Review

Sleep disorders in Alzheimer's disease: the predictive roles and potential mechanisms

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Abstract

Sleep disorders are common in patients with Alzheimer's disease, and can even occur in patients with amnestic mild cognitive impairment, which appears before Alzheimer's disease. Sleep disorders further impair cognitive function and accelerate the accumulation of amyloid-β and tau in patients with Alzheimer's disease. At present, sleep disorders are considered as a risk factor for, and may be a predictor of, Alzheimer's disease development. Given that sleep disorders are encountered in other types of dementia and psychiatric conditions, sleep-related biomarkers to predict Alzheimer's disease need to have high specificity and sensitivity. Here, we summarize the major Alzheimer's disease-specific sleep changes, including abnormal non-rapid eye movement sleep, sleep fragmentation, and sleep-disordered breathing, and describe their ability to predict the onset of Alzheimer's disease at its earliest stages. Understanding the mechanisms underlying these sleep changes is also crucial if we are to clarify the role of sleep in Alzheimer's disease. This paper therefore explores some potential mechanisms that may contribute to sleep disorders, including dysregulation of the orexinergic, glutamatergic, and γ-aminobutyric acid systems and the circadian rhythm, together with amyloid-β accumulation. This review could provide a theoretical basis for the development of drugs to treat Alzheimer's disease based on sleep disorders in future work.

Key Words: Alzheimer's disease; amyloid-β accumulation; circadian rhythm; GABAergic system; glutamatergic system; non-rapid eye movement sleep; orexinergic system; sleep disorders; sleep fragmentation; sleep-disordered breathing

Introduction

Sleep is beneficial to cognitive function and the central nervous system; in particular, sleep can enhance learning and memory in humans (Diekelmann and Born, 2010; Porter et al., 2015). Sleep disorders are prevalent in healthy older people, and can include daytime sleepiness, napping, and nighttime sleep duration reduction. However, these disorders have been found to be more pronounced in patients with Huntington's disease, epilepsy, and Alzheimer's disease (AD) (Baker et al., 2016; Shen et al., 2017; Fujisawa et al., 2019). Sleep disorders in AD mainly manifest as insomnia, an altered wake-sleep rhythm, sleep fragmentation, sleep-disordered breathing, restless legs syndrome, and rapid eye movement (REM) sleep behavior disorder (Cordone and De Gennaro, 2020). AD is the most widespread form of dementia; it is most prevalent in older people, and its primary clinical manifestations are memory and cognitive impairment. Given that the pathogenesis of AD has not been fully elucidated, the current research focus is on AD prevention. For this, finding predictors of AD and developing proper interventions will be essential.

Sleep disorders have been found to be effective in predicting the occurrence of AD (Most et al., 2012; Hahn et al., 2014). Additionally, sleep disorders promote the accumulation of amyloid-β (Aβ) and phosphorylated tau (Bubu et al., 2017; Spira et al., 2018); in turn, the levels of these two pathological biomarkers of AD can be reduced by improving sleep quality. Although sleep disorders can occur at any stage of AD, they most frequently occur in the pre-clinical phase of AD, such as during mild cognitive impairment (MCI), especially the amnestic MCI (aMCI) type. aMCI is a transitional stage between healthy aging and AD, and patients with aMCI are approximately 10 times more likely to develop AD than healthy individuals (Petersen et al., 2001).

Sleep electroencephalography (EEG) is an essential tool for detecting and evaluating sleep disorders. It reveals specific sleep changes in patients with AD with aMCI, which can be used to predict the progression of AD (Zhang et al., 2019). Abnormal sleep EEG mainly occurs during non-rapid eye movement (NREM). NREM sleep is mainly characterized by slow-wave sleep (SWS), sleep spindles, K-complexes, and slow-wave activity, which are altered in both aMCI and AD (Ju et al., 2017; Kam et al., 2019). Levels of Aβ and tau are usually abnormal in NREM sleep (Kam et al., 2019). Sleep fragmentation can occur in cognitively unimpaired older adults but is more pronounced in those with AD (Mander et al., 2017). Indeed, increased sleep fragmentation has been associated with cognitive impairment and a high risk of AD (Lim et al., 2013; Minakawa et al., 2017). Sleep-disordered breathing (SDB) is closely related to AD, and patients with

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aMCI with SDB are more likely to develop AD (Sanderlin et al., 2017). Moreover, obstructive sleep apnea (OSA) occurs in the majority of patients with SDB, accompanied by increased levels of Aβ and tau (Bubu et al., 2019). Continuous positive airway pressure has been reported to improve OSA and prevent AD development, thereby improving memory and cognitive impairment in patients with AD (Richards et al., 2019). This implies that targeting SDB may be a potential approach to prevent AD.

To better identify which strategies could prevent AD, it is important to explore the mechanisms underlying sleep disorders. Many studies have reported that changes in the characteristics of brain neurons, which occur in AD, are related to sleep function and multiple factors that contribute to sleep disorders. Dysregulation of the orexinergic, glutamatergic, and γ-aminobutyric acid systems and the circadian rhythm, together with Aβ accumulation, have been reported to be involved in sleep disorders during AD. These factors are not independent, and their interactions are thought to lead to sleep disorders in AD.

This article summarizes what is known about the relationships between sleep disorders and AD according to recent studies. Specifically, we focus on the roles of sleep disorders in predicting the occurrence of AD. Several potential mechanisms of sleep disorders in AD are described in this paper; these mechanisms provide a theoretical basis for the clinical prevention of AD, which is associated with sleep disorders.

Search Strategy and Selection Criteria

The studies reviewed in this manuscript were retrieved by an electronic search of the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/) for literature focused on sleep disorders in AD, between January 2015 and March 2020. The search terms used were “sleep”, “sleep disorders”, “Alzheimer’s disease”, “circadian rhythm”, and “non-rapid eye movement sleep”.

Potential Predictive Roles of Sleep Disorders in Alzheimer’s Disease

Abnormal NREM sleep

Compelling evidence has indicated that abnormal sleep architecture changes, such as changes in NREM sleep, occur in AD. Abnormal NREM sleep is characterized by several EEG changes, including decreased SWS activity, decreased sleep spindle activity, disrupted slow-wave activity, and K-complex density. Changes in specific components of NREM sleep have been related to the preclinical stage of AD (Cordone and De Gennaro, 2020).

EEG can be used to monitor and explore electrophysiological activity of the brain during sleep. The EEG spectrum can be divided into the following three frequency bands: 0–4 Hz, which comprises the delta band, 4–7 Hz (the theta band), and 8–13 Hz (the alpha band) (Bell, 2002; Ang et al., 2014). In recent years, EEG has been widely applied to study neurological diseases, such as epilepsy (Horvath et al., 2017). Although there is not yet any direct evidence of a causal relationship between sleep disorders and AD, the observed association between EEG changes and AD pathology has highlighted the various components of NREM sleep as possible targets for future innovative treatments (Cordone and De Gennaro, 2020). Changes in sleep EEG have been proposed as markers for the early prediction of AD development because they precede the occurrence of AD and may differ in various stages of AD (Horvath et al., 2018; Zhang et al., 2019). For example, amyloid precursor protein (APP) swe/PS1ΔE9 transgenic AD mice at 4 months of age (without any accumulation of Aβ or tau in brain) have been found to exhibit a 9.1% decrease in wakefulness and a 73.1% increase in NREM sleep in a 12-hour dark session, and a 22.5% increase in wakefulness and an 18.2% decrease in NREM sleep in a 12-hour light session when compared with wild-type mice. Furthermore, the sleep EEG changes observed were different to those of 6-month-old AD mice (Aβ depositions and obvious tau phosphorylation in the cortex and hippocampus were found) (Zhang et al., 2019). To be specific, 6-month-old AD mice exhibited an 8.1% decrease in wakefulness and a 46.7% increase in NREM sleep in a 12-hour dark session, and a 21.2% increase in wakefulness and 18.2% decrease in NREM sleep in a 12-hour light session. Moreover, the study found that AD mice had an overall lower theta and delta rhythm power during NREM sleep than the wild-type mice. In other work, both AD mice at 8–10 months and the Tg2576 mice at 12 months of age exhibited stage-dependent decreased in theta and delta power, and shifted in the power spectra toward higher frequencies, with a significant reduction in the slow-wave delta power in NREM sleep compared with wild-type mice (Kent et al., 2018; Kent et al., 2019). Reduced delta power during NREM sleep represents a sensitive and modifiable measure to evaluate disrupted sleep in AD. Further research is required to clarify the significance and molecular mechanisms of these early sleep EEG alterations in the development of AD.

It has been reported that patients with AD have decreased SWS, and that SWS duration was positively correlated with memory consolidation and negatively correlated with cognitive decline (Rauchs et al., 2013; Colby-Milley et al., 2015; Maestri et al., 2015; Cavuoto et al., 2019). SWS enhancers, such as trazodone, have been administered to improve NREM sleep and delay cognitive deterioration in patients with aMCI and AD, which has been found to stabilize the circadian rhythm in patients with AD (Grippe et al., 2015; La et al., 2019). Thus, a decrease in SWS could be considered as a potential marker of AD and a therapeutic target for AD prevention. However, a decrease in SWS is also a characteristic of healthy aging (Pace-Schott and Spencer, 2015), and so this alone may not be an independent predictor of AD; better predictive results could perhaps be achieved by combining this feature with other AD-specific NREM components. Regarding sleep EEG, patients with AD have been found to have faster mean theta frequency during SWS than age-matched controls, and correlation analysis revealed that this change was associated with better delayed episodic recall (Hot et al., 2011). Notably, the authors found that abnormal NREM sleep was associated with AD pathological features, Aβ and tau. During SWS, the clearance of neuronal metabolites was high, and its dysregulation could therefore lead to metabolic dysfunction. Thus, targeting SWS could be an ideal method to regulate the levels of Aβ and tau. In cognitively normal older people, reduced SWS has been associated with increased cerebrospinal fluid Aβ (Varga et al., 2016; Ju et al., 2017), which suggests that the reduction of SWS leads to the conversion of soluble brain Aβ levels prior to Aβ accumulation (Varga et al., 2016). Furthermore, the disruption of slow-wave activity (0.6–1 Hz) during NREM sleep also significantly increased the levels of Aβ and tau. Another recent study found that, in healthy subjects, the reduction of slow-wave activity was associated with increased Aβ accumulation and hippocampal-neocortical memory transformation (Mander et al., 2015). Cortical sleep spindles display 11–16 Hz bursts of activity generated within the thalamocortical network during NREM sleep (N2-3) (Luthi, 2014). Both patients with aMCI and AD have been found to show significant spindle density reduction (Gorgoni et al., 2016). A decreased spindle activity has been associated with tau level and could represent early tau-related dysfunction in AD, reflecting axonal damage or altered tau secretion, and could thus hold potential as a new biomarker for the early detection of neuronal dysfunction in AD (Kam et al., 2019). A reduction in sleep spindles has also been associated with the decline in sleep-dependent memory

and learning ability, with a specific decline in fast spindles in aMCI and AD (Lustenberger et al., 2015; Laventure et al., 2016). Furthermore, the K-complex – one of the hallmarks of NREM sleep – is regarded as a foundation of SWS (De Gennaro et al., 2000). A significant decrease in K-complex density during NREM sleep (N2) has been found in AD, and K-complex density has also been found to be positively correlated with cognitive decline (De Gennaro et al., 2017; Reda et al., 2017). Moreover, patients with AD have been reported to exhibit a significant decrease in K-complex density in the frontal lobe compared with patients with aMCI and healthy controls, while no differences were observed between patients with aMCI and healthy controls (Lucey, 2017; Reda et al., 2017). This indicates that while the decrease in K-complex density cannot discriminate MCI from healthy aging, it can distinguish patients with AD from healthy people.

Sleep fragmentation

Objective changes of sleep architecture in polysomnography manifest as a decreased total sleep time and sleep efficiency. The number of sleep phase transitions has been reported to be increased in those with sleep disorders, with sleep fragmentation (Peter-Derex et al., 2015). Sleep fragmentation refers to the phenomenon of repeated awakenings during sleep, whereby the duration between each awakening becomes shorter (Guzman-Marin et al., 2007). Sleep fragmentation is a hallmark of several sleep disorders, and often indicates a decline in sleep quality. Increased sleep fragmentation due to intermittent nocturnal arousal can result in a reduction of total sleep time and sleep efficiency, which is common among individuals with normal cognitive function (Li et al., 2018). However, this symptom is more prevalent in patients with aMCI and AD (Sethi et al., 2015; Mander et al., 2017; Palmer et al., 2018). Sleep fragmentation has been found to be correlated with cognitive and memory decline, whereby more sleep fragmentation was associated with a greater memory decline (Shin et al., 2014; Sethi et al., 2015; Manousakis et al., 2018). Furthermore, epidemiological data have shown an association between high levels of sleep fragmentation and the risk of AD. For example, a prospective cohort study based on 737 community-dwelling older people without dementia revealed that individuals with more sleep fragmentation had a 1.5-fold risk of developing AD compared with subjects with less sleep fragmentation, and that increased sleep fragmentation was positively associated with cognitive decline (Lim et al., 2013). Notably, sleep fragmentation was associated with increased Aβ accumulation in that study. Altered proteostasis caused by increased sleep fragmentation may lead to high levels of Aβ in the brain; moreover, the severity of Aβ deposition has been found to be significantly positively correlated with the degree of sleep fragmentation (Minakawa et al., 2017). Nevertheless, the mechanism underlying the exacerbation of Aβ deposition during sleep fragmentation has yet to be elucidated. In cognitively normal older subjects, sleep fragmentation was found to mediate the relationship between fronto-hippocampal hypometabolism and lower executive functioning (Andre et al., 2019). Furthermore, increased sleep fragmentation was associated with thalamic atrophy and ventromedial prefrontal Aβ burden; the thalamus and ventromedial prefrontal cortex are particularly sensitive to aging and are affected in the early stages of AD. However, in participants with cognitive decline, sleep fragmentation did not contribute to their cognitive deficits. These findings suggest that sleep fragmentation may directly contribute to a lower cognitive performance in cognitively normal older subjects. Therefore, treating sleep disorders in healthy older people by improving sleep quality before the onset of cognitive deficits may help to lower the risk of developing AD and maintain cognitive function.

Sleep-disordered breathing

SDB is characterized by abnormal breathing patterns or insufficient ventilation during sleep. It is a common sleep disorder that is associated with numerous adverse health consequences, such as cardiovascular risk (Stadler et al., 2018), diabetes (Lee et al., 2019a), hypertension (Lombardi et al., 2018), and cognitive impairment (Osorio et al., 2015). In recent years, epidemiological studies have shown a relationship between SDB and AD, and reported that SDB may predict the risk of AD (Lutsey et al., 2018; Shi et al., 2018). Indeed, patients with SDB (and MCI) reportedly have a higher susceptibility to AD (Sanderlin et al., 2017), and to be almost 1.58-fold more likely to develop AD than those without SDB (Lee et al., 2019b). OSA accounts for the majority of SDB cases and is estimated to affect 3–7% of men and 2–5% of women in the general population. OSA is characterized by intermittent hypoxemia during nocturnal sleep, which is repetitive partial or complete airway collapse, resulting in sleep fragmentation and poor sleep quality (Lam et al., 2010). Several factors can cause OSA and increase the risk of AD development, such as abnormal sleep architecture (Menon et al., 2019), the APOE ε4 genotype (Ding et al., 2016; Elias et al., 2018), oxidative stress (Andrade et al., 2018), intermittent hypoxia (Sharma et al., 2018), cardiovascular comorbidities (Berger et al., 2019), and neuroinflammation resulting from the aberrant proliferation of astrocytes (Macheda et al., 2019). Notably, patients with AD have a 5-fold higher incidence of developing OSA than cognitively normal subjects of a similar age (Emamian et al., 2016). More importantly, OSA may accelerate the progression of AD-induced cognitive impairment. Accordingly, continuous positive airway pressure treatment of OSA has been reported to significantly reduce and delay cognitive decline in patients with aMCI and AD (Troussiere et al., 2014; Richards et al., 2019). Furthermore, OSA has been associated with the accumulation of pathological biomarkers of AD such as Aβ. For example, it has been reported that patients with OSA exhibit significantly higher serum levels of $A\beta_{40}$, $A\beta_{42}$, and total Aβ levels than patients without OSA, and all three biomarkers were positively correlated with the severity of OSA (Bu et al., 2015). However, cerebrospinal fluid $A\beta_{40}$ and $A\beta_{42}$ levels were lower, while the cerebrospinal fluid tau level was higher in patients with OSA than in controls (Bubu et al., 2019; Liguori et al., 2019). OSA has also been found to accelerate Aβ accumulation and contribute to the development of AD (Yun et al., 2017). Given the high incidence of SDB in patients with MCI and AD, more clinical attention should be paid to this condition.

Potential Mechanisms of Sleep Disorders in Alzheimer's Disease

Orexinergic system dysregulation

The orexinergic system is involved in the regulation of the sleep-wake cycle, and is mainly located in the lateral hypothalamus (Ma et al., 2016; Wang et al., 2018). Orexin, also known as hypocretin, is a hypothalamic neurotransmitter that plays a central and critical role in this system (Roohbakhsh et al., 2018). The concentration of cerebrospinal fluid orexin has been found to be abnormally elevated in patients with aMCI, and this elevation has been associated with hypothalamic dysfunction (Liguori et al., 2016, 2017b). Dysregulation of the orexinergic system has also been implicated in sleep disruption and AD pathology; this dysregulation has been found to be involved in even the earliest stages of AD, during which it causes an increased sleep latency, sleep fragmentation, and REM sleep disruption (Liguori et al., 2016, 2018). Additionally, dysregulation of the orexinergic system was reported to be closely associated with increased Aβ, and the interaction had a significant impact on sleep disorders (Gabelle et al., 2017). In other work, the administration of $A\beta_{25–35}$ was found to significantly decrease NREM sleep duration, while it increased

wakefulness in mice; the levels of tau, p-tau, orexin, and orexin neurons expressing the adenosine A1 receptor were markedly up-regulated in the brain tissue of AD mice, and the adenosine A1 receptor or orexin knockdown inhibited the increase of tau expression levels induced by $A\beta_{25-35}$ in AD mice (Liu et al., 2019). Furthermore, injection of orexin into the lateral ventricle increased wakefulness and interstitial fluid Aβ levels (Liao et al., 2015). These experimental results suggest that sleep disorders are regulated by the interaction between Aβ and orexin.

One newly proposed mechanism connecting AD and sleep disorders is that orexin might hinder Aβ degradation by suppressing phagocytosis and autophagic flux in microglia (An et al., 2017), which suggests that subdued microglial function induced by sleep disturbance may increase Aβ accumulation in the brain. Moreover, the modulation of orexin and its effects on sleep appear to regulate Aβ levels. For example, in one study, APP/PS1 transgenic mice whose orexin gene was knocked out showed a significant decrease in the expression of Aβ and an increase in sleep duration; however, sleep deprivation or increasing wakefulness by rescue of orexinergic neurons increased Aβ levels in the brain (Roh et al., 2014). Interestingly, poor sleep quality, such as intermittent short sleep, which triggers sustained interruption of sleep-wake activity, can adversely affect the orexinergic system function in patients with AD (Zhu et al., 2016; Liguori et al., 2017a). The reduction of intermittent short sleep-induced orexinergic neuron projections may stimulate the release of orexin, which strengthens the interconnection between the orexinergic system and its outputs (Liguori et al., 2017a). On the basis of the above results, we can speculate that there is a bi-directional relationship between sleep disorders and orexinergic system dysregulation, which should be investigated further in future work.

Glutamatergic and GABAergic system dysregulation

Glutamatergic and GABAergic system dysregulation is closely related to the development of AD. Glutamate and GABA are the main excitatory and inhibitory neurotransmitters in glutamatergic and GABAergic systems, respectively. Data from prior studies have indicated that GABAergic neurons in the ventrolateral preoptic nucleus and the parabrachial nucleus (PBN) activate and maintain sleep. Glutamatergic neurons in the PBN are also thought to play a significant role in wakefulness (Torterolo et al., 2011; Scammell et al., 2017). Glutamatergic neurons in the PBN receive the inhibitory inputs from GABAergic neurons via the ventrolateral preoptic nucleus to promote the consolidation of NREM sleep, while GABAergic neurons in the PBN are active during NREM sleep and control the NREM sleep state (Qiu et al., 2016). GABAergic neurons are also vital to the NREM-REM transition and REM sleep maintenance (Lu et al., 2018). One study found that AD mice exhibited sleep disorders in which wakefulness was increased and NREM and REM sleep were decreased. Activity of GABAergic neurons was suppressed in the ventrolateral preoptic nucleus; in the PBN, GABAergic activity was suppressed, while glutamatergic activity was elevated. A neurotransmitter analysis also revealed a reduction of GABA in the ventrolateral preoptic nucleus and PBN, and an elevation of glutamate in the PBN; furthermore, micro-injection of GABA into the PBN improved sleep disorders (Cui et al., 2018). GABAergic neurons in the parafacial zone also reportedly participate in the initiation and maintenance of SWS and cortical slow-wave activity during NREM sleep (Anaclet et al., 2014; Saper and Fuller, 2017). However, GABAergic neurons in the parafacial zone have been found to obviously decrease 7 days after the establishment of AD rats induced via intracerebroventricular injection of streptozotocin, which was accompanied by increased wakefulness and decreased REM and NREM sleep from 14 days (Song et al., 2018). Slow-wave oscillations are a prominent feature during NREM sleep, and play an important role in memory consolidation, but this feature is abnormal in AD. Its dysfunction can be rescued by application of GABA, which strengthens the inhibitory effect of the GABAergic system (Busche et al., 2015; Kastanenka et al., 2017). This finding indicates that neurotransmitter replacement therapy (such as replacement of GABA) could help to treat sleep disorders and prevent AD, but this possibility requires further investigation. Moreover, inhibition of metabotropic glutamate receptors (mGluR5) have been found to consolidate deep sleep and elicit functional activity in slow-wave oscillations, while activation of mGluR5 increased wakefulness and decreased deep sleep (Ahnaou et al., 2015).

Although few studies have examined the role of the glutamatergic and GABAergic systems in AD-associated sleep disorders, this does not obscure their evidently important roles in sleep disorders and AD. Future work should be conducted to better understand the impact of the balance between glutamate and GABA on normal sleep, as well as the role of neurons that contain them. It seems likely that treating sleep disorders with these two transmitters may help to delay AD.

Circadian rhythm dysregulation

AD is often accompanied with sleep-wake cycle disruption. It has been reported that the circadian rhythm changes before AD development (Oyegbami et al., 2017). The sleep-wake cycle is controlled by mechanisms underlying the regulation of the circadian rhythm (Weissova et al., 2016). The circadian rhythm is modulated by the endogenous circadian clock system, which is housed within the suprachiasmatic nucleus (SCN) of the hypothalamus (Coogan et al., 2013). The mammalian circadian clock and its related clock genes play a significant role in regulating the sleep-wake cycle. A dysregulated circadian rhythm has been reported in aMCI and AD (Oyegbami et al., 2017; Brown et al., 2018; Petrasek et al., 2018). Circadian rhythm changes in AD have been associated with sleep disorders, such as sleep fragmentation at night, increased sleep, and decreased activity in the daytime (Manousakis et al., 2018; Kaladchibachi et al., 2019). Specific sleep changes caused by circadian disruption include an imbalance between NREM and REM sleep (Moreira et al., 2017; Venner et al., 2019). Recent data have indicated that clock gene expression levels are abnormally altered in AD. For example, one study found that the expression of Per1, Per2, Cry1, and Cry2 in the medulla/pons was increased at night in 2-month-old APP/PS1 transgenic mice compared with wild-type mice (Oyegbami et al., 2017). Moreover, another study reported that the expression of clock gene Bmal1 was increased in the parietal cortex and cerebellum, while Prok2 was increased in the parietal cortex and the hippocampus of the AD mice (Petrasek et al., 2018). The expression of clock genes in the SCN has also been found to be disrupted in AD mice (Bellanti et al., 2017). Although the AD mice had no noticeable pathological alterations, this study revealed aberrant Per gene expression in the SCN. Accordingly, the AD mice showed a phase delay in the expression of Per1 and Per2 mRNA in the SCN, whereby Per1 and Per2 mRNA levels were significantly decreased (Wu et al., 2018). Disruption of the circadian rhythm impairs sleep and contributes to AD pathology by regulating brain regions that control the circadian rhythm. The circadian rhythm also plays a critical role in AD development by increasing the cleavage of APP, which produces Aβ, thereby severely disrupting the circadian rhythm and reducing the expression of clock protein PER in the SCN (Blake et al., 2015). Additionally, there was a significant Aβ toxicity that triggered morphological and functional signaling deficits in central clock neurons in a Drosophila model of AD (Chen et al., 2014). Tau lesions can also disrupt the circadian rhythm. Indeed, the presence of tauopathy in the SCN has been reported, and the expression of PER2 and BMAL1 was disrupted in the hypothalamus of AD mice (Stevanovic et al., 2017).

Melatonin is considered to be the most effective regulator of the circadian rhythm, and its secretion is regulated by light signals (Lok et al., 2019). Melatonin exerts biological effects by regulating SCN activity (Pevet et al., 2017). Previous work has confirmed that the levels of melatonin are decreased in patients with AD, and this has been related to the dysregulation of the circadian rhythm (Zhang et al., 2016). Clinical trials and meta-analysis have also shown that treatment with melatonin effectively improved sleep disorders in patients with AD, including prolonging total sleep time, improving REM sleep behavior disorder symptoms, and reducing sleep fragmentation (Kwon et al., 2015; Zhang et al., 2016; Wang et al., 2017; Cruz-Aguilar et al., 2018). Genetic susceptibility is also thought to be involved in circadian rhythm dysregulation. The APOE ε4 allele is an ordinary genetic risk factor for AD, and its gene dosage has been found to have an effect on AD. For instance, heterozygotes (one copy) carrying the ε4 allele has been estimated to increase the risk of AD by 3-fold, while homozygotes (two copies) has been found to increase the risk by 8–15 times (Corder et al., 1993; Farrer et al., 1997; Burke et al., 2016). However, in AD mice, APOE ε4 deficiency has been found to cause the degeneration and disturbance of SCN neurons (Zhou et al., 2016).

To summarize, circadian rhythm dysregulation leads to sleep disorders and is involved in various factors associated with AD, including the disrupted expression of circadian clock gene (especially in the SCN), AD pathology (Aβ and tau), genetic susceptibility (APOE ε4), and the disrupted expression of melatonin. However, there also seem to be correlations between these factors. Future research is needed to determine which factors initiate circadian rhythm dysregulation.

Aβ accumulation

Does sleep disturbance drive Aβ, or does Aβ drive sleep disturbance? Clinical studies have confirmed that there is a bi-directional relationship between sleep disorders and Aβ; sleep disorders promote the production and accumulation of Aβ (Chen et al., 2017, 2018; Ju et al., 2017; Shokri-Kojori et al., 2018; Zhao et al., 2019), and the accumulation of Aβ may trigger sleep disorders (Brown et al., 2016; Kincheski et al., 2017), which may create a positive feedback loop for AD development. This article describes the molecular mechanisms of Aβ-induced sleep disorders at the cellular level. $A\beta_{42}$-mediated c-Jun N-terminal kinase (JNK) activation has been found to induce aberrant axonal arborization of wake-promoting pigment-dispersing factor (PDF) neurons, and may thus be a possible mechanism underlying sleep disorders (Song et al., 2017). The authors found that $A\beta_{42}$ significantly reduced sleep in a Drosophila model of AD, and this was accompanied by the post-developmental axonal arborization of PDF neurons associated with JNK activation, which can regulate sleep arousal activity. PDF neurons over-released PDF, which caused sleep impairment, while inhibition of JNK activation restored nighttime sleep loss and decreased $A\beta_{42}$ accumulation (Song et al., 2017). Additionally, a transgenic Drosophila model expressing $A\beta_{42}$ in neurons displayed significantly low levels of consolidated sleep, an effect that was associated with the expression of fatty acid-binding proteins (Fabp). In other work, it was found that Fabp ameliorated $A\beta_{42}$-induced sleep disruption in a Drosophila model of AD (Gerstner et al., 2017). However, this study did not investigate whether Fabp expression was associated with Aβ. Therefore, future work should examine whether the loss of Fabp expression mediates Aβ-induced sleep disorders, and the use of hFabp7 transgenic Drosophila may help to explore this relationship.

Moreover, increased neuronal excitability is thought to be associated with sleep disorders in AD. However, recent research has demonstrated that neuronal hyperexcitability may simply be a mediator of Aβ toxicity. Aβ expression has been found to enhance neuronal excitability in a Drosophila model of AD, and this was caused by defects of specific K^+ currents (Tabuchi et al., 2015). APP has also been reported to affect the regulation of the sleep-wake cycle in AD. In one study, the overexpression of APP in glial cells led to reduced nighttime sleep and prolonged sleep duration, which was associated with the up-regulation of glutamine synthase and innexin2 expression; furthermore, down-regulating the expression of glutamine synthase or increasing the expression of dEaat1 (the glutamate transporter protein) reversed the sleep disorders caused by APP (Farca Luna et al., 2017). These results suggest that APP regulates sleep by affecting glutamine recycling. In conclusion, Aβ, one of the pathological markers of AD, is closely related to sleep disorders. Moreover, Aβ could also affect sleep by interacting with other sleep regulation mechanisms, such as the orexinergic system and the SCN (**Figure 1**).

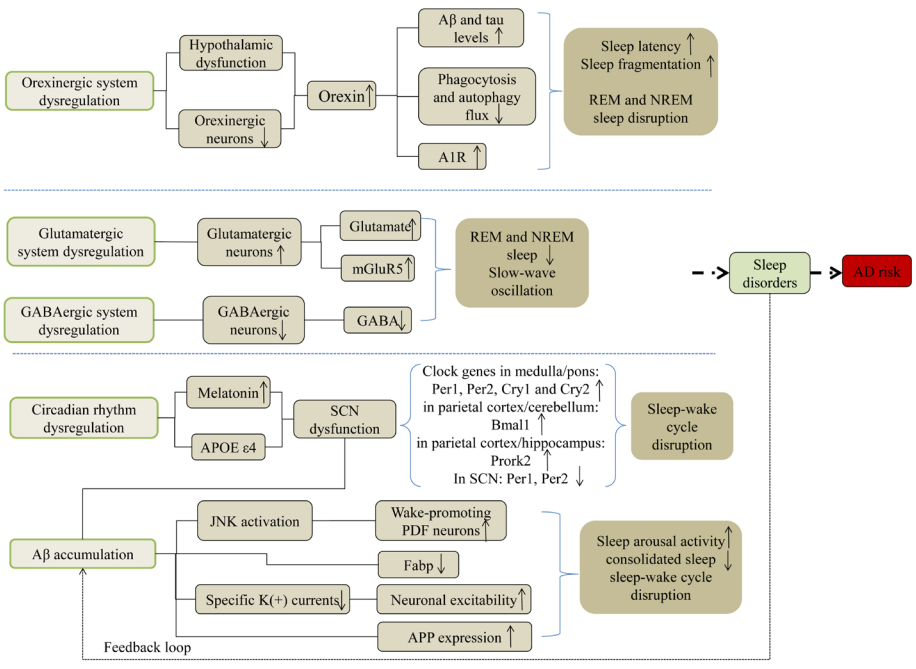

Figure 1 | Candidate mechanisms of sleep disorders in AD.
There are several potential mechanisms of sleep disorders in AD, including dysregulation of the orexinergic, glutamatergic, and γ-aminobutyric acid systems and the circadian rhythm, together with Aβ accumulation. Notably, Aβ accumulation and sleep disorders appear to constitute a vicious feedback loop that promotes AD. A1R: Adenosine A1 receptor; AD: Alzheimer's disease; APOE: apolipoprotein E; APP: amyloid precursor protein; Aβ: amyloid-β; Fabp: fatty acid-binding protein; GABA: γ-aminobutyric acid; JNK: c-Jun N-terminal kinase; mGluR5: metabotropic glutamate receptors; NREM: non-rapid eye movement; PDF: pigment-dispersing factor; REM: rapid eye movement; SCN: suprachiasmatic nucleus.

Conclusions and Future Directions

Sleep disorders are pervasive in AD, and can seriously affect the quality of life of patients with AD. Many epidemiological and experimental results have indicated that sleep disorders may promote the accumulation of Aβ and tau, leading to a decline in memory and cognitive function, thus accelerating and worsening the course of AD. In the current review, we present evidence on the roles of sleep in AD from two aspects: the predictive effects of sleep disorders in AD, and candidate underlying mechanisms. There are various forms of sleep disorders, and a single altered indicator has a low sensitivity and specificity for predicting AD. Thus, it may be necessary to establish a large-sample, multivariable, longitudinal cohort study in the future to evaluate the effectiveness of the combination of multiple sleep disorder predictors in the early prediction of AD. Furthermore, randomized controlled clinical trials on interventions for sleep disorders during the pre-clinical stage of AD could help to determine whether sleep disorders are reliable biomarkers for AD prediction. We have also reviewed the potential underlying mechanisms of sleep disorders, the understanding of which could help to establish drug treatment targets for AD prevention. To be specific, apart from melatonin mentioned above, trazodone (sedating antidepressant) has been shown to have a good efficacy in improving sleep disorders for the treatment of AD (Camargos et al., 2014). Regarding other pharmacological treatments, such as melatonin receptor agonists, hypocretin receptor antagonists, and circadian clock modification, relevant drugs are under development (Urrestarazu and Iriarte, 2016). Future studies should try to identify upstream targets of sleep disorders from various perspectives, such as the circadian rhythm and orexinergic system.

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