*Review Article*

# Does sleep disturbance affect the amyloid clearance mechanisms in Alzheimer's disease?

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Sleep is an important factor that plays a key role in Alzheimer's disease pathogenesis. However, it is still unclear whether poor-quality sleep may overlap with sleep disturbances in the underlying dysfunctional mechanisms of amyloid beta (Aβ) clearance metabolism. Here, we aimed to evaluate the current evidence on the role of sleep deprivation in Aβ clearance metabolism. To that end, we discuss possible mechanisms underlying the bidirectional interaction between the sleep deprivation and Aβ clearance pathways.

**Key words:** Alzheimer's disease, amyloid beta clearance, glymphatic system, sleep, sleep deprivation.

ALZHEIMER'S DISEASE (AD) IS a progressive, neurodegenerative disorder that gradually disrupts neural circuits that are responsible for underlying neurocognitive symptoms. There is rapidly replicating evidence indicating that the key factor in AD pathogenesis is the aggregation of amyloid beta (Aβ) protein within critical regions of the brain. The principal underlying mechanism for the aggregation is the imbalance between clearance and production of Aβ that results in synaptic and neuronal loss due to the accumulation of toxic amyloid aggregates.[1,2] It has been shown previously that individuals with AD may present with sleep and circadian rhythm disturbances. However, it is still unclear whether there is a dual interaction implying that the sleep–wake cycle itself may directly play a key role in the pathogenesis of AD.

## EVIDENCE FROM HUMAN STUDIES

Sleep is an important factor that plays a key role in AD pathogenesis. Apart from studies showing that individuals with AD may present with sleep and circadian rhythm disturbances,[1,3] it is still unclear whether poor-quality sleep may overlap with sleep and circadian rhythm disturbances in the underlying dysfunctional mechanisms of Aβ metabolism. There are various theories hypothesizing that sleep disturbances might worsen the AD pathology through increased wakefulness and related excitotoxicity.[4,5] Moreover, recent studies indicate that altered function of brainstem neurotransmitter pathways secondary to sleep impairment might lead to the impairment of the 'default mode' brain network, which is a key pathophysiological mechanism in AD.[6,7] In recent years, human Aβ metabolism has received considerable critical attention in regards to clarifying the pathophysiological relation between sleep and AD pathogenesis. Furthermore, understanding human Aβ physiology may also help us to establish the utility of cerebrospinal fluid (CSF) Aβ42 levels as a surrogate marker for amyloid plaque deposition. In this context, Bateman *et al.* have already shown that CSF and blood Aβ metabolism are regulated in a circadian manner in healthy adults.[8] These results were further confirmed by the following study indicating that age-related impairment in physiological CSF dynamics was strongly correlated with the amyloidosis.[9]

There are rapidly increasing data showing deleterious effects of sleep disruption on cognition and amyloid burden in normative populations.[2,3,10–14]

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Although it is hard to validate the causal relationship between disturbed sleep and the pathogenesis of AD in humans, short-term prospective studies have already provided fruitful data revealing that sleep disruption increases the risk of incident dementia.[2,3,10,11] In their prospective cohort study of older adults without dementia, Lim *et al.* revealed that sleep fragmentation was correlated with increased risk of AD and cognitive decline, which was abolished with improved sleep consolidation.[10,11] Subsequent longitudinal studies have indicated that insomnia, prolonged sleep duration, and excessive daytime sleepiness are also associated with risk of developing cognitive decline.[15–17] These clinical study results were confirmed by a recent long-term follow-up study showing that there is a significant relation between insomnia and AD in cognitively normal adults.[18] In evaluating the underlying pathophysiological mechanisms, Ju *et al.* established that poor sleep quality increased the brain amyloid aggregation in cognitively normal adults.[14] These results were in line with the following study of 26 cognitively healthy adults showing that short-term sleep deprivation significantly elevated the CSF amyloid-β levels, which were reversed with a night of good sleep.[12] Consistent with this finding, recent amyloid–positron emission tomography studies of cognitively normal populations indicated that there is a strong association between longer sleep latency, self-reported sleep quality, and brain Aβ burden[19,20] that was independent of apolipoprotein E (ApoE) ε4 genotype.[20]

## EVIDENCE FROM ANIMAL STUDIES

There are strong preclinical data indicating that sleep–wake dysregulation leads to a slight increase in extracellular Aβ in Tg2576 mice during wakefulness, which was persistently increased after sleep deprivation. In their interesting study, Kang *et al.* revealed that prolonged sleep deprivation was associated with significant increase in Aβ levels.[1] These results were also confirmed with an amyloid precursor protein (APP)/PS1 mutant line, indicating that the duration of sleep deprivation may play a critical role in determining the amyloid plaque load within the brain.[1] These data suggest that pharmacological interventions aimed to increase the total sleep time may help to reduce the AD pathology. In this context, inhibiting the orexin receptors through almorexant resulted in significant increases in total sleep time, which was

associated with reduced Aβ plaque load in mice.[1] Following transgenic mice, studies focusing on the role of amyloid plaques and tau tangles have also revealed interesting results. Di Meco *et al.* showed that impaired circadian response to light showed significantly increased insoluble tau that was associated with synaptic and cognitive impairment compared with normal circadian controls.[21] Although the role of sleep deprivation was not directly examined in this study, these data are important in suggesting the role of impaired circadian rhythm in the pathophysiology of AD. From another point of view, recent transgenic mice studies have revealed that locus coeruleus (LC) degeneration and related loss of cortical noradrenergic innervation resulted in increased neuroinflammatory response that was correlated with increased amyloid plaques and memory deficits.[22,23] As LC is a well-known region affecting the sleep–wake cycle,[22,23] these preclinical data suggest that sleep disorders might contribute to amyloid pathology. Despite these promising preclinical data, it should also be noted that the results of transgenic animal species should be interpreted cautiously because most transgenic mice models are using the human-derived APP instead of a murine APP.

## A POSSIBLE ROLE OF TRANSPORT MECHANISMS?

Studies have already indicated that a significant portion of Aβ clearance has been attributed to the blood–brain barrier (BBB) transport of Aβ, which is mediated by multi-drug resistant proteins (i.e., ATP-binding cassette transporters, such as p-glycoprotein, and low-density lipoprotein receptor family members) in an ApoE-dependent and -independent manner.[24,25] Beyond its critical role in BBB, ApoE also has a special role in the elimination of Aβ through its interaction with astrocytes, which play a critical role in sleep regulation. Recent studies have indicated that sleep disturbances might affect astrocyte–ApoE Aβ clearance pathways in the manner of a feed-forward mechanism that results in increased Aβ accumulation.[2,3] This is in agreement with recent data showing that sleep deprivation suppresses the glymphatic distribution of CSF-derived ApoE into the brain and its elimination.[26] Several reports indicate that sleep deprivation also leads to systemic inflammation and secondary release of inflammatory mediators, which promote significant alterations in the molecular components of the BBB.[27] However, there is no evidence

in the literature showing that inflammatory molecules exert a local effect on specific BBB transport mechanisms that would increase the risk of developing neurodegenerative diseases. Although there is rapidly replicating evidence indicating the role of p-glycoprotein to Aβ clearance across the BBB,[28] there is only one molecular positron emission tomography study in the literature that has indicated that there is no association between sleep disturbance and p-glycoprotein expression in rodents.[29] Considering all of this evidence, special interest has been given to molecular transport mechanisms by which sleep deprivation might affect the clearance of Aβ through the interstitial fluid (ISF) bulk-flow-dependent process. Compared to peripheral tissue where lymph vessels drain the excess interstitial products to the general circulation,[30] the brain, which has a high metabolic rate and related toxic byproducts, does not have a conventional lymphatic system. Instead of this, there is an interesting glymphatic clearance mechanism of the brain that enables the removal of interstitial toxic proteins, such as Aβ, through a dynamic interaction between the CSF and ISF, which is located around the cerebral vasculature.[31–33] This ISF bulk-flow-dependent process drains Aβ containing ISF from the interstitium via ISF bulk flow into the CSF and perivascular space through the perivascular and glymphatic pathways.[24,34,35] According to this hypothesis, toxic chemicals are cleared from the ISF by a complex process that requires astrocytic water-permeant channel aquaporin-4 (Aqp4) during sleep. Aqp4 is a well-known water transporter that is majorly expressed on the astrocytic endfeet.[36] Studies in the last decade have already shown the pivotal role of astrocytes in 'cleaning the brain' through the glymphatic pathway and indicate the specific modulatory role of astrocytic Aqp4 expression during the sleep.[36] Moreover, there have been interesting studies during recent years evaluating the distribution and expression of Aqp4 in preclinical and clinical AD studies.[37] In this context, experimental studies have already shown the role of Aqp4-dependent trans-astrocytic ISF bulk flow in the clearance of Aβ through the glymphatic system.[24,37,38] These results were confirmed with subsequent studies using Aqp4-knockout mice showing reduced A 40 clearance that resulted in Aβ deposition in the cortex and hippocampus.[32] Although there are no actual data indicating the modulatory role of sleep–wake cycles on the Aqp4 expression, awakened mice showed much-decreased clearance of exogenously applied Aβ from the interstitial space that was

significantly reversed during sleep.[31] Subsequent studies have confirmed the key role of the glymphatic system in Aβ clearance and have revealed that the degradation of Aβ is minimal during these transport clearance measurements.[31,34,39] Additional evidence for the transport failure during sleep–wake impairment was provided from Xie *et al.*, who revealed that the sleep–wake state rather than the circadian rhythm enhanced the glymphatic-system-dependent clearance of the exogenously applied Aβ.[31] In evaluating the underlying mechanisms, they underlined the role of adrenergic signaling during wakefulness, which was responsible for increased tissue resistance to the interstitial fluid flux that resulted in decreased size of the interstitial space that was reversed with adrenergic receptor blockage. Taken together, all of these studies suggest that the astrocytic, sleep-dependent contribution to the glymphatic pathway is a locus of clearance impairment in AD. This also supports that the impairment of the efflux of Ab1-42 from the glymphatic pathway to the circulation is a critical step.

## CONCLUSION

Because Aβ accumulation in the affected regions of the AD brain begins years before any signs of the disease are prominent, a therapeutic approach effectively enhancing clearance mechanisms would exert huge benefits in the progress of this disease. Among the many transport mechanisms that have been mentioned above, the most specific transport mechanism that is tightly linked to sleep disturbance seems to be the glymphatic system (Fig. 1). This
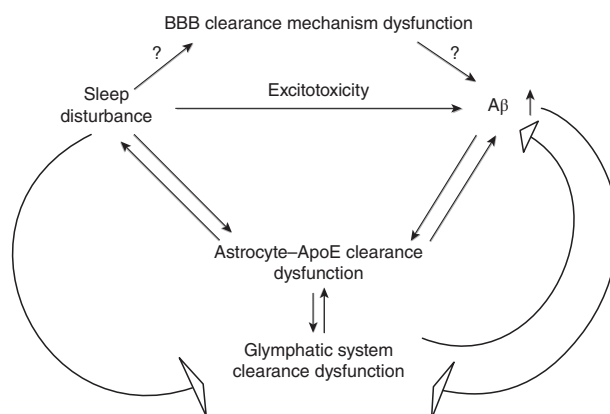


**Figure 1.** Possible role of sleep deprivation on amyloid-beta (Aβ) clearance mechanisms in the brain. ApoE, apolipoprotein E; BBB, blood–brain barrier.

system is characterized by astrocytic Aqp4, which plays an important role in the elimination of Aβ. Future studies evaluating the effects of sleep deprivation on Aqp4 expression would be the logical future steps to be taken in the field of AD research.

## DISCLOSURE STATEMENT

There is no conflict of interest in this study.

## AUTHOR CONTRIBUTIONS

B.Y.: Conception and design of the study, acquisition and analysis of data. L.H.: Drafting the manuscript or figures. E.K.: Acquisition and analysis of data.

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