Hypocretin/Orexin, Sleep and Alzheimer's Disease

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Abstract

Advances in translational research provide key opportunities to explore the physiological and pathological effects of sleep in different neurodegenerative diseases. Recent findings suggest that sleep-wakefulness dysfunctions may predispose to neurodegenerative disorders such as Alzheimer's disease (AD), and vice versa. New theories on the link between sleep and β-amyloid and tau secretion, accumulation and clearance, and its interaction with hypocretins/orexins (key neuropeptides regulating wakefulness) suggest mechanistic ways to better understand the impact of sleep alterations in the pathogenesis of AD. Further studies should validate whether changes in circadian rhythm and sleep-wakefulness patterns could be used for early AD diagnosis and as prognostic markers for cognitive decline. Longitudinal studies are needed, not only to validate these biomarker interactions and to determine the cause-effect relationship and the role of sleep-wakefulness behavior in the regulation of amyloid plaque and neurofibrillary tangle formation, but also to identify the best sleep therapies and related preventive strategies for AD.

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Introduction

Sleep-wake behavior is a fundamental brain function that is substantially associated with cognition and synaptic plasticity [1]. A seminal study in mice reported that sleep is critical for ensuring brain metabolic homeostasis, associated with large increases in the cortical interstitial space compared to wake, resulting in convective exchange between cerebrospi-
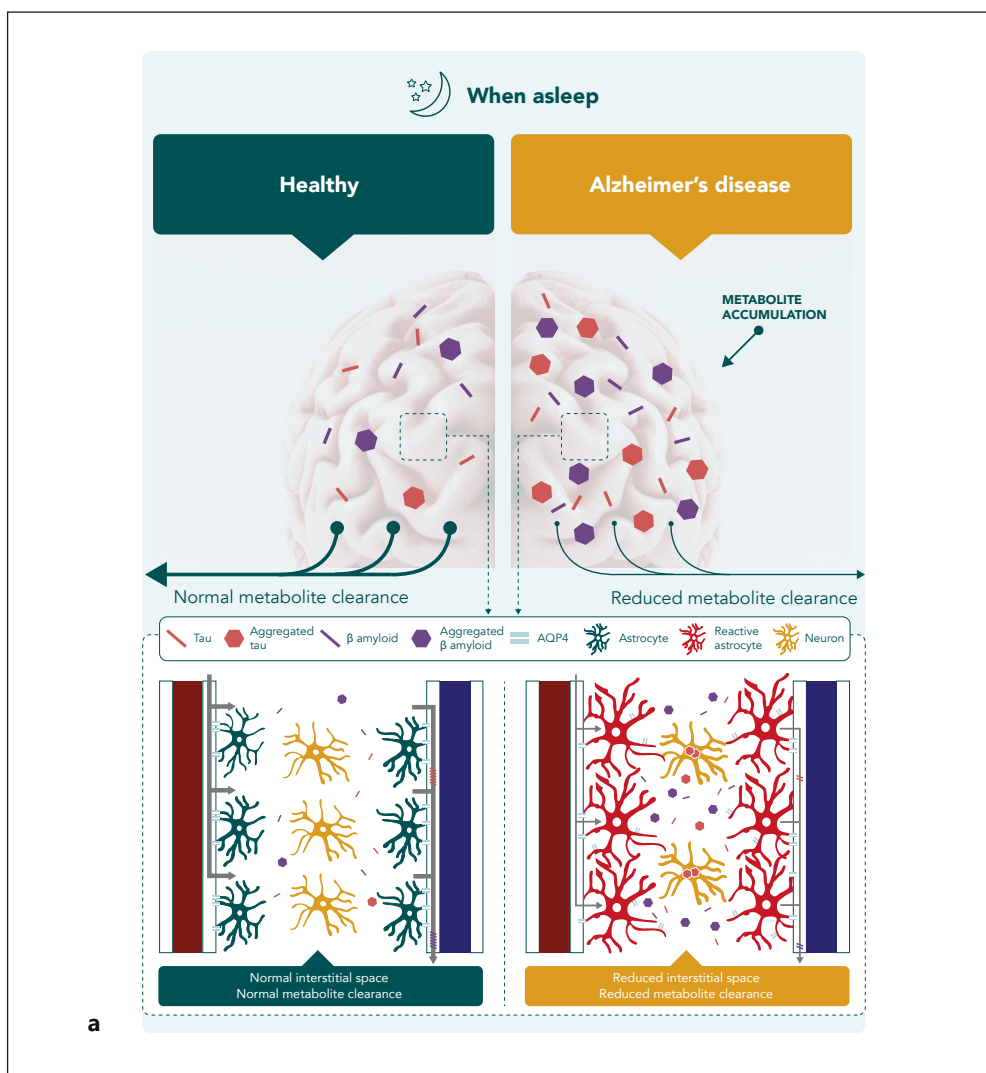
Fig. 1. The interrelation between the brain's glymphatic clearance, Alzheimer's disease, and sleep disturbances. **a** A schematic representation of the glymphatic system during sleep in healthy conditions and in Alzheimer's disease. The glymphatic pathway clears waste by active fluid transport from para-arterial to paravenous space through aquaporin-4 (AQP4) water channels in astrocyte end-feet. Sleep (non-rapid eye movement sleep) is a primary driver of glymphatic clearance. During natural NREM sleep, levels of several neurotransmitters (e.g., orexin and norepinephrine) decline leading to an expansion of the brain's extracellular space, and consequent heightened interstitial clearance of β-amyloid and tau proteins from the brain. Impaired glymphatic clearance has been linked to neurodegenerative diseases. In Alzheimer's disease, reactive astrocytes are a characteristic feature; interstitial space is consequently reduced, leading to a reduction in metabolic clearance by approximately 60% [2]. β-Amyloid deposits accumulate in the extracellular space, and tau protein aggregates form in the neurons. **b** Disturbed nighttime sleep may impair glymphatic clearance and promote abnormal secretion and clearance of β-amyloid and tau, and the spread of Alzheimer's disease pathology.

(Figure continued on next page.)

b

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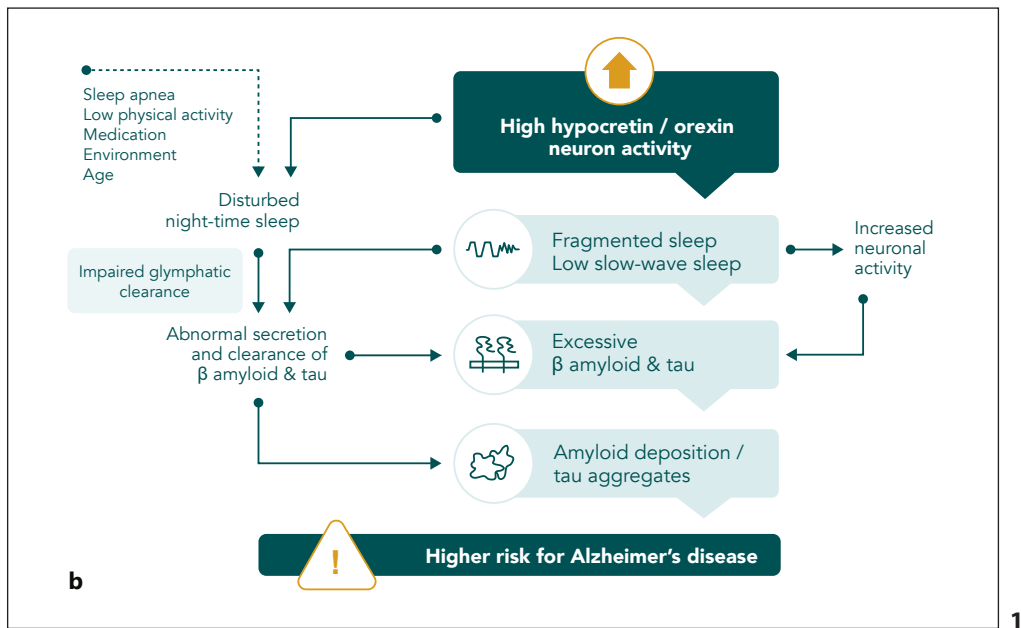
nal fluid (CSF) and the interstitial fluid [2]. The restorative function of sleep may therefore be related to increased clearance of potentially neurotoxic degradation products of neuronal activity that accumulate in the awake brain, such as β-amyloid (Aβ) [2].

Alzheimer's disease (AD) is a multifactorial and complex illness with pathological processes that begin many years before the first clinical symptoms [3]. The pathological process is characterized by extracellular aggregation of Aβ peptides in senile plaques resulting from excessive production and/or cleavage of amyloid precursor protein (APP), and by intraneuronal hyperphosphorylated and aggregated tau proteins arranged into filaments that form neurofibrillary tangles in particular brain regions (Fig. 1a). Positron emission tomography imaging with tracers that bind specifically Aβ aggregates was able to quantify accumulation of amyloid plaques, years or even decades before clinical symptoms of AD [3]. The dynamics of Aβ changes and the large variability in progressive cognitive decline in subjects at risk for AD remain mostly unclear. Recent findings suggest that sleep-wakefulness dysfunctions may predispose to neurodegenerative disorders such as AD, and vice versa. I will focus in this review on sleep-wake dysfunction and AD.

Sleep Changes in Patients with Cognitive Decline and Alzheimer's Disease

In recent years, there has been growing clinical evidence that circadian and sleep disorders play a role in the pathophysiology of AD [4]. Sleep disturbances are frequently reported early on in AD, with both daytime sleepiness and increased frequency of nighttime awakenings [5–7]. Markers of poor sleep quality, such as low sleep efficiency, long wake time

after sleep onset, as well as short and long sleep, daytime napping and sleep apnea syndrome, have been associated with cognitive decline in older adults [8–11]. Excessive daytime sleepiness has also been associated with higher risk of cognitive decline in elderly populations. In the Honolulu-Asia Aging Study, excessive daytime sleepiness increased the risk of cognitive decline by up to 44% [12]. In the French Three-City population based-study with an 8-year follow-up, excessive daytime sleepiness was independently associated with the risk of cognitive decline, especially in patients who later developed dementia [13]. Similarly, incident dementia cohort studies showed that sleep problems increase the risk of developing dementia. Reciprocally, sleep disorders are common in patients with AD (around 35%), and their frequency increases with the disease severity, thus affecting the quality of life of patients and caregivers [5, 14–17]. Clinically, patients with AD present frequent and prolonged episodes of daytime sleepiness, sleep maintenance insomnia, fragmented sleep with frequent awakening periods and a typical phase-advance of the nocturnal sleep period. At an advanced AD stage, sleep alterations may lead to a virtual reversal of the day-night sleep pattern and become a predictive factor of mortality and institutionalization, especially in the context of sundowning syndrome (i.e., the exacerbation of behavioral symptoms in the afternoon and evening) [15, 16].

Several studies evaluated the relationship between sleep quantity and quality and Aβ deposition in the brain of healthy controls and patients with AD at different clinical stages. The Baltimore Longitudinal Study of Aging found that, in community-dwelling older adults without cognitive troubles, self-reported sleep duration correlated with Aβ deposition in the brain [6]. Specifically, shorter sleep duration (<6 vs. >7 h) was associated with higher Aβ deposition in the cortex and precuneus, measured by using $[^{11}C]$ Pittsburgh compound B PET. However, another study carried out in Montpellier, France, did not confirm the association between amyloid-PET burden and self-reported poor sleep quantity/quality when twice the number of subjects were included as compared to the previous study [18], suggesting that the interplay between sleep and amyloid is more complex than previously described. Moreover, cognitively healthy elderly subjects who reported greater somnolence had higher Aβ burden in the precuneus, angular and cingulate gyrus and frontal medial orbital cortex [19]. Another study showed that baseline self-reported sleepiness was associated with increased longitudinal Aβ accumulation in elderly persons without dementia, suggesting that those with sleepiness may be more vulnerable to pathological changes associated with AD [20]. Based on actigraphy measurements of sleep efficiency and wake time after sleep onset, one study showed that cognitively normal subjects at risk of AD due to low CSF $A\beta_{42}$ levels (≤500 pg/mL) presented poor sleep efficiency and frequent napping but no change in sleep quantity, even after adjustment for age, gender and apolipoprotein E (APOE) genotype [7]. One study in 2020 also showed that cognitively unimpaired elderly subjects with sleep-disordered breathing had greater amyloid deposition in AD-sensitive brain regions, notably the posterior cingulate cortex and precuneus [21]. However, no association was found with cognition, self-reported cognitive and sleep difficulties, or excessive daytime sleepiness symptoms.

Taken together, most of these studies suggested that sleep alterations could be considered as a marker of early AD stages; however, the changes in sleep patterns from preclinical to clinical AD and the causality link with AD remain unclear. The neurobiological basis to explain the relationships between sleep disturbances and cognitive decline/AD remains to be elucidated.

Interaction between β-Amyloid, Tau and Sleep-Wake Regulation: A Role for Hypocretin/Orexin?

The neurobiological basis of fragmented sleep in AD remains unknown. Some authors have suggested a role of non-rapid eye movement (NREM) sleep networks, particularly for GABAergic and galanin neurons of the ventrolateral preoptic area, as well as the role of acetylcholine neurons in the basal forebrain [22]. A postmortem study on adults showed that patients with AD had fewer galanin-containing neurons in the intermediate nucleus, which may be the human homologue of the rodent ventrolateral preoptic area nucleus [23]. Moreover, subjects (with or without AD) with more galanin-positive intermediate nucleus neurons showed less fragmented sleep.

Among the many neurotransmitters involved in the regulation of the sleep-wake cycle, orexins (also called hypocretins), which promote wakefulness but also energy homeostasis, stress adaptation, and reward behaviors [24], may have a direct link with the amyloid and tau pathways (Fig. 1b). The orexin system contributes to sleep-wake regulation by sustaining long periods of wakefulness in humans and animals. Although orexin neurons are a restricted group of cells that are localized exclusively in the lateral hypothalamus, their projections are widely distributed throughout the brain [25]. In the flip-flop model of reciprocal interactions between sleep- and wake-promoting brain regions, aminergic regions promote wakefulness through direct excitatory effects on the cortex and inhibition of sleep-promoting neurons of the ventrolateral preoptic nucleus [26]. Orexin neurons increase the activity of aminergic neurons, thus supporting the inhibition of sleep-promoting neurons.

In rats, orexin-A release shows a 24-h fluctuation similar to that of brain interstitial fluid Aβ [27]. Similar data have been found in young healthy subjects, with peak CSF Aβ concentrations in the evening and lower concentrations overnight [28, 29]. In young patients with AD carrying presenilin mutations, CSF Aβ fluctuation disappeared after amyloid plaque formation. In transgenic mice that overexpress a mutated form of human amyloid precursor protein (APP), brain interstitial fluid Aβ concentration correlated with wakefulness and significantly increased during acute sleep deprivation and during orexin-A infusion. Conversely, the amount of interstitial fluid Aβ decreased during sleep and after infusion of a dual orexin receptor antagonist (almorexant) [29]. Chronic sleep restriction also significantly increased, and almorexant decreased the formation of Aβ plaques in several brain regions in these mice. Another study aimed to determine whether orexin release or secondary changes in sleep via orexin modulation affect Aβ pathology [30]. In transgenic mice that overexpress APP/presenilin1, in which the orexin gene is

knocked out, a marked decrease in the amount of Aβ deposition in the brain was found together with an increase in sleep time [30]. A focal overexpression of orexin in the hippocampus in these mice did not change the total duration of sleep/wakefulness and the levels of Aβ pathology. However, increasing wakefulness by the rescue of orexinergic neurons in the hypothalamus of these mice lacking orexin increased the amount of Aβ pathology in the brain. After sleep deprivation, these mice had a significant increase in Aβ plaque pathology, demonstrating the presence of hypothalamic factors other than orexin to modulate Aβ metabolism [30].

Conversely, in humans, results are more conflicting, especially concerning CSF orexin-A levels in AD patients. In a postmortem analysis, like other neurons, the number of orexin neurons in the hypothalamus and the concentration of orexin in ventricular CSF were reduced in patients with AD compared with controls [31]. However, we and other authors found higher CSF orexin-A levels in patients with AD than in controls [32–35], possibly related to sleep deterioration and neurodegeneration which may destabilize the regulation of the activity and number of orexin neurons. Different studies have also highlighted correlations between orexin-A, $A\beta_{42}$ and total tau levels in patients with AD [32–34]. We found higher CSF orexin-A levels in patients with mild cognitive impairment than in patients with other dementia syndromes, suggesting a pathophysiological link between $A\beta_{42}$ and orexin-A in early AD stages [32, 33]. Another case-control study compared the CSF levels of orexin with those of tau and $A\beta_{42}$, and with sleep parameters and cognition in drug-naive patients with AD and in controls without dementia. Patients with moderate to severe AD presented with higher mean CSF orexin-A levels than controls [34] that parallel sleep deterioration. Moreover, the cognitive performances were negatively correlated with REM sleep latency and wake time after sleep onset, and positively correlated with sleep efficiency in patients with AD.

Taken together, these data suggest that the orexin system is progressively dysregulated during the neurodegenerative process in AD; however, whether the observed changes in orexin-A levels are linked to the underlying neurodegenerative process or are secondary to sleep-wake cycle alterations remains unclear. The degeneration of key sleep and wake regulatory systems in AD, which is responsible for a marked increase in nighttime wakefulness and daytime sleepiness, may interfere with neuronal metabolism and ultimately lead to enhanced and accelerated Aβ aggregation [36]. Although the whole process is largely unclear, amyloid plaque formation, a pathological hallmark of AD, is modulated by the amount of wakefulness, which is by itself regulated by the endogenous orexins.

Narcolepsy Type 1: A Model of Orexin Deficiency

Narcolepsy type 1 (NT1) is an orphan chronic disease characterized by excessive daytime sleepiness, cataplexy, and orexin deficiency and can serve as an interesting model to improve our understanding of the relationship between amyloid and orexin pathways [37].

NT1 typically occurs in the teens or twenties, with normal durations of sleep and wakefulness but with frequent instability of both wakefulness and sleep.

A low CSF orexin-A level is the gold standard (highly specific and sensitive) for the diagnosis of NT1 [37]. In NT1, the irreversible loss of orexin neurons, probably due to an autoimmune process, results in irresistible transitions to sleep (especially REM sleep) during the day, difficulties in maintaining long wakefulness periods, fragmented nighttime sleep with frequent shifts between sleep stages, and arousals [37, 38]. Behavioral state instability caused by orexin deficiency has been well studied in rodents. Compared with wild-type mice, orexin knockout mice have normal amounts of sleep and wake, but wake and NREM sleep bouts are very brief, with many more transitions between states [39, 40]. Survival analysis of wake bouts showed that orexin is necessary for the maintenance of long wake bouts, and that orexin deficiency has little impact on wake bouts <1 min. A human study also showed an association between CSF orexin levels and markers of nocturnal sleep stability (sleep and wake bouts, and sleep-wake transitions) in patients with hypersomnolence [41]. Taken together, sleep and wake bouts are reliable markers of nocturnal sleep stability that correlate with CSF orexin-A levels in a dose-dependent way.

Due to the complex relationships between amyloid, orexin and sleep-wakefulness, and the definite effect of a dual orexin receptor antagonist on decreasing the formation of Aβ plaques in transgenic mice, some have hypothesized that chronic loss of orexin early in life may alter the balance between Aβ production and degradation/clearance, and then prevent or delay the accumulation of Aβ in the human brain [42]. One study addressed this hypothesis by analyzing the presence of neuropathological lesions consistent with AD in the postmortem brain tissues of 12 patients with narcolepsy-cataplexy; 33% had AD lesions, a proportion similar to that expected in the general population [43]. However, details regarding the phenotype of narcolepsy, CSF orexin levels, and orexin neuron quantification were only available for one case. Another study readdressed this hypothesis by determining whether elderly patients with NT1 have a lower amyloid brain burden than controls, as measured with ^{18}F-florbetapir-PET [44]. We indeed found lower levels of cortical amyloid burden in patients with NT1 compared to two age- and sex-matched control groups. Only one NT1 patient (4.3% of the sample) had a positive PET compared to 27.5 and 30.4% of the control groups. Our results suggest that the chronic loss of orexin signaling may disturb the balance between Aβ production and degradation/clearance in patients with NT1, and as a result, the risk of developing AD could be reduced or the appearance of amyloid plaques and related disease symptoms delayed.

Medication Targeting the Orexin System

A number of orexin receptor agonists are under development and have received large attention as promising arousal-promoting agents to first treat patients with NT1. Orexin receptor agonists are expected to stimulate the deficient orexin system in NT1 but also to improve wakefulness in other forms of central hypersomnolence. In contrast, dual orexin-

receptor antagonists (DORAs) promote sleep, are used to treat insomnia, and several of them have already been approved or are under development with promising results (e.g., suvorexant, lemborexant, daridorexant) [45–48]. Patients with insomnia taking one of these drugs returned to sleep from their longest awakening more than twice faster than those on placebo [49]. Moreover, the number of, and time spent in, long wake bouts were reduced in the treated group, suggesting that DORAs may reduce wake time after sleep onset by decreasing long wake bouts. Taken altogether, we may further consider the potential positive effect of the orexin receptor antagonists on nighttime sleep and, consequently, on reducing brain amyloid load in subjects at risk for developing AD.

Interaction between Tau and Sleep-Wake Regulation

The majority of studies in the mice mentioned above support a key role of sleep in the regulation of Aβ accumulation; however, tau also increases in the interstitial fluid in mice during periods of wakefulness. Sleep-deprived mice had an increase in tau release in the interstitial fluid during the light period when mice typically sleep and have low levels of extracellular tau [50]. Other approaches that selectively activate neurons stimulating wakefulness in the hypothalamus confirmed the increased levels of both Aβ and tau in the brains of mice [50]. In human, CSF tau increased more than 50% during sleep deprivation when compared to baseline [50]. The lack of sleep also alters the process of tau phosphorylation in humans which is a key early stage in tau aggregation and tau-mediated neurodegeneration [51]. Altogether, this increased release of tau and its hyperphosphorylation indicate that sleep disruption may promote the spread of tau pathology that is highly correlated with synaptic loss, neuronal dysfunction, and the severity of cognitive symptoms in AD [52]. Another study found that the decreased slow-wave activity in NREM sleep was associated with increased Aβ and tau accumulation assessed by AV-45 amyloid and AV-1451 tau PET and with biomarkers measured in CSF [53]. Finally, a few studies have reported positive correlations between orexin and total or phosphorylated tau protein levels in either patients with AD [34] or cognitively normal elderly subjects [54].

Conclusion

The associations between Aβ, tau, sleep, and wakefulness are complex and potentially bidirectional, and our knowledge remains limited. Advances in translational research provide key opportunities to explore the physiological and pathological effects of sleep in different neurodegenerative diseases such as AD, and vice versa. The recent theories on the link between sleep and amyloid clearance suggest new mechanisms that could link amyloid pathogenesis with sleep-wake neurobiology. The hypothesis that amyloid proteins are washed out via the brain glymphatic system during sleep and the notion of Aβ, tau, and phosphorylated tau accumulation and deposition in the brain and its interaction

with sleep, influenced by orexins, should encourage clinicians and scientists to develop integrative models that include biorhythm markers in AD. Changes in circadian rhythm and sleep-wakefulness patterns could possibly be used for early AD diagnosis and as prognostic markers for cognitive decline and ought to be validated. Moreover, longitudinal studies are needed, not only to confirm these biomarker interactions and to determine the cause-effect relationship and the role of sleep-wakefulness behavior in the regulation of amyloid plaque formation and tau aggregates, but also to identify the best therapies and preventive strategies for AD. Finally, it could be interesting to test the effect of orexin receptor antagonists for reducing Aβ and tau burden in patients with early AD or in subjects at risk of developing AD.

Key Take-Home Points

- Sleep disturbances may predispose to neurodegenerative disorders such as AD.
- The link between sleep and Aβ and tau secretion, accumulation, and clearance and its interaction with hypocretins/orexins suggest mechanistic ways to better understand the impact of sleep alterations in the pathogenesis of AD.
- Further studies are required to determine whether managing sleep problems and increasing slow-wave sleep may alter amyloid plaque and neurofibrillary tangle formation, and thus prevent the risk of dementia.
- The effects of orexin receptor antagonists on nighttime sleep and, consequently, on the reduction in the accumulation of Aβ and tau deserve to be studied in detail in subjects at risk of developing AD.

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Conflicts of Interest Statement

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