Cellular Signalling 64 (2019) 109420

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Review

Alzheimer's disease pathogenesis: The role of disturbed sleep in attenuated brain plasticity and neurodegenerative processes

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ARTICLE INFO

Keywords:
Hippocampus
Sleep
Memory
Alzheimer
Amyloid-beta
Orexin
Locus coeruleus
Cytokines
Inflammation
Cofilin

ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive impairments. The classical symptoms of the disease include gradual deterioration of memory and language. Epidemiological studies indicate that around 25–40% of AD patients have sleep-wake cycle disturbances. Importantly, a series of studies suggested that the relationship between AD and sleep disturbance may be complex and bidirectional. Indeed, accumulation of the extracellular neuronal protein amyloid-beta (Aβ) leads to altered sleep-wake behavior in both mice and humans. At the same time, disturbances of the normal sleep-wake cycle may facilitate AD pathogenesis. This paper will review the mechanisms underlying this potential interrelated connection including locus coeruleus damage, reductions in orexin neurotransmission, alterations in melatonin levels, and elevated cytokine levels. In addition, we will also highlight how both the development of AD and sleep disturbances lead to changes in intracellular signaling pathways involved in regulating neuronal plasticity and connectivity, particularly extremes in cofilin phosphorylation. Finally, current pharmacological and nonpharmacological therapeutic approaches will be discussed.

1. Introduction

In 2015 more than 47 million people worldwide were affected by Alzheimer's disease (AD) and other forms of dementia, and according to the World Health Organization the number is expected to rise to approximately 150 million by 2050. Clinically, this form of dementia is hallmarked by cognitive decline, learning and memory problems, and personality disorders [1]. AD negatively impacts both life quality and expectancy [2]. AD is also one of the most common progressive neurodegenerative disorders, associated with irreversible degeneration of the brain [3]. It takes many years for AD to progress from mild cognitive impairments (MCI) to advanced dementia [4]. However, the first (positron emission tomography) (PET)-based detectable pathology of the disease occurs about 15 years before any cognitive symptoms appear, a period referred to as preclinical AD [4]. To date, no treatments exist despite over a hundred agents being tested in phase I and II clinical trials, which act as either disease-modifying therapies or symptomatic cognitive enhancers [5]. Because of the increase in human longevity, the disease has become a major health and economic challenge worldwide [6]. As a result, major efforts are undertaken to identify markers and symptoms to detect AD in its earliest stages.

The neuropathological diagnosis of AD is quite often not confirmed until postmortem, diagnosed by characteristic cortical degeneration shown on MRI/CT scans, and determined by the presence of neurofibrillary tangles (NFTs) and amyloid-β (Aβ) plaques in neocortical and subcortical regions of the brain [7,8]. NFTs are composed of highly phosphorylated forms of the tubulin-associated unit protein (tau) [9]. As indicated by correlational PET scan studies, the accumulation of NFTs and tau phosphorylation are associated with neuronal dysfunction and cognitive deterioration in AD [9]. The occurrence of these neuropathological hallmarks is most prominent in brain regions essential for cognitive function such as the entorhinal cortex and hippocampus [10].

The second main feature in AD pathogenesis is the composition of strings of Aβ peptides that can form beta sheets. These sheets can then accumulate further to form Aβ plaques [7]. Aβ plaques occur in the brain during the earliest stage of preclinical AD [11,12]. The Aβ plaques can be detected in humans by PET [13], and evaluated in cerebrospinal fluid (CSF). Other hallmarks like tau aggregation into intracellular NFTs, synaptic dysfunction, neuronal loss, and cognitive impairment have all been correlated with Aβ accumulation [11,12]. In

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https://doi.org/10.1016/j.cellsig.2019.109420
Received 26 July 2019; Accepted 15 September 2019
Available online 16 September 2019

fact, due to a series of harmful risk factors, which we will describe below, Aβ can aggregate and start the progression of the AD [14].

The risk factors of AD partly depend on the form of the disease. There are currently two known forms of AD: the most common late-onset AD (LOAD) and early-onset AD (EOAD), the latter occurring in around 1% - 6% of all cases [15]. LOAD is characterized by an age higher than 65 years, whereas EOAD ranges from 30 years to 65 years [15]. Genetically, AD can be distinguished into familial form and sporadic form [15]. The familial AD is associated with amyloid APOE genotype and genetic alterations in genes including amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) [16]. Sporadic AD, which accounts for over 90% of all AD patients, is a multifactorial disease resulting from a combination of genetic and environmental factors [17]. The main factor in the sporadic form is age [17].

Interestingly, disturbed sleep is another factor of importance that can accelerate AD pathology [18,19]. For example, amyloid plaques and tau tangles are also commonly found in brain regions critical for the regulation and modulation of the sleep-wake cycle, including locus coeruleus, hypothalamus, and the cortical layers [20]. Importantly, the connection between AD pathogenesis at the level of Aβ and the disruption of the sleep-wake cycle is thought to be reciprocal [19]. Indeed, even a single night of sleep deprivation elevates Aβ levels in the human brain [21]. This clinical evidence is biologically backed up by rodent students showing that chronic sleep restriction in AD mouse models leads to elevated Aβ levels in interstitial fluid [22], whereas chronic sleep deprivation leads to Aβ accumulation [23]. Because loss of sleep has become a common feature of our modern society, it may be an increasingly important risk factor accelerating the development of AD. For this reason, the current review will describe recent work underscoring the potential interrelationship between disrupted sleep and the development of AD. It will also describe some of the potentially underlying molecular mechanisms and related therapeutic strategies (Fig. 1).

2. Alzheimer pathology and sleep wake cycle disturbances

To understand how AD and poor sleep interact with one another it is important to understand the basic properties of the two common sleep stages: rapid eye movement (REM) and non-rapid eye movement (NREM). In humans NREM sleep can be subdivided into three stages: N1, N2 and N3 [24]. During the N1 and N2 stage, EEG background consists of low amplitude and high-frequency waves, which gradually progress to high voltage and low frequency waves during the N3 [24,25]. The latter stage is also known as slow wave sleep (SWS) [24]. Further, NREM sleep is associated with behavioral quiescence, and a general decrease of synaptic activity [24]. REM sleep is characterized by low amplitude and high-frequency EEG background similar to the awake state. For this reason, REM is also called paradoxical sleep [24].

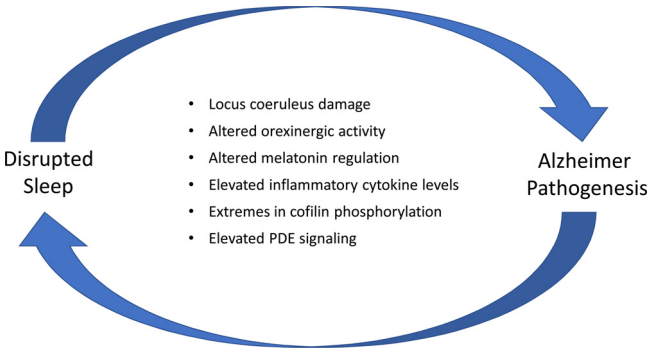

Fig. 1. The potential relationship between sleep disturbances and the development of Alzheimer's disease.
Multiple signaling mechanisms, affect both sleep homeostasis and quality as well as the development and progression of Alzheimer's disease (AD). Because of the potential bidirectional interrelationship between poor sleep and progression of AD, misregulation of these signaling mechanisms may not only directly accelerate the development of AD, which indirectly affects sleep quality. It may also affect sleep hygiene directly and through these mechanisms indirectly further accelerate the further development of AD.

Despite the reports that a large proportion of the patients perceive their sleep quality as satisfactory [26,27], approximately 25–40% of all patients with AD show impairments of sleep and circadian rhythms. Specifically, most of the AD patients have an increased latency to fall sleep and experience more frequent nocturnal awakenings leading to increased wakefulness at night [28,29]. The latter observation could very well relate to the in parallel reported daytime sleepiness [28,29]. Even individuals with the early hallmarks of AD show a decline in the duration of both REM and NREM sleep [30]. Most studies have reported similar decreases in REM sleep duration or percentages, although such changes were not observed in every study [31–33]. Regarding NREM sleep, alterations in slow-wave sleep and slow-wave activity have been observed in patients with early AD [34] and as such have been proposed as a potential biomarker to detect the early stages of AD [35]. For a comprehensive overview of specific EEG alterations during different stages of sleep see the recent report by Winsky-Sommerer and colleagues [25]. Finally, sleep disorders such as insomnia and sleep apnea are commonly observed in AD patients [28,29].

Examining the mechanisms underlying sleep phenotypes in AD is challenging, due to experimental limitations [36]. Nevertheless, correlative studies use actigraphy, a noninvasive method to assess rest and activity cycles, showed that cognitively normal individuals with Aβ deposition (detected by PiB PET imaging), have an increased nap frequency and decreased sleep efficiency in comparison with individuals without Aβ plaques [37]. It is suggested that those individuals with Aβ deposition have preclinical AD, and cognitive symptoms will develop in time [37]. Using (PET-scan in combination with amyloid imaging traces, Spira et al. indicated that older individuals with a shorter sleep duration were more likely to have Aβ depositions in cortical layers including the precuneus, the portion of the superior parietal lobe involved in memory function [38]. It is important to note, however, that some individuals with high loads of Aβ do not have any memory complaints or show neuronal degeneration. The latter may be a result of compensatory factors or potentially through an alternative mechanism through which cognitive capacity is maintained (for discussion see [39]).

Because the neural circuits and neurotransmitters responsible for sleep regulation are highly conserved between mammals [36], experimental animal models are widely used to understand associations between sleep disturbances and AD [40]. From these studies, a direct link between AD pathology and sleep disturbances was inferred using genetically engineered mice expressing amyloid and/or tau aggregates in the brain [41,42]. For example, in mice expressing APP, known as Swedish mutation Tg2576 line, accumulation of amyloid plaques was detected in brain regions critical for sleep/wake regulation, leading to sleep and circadian rhythm abnormalities [41–43]. A hallmark of recovery sleep following sleep deprivation is an increase in delta (1-4 Hz) power during non-REM sleep. Such a physiological response during recovery sleep is absent in APP mice, underscoring the affected sleep homeostasis in the mutant mice [42]. Furthermore, at 22 months of age (equivalent of approximately 65 years of age in humans), time-of-day-dependent modulation of sleep was blunted and the percentage of REM sleep was reduced in the same animals [42]. Even at the age of 12 months (equivalent of 40 years of age in humans), these mice already exhibited stage-dependent decreases in both theta and delta power, and shifts in the power spectra towards higher frequencies [43]. Also, APP/PS1 transgenic mice show an increase in wakefulness and reduced sleep time as early as 6 months of age. These behavioral phenotypes are accompanied by Aβ plaque formation in the hippocampus and neocortex [44]. At 9 months of age, plaque formation was observed

throughout the brain leading to an even more prominent disruption of the sleep-wake cycle with significantly increased wakefulness and decreased REM and NREM sleep [44]. Likewise, triple knock-in mice, generated by Platt and colleagues [45], were designed by targeted insertion of human amyloid and tau transgenes and crossed with an existing presenilin mutant mouse line. The triple transgenic mice expressed intra-neuronal amyloid deposits and hyperphosphorylated tau in hippocampus and cortex starting from 6 months of age. In line with the other models, the triple mutant mice exhibited enhanced wakefulness alongside with reduced NREM sleep, increased sleep fragmentation, and higher delta power during wakefulness and REM sleep. These phenotypes preceded deficits in hippocampal synaptic plasticity and memory formation, all emerging at approximately 12 months of age. Using a different AD mouse model harboring three mutations, including APP, PS1, and tau, Manaye and colleagues found that the age-related loss of noradrenergic neurons was observed in the locus coeruleus, a region critically responsible for orchestrating normal wakefulness [46]. Altogether, these studies show that the development of Alzheimer-like pathologies in murine animal models are associated with prolonged wakefulness, decreased sleep, and sleep quality (e.g. alterations in sleep architecture/ homeostasis). Together, the data from clinical studies in AD patients and from animal models of AD pathology underscore that Aβ deposition affects both sleep quality and duration and that specific sleep disturbances might be used as a potential biomarker to detect early AD pathology. In the next paragraphs, we will describe studies, which support evidence for a role in sleep-wake disturbances and sleep loss and the development of AD pathogenesis.

3. Sleep loss exacerbates AD pathology in animal models and humans

In the previous paragraphs, we described work in humans and animal models indicating that Aβ accumulation in the brain may affect both sleep duration and sleep quality [38,41,42,44–47]. However, sleep disturbance in turn may exacerbate the development of AD pathology. Indeed, a first hint that sleep and wakefulness influence the levels of soluble Aβ and plaque formation was obtained from animal studies. Kang et al., assessed the levels of soluble Aβ in the brain interstitial fluid (ISF) during the sleep-wake cycle in the APP (Tg2576) transgenic mouse model [22]. Mice were kept under standard light/dark (12 h/12 h) conditions and a diurnal Aβ pattern was observed [22]. Specifically, they found that the levels of soluble Aβ in the brains were around 25% higher in the dark phase (i.e. the period in which mice spend the majority of the time awake) than in the light phase (i.e. their inactive phase) [22]. Strikingly, the formation of amyloid plaques increased by two-fold, when sleep was disrupted for 4 h every day for 21 days [22]. These findings were replicated in two other frequently used Alzheimer mouse models [22]. Finally, using almorexant, an orexin receptor antagonist, to increase sleep time in mice, the authors found that Aβ plaque formation significantly reduced as a result of increased sleep time [22]. This elegant set of experiments suggests a direct relationship between the sleep-wake cycle, soluble Aβ, and Aβ plaque formation.

In human studies, a diurnal Aβ pattern in CSF was also observed [48]. As reported in the rodent studies, the soluble Aβ levels in CSF were higher during the waking phase, and lower during sleep [48]. While the levels fluctuated in young participants in a circadian fashion, they decreased in older participants with and without amyloid deposition [48]. Individuals with amyloid deposition lacked diurnal variation in the levels of soluble Aβ, especially in the level of $A\beta_{42}$ [48]. Furthermore, it is interesting to note that individuals with a PSEN1 or PSEN2 mutation but without Aβ aggregates have a normal diurnal variation of Aβ in CSF, while diurnal variation was disturbed in those expressing Aβ aggregates [48]. Furthermore, using PET and ^{18}F-florbetaben to measure brain Aβ burden in the brains of healthy controls, Shokri-Kojori and colleagues showed that Aβ accumulation was observed in the right hippocampus and thalamus following just a single night of sleep deprivation [21]. Related to these observations, Heneka and colleagues [49] examined in transgenic mice whether plaque formation was affected by experimentally-induced locus coeruleus degeneration, a common hallmark of early AD pathogenesis that diminishes cortical noradrenergic innervation [50]. The authors observed significantly more plaque formation in mice following early locus coeruleus degeneration than in age-matched control mice. Because the locus coeruleus region contributes to the regulation of the sleep-wake cycle, these findings suggest that disruption of the normal sleep-wake cycle may directly contribute to Aβ deposition [49]. In addition to these studies in which the indirect impact of sleep disturbances (by means of locus coeruleus damage) on the development of AD pathologies was assessed, many laboratories have examined the direct impact of sleep deprivation on the development of AD pathologies in rodent models. For example, Chen et al showed that as little as 2 to 4 days of sleep deprivation using the flowerpot method (a method that omits REM sleep and some non-REM sleep) not only causes cognitive impairments [51]. It also leads to increased levels of Aβ peptide. Likewise, hibernation studies in ground squirrels revealed that Aβ could reversibly be formed during periods of sleep loss-hibernation [52]. A likely explanation for the increase in Aβ peptide was the observed parallel elevation of the APP-cleaving enzyme 1 (BACE1, β-secretase). Together with the absence of changes in the levels of Aβ-degradation enzymes, this may ultimately lead to elevated $A\beta_{42–44}$ deposits [51].

In addition to examining the direct impact of sleep deprivation on the development of AD phenotypes in rodents, a few laboratories have attempted to replicate such studies in humans. For example, a study including 26 cognitively healthy male subjects, indicated that even a single night of sleep deprivation significantly increases the levels of $A\beta_{42}$ in CSF [53]. In addition, the authors observed that the levels of $A\beta_{42}$ decreased by 6% if sleep was normalized [53]. In line with these observations, others have reported that 36 h of sleep deprivation lead to a 25–30% increase in CSF $A\beta_{38}$, $A\beta_{40}$, and $A\beta_{42}$ concentration as a result of increased overnight production of Aβ [54]. Recent work using a PET approach by Shokri-Kojori and colleagues indicated that even a single night of sleep deprivation is sufficient to elevate Aβ levels, especially in the right hippocampus and thalamus [21].

An important question that remained unanswered was which aspect of sleep modulates Aβ levels in the human brain. Jiu and colleagues addressed this question by specifically disrupting slow-wave activity in healthy volunteers [55]. They found that the specific disruption of slow waves correlated with an increase in CSF $A\beta_{40}$ without affecting total protein, tau, or hypocretin levels. This effect was not correlated with sleep duration or sleep efficiency. Interestingly, the authors also observed that poor home sleep quality (assessed using actigraphy) is associated with increases in CSF tau. Related to these observations, the lab of David Holtzman recently showed that tau seeding and spreading are influenced by the sleep-wake cycle and sleep deprivation. ISF tau in mice and CSF tau in humans were elevated following sleep deprivation. Even more striking is the finding that chronic sleep deprivation increased tau pathology spreading [56]. These findings underscore the importance of unraveling the molecular underpinnings by which sleep loss and sleep disturbance facilitate the tau pathology.

In summary, the level of soluble Aβ and tau are fluctuating in a diurnal pattern with levels rising during wakefulness and decreasing during sleep. Disrupted sleep and sleep loss can lead to increased Aβ accumulation in both humans and rodents with poor sleep hygiene even leading to increased tau levels in the CSF. The underlying mechanisms connecting sleep-wake cycle disturbances and AD pathogenesis are still under investigation [57], although the aforementioned studies suggest that a dysregulation of Aβ kinetics may facilitate the AD pathogenesis in the sleep-deprived brain.

4. Potential molecular mechanisms underlying the relationship between disturbed sleep and AD pathology

Given the potential importance of disturbed sleep in the development and progression of AD, it is important to get a better understanding of the neurobiological, cellular and molecular mechanisms underlying the complex relationship between sleep and AD pathology [58]. Several molecular underpinnings have been described that may explain this potential relationship between sleep-wake cycle and AD pathogenesis. In the next set of paragraphs, we will discuss several of these potential mechanisms.

One possible mechanism is that oscillations in neuronal activity as observed during specific sleep stages and wakefulness lead to fluctuations in Aβ concentrations. At the neuronal level, non-REM sleep is associated with the quiescent state [22]. PET imaging can successfully be used to assess the cerebral metabolic rate during specific sleep/wake stages by measuring glycolysis levels of individuals during awake, REM, and non-REM state [59,60]. Glycolysis was similar in awake and REM stages, whereas it was decreased by 43.8% during the SWS stage [59,60]. These findings indicate that the differences between awake and deep-sleep stages are in part associated with the level of neuronal activity [59,60]. Indeed, in awake and REM stages, cortical neurons continuously fire, which leads to low amplitude and high-frequency EEG background [61,62]. In contrast, during the SWS stage, more high amplitude and low-frequency waves in EEG are detected due to neural oscillation between silent periods of hyperpolarization and depolarization [61]. Aβ is released into the brain ISF during neuronal firing or synaptic activity [63], suggesting that increased neuronal activity leads to a higher concentration of Aβ in ISF [63]. Because neurons spend most time in their 'silent stage' during SWS, it is believed that they release less Aβ at this stage, whereas the opposite effect is expected during other sleep or awake stages [63]. Indeed, Aβ levels are lower during sleep in both the ISF of mice and CSF of humans [22,42].

The aforementioned mechanism suggests that sleep may influence Aβ production through neuronal activity. However, one of the other mechanisms contributing to the AD pathogenesis is a failure to clear Aβ from the brain [4]. Different clearance systems are known to be responsible for soluble Aβ elimination from the brain [64]. Several rodent studies suggested, that around 75% of the extracellular Aβ is removed from the brain by the blood-brain barrier transport system, whereas merely 10% by means of the ISF bulk flow system [65]. However, the notion that the ISF bulk flow system only contributes to a minor portion of the Aβ removal was challenged by others. Using two-photon imaging studies, they showed that a specialized ISF bulk flow system, known as glymphatic system, which depends on astrocytic aquaporin-4 (AQP4) water channels, is responsible for more amounts of Aβ clearance than previously thought [66,67]. In the brain, this system channels ISF through astrocytes into the peripheral lymphatic system [67]. Iliff and his group injected radiolabeled Aβ into the mouse striatum, which allowed them to assess the activity of the clearance system. The authors showed that the rate by which this radioactive Aβ probe was removed from the brain was two times higher in control animals compared to AQP4 knockout mice, underscoring the importance of the AQP4 expressed in astrocytes for Aβ clearance [66].

Because sleep is one of the factors affecting the glymphatic system [68], it is interesting to speculate that the clearance of Aβ is higher during sleep and that, as a result, the sleep-wake cycle may influence the glymphatic clearance of Aβ [69]. Using two-photon imaging, Xie et al compared the level of cortical CSF influx during wakefulness, anesthesia, and sleep in mice [69]. Both sleep and anesthesia lead to a 60% increase in the interstitial space, indicating that the exchange between CSF with ISF during both sleep and anesthesia is altered [69]. As such, these results support the hypothesis, that brain clearance of Aβ (and other molecules) is indeed increased during sleep [69].

Orexin critically contributes to the organization of sleep-wake cycles. Orexin is a neuropeptide produced in the hypothalamus [70], and its levels in- and decrease during respectively wakefulness and REM sleep. Because impairments in the orexinergic system alter the dynamics of Aβ and tau proteins, orexin is also considered a possible mediator of the disrupted sleep-wake cycles in AD patients [70]. Indeed, intracerebroventricular administration of orexin in mice leads to increased wakefulness and significantly higher Aβ levels in the brain ISF [22]. Furthermore, application of an orexin receptor antagonist over a period of 24 h showed significantly reduced levels of Aβ [22]. Moreover, reduced plaque formation was observed, when the same antagonist was administered for an additional 8 weeks [22]. Based on these observations, Kang and colleagues hypothesized that orexin not only promotes wakefulness, which in turn is related to higher levels of Aβ in the brain, it also has a direct effect on Aβ dynamics [18,22].

To understand the molecular underpinnings mediating these effects, additional animal studies were performed to determine whether disruptions of the sleep-wake cycle or orexin-mediated wakefulness are causally related with abnormal Aβ metabolism. Using APP/PS1, the Holtzman lab examined whether orexin release directly or indirectly through the modulation of sleep affected development of AD pathology. Genetic ablation of the orexin gene in the APP/PS1 mutant mice reduced the amount of Aβ pathology in the brain and in parallel led to an increased sleep time. Furthermore, increasing wakefulness by restoring orexin receptor expression in the brains of APP/PS1 orexin knock-out mice or application of sleep deprivation elevated the amount of Aβ pathology in the brain [18]. Altogether, their important findings support the idea that orexin, through its role in wake regulation and neuronal activity, impacts the development of Aβ pathology [18]. As such, the orexinergic system remains a promising target for human studies to interrogate the relation between sleep and Aβ pathology in preclinical stage AD patients.

Melatonin is thought to be involved in regulating human sleep, and loss of it can lead to disturbances of both the sleep-wake cycle as well as circadian rhythms. Because the levels of melatonin are more than ten-fold higher during darkness [71], it is often referred to as a "dark" hormone. Melatonin is produced by the pineal gland [72] and is associated with neurodegenerative diseases including AD due its neuroprotective effects [73–75]. Indeed, administration of melatonin in mice decreased the production of Aβ [76]. Melatonin directly regulates the metabolism of APP, leading to lower levels of Aβ production [76]. Importantly, decreased levels of CSF melatonin were observed in patients carrying the ApoE4 allele (one of the main risk factors of AD) [76]. In parallel to the disturbances in the sleep-wake cycle, decreased levels of CSF melatonin are already detected during the preclinical stage of AD [77,78]. Altogether, these interesting findings corroborate the idea that the reduction of melatonin may indeed contribute to plaque formation by increasing Aβ levels in the brain [76], while in parallel negatively impacting the sleep-wake cycle. It is unclear, however, whether melatonin merely independently modulates both processes in parallel or whether the progression of AD and poor sleep quality by means of changed melatonin levels is directly interrelated.

The association between sleep deprivation and inflammatory responses has also been discussed in various conditions including AD [79]. The most frequently used approach to examine the relationship between sleep and inflammatory responses is by means of applying sleep deprivation. For example, total sleep deprivation for four nights increases levels of C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factors (TNF), with the increases of TNF already emerging after as little as two nights [80–82]. For a comprehensive overview of the impact of sleep deprivation on innate immunity see [83]. A second approach that has been used to study the link between sleep and inflammatory processes is by studying how inflammatory cytokines behave in insomnia [79]. Motivala et al. summarized that more chronic sleep disturbances also increases the expression of inflammatory cytokines like IL-6, CRP, and TNF-α in humans [84]. Furthermore, Chen et al. indicated that patients with mild or moderate stages of AD have increased levels of IL-1β and TNF-α [85]. In Alzheimer mouse models,

high levels of TNF-α are associated with increased Aβ production and decreased Aβ clearance. In contrast, TNF-α neutralization leads to opposite effects [86]. Inhibition of TNF-α signaling before the Aβ plaque formation, prevents hyperexcitability of glutamine synapse which relates with cognitive decline [87]. However, there is no evidence that TNF-α levels are increased at least in the preclinical stage of AD [88,89].

Another hypothesis related to AD and inflammation, is that the reciprocal association between sleep and immune responses is promoted by low-grade inflammation in aging [79]. The low-grade inflammation is characterized by multiple factors such as increased production of reactive oxygen species, and elevated levels of proinflammatory cytokines, like IL-6 and TNF [79]. Bjurstrom et al. indicated that increased expression of TNF-α and IL-6 correlates with better sleep maintenance and higher SWS percentage in older adults, while lower expression of proinflammatory cytokines were observed in the morning [90]. A period of sleep deprivation is normally accompanied by a typical homeostatic rebound with an increase in SWS and slow-wave activity. In elderly people, however, such a homeostatic rebound was reported to be absent [91]. As a result, long-term changes in sleep may elevate the amount of circulating proinflammatory compounds in the morning thereby facilitating inflammation [92]. At the same time, such increased levels of inflammatory markers may inhibit further activation of immune cells, which undermines a relationship between sleep maintenance and -depth with evening and morning fluctuations in cytokines production [93]. In line with this hypothesis, it should be noted that elderly people do not exhibit the increase in inflammatory cytokine production, while this is observed in young adults following acute sleep restriction [94].

In turn, proinflammatory cytokines as well as Aβ in AD brains are linked to increased levels of cytoplasmic rod-shaped bundles of filaments that are composed of ADF/cofilin-actin and conveniently called rods [95]. Cofilin, the major ADF/cofilin isoform in mammalian neurons, severs actin filaments at low cofilin/actin ratios and stabilizes filaments at high cofilin/actin ratios. Cofilin's phosphoregulation is a downstream target of many transmembrane signaling processes and its misregulation in neurons has been linked to AD in rodent models [96]. Cofilin is activated by dephosphorylation and is thought to be oxidized in stressed neurons bundling cofilin-actin filaments into stable rods. Rods form within neurites causing synaptic dysfunction by sequestering cofilin, disrupting normal actin dynamics, blocking transport, and exacerbating mitochondrial membrane potential loss [95,97,98]. Interestingly, recent work indicated that hippocampal cofilin activity is elevated following sleep deprivation [99]. Suppressing cofilin activity selectively in hippocampal neurons was sufficient to prevent the cognitive deficits and plasticity impairments associated with sleep deprivation, underscoring an important and causal role for cofilin signaling in the phenotypes associated with sleep loss. In this way, misregulation of cofilin signaling as a result of sleep deprivation may exacerbate the progression of AD at the molecular level. Cofilin signaling and its upstream signaling pathways may therefore also be valuable targets to combat the progression of AD as a result of sleep disturbances and sleep loss (Fig. 1).

5. Current therapies

At present, there are very limited therapies for AD patients with reported disturbances of their sleep-wake cycle [36]. Therapeutic approaches with emphasis on sleep hygiene may be a fruitful approach to slow the progression of AD. For this reason, it is important to further elucidate the interrelationship between AD and poor sleep quality, which eventually might contribute to new therapeutic approaches [58]. In order to fully understand the therapeutic potential of sleep therapy, longitudinal sleep studies should include patients with preclinical AD or individuals with genetic mutations, which are associated with a familial form of AD [100].

Current nonpharmacological strategies focus in some cases on “sleep hygiene” [101,102]. Recommendations for patients include limitations of caffeine and alcohol usage, keeping regular sleep-wake times, as well as avoidance of light exposure during the night time [101,102]. A major problem for institutionalized patients is insufficient light exposure during daytime [101,102]. A study by Shochat et al., indicated that the average time of natural sun light in a nursing home was as little as 1 min [102]. Unfortunately, the effect of morning bright light treatment for rest-activity disruption in AD patients seemed rather modest. Only in subjects with the most impaired rest-wake activity, a positive and significant impact of a brief (one hour) light treatment was observed [103].

The number of available pharmacological strategies focusing on enhancing sleep quality to combat AD are unfortunately limited [36]. Melatonin, trazodone, and ramelteon were tested in randomized studies as possible drugs to improve sleep quality [104]. Patients with moderate or severe AD stages were included in melatonin and trazodone trials, and mild and moderate stages patients were included in ramelteon studies [105–107]. Unfortunately, melatonin and ramelteon treatment did not lead to increased quality of sleep in patients [105–107]. In the trazodone studies, improvements were observed in sleep efficiency and total sleep time, but no changes were reported for daytime sleep [108]. Another interesting class of drugs with therapeutic potential that is linked to both AD and sleep are the type 4 phosphodiesterase inhibitors (PDE4 inhibitors). PDE4 inhibitors have shown to be promising cognition enhancers in clinical studies [109,110] and animal models [111]. Indeed, treatment with the PDE4 inhibitor rolipram was shown to make synapses and neurons more resistant to the damaging effects of Aβ, although the protective effects seem to be working through pathways bypassing Aβ itself [112,113]. In addition, more recent work highlighted the possibility that rolipram may also promote the clearance of aggregated tau [114]. Moreover, attenuated cAMP signaling, as a result of elevated activity of the PDE4 family, seems to be a causal factor in the detrimental effects of sleep loss on memory function [99,115–118]. Specifically, sleep loss upregulates the levels of PDE4A5 isoform in the hippocampus [115], which facilitates the dephosphorylation and activation of cofilin [99,117]. The increase in cofilin activity ultimately leads to spine loss, impairments in synaptic plasticity and memory storage [99,117]. Because suppressing cofilin function is sufficient to prevent these memory deficits [99,117], and the direct interaction between cofilin and PDE4 signaling [99,117,119], PDE4 inhibitors may be particularly promising as potential therapeutic tools to combat the impact of both sleep deprivation as well as AD. As such, therapy for AD patients with sleep disturbances focusing on PDE4-cofilin signaling still remains a promising area for future therapeutic development.

6. Conclusions

AD is the most common cause of dementia and includes around 50–70% of all dementia cases [3]. Around 50% of people by age 85 suffer from AD, since the risk of the disease highly increases with age [3]. Clinically, AD is associated with a gradual decline in cognitive function. It takes many years of progression from mild cognitive symptoms to develop severe dementia [4]. In the preclinical stage of AD, there are no cognitive symptoms yet as they appear only around 15 years later [4]. However, an increased level of Aβ peptide, as well as plaque formation, is already detected. Interestingly, during the preclinical AD, disruption of sleep-wake cycles is often observed. Indeed, around 25–40% of AD patients suffer from sleep disturbances, including reduced sleep efficiency, sleep fragmentation, and increased daytime napping. Earlier, multiple studies suggested that disrupted sleep-wake cycles are one of the potential risk factors for AD [58]. However, ongoing research underscored the idea that an impaired sleep-wake cycle is not only a result of the AD pathology, it in fact also exacerbates the AD pathology. Indeed, studies in both humans and animal models, have

indicated that accumulation of Aβ negatively impacts sleep quality. Furthermore, levels of soluble Aβ increase following sleep deprivation, which results in exacerbation of AD pathology. All these studies suggest that there are multiple mechanisms that impact both AD pathology and sleep-wake cycle. Decreased neuronal activity, altered activity of the glymphatic system affecting the transport of Aβ out of the brain, changed melatonin, orexinergic, cAMP-PDE and cofilin signaling, as well as increased inflammatory responses in the brain are potentially critical mechanisms associated with AD pathology and alterations in the sleep-wake cycle. Further studies are necessary in order to fully elucidate the underlying mechanisms, which explain the associations between altered sleep-wake cycles and Aβ accumulation. The outcome of such studies may clarify how sleep interacts with the AD pathogenesis, and ultimately dictate how modulation of specific pathways can be used to target both poor sleep hygiene and AD pathogenesis.

Declaration of Competing Interest

None.

References

[1] W. Jaroudi, J. Garami, S. Garrido, M. Hornberger, S. Keri, A.A. Moustafa, Factors underlying cognitive decline in old age and Alzheimer's disease: the role of the hippocampus, Rev. Neurosci. 28 (7) (2017) 705–714.

[2] C.P.C. Galts, L.E.B. Bettio, D.C. Jewett, C.C. Yang, P.S. Brocardo, A.L.S. Rodrigues, J.S. Thacker, J. Gil-Mohapel, Depression in neurodegenerative diseases: common mechanisms and current treatment options, Neurosci. Biobehav. Rev. 102 (2019) 56–84.

[3] A. Alzheimer, A contribution concerning the pathological anatomy of mental disturbances in old age, 1899, Alzheimer Dis. Assoc. Disord. 5 (2) (1991) 69–70.

[4] R.A. Sperling, P.S. Aisen, L.A. Beckett, D.A. Bennett, S. Craft, A.M. Fagan, T. Iwatsubo, C.R. Jack Jr., J. Kaye, T.J. Montine, D.C. Park, E.M. Reiman, C.C. Rowe, E. Siemers, Y. Stern, K. Yaffe, M.C. Carrillo, B. Thies, M. Morrison-Bogorad, M.V. Wagster, C.H. Phelps, Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement. 7 (3) (2011) 280–292.

[5] J. Cummings, K. Blennow, K. Johnson, M. Keeley, R.J. Bateman, J.L. Molinuevo, J. Touchon, P. Aisen, B. Vellas, Anti-tau trials for Alzheimer's disease: a report from the EU/US/CTAD task force, J. Prev. Alzheimers. Dis. 6 (3) (2019) 157–163.

[6] R.S. Wilson, S.E. Arnold, J.A. Schneider, J.F. Kelly, Y. Tang, D.A. Bennett, Chronic psychological distress and risk of Alzheimer's disease in old age, Neuroepidemiology 27 (3) (2006) 143–153.

[7] D.A. Butterfield, D. Boyd-Kimball, Amyloid beta-peptide(1-42) contributes to the oxidative stress and neurodegeneration found in Alzheimer disease brain, Brain Pathol. 14 (4) (2004) 426–432.

[8] L.M. Ittner, Y.D. Ke, F. Delerue, M. Bi, A. Gladbach, J. van Eersel, H. Wolfing, B.C. Chieng, M.J. Christie, I.A. Napier, A. Eckert, M. Staufenbiel, E. Hardeman, J. Gotz, Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models, Cell 142 (3) (2010) 387–397.

[9] J.P. Brion, Neurofibrillary tangles and Alzheimer's disease, Eur. Neurol. 40 (3) (1998) 130–140.

[10] P.I. Moreira, C. Carvalho, X. Zhu, M.A. Smith, G. Perry, Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology, Biochim. Biophys. Acta 1802 (1) (2010) 2–10.

[11] J. Hardy, D.J. Selkoe, The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics, Science 297 (5580) (2002) 353–356.

[12] C.R. Jack Jr., D.S. Knopman, W.J. Jagust, L.M. Shaw, P.S. Aisen, M.W. Weiner, R.C. Petersen, J.Q. Trojanowski, Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade, Lancet Neurol. 9 (1) (2010) 119–128.

[13] M.A. Mintun, G.N. Larossa, Y.I. Sheline, C.S. Dence, S.Y. Lee, R.H. Mach, W.E. Klunk, C.A. Mathis, S.T. DeKosky, J.C. Morris, [11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease, Neurology 67 (3) (2006) 446–452.

[14] M.A. Findeis, The role of amyloid beta peptide 42 in Alzheimer's disease, Pharmacol. Ther. 116 (2) (2007) 266–286.

[15] L.M. Bekris, C.E. Yu, T.D. Bird, D.W. Tsuang, Genetics of Alzheimer disease, J. Geriatr. Psychiatry Neurol. 23 (4) (2010) 213–227.

[16] L. Bertram, C.M. Lill, R.E. Tanzi, The genetics of Alzheimer disease: back to the future, Neuron 68 (2) (2010) 270–281.

[17] R. Mayeux, Y. Stern, Epidemiology of Alzheimer disease, Cold Spring Harb. Perspect. Med. 2 (8) (2012).

[18] J.H. Roh, H. Jiang, M.B. Finn, F.R. Stewart, T.E. Mahan, J.R. Cirrito, A. Heda, B.J. Snider, M. Li, M. Yanagisawa, L. de Lecea, D.M. Holtzman, Potential role of orexin and sleep modulation in the pathogenesis of Alzheimer's disease, J. Exp. Med. 211 (13) (2014) 2487–2496.

[19] J. Dufort-Gervais, V. Mongrain, J. Brouillette, Bidirectional relationships between sleep and amyloid-beta in the hippocampus, Neurobiol. Learn. Mem. 160 (2019) 108–117.

[20] R.D. Rudelli, M.W. Ambler, H.M. Wisniewski, Morphology and distribution of Alzheimer neuritic (senile) and amyloid plaques in striatum and diencephalon, Acta Neuropathol. 64 (4) (1984) 273–281.

[21] E. Shokri-Kojori, G.J. Wang, C.E. Wiers, S.B. Demiral, M. Guo, S.W. Kim, E. Lindgren, V. Ramirez, A. Zehra, C. Freeman, G. Miller, P. Manza, T. Srivastava, S. De Santi, D. Tomasi, H. Benveniste, N.D. Volkow, beta-Amyloid accumulation in the human brain after one night of sleep deprivation, Proc. Natl. Acad. Sci. U. S. A. 115 (17) (2018) 4483–4488.

[22] J.E. Kang, M.M. Lim, R.J. Bateman, J.J. Lee, L.P. Smyth, J.R. Cirrito, N. Fujiki, S. Nishino, D.M. Holtzman, Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle, Science 326 (5955) (2009) 1005–1007.

[23] M. Tabuchi, S.R. Lone, S. Liu, Q. Liu, J. Zhang, A.P. Spira, M.N. Wu, Sleep interacts with abeta to modulate intrinsic neuronal excitability, Curr. Biol. 25 (6) (2015) 702–712.

[24] T. Deboer, Behavioral and electrophysiological correlates of sleep and sleep homeostasis, Curr. Top. Behav. Neurosci. 25 (2015) 1–24.

[25] R. Winsky-Sommerer, P. de Oliveira, S. Loomis, K. Wafford, D.J. Dijk, G. Gilmour, Disturbances of sleep quality, timing and structure and their relationship with other neuropsychiatric symptoms in Alzheimer's disease and schizophrenia: insights from studies in patient populations and animal models, Neurosci. Biobehav. Rev. 97 (2019) 112–137.

[26] S. Ancoli-Israel, M.R. Klauber, J.C. Gillin, S.S. Campbell, C.R. Hofstetter, Sleep in non-institutionalized Alzheimer's disease patients, Aging (Milano) 6 (6) (1994) 451–458.

[27] F.F. de Oliveira, P.H. Bertolucci, E.S. Chen, A. Smith Mde, Assessment of sleep satisfaction in patients with dementia due to Alzheimer's disease, J. Clin. Neurosci. 21 (12) (2014) 2112–2117.

[28] C.F. Hatfield, J. Herbert, E.J. van Someren, J.R. Hodges, M.H. Hastings, Disrupted daily activity/rest cycles in relation to daily cortisol rhythms of home-dwelling patients with early Alzheimer's dementia, Brain 127 (2004) 1061–1074 Pt 5.

[29] M. Moran, C.A. Lynch, C. Walsh, R. Coen, D. Coakley, B.A. Lawlor, Sleep disturbance in mild to moderate Alzheimer's disease, Sleep Med. 6 (4) (2005) 347–352.

[30] P.N. Prinz, E.R. Peskind, P.P. Vitaliano, M.A. Raskind, C. Eisdorfer, N. Zemcuznikov, C.J. Gerber, Changes in the sleep and waking EEGs of non-demented and demented elderly subjects, J. Am. Geriatr. Soc. 30 (2) (1982) 86–93.

[31] D.L. Bliwise, Sleep in normal aging and dementia, Sleep 16 (1) (1993) 40–81.

[32] R.J. Loewenstein, H. Weingartner, J.C. Gillin, W. Kaye, M. Ebert, W.B. Mendelson, Disturbances of sleep and cognitive functioning in patients with dementia, Neurobiol. Aging 3 (4) (1982) 371–377.

[33] M.V. Vitiello, J.A. Bokan, W.A. Kukull, R.L. Muniz, R.G. Smallwood, P.N. Prinz, Rapid eye movement sleep measures of Alzheimer's-type dementia patients and optimally healthy aged individuals, Biol. Psychiatry 19 (5) (1984) 721–734.

[34] B.A. Mander, S.M. Marks, J.W. Vogel, V. Rao, B. Lu, J.M. Saletin, S. Ancoli-Israel, W.J. Jagust, M.P. Walker, beta-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation, Nat. Neurosci. 18 (7) (2015) 1051–1057.

[35] B.A. Mander, J.R. Winer, W.J. Jagust, M.P. Walker, Sleep: a novel mechanistic pathway, biomarker, and treatment target in the pathology of Alzheimer's disease? Trends Neurosci. 39 (8) (2016) 552–566.

[36] M.M. Lim, J.R. Gerstner, D.M. Holtzman, The sleep-wake cycle and Alzheimer's disease: what do we know? Neurodegener. Dis. Manag. 4 (5) (2014) 351–362.

[37] Y.E. Ju, D.M. Holtzman, Sleep evaluation by actigraphy for patients with Alzheimer disease–reply, JAMA Neurol. 70 (8) (2013) 1074–1075.

[38] A.P. Spira, A.A. Gamaldo, Y. An, M.N. Wu, E.M. Simonsick, M. Bilgel, Y. Zhou, D.F. Wong, L. Ferrucci, S.M. Resnick, Self-reported sleep and beta-amyloid deposition in community-dwelling older adults, JAMA Neurol. 70 (12) (2013) 1537–1543.

[39] J. Avila, G. Perry, B.A. Strange, F. Hernandez, Alternative neural circuitry that might be impaired in the development of Alzheimer disease, Front. Neurosci. 9 (2015) 145.

[40] S. Huitron-Resendiz, M. Sanchez-Alavez, R. Gallegos, G. Berg, E. Crawford, J.L. Giacchino, D. Games, S.J. Henriksen, J.R. Criado, Age-independent and age-related deficits in visuospatial learning, sleep-wake states, thermoregulation and motor activity in PDAPP mice, Brain Res. 928 (1–2) (2002) 126–137.

[41] B. Zhang, S.C. Veasey, M.A. Wood, L.Z. Leng, C. Kaminski, S. Leight, T. Abel, V.M. Lee, J.Q. Trojanowski, Impaired rapid eye movement sleep in the Tg2576 APP murine model of Alzheimer's disease with injury to pedunculopontine cholinergic neurons, Am. J. Pathol. 167 (5) (2005) 1361–1369.

[42] J.P. Wisor, D.M. Edgar, J. Yesavage, H.S. Ryan, C.M. McCormick, N. Lapustea, G.M. Murphy Jr., Sleep and circadian abnormalities in a transgenic mouse model of Alzheimer's disease: a role for cholinergic transmission, Neuroscience 131 (2) (2005) 375–385.

[43] B.A. Kent, S.M. Strittmatter, H.B. Nygaard, Sleep and EEG power spectral analysis in three transgenic mouse models of Alzheimer's disease: APP/PS1, 3xTgAD, and Tg2576, J. Alzheimers Dis. 64 (4) (2018) 1325–1336.

[44] J.H. Roh, Y. Huang, A.W. Bero, T. Kasten, F.R. Stewart, R.J. Bateman, D.M. Holtzman, Disruption of the sleep-wake cycle and diurnal fluctuation of beta-amyloid in mice with Alzheimer's disease pathology, Sci. Transl. Med. 4 (150) (2012) 150ra122.

[45] B. Platt, B. Drever, D. Koss, S. Stoppelkamp, A. Jyoti, A. Plano, A. Utan, G. Merrick, D. Ryan, V. Melis, H. Wan, M. Mingarelli, E. Porcu, L. Scrocchi, A. Welch, G. Riedel, Abnormal cognition, sleep, EEG and brain metabolism in a novel knock-in Alzheimer mouse, PLB1, PLoS One 6 (11) (2011) e27068.

[46] K.F. Manaye, P.R. Mouton, G. Xu, A. Drew, D.L. Lei, Y. Sharma, G.W. Rebeck, S. Turner, Age-related loss of noradrenergic neurons in the brains of triple transgenic mice, Age (Dordr.) 35 (1) (2013) 139–147.
[47] Y.E. Ju, J.S. McLeland, C.D. Toedebusch, C. Xiong, A.M. Fagan, S.P. Duntley, J.C. Morris, D.M. Holtzman, Sleep quality and preclinical Alzheimer disease, JAMA Neurol. 70 (5) (2013) 587–593.
[48] Y. Huang, R. Potter, W. Sigurdson, A. Santacruz, S. Shih, Y.E. Ju, T. Kasten, J.C. Morris, M. Mintun, S. Duntley, R.J. Bateman, Effects of age and amyloid deposition on Abeta dynamics in the human central nervous system, Arch. Neurol. 69 (1) (2012) 51–58.
[49] M.T. Heneka, M. Ramanathan, A.H. Jacobs, L. Dumitrescu-Ozimek, A. Bilkei-Gorzo, T. Debeir, M. Sastre, N. Galldiks, A. Zimmer, M. Hoehn, W.D. Heiss, T. Klockgether, M. Staufenbiel, Locus ceruleus degeneration promotes Alzheimer pathogenesis in amyloid precursor protein 23 transgenic mice, J. Neurosci. 26 (5) (2006) 1343–1354.
[50] W. Bondareff, C.Q. Mountjoy, M. Roth, Selective loss of neurones of origin of adrenergic projection to cerebral cortex (nucleus locus coeruleus) in senile dementia, Lancet 1 (8223) (1981) 783–784.
[51] L. Chen, J. Huang, L. Yang, X.A. Zeng, Y. Zhang, X. Wang, M. Chen, X. Li, Y. Zhang, M. Zhang, Sleep deprivation accelerates the progression of alzheimer's disease by influencing Abeta-related metabolism, Neurosci. Lett. 650 (2017) 146–152.
[52] T. Arendt, J. Stieler, A.M. Strijkstra, R.A. Hut, J. Rudiger, E.A. Van der Zee, T. Harkany, M. Holzer, W. Hartig, Reversible paired helical filament-like phosphorylation of tau is an adaptive process associated with neuronal plasticity in hibernating animals, J. Neurosci. 23 (18) (2003) 6972–6981.
[53] S. Ooms, S. Overeem, K. Besse, M.O. Rikkert, M. Verbeek, J.A. Claassen, Effect of 1 night of total sleep deprivation on cerebrospinal fluid beta-amyloid 42 in healthy middle-aged men: a randomized clinical trial, JAMA Neurol. 71 (8) (2014) 971–977.
[54] B.P. Lucey, T.J. Hicks, J.S. McLeland, C.D. Toedebusch, J. Boyd, D.L. Elbert, B.W. Patterson, J. Baty, J.C. Morris, V. Ovod, K.G. Mawuenyega, R.J. Bateman, Effect of sleep on overnight cerebrospinal fluid amyloid beta kinetics, Ann. Neurol. 83 (1) (2018) 197–204.
[55] Y.S. Ju, S.J. Ooms, C. Sutphen, S.L. Macauley, M.A. Zangrilli, G. Jerome, A.M. Fagan, E. Mignot, J.M. Zempel, J. Claassen, D.M. Holtzman, Slow wave sleep disruption increases cerebrospinal fluid amyloid-beta levels, Brain 140 (8) (2017) 2104–2111.
[56] J.K. Holth, S.K. Fritschi, C. Wang, N.P. Pedersen, J.R. Cirrito, T.E. Mahan, M.B. Finn, M. Manis, J.C. Geerling, P.M. Fuller, B.P. Lucey, D.M. Holtzman, The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans, Science 363 (6429) (2019) 880–884.
[57] E.S. Musiek, D.D. Xiong, D.M. Holtzman, Sleep, circadian rhythms, and the pathogenesis of Alzheimer disease, Exp. Mol. Med. 47 (2015) e148.
[58] Y.E. Ju, B.P. Lucey, D.M. Holtzman, Sleep and Alzheimer disease pathology–a bidirectional relationship, Nat. Rev. Neurol. 10 (2) (2014) 115–119.
[59] P. Maquet, D. Dive, E. Salmon, B. Sadzot, G. Franco, R. Poirrier, R. von Frenckell, G. Franck, Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and [18F]2-fluoro-2-deoxy-D-glucose method, Brain Res. 513 (1) (1990) 136–143.
[60] T.T. Dang-Vu, M. Schabus, M. Desseilles, V. Sterpenich, M. Bonjean, P. Maquet, Functional neuroimaging insights into the physiology of human sleep, Sleep 33 (12) (2010) 1589–1603.
[61] Y. Nir, R.J. Staba, T. Andrillon, V.V. Vyazovskiy, C. Cirelli, I. Fried, G. Tononi, Regional slow waves and spindles in human sleep, Neuron 70 (1) (2011) 153–169.
[62] T. Abel, R. Havekes, J.M. Saletin, M.P. Walker, Sleep, plasticity and memory from molecules to whole-brain networks, Curr. Biol. 23 (17) (2013) R774–R788.
[63] J.R. Cirrito, K.A. Yamada, M.B. Finn, R.S. Sloviter, K.R. Bales, P.C. May, D.D. Schoepp, S.M. Paul, S. Mennerick, D.M. Holtzman, Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo, Neuron 48 (6) (2005) 913–922.
[64] J.M. Tarasoff-Conway, R.O. Carare, R.S. Osorio, L. Glodzik, T. Butler, E. Fieremans, L. Axel, H. Rusinek, C. Nicholson, B.V. Zlokovic, B. Frangione, K. Blennow, J. Menard, H. Zetterberg, T. Wisniewski, M.J. de Leon, Clearance systems in the brain-implications for Alzheimer disease, Nat. Rev. Neurol. 11 (8) (2015) 457–470.
[65] M. Shibata, S. Yamada, S.R. Kumar, M. Calero, J. Bading, B. Frangione, D.M. Holtzman, C.A. Miller, D.K. Strickland, J. Ghiso, B.V. Zlokovic, Clearance of Alzheimer's amyloid-ss(1-40) peptide from brain by LDL receptor-related protein-1 at the blood-brain barrier, J. Clin. Invest. 106 (12) (2000) 1489–1499.
[66] J.J. Iliff, M. Wang, Y. Liao, B.A. Plogg, W. Peng, G.A. Gundersen, H. Benveniste, G.E. Vates, R. Deane, S.A. Goldman, E.A. Nagelhus, M. Nedergaard, A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta, Sci. Transl. Med. 4 (147) (2012) 147ra111.
[67] B.T. Kress, J.J. Iliff, M. Xia, M. Wang, H.S. Wei, D. Zeppenfeld, L. Xie, H. Kang, Q. Xu, J.A. Liew, B.A. Plog, F. Ding, R. Deane, M. Nedergaard, Impairment of paravascular clearance pathways in the aging brain, Ann. Neurol. 76 (6) (2014) 845–861.
[68] B.P. Lucke-Wold, K.E. Smith, L. Nguyen, R.C. Turner, A.F. Logsdon, G.J. Jackson, J.D. Huber, C.L. Rosen, D.B. Miller, Sleep disruption and the sequelae associated with traumatic brain injury, Neurosci. Biobehav. Rev. 55 (2015) 68–77.
[69] L. Xie, H. Kang, Q. Xu, M.J. Chen, Y. Liao, M. Thiyagarajan, J. O'Donnell, D.J. Christensen, C. Nicholson, J.J. Iliff, T. Takano, R. Deane, M. Nedergaard, Sleep drives metabolite clearance from the adult brain, Science 342 (6156) (2013) 373–377.
[70] C. Liguori, M. Nuccetelli, F. Izzi, G. Sancesario, A. Romigi, A. Martorana, C. Amoroso, S. Bernardini, M.G. Marciani, N.B. Mercuri, F. Placidi, Rapid eye movement sleep disruption and sleep fragmentation are associated with increased orexin-A cerebrospinal-fluid levels in mild cognitive impairment due to Alzheimer's disease, Neurobiol. Aging 40 (2016) 120–126.
[71] J. Arendt, Melatonin and the pineal gland: influence on mammalian seasonal and circadian physiology, Rev. Reprod. 3 (1) (1998) 13–22.
[72] A.F. Wiechmann, D.M. Sherry, Role of melatonin and its receptors in the vertebrate retina, Int. Rev. Cell Mol. Biol. 300 (2013) 211–242.
[73] J. Zhou, S. Zhang, X. Zhao, T. Wei, Melatonin impairs NADPH oxidase assembly and decreases superoxide anion production in microglia exposed to amyloid-beta1-42, J. Pineal Res. 45 (2) (2008) 157–165.
[74] J.M. Olcese, C. Cao, T. Mori, M.B. Mamcarz, A. Maxwell, M.J. Runfeldt, L. Wang, C. Zhang, X. Lin, G. Zhang, G.W. Arendash, Protection against cognitive deficits and markers of neurodegeneration by long-term oral administration of melatonin in a transgenic model of Alzheimer disease, J. Pineal Res. 47 (1) (2009) 82–96.
[75] E. Matsubara, T. Bryant-Thomas, J. Pacheco Quinto, T.L. Henry, B. Poeggeler, D. Herbert, F. Cruz-Sanchez, Y.J. Chyan, M.A. Smith, G. Perry, M. Shoji, K. Abe, A. Leone, I. Grundke-Ikbal, G.L. Wilson, J. Ghiso, C. Williams, L.M. Refolo, M.A. Pappolla, D.G. Chain, E. Neria, Melatonin increases survival and inhibits oxidative and amyloid pathology in a transgenic model of Alzheimer's disease, J. Neurochem. 85 (5) (2003) 1101–1108.
[76] T. Ali, M.O. Kim, Melatonin ameliorates amyloid beta-induced memory deficits, tau hyperphosphorylation and neurodegeneration via PI3/Akt/GSk3beta pathway in the mouse hippocampus, J. Pineal Res. 59 (1) (2015) 47–59.
[77] Y.H. Wu, M.G. Feenstra, J.N. Zhou, R.Y. Liu, J.S. Torano, H.J. Van Kan, D.F. Fischer, R. Ravid, D.F. Swaab, Molecular changes underlying reduced pineal melatonin levels in Alzheimer disease: alterations in preclinical and clinical stages, J. Clin. Endocrinol. Metab. 88 (12) (2003) 5898–5906.
[78] J.N. Zhou, R.Y. Liu, W. Kamphorst, M.A. Hofman, D.F. Swaab, Early neuropathological Alzheimer's changes in aged individuals are accompanied by decreased cerebrospinal fluid melatonin levels, J. Pineal Res. 35 (2) (2003) 125–130.
[79] M. Atienza, J. Ziontz, J.L. Cantero, Low-grade inflammation in the relationship between sleep disruption, dysfunctional adiposity, and cognitive decline in aging, Sleep Med. Rev. 42 (2018) 171–183.
[80] H.K. Meier-Ewert, P.M. Ridker, N. Rifai, M.M. Regan, N.J. Price, D.F. Dinges, J.M. Mullington, Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk, J. Am. Coll. Cardiol. 43 (4) (2004) 678–683.
[81] M. Chennaoui, F. Sauvet, C. Drogou, P. Van Beers, C. Langrume, M. Guillard, B. Gourby, C. Bourrilhon, G. Florence, D. Gomez-Merino, Effect of one night of sleep loss on changes in tumor necrosis factor alpha (TNF-alpha) levels in healthy men, Cytokine 56 (2) (2011) 318–324.
[82] W.T. Shearer, J.M. Reuben, J.M. Mullington, N.J. Price, B.N. Lee, E.O. Smith, M.P. Szuba, H.P. Van Dongen, D.F. Dinges, Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight, J. Allergy Clin. Immunol. 107 (1) (2001) 165–170.
[83] M.R. Irwin, Why sleep is important for health: a psychoneuroimmunology perspective, Annu. Rev. Psychol. 66 (2015) 143–172.
[84] S.J. Motivala, Sleep and inflammation: psychoneuroimmunology in the context of cardiovascular disease, Ann. Behav. Med. 42 (2) (2011) 141–152.
[85] R. Chen, Y. Yin, Z. Zhao, L. Huang, S. Huang, J. Zhuang, H. Wu, H. Peng, P. Li, Elevation of serum TNF-alpha levels in mild and moderate Alzheimer patients with daytime sleepiness, J. Neuroimmunol. 244 (1–2) (2012) 97–102.
[86] R. Chang, K.L. Yee, R.K. Sumbria, Tumor necrosis factor alpha inhibition for Alzheimer's Disease, J. Cent. Nerv. Syst. Dis. 9 (2017) (1179573517709278).
[87] C. Cavanagh, Y.C. Tse, H.B. Nguyen, S. Krantic, J.C. Breitner, R. Quirion, T.P. Wong, Inhibiting tumor necrosis factor-alpha before amyloidosis prevents synaptic deficits in an Alzheimer's disease model, Neurobiol. Aging 47 (2016) 41–49.
[88] K. Morimoto, J. Horio, H. Satoh, L. Sue, T. Beach, S. Arita, I. Tooyama, Y. Konishi, Expression profiles of cytokines in the brains of Alzheimer's disease (AD) patients compared to the brains of non-demented patients with and without increasing AD pathology, J. Alzheimers Dis. 25 (1) (2011) 59–76.
[89] N.L. Monson, S.J. Ireland, A.J. Ligocki, D. Chen, W.H. Rounds, M. Li, R.M. Huebinger, C. Munro Cullum, B.M. Greenberg, A.M. Stowe, R. Zhang, Elevated CNS inflammation in patients with preclinical Alzheimer's disease, J. Cereb. Blood Flow Metab. 34 (1) (2014) 30–33.
[90] M.F. Bjurstrom, R. Olmstead, M.R. Irwin, Reciprocal relationship between sleep macrostructure and evening and morning cellular inflammation in rheumatoid arthritis, Psychosom. Med. 79 (1) (2017) 24–33.
[91] M. Munch, V. Knoblauch, K. Blatter, C. Schroder, C. Schnitzler, K. Krauchi, A. Wirz-Justice, C. Cajochen, The frontal predominance in human EEG delta activity after sleep loss decreases with age, Eur. J. Neurosci. 20 (5) (2004) 1402–1410.
[92] A.N. Vgontzas, M. Zoumakis, E.O. Bixler, H.M. Lin, P. Prolo, A. Vela-Bueno, A. Kales, G.P. Chrousos, Impaired nighttime sleep in healthy old versus young adults is associated with elevated plasma interleukin-6 and cortisol levels: physiologic and therapeutic implications, J. Clin. Endocrinol. Metab. 88 (5) (2003) 2087–2095.
[93] M.R. Irwin, M.R. Opp, Sleep health: reciprocal regulation of sleep and innate immunity, Neuropsychopharmacology 42 (1) (2017) 129–155.
[94] J.E. Carroll, C. Carrillo, R. Olmstead, T. Witarama, E.C. Breen, M. Yokomizo, T. Seeman, M.R. Irwin, Sleep deprivation and divergent toll-like receptor-4 activation of cellular inflammation in aging, Sleep 38 (2) (2015) 205–211.
[95] J.R. Bamburg, B.W. Bernstein, Actin dynamics and cofilin-actin rods in alzheimer disease, Cytoskeleton (Hoboken) 73 (9) (2016) 477–497.
[96] A.E. Shaw, J.R. Bamburg, Peptide regulation of cofilin activity in the CNS: a novel therapeutic approach for treatment of multiple neurological disorders, Pharmacol.

Ther. 175 (2017) 17–27.
[97] M.T. Maloney, J.R. Bamburg, Cofilin-mediated neurodegeneration in Alzheimer's disease and other amyloidopathies, Mol. Neurobiol. 35 (1) (2007) 21–44.
[98] T. Rush, J. Martinez-Hernandez, M. Dollmeyer, M.L. Frandemiche, E. Borel, S. Boisseau, M. Jacquier-Sarlin, A. Buisson, Synaptotoxicity in Alzheimer's disease involved a dysregulation of actin cytoskeleton dynamics through Cofilin 1 phosphorylation, J. Neurosci. 38 (48) (2018) 10349–10361.
[99] R. Havekes, T. Abel, The tired hippocampus: the molecular impact of sleep deprivation on hippocampal function, Curr. Opin. Neurobiol. 44 (2017) 13–19.
[100] D.P. Cardinali, D.E. Vigo, N. Olivar, M.F. Vidal, A.M. Furio, L.I. Brusco, Therapeutic application of melatonin in mild cognitive impairment, Am. J. Neurodegener. Dis. 1 (3) (2012) 280–291.
[101] S. Ancoli-Israel, M.R. Klauber, D.W. Jones, D.F. Kripke, J. Martin, W. Mason, R. Pat-Horenczyk, R. Fell, Variations in circadian rhythms of activity, sleep, and light exposure related to dementia in nursing-home patients, Sleep 20 (1) (1997) 18–23.
[102] T. Shochat, J. Martin, M. Marler, S. Ancoli-Israel, Illumination levels in nursing home patients: effects on sleep and activity rhythms, J. Sleep Res. 9 (4) (2000) 373–379.
[103] G.A. Dowling, E.M. Hubbard, J. Mastick, J.S. Luxenberg, R.L. Burr, E.J. Van Someren, Effect of morning bright light treatment for rest-activity disruption in institutionalized patients with severe Alzheimer's disease, Int. Psychogeriatr. 17 (2) (2005) 221–236.
[104] J. McCleery, D.A. Cohen, A.L. Sharpley, Pharmacotherapies for sleep disturbances in Alzheimer's disease, Cochrane Database Syst. Rev. (3) (2014) CD009178.
[105] M. Serfaty, S. Kennell-Webb, J. Warner, R. Blizard, P. Raven, Double blind randomised placebo controlled trial of low dose melatonin for sleep disorders in dementia, Int. J. Geriatr. Psychiatry. 17 (12) (2002) 1120–1127.
[106] C. Singer, R.E. Tractenberg, J. Kaye, K. Schafer, A. Gamst, M. Grundman, R. Thomas, L.J. Thal, S. Alzheimer's Disease Cooperative, A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease, Sleep 26 (7) (2003) 893–901.
[107] P.R. Gehrman, D.J. Connor, J.L. Martin, T. Shochat, J. Corey-Bloom, S. Ancoli-Israel, Melatonin fails to improve sleep or agitation in double-blind randomized placebo-controlled trial of institutionalized patients with Alzheimer disease, Am. J. Geriatr. Psychiatry 17 (2) (2009) 166–169.
[108] E.F. Camargos, L.L. Louzada, J.L. Quintas, J.O. Naves, F.M. Louzada, O.T. Nobrega, Trazodone improves sleep parameters in Alzheimer disease patients: a randomized, double-blind, and placebo-controlled study, Am. J. Geriatr. Psychiatry 22 (12) (2014) 1565–1574.
[109] P.R.A. Heckman, A. Blokland, E.P.P. Bollen, J. Prickaerts, Phosphodiesterase inhibition and modulation of corticostriatal and hippocampal circuits: clinical overview and translational considerations, Neurosci. Biobehav. Rev. 87 (2018) 233–254.
[110] A. Blokland, M.A. Van Duinen, A. Sambeth, P.R.A. Heckman, M. Tsai, G. Lahu, T. Uz, J. Prickaerts, Acute treatment with the PDE4 inhibitor roflumilast improves verbal word memory in healthy old individuals: a double-blind placebo-controlled study, Neurobiol. Aging 77 (2019) 37–43.
[111] P.R. Heckman, C. Wouters, J. Prickaerts, Phosphodiesterase inhibitors as a target for cognition enhancement in aging and Alzheimer's disease: a translational overview, Curr. Pharm. Des. 21 (3) (2015) 317–331.
[112] B. Gong, O.V. Vitolo, F. Trinchese, S. Liu, M. Shelanski, O. Arancio, Persistent improvement in synaptic and cognitive functions in an Alzheimer mouse model after rolipram treatment, J. Clin. Invest. 114 (11) (2004) 1624–1634.
[113] T.A. Comery, R.L. Martone, S. Aschmies, K.P. Atchison, G. Diamantidis, X. Gong, H. Zhou, A.F. Kreft, M.N. Pangalos, J. Sonnenberg-Reines, J.S. Jacobsen, K.L. Marquis, Acute gamma-secretase inhibition improves contextual fear conditioning in the Tg2576 mouse model of Alzheimer's disease, J. Neurosci. 25 (39) (2005) 8898–8902.
[114] N. Myeku, C.L. Clelland, S. Emrani, N.V. Kukushkin, W.H. Yu, A.L. Goldberg, K.E. Duff, Tau-driven 26S proteasome impairment and cognitive dysfunction can be prevented early in disease by activating cAMP-PKA signaling, Nat. Med. 22 (1) (2016) 46–53.
[115] C.G. Vecsey, G.S. Baillie, D. Jaganath, R. Havekes, A. Daniels, M. Wimmer, T. Huang, K.M. Brown, X.Y. Li, G. Descalzi, S.S. Kim, T. Chen, Y.Z. Shang, M. Zhuo, M.D. Houslay, T. Abel, Sleep deprivation impairs cAMP signalling in the hippocampus, Nature 461 (7267) (2009) 1122–1125.
[116] R. Havekes, V.M. Bruinenberg, J.C. Tudor, S.L. Ferri, A. Baumann, P. Meerlo, T. Abel, Transiently increasing cAMP levels selectively in hippocampal excitatory neurons during sleep deprivation prevents memory deficits caused by sleep loss, J. Neurosci. 34 (47) (2014) 15715–15721.
[117] R. Havekes, A.J. Park, J.C. Tudor, V.G. Luczak, R.T. Hansen, S.L. Ferri, V.M. Bruinenberg, S.G. Poplawski, J.P. Day, S.J. Aton, K. Radwanska, P. Meerlo, M.D. Houslay, G.S. Baillie, T. Abel, Sleep deprivation causes memory deficits by negatively impacting neuronal connectivity in hippocampal area CA1, eLife 5 (2016).
[118] R. Havekes, P. Meerlo, T. Abel, Animal studies on the role of sleep in memory: from behavioral performance to molecular mechanisms, Curr. Top. Behav. Neurosci. 25 (2015) 183–206.
[119] F. Raven, E.A. Van der Zee, P. Meerlo, R. Havekes, The role of sleep in regulating structural plasticity and synaptic strength: implications for memory and cognitive function, Sleep Med. Rev. 39 (2018) 3–11.