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# *Research Advances and Assumptions in Metformin Improving Cognitive Functions by Regulating Circadian Rhythms*

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***Abstract.*** Metformin, a first-line drug for type 2 diabetes, has been increasingly linked to delayed aging and improved cognitive functions. Circadian rhythm disorders are closely linked to cognitive decline and microglia-driven neuroinflammation, especially in neurodegenerative diseases like Alzheimer's disease (AD). This article reviews how metformin regulates the expression of core clock genes by activating the AMPK signaling pathway, thereby reshaping circadian rhythms and potentially restoring microglial rhythmic activity. This paper proposes the systematic axis of "Metformin–Circadian Rhythms–Cognition" to provide a new perspective for interpreting its neuroprotective effects and to call for experimental studies to directly verify the relationships among the three. If this chain is verified, it will facilitate a shift in treatment strategies for cognitive aging and neurodegenerative diseases.

***Keywords:*** Metformin, Circadian Rhythms, Cognition, AMPK, Microglia

## 1. Introduction

Metformin is currently the first-line drug for type 2 diabetes, and it also partially acts through the activation of 5′-AMP-activated protein kinase (AMPK) [1,2]. In recent years, studies have found that it has the potential to delay aging, including by improving cognition [3,4].

Circadian rhythms are approximately 24-hour endogenous biological rhythms and consist of two main kinds of clocks. One is the central clock in the suprachiasmatic nucleus (SCN) and the other is the peripheral clock in most organs and tissues. Its molecular mechanism primarily involves a negative feedback loop (TTFL) formed by four core gene groups: Clock, Bmal1, Per1-3, and Cry1-2 [5]. Circadian rhythms are significant for cognitive functions, as circadian clock genes regulate the memory formation systemically and locally [6]. Circadian rhythm disorders often lead to cognitive impairment. For example, patients with Alzheimer's disease commonly have circadian rhythm disorders even before Amyloid-β (Aβ) plaques appear [7]. In addition, as intrinsic immune cells of the brain, microglia also function according to circadian rhythms [8]. When circadian rhythms are weakened, microglia are activated throughout the day, expressing many pro-inflammatory factors and excessively phagocytosing neurons, leading to cognitive impairment [9]. The combination of metformin-activated AMPK can influence Bmal1 and CRY1 [10], thereby regulating circadian rhythms. Along with evidence that metformin improves cognition [11,12], this suggests the possible existence of a "Metformin-Circadian rhythms-Cognition" pathway.

This review summarizes potential pathways by which metformin may improve cognition through circadian rhythms, aiming to promote research directly verifying the relationship among the three. If this pathway exists, the role of metformin could shift from merely repairing "brain cell components" to systematically repairing the "central clock," thereby enabling the development of more effective drugs.

## 2. Interactions among circadian rhythms, neuroinflammation, and cognitive functions

### 2.1. Regulation of nervous system functions by circadian rhythms

Circadian rhythms are endogenous rhythms with a cycle of approximately 24 hours present in most organisms, driving periodic changes in physiological processes such as autonomic nervous system activity, hormone secretion, and sleep/wake cycles [13]. In mammals, the primary circadian rhythm oscillator is the SCN, located in the hypothalamus, composed of approximately 20,000 autonomously oscillating neurons that regulate peripheral oscillators throughout the body [5]. At the molecular level, they were created from a negative transcription-translation feedback loop (TTFL), made up of four core gene groups: Circadian Locomotor Output Cycles Kaput (Clock), Brain Muscle ARNT-Like 1 (Bmal1), Period (Per1-3), and Cryptochrome (Cry1-2). Specifically, the heterodimer of the two transcription factors, BMAL1 and CLOCK, first binds to E-box sequences upstream of the Per and Cry genes, thereby driving their transcription. After forming heterodimers and entering the nucleus in the cytoplasm, the translated PER and CRY repress the transcription of the Per and Cry genes by blocking BMAL1/CLOCK activity. Subsequently, CRY and PER are phosphorylated, ubiquitinated, and broken down, removing the inhibition on BMAL1 and CLOCK, and initiating a new cycle. The other auxiliary feedback loop involves REV-ERB nuclear receptors and the RAR-related orphan receptor (ROR) [6,14].

Circadian rhythms play an important regulatory role in cognition. At the molecular level, knocking out the four core circadian rhythm genes disrupts memory, indicating that circadian rhythm genes are indispensable for memory formation [6]. Notably, Bmal1 may influence memory formation by regulating the cAMP/mitogen-activated protein kinase (MAPK; also known as ERK) signaling pathway in the hippocampus [15]. PER1 may regulate the activity of cAMP response element-binding protein (CREB) by interacting with CREB kinase, thereby affecting the MAPK/CREB cascade, a key process in memory consolidation [6]. PER2 may similarly influence memory by regulating CREB activation through modulation of the dopamine receptor D1 (DRD1) [16].

Microglia are the resident immune cells of the central nervous system. Apart from their traditional roles in injury repair, phagocytosis and clearance of waste products in the central nervous system, and secretion of inflammation factors and chemokines, microglia play a significant role in supporting neurons and oligodendrocytes, pruning synapses as well as normal developmental processes within homeostatic brain functioning [17,18]. Microglia exhibit two phenotypes: M1 and M2. M1-type microglia are generally considered to exert neurotoxicity by secreting pro-inflammatory cytokines such as interleukin IL-1β, IL-6, and reactive oxygen species (ROS), whereas M2-type microglia release factors that protect neutron such as insulin-like growth factor-1 (IGF-1), fibroblast growth factor (FGF), and colony-stimulating factor-1 (CSF1), as well as anti-inflammatory cytokines like IL-10 and TGF-β [19,20]. Microglia also express circadian rhythm genes like Per1, Per2, Rev-erbα, and Bmal1, and their expression exhibits circadian rhythms [21].

Circadian rhythms regulate various microglial functions, including cytokine release, phagocytic activity, and metabolic state [8]. Under healthy conditions, the inflammatory response of microglia shows rhythmic fluctuations; for example, in rats, microglia respond more strongly to LPS stimulation during the light phase than during the dark phase [21]. Core circadian genes also regulate microglial activity and the inflammatory response. For example, in human glioblastoma tissue microarrays (TMA), Clock and Bmal1 signaling influences the expression of C-X3-C motif chemokine receptor 1 (CX3CR1) and transmembrane protein 119 (TMEM119), two markers of microglia. Clock can upregulate the transcription caused by the main inflammation transcription factor NF-κB. Bmal1 deficiency improves microglia phagocytic function, reduces pro-inflammatory cytokines, and increases antioxidant and anti-inflammatory factors [9].

### 2.2. Circadian rhythm disorders lead to cognitive impairment

Circadian rhythm disorders are often associated with cognitive decline. At the macroscopic level, patients with Alzheimer's disease frequently exhibit sleep fragmentation and excessive daytime somnolence in the early stages. Studies have found that fragmentation of the 24-hour activity rhythm may precede Aβ pathology [7]. At the microscopic level, studies in mice have already identified evidence that behavioral circadian rhythm disorders precede the formation of Aβ plaques. At the microscopic level, weakened gene expression of the circadian rhythms may lead to the onset or exacerbation of cognitive impairment. Research has shown that in the SCN territory, in 2-month-old AD mice—early-stage AD mice exhibiting behavioral circadian rhythm disorders but not yet forming Aβ plaques—the core circadian clock gene Bmal1 has lost its circadian rhythms. In 10-month-old AD mice, there is additional loss of rhythm in the Clock genes Per2 and Cry2. In the hippocampal territory, early loss of rhythmicity in circadian clock genes was similarly observed, and with aging, more circadian clock genes exhibited rhythmicity loss [22]. Microglia circadian rhythm disorders are particularly noteworthy. Microglia exhibit disrupted rhythmic expression of Per1 and Per2, exhibiting daytime activation and high levels of pro-inflammatory cytokines like TNF-α and IL-1β mRNA. The response to stimuli loses its diurnal variation, unlike in young individuals, who exhibit rhythmic expression of pro-inflammatory factors and stimulus responses [23,24]. The release of pro-inflammatory cytokines like TNF-α and IL-1β, as well as excessive microglial activation, may damage neurons, inhibit long-term potentiation (LTP), and impair synaptic plasticity and memory consolidation. Overactivated microglia may excessively phagocytose synapses or neurons, disrupting normal neural networks. Previous studies have found that circadian rhythm disorders raise the number of microglia in the mouse hippocampus and raise pro-inflammatory TNF-α levels. In contrast, neurogenesis and synaptic protein levels decrease, which may affect learning and memory [25]. However, it should be noted that most studies only indicate a close association between circadian rhythm disorders and microglial activation. In contrast, direct causal evidence showing that restoring microglial rhythmicity alone leads to cognitive improvement remains limited.

## 3. The circadian rhythms regulatory effect of metformin

### 3.1. AMPK-BMAL1: the hub of energy sensing and clock regulation

AMP-activated kinase (AMPK) senses energy in organisms. When cellular energy is insufficient, indicated by decreased ATP levels and an increased AMP/ATP ratio, AMPK is activated to maintain cellular energy homeostasis by inhibiting anabolic processes (such as lipid synthesis) and promoting catabolic processes (such as glucose utilization) [2,26]. Two serine/threonine protein kinases regulate AMPK: LKB1 and Ca2+/calmodulin-dependent protein kinase b (CaMKKb). Moreover, sirtuin-1, a nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase encoded by the proposed anti-aging gene SIRT1, positively regulates it [2]. Metformin, a component abundantly found in Galega officinalis L., has become a first-line oral hypoglycemic agent for treating type 2 diabetes [1]. In recent years, studies have found that metformin has the potential to delay aging, including by improving cognitive functions [4,27]. Metformin primarily exerts its effects by activating AMPK. Metformin activates AMPK by blocking the electron transport chain of mitochondrial complex I that lowers ATP levels and raises the AMP/ATP ratio [2]. The activation of AMPK can upregulate the expression of Bmal-1, thereby participating in the regulation of the TTFL of the biological clock, reshaping the rhythm amplitude and phase, and improving circadian rhythm disorders [11,28]. In addition, studies have shown that activated AMPK can facilitate the degradation of CRY and PER proteins, thereby alleviating the inhibitory effect on BMAL/CLOCK [10,12]. However, current evidence linking metformin to circadian rhythm regulation mainly comes from peripheral tissues or metabolic disease models, and whether similar effects occur in the central nervous system has not been thoroughly investigated. Furthermore, most studies examine circadian rhythm gene expression or metabolic outcomes independently, rather than within an integrated framework of cognition or neuroinflammation.

### 3.2. Microglia: from the state of "persistent activation" to a state of "rhythmic response"

In addition to acting on TTFL, metformin may also modulate microglial state. Studies have found that metformin treatment can inhibit the activation of M1-type microglia and promote the transition of microglia from M1 type to M2 type [29,30]. Previous studies have demonstrated that the metabolic change of microglia from glycolysis to oxidative phosphorylation drives the inflammatory response. Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases have also been linked to this metabolic change [31]. Since metformin can regulate cellular energy metabolism through mitochondrial complex I (Complex I), and glycolysis inhibition and promotion of the tricarboxylic acid cycle by ramelteon, a melatonin receptor agonist, regulates microglia metabolic reprogramming thereby suppressing neuroinflammation, metformin may similarly shift the metabolic pattern of microglia from pro-inflammatory glycolysis back to oxidative phosphorylation thus restoring homeostasis [20]. However, this has not yet been studied. Metformin can also inhibit NF-κB activation through AMPK-dependent or independent pathways, and therefore may decrease the release of pro-inflammatory factors like TNF-α and IL-6 in microglia. In addition, mTOR is a serine/threonine kinase that can inhibit autophagy by phosphorylating autophagy-related proteins [32]. Metformin-activated AMPK can inhibit mTOR1 activity, promoting autophagy [33]. This may facilitate the clearance of damaged components within microglia and enhance their phagocytic capacity for key proteins involved in neurodegenerative diseases like Aβ and tau. Although the aforementioned effects of inhibiting pro-inflammatory factor release and promoting autophagy may appear to be less associated with the circadian rhythms, given that pro-inflammatory factors may in turn affect the circadian system, and that microglia are activated uniformly throughout the day when the rhythm is weakened, these effects are important for eliminating existing negative impacts and restoring microglia to homeostasis [34,35]. However, there is still a lack of experimental verification of rhythmic changes in microglia before and after metformin treatment, as well as studies on the mechanisms underlying metformin's effects on microglia.

## 4. Frontier prospects and translational significance of the "metformin-circadian rhythms-cognition" axis

Currently, therapeutic strategies for neurodegenerative cognitive impairment primarily focus on directly intervening in pathological changes at the neuronal level. Taking Alzheimer's disease as an example, the currently approved drugs include cholinesterase inhibitors (such as donepezil, rivastigmine, and galantamine), which improve synaptic function, and N-methyl-D-aspartate (NMDA) receptor antagonists (such as memantine), which mitigate neurotoxicity. However, these therapies can only alleviate symptoms and cannot prevent or cure the disease. Moreover, for neurodegenerative cognitive impairment with complex pathology, therapies targeting a single mechanism are insufficient [36]. Circadian rhythms coordinate systemic physiological processes, including metabolism, immune responses, and neural activity, and their disruption represents an early and potentially upstream driver of cognitive decline [37-39]. Incorporating circadian regulation into therapeutic strategies may therefore shift current approaches from targeting isolated pathological features to correcting systemic dysregulation. Metformin demonstrates translational potential in this context. It is not merely a hypoglycemic agent; its multi-target mechanism of action, such as inhibiting mitochondrial complex I and activating AMPK, allow it to directly modulate core biological molecules, thereby offering the potential to reshape the rhythmicity of downstream physiological processes, including the microglial immune response.

Future research may focus on the following directions:

(1) Development of combined circadian rhythms intervention strategies: Explore the synergistic effects of metformin with other non-pharmacological circadian interventions (such as phototherapy, melatonin therapy, and lifestyle modifications) to confirm whether combined strategies of pharmacological and behavioral interventions can more effectively correct circadian rhythms and improve cognitive functions [40].

(2) Development of drugs targeting microglia: Investigate the rhythmic changes of microglia before and after the action of metformin, and verify whether metformin affects the rhythm of its immune response through metabolic reprogramming (such as the shift from glycolysis to oxidative phosphorylation). Specifically elucidating the molecular pathways by which metformin regulates the rhythm of microglia, providing targets for the development of new microglia modulators with higher specificity and cognitive therapeutic drugs targeting microglia.

(3) Biomarker-driven interventions: Develop and apply circadian rhythm biomarkers (such as melatonin) to identify individuals at risk of cognitive decline due to circadian rhythm disorders and to enable early intervention [41]. For these patients, metformin or other chronotherapeutic agents may be more effective.

## 5. Conclusion

This review systematically demonstrates the potential pathways through which metformin may improve cognition by restoring circadian rhythms, provides insights into the interpretation of its anti-aging and neuroprotective effects, and offers new perspectives for better treatment of neurodegenerative cognitive impairment. Metformin inhibits mitochondrial complex I of the electron transport chain, leading to increased AMP/ATP levels, activated AMPK, enhanced expression of Bmal1, and accelerated degradation of PER and CRY proteins, thereby remodeling amplitude and phase. In addition, metformin can regulate microglial homeostasis by inhibiting M1-type microglial activation, suppressing NF-κB activation, and promoting microglial autophagy. Therefore, metformin may constitute a "Metformin–Circadian rhythms–Cognitive improvement" pathway at the cellular, tissue, and whole-organism levels, providing a framework for interpreting its anti-aging and neuroprotective effects.

However, the number of references in this review is insufficient, and most of the existing evidence is derived from cellular and rodent models, lacking data from primates and long-term follow-up. Moreover, many aspects of the mechanisms remain to be verified, such as the circadian rhythms of microglia before and after metformin intervention, and whether the effect of metformin on the M1/M2 phenotype transition of microglia is mediated by the regulation of energy metabolism. There is also a lack of direct experimental verification of the "Metformin-Circadian rhythms-Cognition" pathway. These may be potential directions for future research.

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