

# Potential Protective Effects of Melatonin on Alzheimer's Disease Through Regulating Sleep and Circadian Rhythms

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**Abstract:** The disorder of sleep and rhythm has long been considered as the pathological manifestations of Alzheimer's disease (AD). The growing evidence has been showing the potential relationship between sleep and circadian rhythm regulations with the occurrence and development of AD. Therefore, it is crucial to improve sleep and circadian rhythms. Melatonin, a hormone secreted by the pineal gland, plays an important role in regulating human sleep and circadian rhythm. A potential mechanism is that melatonin improves sleep and rhythm disorders, and thus, indirectly regulates the pathogenesis of AD. Moreover, the pathogenesis of AD includes free radical oxidative damage, as well as neuroinflammation. In recent years, many studies have proved neuroendocrine immunomodulatory activity and free radical scavenging antioxidant capacity of melatonin. As a free radical scavenger, melatonin participates in the antioxidant system and regulates the symptoms of AD. This review summarizes signaling pathways leading to the pathogenesis of AD, such as neuroinflammation, A $\beta$  burden and increasing Tau level. Apart from pathogenesis of AD, effects of melatonin on the regulation of clock genes and the role of its receptors MT1 and MT2 in improving sleep disorders and circadian rhythm deterioration are discussed. Clinical trials show melatonin may also improve the cognitive ability of AD patients. This review attempts to provide a broader perspective and new direction for prevention and treatment of AD with melatonin.

## 1. Introduction

Alzheimer's disease (AD) is a common neurodegenerative disease in middle-aged and elderly people, accompanied by abundant clinical symptoms, such as mild cognitive impairment (MCI), impaired language functions and behavioral impairment [1]. According to the report from World Health Organization, there were about 50 million AD patients worldwide in 2015, and that figure was estimated to triple in 35 years [2]. Given the increasing number of AD patients, many countries have invested not only plenty of money to lighten the burden of family, but also a huge number of human resources to explore the pathological mechanisms and specific treatments. So far, the etiology of AD remains unclear, and there is a lack of effective treatments to slow down the course of the disease. However, existing studies have shown that the sleep structure of AD patients is different from that of healthy people, such as the decrease of total sleep time, low sleep efficiency and prolonged latency [3]. In clinical cases, circadian rhythm disorders are an early symptom of AD [4]. In fact, growing evidence supports that sleep and circadian rhythm disorders may contribute to the early pathogenesis of AD [5]. In a word, sleep and circadian rhythm disorders, as pathological manifestations, may lead to the pathogenesis of AD, and it is of great significance for the clinical diagnosis and development of new treatments for AD.

The circadian regulation of sleep and wakefulness is organized by a pacemaker located in the suprachiasmatic nucleus (SCN) which serves as a master clock [6]. Melatonin, N-acetyl-5-methoxytryptamine, is one of the most important timing signals generated by the SCN [7, 8]. SCN

controls the influx of sympathetic nerve endings after the dense pineal ganglion. There are two major cell types in pineal gland: neuroglial cells and pinealocytes. The SCN activity is inhibited and the pineal gland produces melatonin during the dark phase; when the SCN is active, melatonin production is inhibited during the light phase. Therefore, melatonin is called “sleep factor”. Studies on circadian system of the North American lizard species green chameleon found that melatonin has a direct inhibitory effect on the chameleon's vitality, implying that the pineal gland can control other circadian clocks through regular synthesis and secretion of melatonin [9]. Moreover, melatonin and melatonin receptor (MT) play an important role in the regulation of circadian rhythm in many animals [10]. There are three types of MT that have been described: MT1, MT2, and MT3. The first two are G-protein-coupled receptors, which respectively inhibit neuronal activity and sleep phase transition in SCN [11]. The MT1 receptor is mainly expressed in SCN and hypophysial pars tuberalis, and MT2 receptor is mainly expressed in retina [12]. The MT3 binding site has been identified as a quinone reductase protein, but its physiological significance remains to be clarified. These studies indicated effects on the circadian regulation of sleep and wakefulness.

Melatonin can regulate sleep and circadian rhythms, while sleep and circadian rhythm disorders may induce the pathogenesis of AD. Therefore, it could be speculated that melatonin may affect and potentially treat AD by regulating sleep and circadian rhythms. However, the relationship between melatonin, sleep, circadian rhythms and AD remains unclear. In this review, the mechanisms of circadian rhythms influencing AD and that of melatonin regulating circadian rhythms are discussed to provide a broader perspective for future research and drug development.

## **2. Possible mechanisms of sleep and circadian rhythms affecting AD**

### **2.1 Sleep and circadian rhythm disorders exacerbate neuroinflammation**

In the central nervous system, neuroinflammation is the immune response activated by microglia and astrocytes under infection and injury. Pathological neuroinflammation due to abnormal activation of microglia and astrocytes will result in nerve degeneration, which is the main pathological feature of AD. Sleep and circadian rhythms are among the key factors to regulate the activation and inhibition of these cells. The specific deletion of clock gene *Bmal1* in astrocytes can induce the activation of astrocytes and promote the expression of inflammation-related genes, which exist both *in vivo* and *in vitro* [13]. Meanwhile, this deletion can also promote the death of cultured neurons *in vitro*, indicating that circadian rhythms may regulate the activation and function of astrocytes [13]. Additionally, in mouse microglial cells, the expression of *Bmal1* is rhythmic (the expression is more at circadian time 4), which encourages the microglia to phagocytize more amyloid  $\beta$ -protein ( $A\beta$ ) [14]. The absence of clock protein Rev-erba could lead to spontaneous activation and proliferation of microglia and astrocytes, as well as aggravation of the neuroinflammation induced by lipopolysaccharide. However, these effects could be rescued by activation of Rev-erba, suggesting that circadian rhythm is a critical factor in regulating neuroinflammation through glial cells [15]. Inhibition of secretory glycoprotein *Chi3l1* improved the phagocytosis of  $A\beta$  in microglia and astrocytes *in vitro*, while knockout of bioclock gene *Baml1* or *Clock/Npas2* strongly inhibited the expression of *Chi3l1*, indicating that circadian rhythm plays an important role in regulating neuroinflammation [16]. After the sleep deprivation of the animal model with cognitive impairment, the expression of inflammatory cytokines IL-1 $\beta$  and IL-6 in the hippocampus increased, with the aggravated pathological damage of neurons and the activation of astrocytes [17]. Taken together, these studies suggest that sleep and circadian rhythms are vital factors in the regulation of neuroinflammatory response in AD.

### **2.2 Sleep and circadian rhythm disorders induce oxidative damage**

Oxidative damage is a reaction in which a large number of oxides and free radicals cause cytotoxicity and neurotoxicity with the imbalance between oxidation and reduction in the body. It is reported that the 53 MCI-AD patients and 27 healthy controls in which MCI-AD patients showed higher levels of oxidation with the increased oxidative damage level of DNA [18]. Oxidative damage is closely related to sleep and circadian rhythms as well. Whether in eukaryotes such as mice, fruit

flies, *Arabidopsis thaliana* seedlings and filamentous fungi, or in prokaryotes such as cyanobacteria, redox proteins represent a rhythmic cycle [19]. In the mouse model with clock gene *Bmal1* deletion, neurons underwent oxidative damage and the expression of antioxidant genes *Nqo1* and *Aldh2* were impaired; in primary cultured cells, the decrease of *Bmal1* expression also promoted oxidative stress injury [20]. After 24 hours of sleep deprivation, there was no increase in reactive oxygen species in the brain of the mice. However, when the experimental animals were deprived of sleep for 5-11 days, the activity of superoxide dismutase in hippocampus and brainstem decreased significantly, resulting in oxidative damage [21]. This experiment revealed that short-term sleep deprivation may not have much effect on oxidative damage, while long-term wakefulness would inhibit the process of antioxidation and cause redox imbalance.

### 2.3 Sleep and circadian rhythm disorder lead to A $\beta$ burden

A $\beta$  is the product of  $\beta$ -secretase and  $\gamma$ -secretase hydrolyzing amyloid precursor protein, whose deposition has strong neurotoxicity. Once the metabolism of A $\beta$  is out of balance, oxidative stress is triggered, neuroinflammation is aggravated, and A $\beta$ -degrading enzyme activity is affected, thus inducing AD. As early as 1992, there was a hypothesis that A $\beta$  deposition would lead to nerve fiber tangles and cell death [22]. Supporting evidence showed that the natural secretion of A $\beta$  oligomer *in vivo* may effectively inhibit the long-term potentiation of hippocampal region, implicating that A $\beta$  oligomer can be used as a target for the treatment of AD [23]. Through animal model experiments and human sample collection, the researchers discovered that A $\beta$  was closely associated with sleep and circadian rhythms. For example, although circadian fluctuations in A $\beta$  levels were observed in both C57BL6 wild-type mice and human *APP* transgenic mice (A $\beta$  levels were the highest in the awakening stage in dark environment, and the lowest in sleep with light exposure), such circadian fluctuations still existed in low light conditions, implying that the difference in A $\beta$  levels is related to the sleep-awakening cycle, while not with light. Similarly, during the 33-hour assessment of cerebrospinal fluid A $\beta$  levels in male volunteers, daily fluctuations were found in A $\beta$  levels as well (the highest at 19:00-21:00 and the lowest at 9:00-11:00) [24]. It was found that the transcription of A $\beta$  scavenger gene *ApoJ* was rhythmic, while the circadian pattern of *ApoJ* was not disturbed by the depletion of female sex hormones, providing a deeper insight into circadian rhythms and the mechanism of A $\beta$  scavenging [25]. Through the directed deletion of clock gene *Baml1* to disrupt the circadian rhythms of mice, research revealed that the disorder of central circadian rhythms accelerated the deposition of A $\beta$ , and the loss of peripheral *Baml1* in the brain parenchyma increased the expression of *ApoE*, the main risk gene of AD, supporting the hypothesis that circadian rhythm dysfunction resulted in A $\beta$  aggregation and confirming that abnormal circadian rhythms may directly affect the pathogenesis of AD [26]. Regarding sleep deprivation, measuring the levels of A $\beta$  of 20 healthy volunteers after a night of normal rest and sleep deprivation, the researchers found that one night of sleep deprivation significantly increased the accumulation of A $\beta$  in the right hippocampus and thalamus [27]. Thus, the negative effect of sleep deprivation on the level of A $\beta$  in the brain was illustrated. Hence, further research may focus on whether regulation of sleep and circadian rhythms in AD patients could rescue the accumulation of A $\beta$ .

### 2.4 Sleep deprivation increases Tau level

The cytoskeleton of nerve cells is composed of microtubule system. Tau, as one of the most important microtubule-associated proteins, its abnormal hyperphosphorylation and aggregation would make nerve cells lose their normal physiological function. Clinical studies showed that there was an obvious Tau deposition in the temporal lobe of AD patients with cognitive impairment [28]. Tau level in brain interstitial fluid increased by about 90% in awake state compared with sleep state, and about 100% in sleep deprivation state [29]. By measuring the concentration of Tau in cerebrospinal fluid of volunteers who were deprived of sleep, treated with sodium hydroxybutyrate (with hypnotic effect), and allowed normal sleep, increased concentration of Tau in cerebrospinal fluid by sleep deprivation was rescued [30]. At present, there are few studies on circadian regulation of Tau, and more evidence

is needed to support that circadian rhythm disorders could affect the abnormal hyperphosphorylation of Tau.

### **3. Mechanisms of melatonin regulating sleep and circadian rhythms**

#### **3.1 Melatonin biosynthesis**

The melatonin produces in marked circadian signals originating in the SCN. The human SCN innervates only a small number of hypothalamic nuclei. The melatonin regulates the circadian rhythms via an indirect inhibitory pathway [31].

In human beings, sympathetic nerve stimulation plays an important role in the secretion of melatonin. When sympathetic excitation stimulates pineal cells to release melatonin, melatonin is synthesized from tryptophan in pineal gland cells and catalyzed to serotonin (5-HT) by tryptophan hydroxylase. 5-HT is converted into N-acetylserotonin by the rate-limiting enzyme arylalkylamine N-acetyltransferase, and then into melatonin by the enzyme hydroxyindole-O-methyltransferase.

The synthetic melatonin usually immediately enters the capillaries and cerebrospinal fluid. The activity of SCN is inhibited at night, and the axons of SCN neurons released  $\gamma$  aminobutyric acid (GABA) applied to the hypothalamus paraventricular nucleus cell. The paraventricular nucleus of the hypothalamus transmits the signal to the medial lateral anterior sympathetic nerve of the spine, and then to the superior cervical ganglion (SCG), which secretes norepinephrine (NE). During darkness at night, NE couples with  $\beta 1$  adrenoceptors and activates the cAMP-protein kinase A (PKA)-CREB and PLC-Ca<sup>2+</sup>-PKC pathways. Thus, the synthesis of adenylate cyclase (AC) is increased and the activity of arylamine nitrogen acetyltransferase or 5-hydroxytryptamine nitrogen is enhanced. This process is further enhanced by stimulations of  $\alpha 1$  adrenoceptors. The intracellular cAMP level to n-acetyltransferase (a rate-rate-regulating enzyme of melatonin synthesis) synthesis is then marked raised and eventually the stimulation of melatonin synthase. Especially when 5-hydroxytryptamine-N-acetyltransferase is accelerated, melatonin is subsequently synthesized [31].

The light signal is the main environmental control factor of pineal melatonin the day. When light reaches the retina containing melanin, nerve cells could detect blue light at a wavelength of 460-480 nm. The release of glutamate and pituitary adenylate cyclase activating polypeptide (PACAP) would then cause the expression of clock genes (*Bmal1*, *Clock*, *Per1*, *Per2* and *Cry*) in SCN, following by inhibiting the secretion of Noradrenaline in downstream pathways, and eventually affecting the synthesis of melatonin [32].

#### **3.2 The CLOCK gene for regulating circadian rhythms**

The molecular mechanism of SCN's involvement in circadian mainly includes a self-sustained molecular clockwork, which is based on autoregulatory transcriptional/translational feedback loops of clock genes, particularly *PER*, *CLOCK*, *BMAL1*, *CRY*, etc. These molecules have been found mainly in pineal gland and represented the synchronizing effect of the hypothalamus and the SCN. Therefore, it is necessary to test the expression and regulation of these clock genes. The two transcription *CLOCK* and *BMAL1* are the core mechanism transcription of other clock genes, for example, both three *Period* (*PER1*, *PER2* and *PER3*) and two *Cryptochrome* (*CRY1* and *CRY2*) genes can be activated by *CLOCK* and *BMAL1* heterodimers [33]. The SCN directly affects clock genes such as *CRY2* and *PER1* through the  $\beta 1$  adrenergic signaling system. Then *PER* and *CRY* proteins would couple complexes that translocate to the nucleus to inhibit *CLOCK* and *BMAL1*-induced transactivation. *PER/CRY* repressor complex is considered as the critical step for a start point of a new cycle of regulation [34].

#### **3.3 The role of Melatonin receptors**

MT1 and MT2 are associated with the activation of a variety of signaling pathways, among which the most common pathway is through inhibition of cAMP formation by G-proteins which are sensitive to pertussis toxin, and consequently inhibition of adenylate cyclase expression [35]. The cAMP response-element binding (CREB) transcription factor, which binds to the regulatory sequences of circadian clock genes, represents the link between melatonin and the biological clock. Therefore, the

PKA/CREB signaling pathway has been shown to play a crucial part in the circadian rhythm. In SCN of rats, melatonin inhibits phosphorylation of cAMP-response element binding protein that is mediated by PACAP. This effect is mainly mediated by the activation of MT1 receptor, which then increases the expression of Bmal1 gene in SCN and makes rats perform regular rhythm. The reaction is almost completely absent in MT1 knockout rats [36, 37]. The expression of MT2 receptor appears to regulate the circadian rhythm of neuron firing by stimulating protein kinase C (PKC) [38].

Melatonin signals clock genes throughout the body, causing them to be expressed synchronously. At the molecular level, the expression of BMAL1 and PER1 regulates the rhythm cycle through negative feedback [39]. In the early morning, the decline in melatonin levels causes a surge in the levels of intracellular cAMP, which leads to the transcription of cAMP-regulated genes, including PER1 [40]. While when melatonin synthesis and secretion decreased, the expression of clock genes such as BMAL1 was not inhibited.

In the heart and liver of elderly rats, the decline in expression of Per and Bmal1 in the evening is even greater compared to middle-aged ones [41]. Clinical AD patients showed lower rhythmic responses in CRY1, BMAL1 and PER1 expression, while control participants showed regular rhythmic responses in these genes [42].

Thus, further research is required to verify if melatonin can restore the normal circadian rhythm of AD by regulating the expression of clock genes.

### **3.4 Effects of melatonin on regulating sleep**

Deficiency secretion of melatonin and rhythm disorders may diminish functions of the body and cause sleep disorders, which would tend to sub-health and seriously induce the occurrence of diseases. Therefore, melatonin is crucial for sleep, and quantitative supplementation of melatonin has been proved to effectively improve insomnia [43]. The clinical use of melatonin in different pathologies was studied. Two forms of exogenous melatonin, with the ability to diffuse across the blood-brain barrier, have been used: an immediate release form and a long release form which could mimic the physiological melatonin secretion rhythm to replace reduced physiological secretion. It has been found a decreased melatonin secretion with age, especially in elderly insomniacs and dementia patients. However, with melatonin therapy as an add-on treatment, there have been found beneficial effects on MCI and AD patients with sleep disorders in improving sleep quality, as well as in regulating the sleep/wake rhythm. Moreover, melatonin may also improve cognitive function in MCI, while showing no effect in moderate to severe patients [43].

Sleep and rhythm disorder is not only the pathogenesis of AD sleep disorder, but also the clinical manifestation of AD. In order to determine the circadian rhythm of AD patients in the early stages of the disease, dim light melatonin onset (DLMO) secretion was calculated. It was found that initial evening secretion of melatonin proved to be delayed and was mildly impaired in patients with a mild/moderate form of AD [44]. Thus, the subclinical altered patterns of melatonin secretion occur in subjects with AD at an early stage of the disease.

## **4. Relationship between melatonin, sleep and circadian rhythms, and AD**

The increasing evidence implies that sleep and rhythm disorders may lead to neuroinflammation, oxidative damage, A $\beta$  burden and a high level of Tau, which can further affect the pathogenesis of AD. Melatonin has also been shown to improve sleep and circadian rhythm disorders by regulating the expression of clock genes. Therefore, a possible speculation is that melatonin may prevent and treat AD by regulating sleep and rhythm, reducing the adverse effects of neuroinflammation, oxidative damage and other pathogenic factors in human body (Fig 1.). However, most of the current studies regulate AD symptoms by directly reducing neuroinflammation, oxidative damage, A $\beta$  burden and the high level of Tau, while there are few studies on the combination of melatonin, sleep and circadian rhythm and AD pathogenesis. Further research may focus on melatonin improving sleep rhythm, sleep rhythm disorder leading to the pathogenesis of AD, and melatonin treating AD.

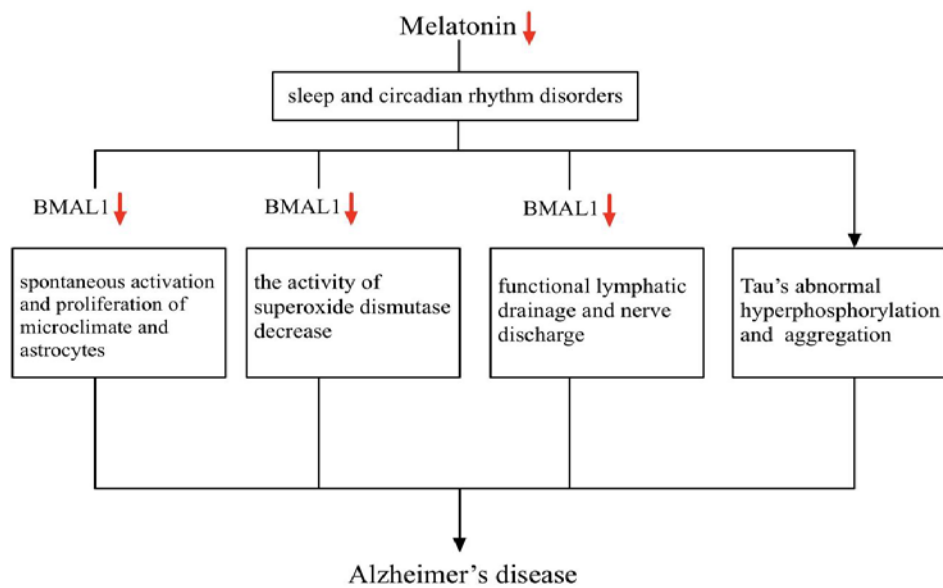


Figure 1. Effects and mechanisms of melatonin and sleep and circadian rhythm dysregulation on Alzheimer's disease

## 5. Melatonin as a therapeutic target to AD

Melatonin has been shown to have many advantages as an adjuvant drug in the treatment of AD. First, the safety and effectiveness of melatonin have been proved by a variety of studies. 12 healthy men were injected with 10 mg melatonin, 100 mg melatonin and placebo, respectively, and no adverse reactions were shown during this period (0-420 min) [45]. Melatonin can improve sleep problems and circadian rhythm disorders in patients with AD, while some studies showed controversial outcomes (Table. 1.). In these clinical trials, most volunteers showed good tolerance to melatonin and no obvious adverse reactions were found, while some showed only mild side effects, such as dizziness, nausea or drowsiness. Furthermore, melatonin also exerts an effective contribution on improving the cognition and memory of patients with AD. 11 AD patients who received 3 mg melatonin treatment for 4 weeks had significantly lower AD Assessment Scale (ADAS) scores than 9 patients in the control group (lower ADAS score showing better cognition function in this test) [46]. In 80 patients with mild to moderate AD, 2 mg add-on prolonged-release melatonin (PRM) treatment for 6 months could improve their ADAS-Cog values [47]. After the long-term melatonin treatment, the spatial learning ability of AD model mice has been improved and the memory impairment has been alleviated [48]. Similarly, exogenous melatonin and its metabolite AFMK may improve the learning and memory ability of streptozotocin-induced AD mice [49]. The related MT agonists also have the same effect, such as the novel MT1/MT2 agonist Neu-P11. Neu-P11 can enhance the object recognition memory of AD model rats when it was taken in the morning or afternoon, while melatonin only works in the afternoon, revealing that MT agonists may have a wider effect than melatonin [50]. MT1 and MT2 played their respective roles in mediating learning and memory by melatonin, but there have been few studies on specific agonists to improve the cognitive ability of patients with AD [51]. Thus, investigation and experimentation into MT1/MT2 specific agonists are strongly recommended. Finally, the price of melatonin on the market is mostly between 70 yuan to 200 yuan, and one bottle can maintain the dosage for at least a month, which would not become a great burden for ordinary families.

The clinical use of melatonin is limited by the absence of enough research. For instance, how specific MT agonists improve cognitive ability, whether melatonin interacts with other drugs to treat AD at the same time, as well as whether long-term use of melatonin could lead to drug tolerance or addiction. Further research is required to better understand these questions to broader the clinical application of melatonin.

Table.1. Clinical trials for melatonin treatment on AD patients

Objectives	Treatment method	Outcomes	Reference
44 AD patients with sleep disturbance	6 mg slow-release melatonin for 7 weeks	Non-significant effects on median total time asleep, wakefulness and sleep efficiency	[52]
157 AD patients with poor sleep	2.5 mg slow-release melatonin for 2 months	Non-significant trends for increase in total overnight sleep time and decrease in wake following onset of sleep	[53]
20 AD patients	3 mg melatonin for 4 weeks	Significantly longer sleep time and decreased nocturnal activity	[46]
24 AD patients	3 mg melatonin for 2 weeks	Significant decrease in nocturnal activity	[54]
50 AD patients	2.5 mg melatonin for a mean of 15 months	Shorter sleep onset latency and longer sleep duration	[55]
50 AD patients	1 hour of light exposure in the morning and 5 mg melatonin in the evening for 10 weeks	Significant improvement in day:night sleep ratio	[56]
41 patients with probable AD	8.5 mg immediate release melatonin and 1.5 mg sustained release melatonin for 10 nights	Non-significant effects on sleep and circadian rhythms	[57]
80 patients with mild to moderate AD	2 mg add-on PRM for 6 months	Better sleep efficiency	[47]
8 patients with mild-to-moderate AD	5 mg fast-release melatonin for 2 nights	Significant decrease of EEG coherences in the $\beta_2$ , $\beta_1$ and $\gamma$ bands in the right hemisphere during NREMS-3	[58]

Abbreviations: AD, Alzheimer's disease; PRM, prolonged-release melatonin; EEG, electroencephalogram; NREMS, non-rapid eye movement sleep.

## 6. Conclusions

In summary, sleep and circadian rhythm disorders may induce AD by exacerbating neuroinflammation, aggravating oxidative damage, promoting A $\beta$  and Tau deposition, while the synthesis and secretion of melatonin can regulate sleep and circadian rhythm changes. Exogenous melatonin supplementation can effectively improve sleep and circadian rhythm disorders. Therefore, melatonin might be used to treat sleep and rhythm disorders, prevent AD, slow down the course of AD, or improve the pathological manifestations of AD. Melatonin has already been recognized by the public for its safety and benefits. Surprisingly, melatonin may probably even improve the cognition and memory of AD patients. However, the current studies are based on a small sample of participants and a lack of enough data. Therefore, more researches are required to further study this promising topic. With the continuous perfection of future research, more melatonin-related drugs may be available to the public and improve the outcome of AD patients.

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