THEORETICAL REVIEW

Candidate mechanisms underlying the association between sleep-wake disruptions and Alzheimer's disease

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SUMMARY

During wakefulness, extracellular levels of metabolites in the brain increase. These include amyloid beta (Aβ), which contributes to the pathogenesis of Alzheimer's disease (AD). Counterbalancing their accumulation in the brain, sleep facilitates the removal of these metabolites from the extracellular space by convective flow of the interstitial fluid from the para-arterial to the para-venous space. However, when the sleep-wake cycle is disrupted (characterized by increased brain levels of the wake-promoting neuropeptide orexin and increased neural activity), the central nervous system (CNS) clearance of extracellular metabolites is diminished. Disruptions to the sleep-wake cycle have furthermore been linked to increased neuronal oxidative stress and impaired blood–brain barrier function – conditions that have also been proposed to play a role in the development and progression of AD. Notably, recent human and transgenic animal studies have demonstrated that AD-related pathophysiological processes that occur long before the clinical onset of AD, such as Aβ deposition in the brain, disrupt sleep and circadian rhythms. Collectively, as proposed in this review, these findings suggest the existence of a mechanistic interplay between AD pathogenesis and disrupted sleep-wake cycles, which is able to accelerate the development and progression of this disease.

Regulation of amyloid and tau levels in the brain across the sleep-wake cycle

The aggregation of amyloid beta (Aβ) peptides (predominantly Aβ peptides 1–40 and 1–42; Aβ40 and Aβ42, respectively) into plaques in the brain is a marker of Alzheimer's disease (AD) and a key component of the 'Amyloid cascade hypothesis' [1]. In recent years, increasing evidence has accumulated to support the hypothesis that the production of Aβ peptides in the brain is closely connected to the 24-hr sleep-wake cycle, with high extracellular levels during wakefulness and low extracellular levels during sleep [2–4] (Fig. 1). A major driver for the production of Aβ appears to be neuronal activity, which is higher during wakefulness as compared with sleep. This hypothesis is supported by the observation that unilateral vibrissal stimulation increases, while unilateral vibrissal

removal decreases, interstitial fluid (ISF) levels of Aβ in the contralateral barrel cortex of transgenic mice (Tg2576) [5]. In humans, ISF Aβ concentrations have been shown to increase in patients with acute brain damage as neurological status improves, and conversely to fall when neurological status declines [6].

During sleep, the brain remains metabolically and electrically active with preservation of cortico-cortical connectivity during light sleep, i.e., non-rapid eye movement (NREM) sleep stage 1 (N1) and NREM sleep stage 2 (N2) [7–9]. However, a reduction occurs in fronto-parietal functional connectivity with increasing depth of NREM sleep to the point of being significantly reduced in deep sleep [7–11], also called NREM sleep stage 3 (N3) or slow-wave sleep (SWS). Therefore, Aβ production could be postulated to decrease during SWS by virtue of the decreased neuronal activity in this sleep stage. Supporting this hypothesis, cerebrospinal fluid (CSF) Aβ42 levels have been shown to be lowest in humans at around 10:00 h (around 25% lower than peak values), corresponding to a nadir in ISF levels at 04:00 h (as there is a 6-h lag for brain soluble Aβ to reach the lumbar space [12,13]). This represents a time point after which most SWS has typically occurred and after

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Abbreviations

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Aβ	amyloid beta
Aβ40	amyloid beta peptide 1–40
Aβ42	amyloid beta peptide 1–42
AD	Alzheimer's disease
ApoE	apolipoprotein E
APP	amyloid precursor protein
AQP4	aquaporin-4
BBB	blood–brain barrier
CNS	central nervous system
CSF	cerebrospinal fluid
EEG	electroencephalogram
GLUT1	glucose transporter 1
ISF	interstitial fluid
LC	locus coeruleus
MCI	mild cognitive impairment
NFT	neurofibrillary tangle
NREM	non-rapid eye movement
N1	NREM sleep stage 1
N2	NREM sleep stage 2
N3	NREM sleep stage 3
PET	positron emission tomography
P-tau	phosphorylated tau
REM	rapid eye movement
RNS	reactive nitrogen species
ROS	reactive oxygen species
SDB	sleep-disordered breathing
SirT3	sirtuin type 3
SCN	suprachiasmatic nucleus
SWA	slow-wave activity
SWS	slow-wave sleep
T-tau	Total tau
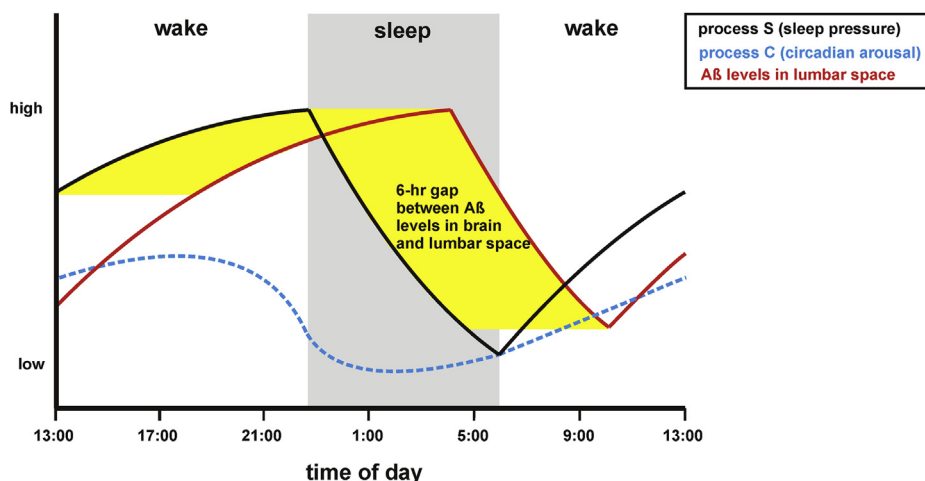
Fig. 1. Temporal association between homeostatic sleep pressure and CSF concentrations of amyloid beta. The propensity to sleep is considered to be regulated by two interacting mechanisms: a circadian process (C) and a homeostatic process (S) [110]. Process C drives arousal and helps time the onset of normal sleep (driven by e.g., environmental light changes and meal patterns), whereas Process S drives sleep pressure and increases as wakefulness continues and decreases during slow-wave sleep (SWS), a sleep stage that predominates during the first 1/3 of the night. In humans, in a study where samples were collected via an indwelling lumbar catheter, both CSF Aβ40 and Aβ42 fluctuated by 25% with a diurnal pattern (labeled as Aβ in the figure) (higher during wakefulness and lower during sleep), with the lowest Aβ42 levels at around 10:00 h [2]. This corresponds to approximately 04:00 h in sleep time as there is a 6-h lag for brain Aβ to reach the lumbar space [12,57]. Abbreviations: Aβ, amyloid beta; Aβ40, amyloid beta peptide 1–40; Aβ42, amyloid beta peptide 1–42 CSF: cerebrospinal fluid.

which sleep is predominated by sleep stages N1-2 and rapid eye movement (REM) sleep.

Neuropeptides involved in the regulation of the sleep-wake cycle may additionally contribute to the characteristic 24-hr pattern of Aβ peptides in the brain. One such candidate is the hypothalamic neuropeptide orexin-A (hypocretin 1), the level of which increases during wakefulness [14]. A study in transgenic APPswe (Tg2576) mice — a mouse model of AD pathology, which carries the Swedish mutation (K595N/M596L) of the amyloid precursor protein (APP) resulting in higher Aβ peptide levels, and which does not develop behavioral signs of AD — showed that intracerebroventricular administration of orexin at the beginning of the light (i.e., inactive) period could acutely increase both wakefulness and Aβ levels in ISF. Conversely, intracerebroventricular treatment over 24 h with a dual orexin receptor antagonist (almorexant) decreased Aβ ISF levels [2]. Further supporting the role of orexin for Aβ accumulation, daily treatment with almorexant for 8 w reduced the formation of Aβ plaques in several brain regions in APPswe/PS1dE9 mice [2]. In a recent study performed in amyloid transgenic mice in which the

orexin gene was knocked out (APP/PS1dE9/OR$^{-/-}$) [15], loss of orexin resulted in decreased wakefulness and a subsequent reduction in amyloid pathology. In contrast to findings of animal studies, evidence from human studies about the role of orexin in the regulation of Aβ production in the brain is less consistent [16–23]. For instance, a recent study involving patients with the sleep disorder narcolepsy — a disease hallmarked by a progressive loss of brain orexin function [24] — revealed that CSF concentration of Aβ was significantly higher in the patient group with normal CSF orexin-A concentration than in those with low orexin-A concentrations [16]. Moreover, in a separate study, CSF levels of Aβ42 were found to be lower in narcoleptic patients compared with healthy controls [25]. Finally, in a case of narcolepsy-cataplexy that occurred post H1N1 vaccination, a strong decrease in CSF beta-amyloid was observed (152 mg/l, normal >500 mg/l [26]). In contrast to these studies involving narcoleptic patients, CSF concentrations of orexin-A and Aβ42 have been found to show no relationship in both AD patients and healthy controls [20].

Another key component of AD pathogenesis is the accumulation of intracellular neurofibrillary tangles (NFTs) composed of