (Lac-Phe) significantly increase during exercise. The biosynthesis of Lac-Phe involves lactate and phenylalanine and occurs in cytosolic nonspecific dipeptidase 2 positive ($CNDP2^{+}$) cells. Notably, this gene is abundant in microglia in the brain (Jansen et al., 2015). These discoveries uncover the potential role of Lac-Phe in the human body and its potential utility in regulating food intake and influencing overall energy balance (Li et al., 2022). Additionally, some studies have also described changes in microglial numbers between "neuroprotective" and "neurotoxic" phenotypes observed in several studies (Kohman et al., 2013; Littlefield et al., 2015), these changes differ across sexes, ages, and brain regions. Clearly, the current understanding of exercise timing within the circadian rhythm and its effects on microglial function remains inadequate.

6. Conclusion and future prospective

The microglial circadian rhythm is a rapidly advancing and emerging field in neurobiology. This review summarizes evidence showing that microglial circadian gene expression affects the health and function of glia and neurons. However, research on microglial circadian rhythms is still in its early stages and numerous questions remain unresolved.

First, global gene deletion approaches are the dominant techniques used, but they may introduce confounding variables in different CNS locations and developmental processes. Experiments involving the deletion of clock genes during embryonic development have limitations because clock genes also affect the development of neural circuits. For instance, Bmal1-deficient mice exhibit arrhythmic circadian behavior and expression of clock target genes. Bmal1-KO mice also have a shortened lifespan and exhibit an early aging phenotype, which is consistent with the increased levels of reactive oxygen species observed in some tissues of Bmal1-KO mice (Bunger et al., 2000). Additionally, these mice exhibit several health problems, including reduced overall activity and weight loss (Bunger et al., 2005; Kondratov et al., 2006; Sun et al., 2006).

Second, the research on the circadian rhythm of microglia in the CNS is relatively scarce, and most of the current research is focused on brain

areas like the cortex, hypothalamus, SCN, and hippocampus. However, there is a lack of research on the diurnal morphological changes, gene expression changes, and functional effects of microglia in areas like the spinal cord.

Moreover, the field of biology has recently shown increased interest in studying sex differences, and this interest also extends into circadian rhythm research. However, the area of microglial circadian function remains largely unexplored, particularly with regards to sex differences. The cyclic differences in immune responses between males and females highlight the need for further research in this area. Such research may lead to future advancements in sex-dependent circadian regulation and personalized medicine.

The emerging field of microglial circadian rhythm is showing great potential to advance our understanding of neurobiology and its effects on health and disease. To further our understanding and develop new treatments, future research should concentrate on improving experimental methods, exploring the circadian rhythms of microglia in various regions of the CNS, and examining sex differences. This knowledge will not only deepen our comprehension of the interplay between circadian rhythms and microglial function, but also lead to the development of personalized medicine strategies.

CRediT authorship contribution statement

Han Jiao: Writing – original draft, Conceptualization. **Andries Kalsbeek:** Writing – review & editing. **Chun-Xia Yi:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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