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Review

Sleep Deprivation, a Link Between Post-Traumatic Stress Disorder and Alzheimer's Disease

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Abstract. An estimated 5 million Americans are living with Alzheimer's disease (AD), and there is also a significant impact on caregivers, with an additional 16 million Americans providing unpaid care for individuals with AD and other dementias. These numbers are projected to increase in the coming years. While AD is still without a cure, continued research efforts have led to better understanding of pathology and potential risk factors that could be exploited to slow disease progression. A bidirectional relationship between sleep deprivation and AD has been suggested and is well supported by both human and animal studies. Even brief episodes of inadequate sleep have been shown to cause an increase in amyloid-β and tau proteins, both well-established contributors to AD pathology. Sleep deprivation is also the most common consequence of post-traumatic stress disorder (PTSD). Patients with PTSD frequently present with sleep disturbances and also develop dementia at twice the rate of the general population accounting for a disproportionate representation of AD among U.S. Veterans. The goal of this review is to highlight the relationship triad between sleep deprivation, AD, and PTSD as well as their impact on molecular mechanisms driving AD pathology.

Keywords: Alzheimer's disease, amyloid-β, post-traumatic stress disorder, sleep deprivation, tau

INTRODUCTION

Sleep is a reoccurring period of restorative unconsciousness necessary for normal human function. The cycle of consciousness and unconsciousness is under the control of the circadian clock, a complex system of endocrine and neuroendocrine processes that input ques from the environment to create a sleep-wake rhythm. Significant variability exists in when people sleep and how frequently, termed chronotypes. However, sleep duration less than 5 hours per night corelates with poor cardiovascular health, type 2 diabetes, and obesity across different populations [1, 2]. Individuals with chronotypes far outside the average are considered to have sleep disorders [3]. Requirement for sleep is evolutionarily conserved and is present in invertebrates and vertebrates [4]. Chronic

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lack of adequate sleep leading to sleep deprivation can cause both systemic and neurological problems ranging from metabolic disruption and obesity to stroke, and impaired learning [5, 6]. Sleep deprivation is associated with neurodegenerative disorders like Alzheimer's disease (AD) [7] as well as neuropsychiatric disorders such as post-traumatic stress disorder (PTSD) [8], but it remains unclear if sleep deprivation is a cause or a consequence for these disorders.

Quality sleep has been shown recently to be necessary in helping coordinate the clearing of metabolic waste and toxic proteins involved in AD and inadequate sleep may therefore accelerate or cause AD. Non-rapid eye movement (Non-REM) sleep presents on an electroencephalogram (EEG) with low-frequency (less than 4 Hz) oscillations, important in supporting consolidations of new memories and neuronal processing [9–11]. During Non-REM sleep, low frequency oscillations in neuronal activity were found to co-occur with large influx of cerebrospinal fluid (CSF) into the brain and hemodynamic changes [12]. In mice, sleep is associated with clearance of metabolic waste from the CSF which is stronger during low-frequency EEG oscillation associated with Non-REM sleep [13, 14]. Sleep has been found to regulate CSF levels of AD related proteins amyloid-β (Aβ) and tau [15, 16]. Even a single night without sleep can cause accumulation of Aβ in otherwise healthy human brains suggesting a close relationship with sleep disruption and key components of AD pathology [17]. AD is the most common neurodegenerative disorder that disrupts neural circuits, leading to a progressive loss of neurological function and death. Disruption of neural circuitry and neurodegeneration is in part driven by accumulation of "senile plaques" made up of misprocessed Aβ protein and also neurofibrillary tangles consisting of hyperphosphorylated tau. Studies suggest that the incidence of AD is higher in those individuals diagnosed with PTSD [18, 19], a psychiatric disorder triggered by exposure to one or more traumatic events which can lead to a number of neurological and physiological problems, though there have been few studies investigating the factors that may contribute to observed correlation between PTSD and AD. While PTSD patients can present with a number of characteristic symptoms, one of the most common complaints is the presences of sleep disturbances. Large studies suggest that sleep disruption is present in 70–87% of patients with PTSD [20–22]. In this review, we discuss the important role of sleep deprivation in the pathogenesis of AD and as a component of PTSD that may drive the higher incidence of AD in PTSD patient population. We examined primary literature over the past two decades spanning human and animal studies on PTSD, sleep deprivation, and AD, that together implicate sleep deprivation as the likely link between PTSD and increased susceptibility to AD.

SLEEP DEPRIVATION

Disruption of sleep-wake cycle is frequently caused by work and lifestyle choices [23]. Persistent disruption of sleep-wake cycle can result in chronic sleep deprivation which has been linked to systemic and neurological problems including disruption of normal metabolism, obesity, heart disease, high blood pressure, and stroke [5, 6]. The consequences of sleep deprivation are not simply a result of wear and tear but also due to long lasting hormonal, genetic, and epigenetic changes [5, 6, 24]. Brain is particularly affected by sleep deprivation, resulting in diminished learning and memory even after brief periods of sleep deprivation [25–27]. Even among college athletes sleep deprivation causes deterioration in learning, vigilance, mood, and athletic performance [28]. By altering gene expression and hormone levels, and by disrupting normal metabolic function, sleep deprivation can predispose, cause, or worsen neurodegenerative and neuropsychiatric disorders including AD.

Sleep deprivation and AD

A bidirectional relationship between sleep disruption and AD has been proposed and is supported by mounting evidence, demonstrating that sleep deprivation increases AD related pathology and that increasing AD pathology further causes sleep disruption [29, 30]. Sleep cycles between non-REM and REM sleep stages, several times during a typical night. Non-REM is the longer of the two sleep stages and is further subdivided into 3 successive sub-stages, that occur before the shorter REM period is reached. Non-REM sleep is characterized by low-frequency (less than 4 Hz) oscillations, important in supporting consolidations of new memories and neuronal processing [9–11]. Non-REM sleep is also accompanied by large influx of cerebrospinal fluid (CSF) into the brain and also with hemodynamic changes [12]. In mice, as in humans, diurnal variation in Aβ levels were found to occur, with higher Aβ levels detected in the CSF during waking hours, that decrease following sleep or in case of mice higher levels of Aβ

were detected during their active dark phase compared to light phase [15]. Chronic sleep disruption in mice resulted in significantly higher levels of Aβ, that decreased following sleep suggesting that Aβ levels are dependent on wakefulness rather than time of day [15]. Orexin is a molecule involved in regulating wakefulness and is released from hypothalamic neurons promoting wakefulness [31]. Diurnal fluctuations in orexin correspond to Aβ. Brain infusion of orexin in mice resulted in increased Aβ levels, while inhibition of orexin receptors abolished diurnal Aβ variation [15]. Chronic sleep deprivation of APP transgenic mice that develop Aβ plaques, resulted in increased plaque burden, while blocking orexin receptors decreased plaque burden [15]. Sleep duration of less than 5 hours or greater than 11 hours per night have been linked to increased risk for cognitive impairment [32, 33]. Prospective study looking at sleep demonstrated that sleep fragmentation increases the risk of developing AD [7]. AD related pathology is thought to start decades before the onset of symptoms and eventual diagnosis. Identifiable pathological changes in AD include reduction of soluble $A\beta_{42}$ levels in the CSF 10–15 years before the onset of cognitive symptoms associated with AD [35]. Asymptomatic individuals with reduced soluble $A\beta_{42}$ levels, which is an indication of Aβ sequestration into insoluble senile plaques, have worse sleep quality compared to their peers with normal $A\beta_{42}$ levels [36]. These clinical observations were replicated in two different mouse models (APPSWE and APPSWE/PS1DE9) where sleep deprivation accelerated deposition of Aβ into amyloid plaques and enhanced sleep showed decrease in Aβ plaque deposition [15].

Sleep deprivation in PTSD as a risk factor AD

Individuals with PTSD are reported to have exaggerated cognitive changes with aging, and increased incidence of AD; however, well-controlled studies in this area are relatively few in number. Administrative data from the Veterans Integrated Service Network (VISN) of Department of Veterans Affairs healthcare facilities revealed that the prevalence and incidence of a dementia diagnosis remained nearly two times as high in Veterans with diagnosed PTSD compared to the control group consisting of Veterans without diagnosed PTSD [18]. Another study of Veterans aimed at determining whether PTSD is associated with increased risk for developing dementia reported that during a 7-year follow-up, Veterans with PTSD had a cumulative incident dementia rate of 10.6% whereas those without PTSD had a rate of 6.6%. These results were similar even after those with a history of head injury, substance abuse, or clinical depression were excluded [19]. While PTSD is common among Veterans, it is also present in the general population. A study of 600 older persons revealed that individuals that were categorized as being in the 90th percentile of "distress-proneness" were 2.7 times more likely to develop AD than those not prone to distress (10th percentile). In this study, "distress-proneness" was also associated with overall cognitive decline [37].

PTSD and AD have also been studied in animal models. Studies in animals have shown that various stressors can be associated with accelerated development of amyloid plaques [38–41], increased levels of Aβ [42, 43], and tau hyperphosphorylation [44–46]. One study in mice found that a PTSD-like induction chronically elevated levels of Aβ in the CSF, exacerbating ongoing AD pathogenesis [47]. They demonstrated that Aβ resulted in hyperexcitation of corticotropin-releasing factor (CRF) neurons and that lowering of Aβ levels attenuated the PTSD-like phenotype. Their data demonstrated that exposure to PTSD-like trauma can drive AD pathogenesis and perturb CRF signaling, important in stress activated responses, thereby enhancing chronic PTSD symptoms and increasing the risk for AD.

PTSD patients can present with a number of psychiatric symptoms, including nightmares and hyperarousal, which invariably impact sleep duration and quality [48]. PTSD and sleep quality deficits are common among combat Veterans. One study of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) Veterans found that 89% were reported as "poor sleepers" according to the Pittsburgh Sleep Quality Index (PSQI) and that sleep quality was worse among Veterans presenting with PTSD symptoms [49].

Neuroimaging studies have long shown that neuronal excitability plays a key role in PTSD pathogenesis [50–52]. One study demonstrated that patients with PTSD exhibited a mean conditioned motor evoked potential amplitude higher than that observed in control groups. They demonstrated that PTSD can give rise to abnormalities in intracortical inhibition which leads to cortical hyperexcitability [53]. Similarly, changes in neuronal excitability may underlie the effects of sleep deficit on AD pathogenesis. In a *Drosophila* model of AD, Aβ accumulation led to fragmented and reduced sleep, while chronic sleep deprivation led to increased Aβ burden.

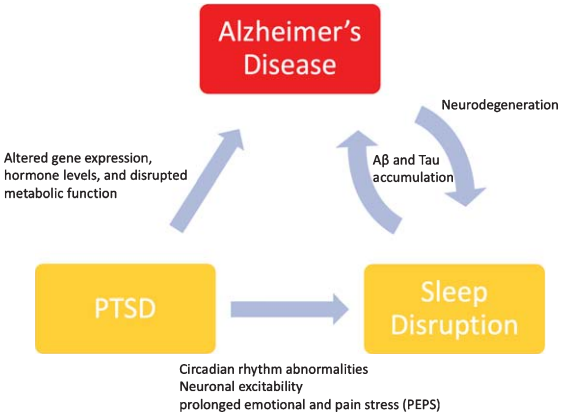

Fig. 1. PTSD can cause altered gene expression, altered hormone levels, and disrupted metabolism, thereby creating an environment that can promote amyloid-β (Aβ) formation and neurodegeneration associated with Alzheimer's disease. Sleep deprivation resulting from PTSD can cause a positive feedback loop where sleep deprivation increases likelihood of Alzheimer's disease and in turn, progression of Alzheimer's disease can result in further sleep disturbances.

Moreover, neuronal excitability was found to mimic the effects of reduced sleep on Aβ accumulation. Additionally, suppressing neuronal excitability reduced the effects of sleep deprivation on Aβ accumulation [54]. These results suggest that both neuronal excitability and sleep deprivation exacerbate the accumulation of Aβ and may provide a link between the neuronal excitability and sleep deprivation in PTSD patient populations which can eventually lead to development of AD. We summarize the relationship between PTSD, sleep deprivation, and AD in Fig. 1.

MOLECULAR MECHANISMS OF AD DRIVEN BY SLEEP DEPRIVATION

The hallmark plaques observed in AD brains are the result of an accumulation and inability to clear the protein Aβ, a metabolic waste product. Though the mechanisms by which Aβ is cleared in healthy human brains is not well understood, there is evidence that sleep may play a role in clearance of waste products such as Aβ [13]. Animal models provide further evidence that Aβ levels and sleep quality and duration are tightly linked. In mice, measurement of hippocampal Aβ levels using *in vivo* microdialysis revealed that Aβ levels were positively correlated with the amount of time spent awake and negatively correlated with the amount of time spent asleep. This negative correlation was even stronger with non-REM sleep [15]. In a human study, even a single unrestricted night of sleep led to a 6% decrease in CSF Aβ levels in cognitively normal middle-aged men and just one night of total sleep deprivation counteracted this decrease, interfering with the physiological morning decrease in Aβ levels [55].

The increased risk for AD in chronic sleep deficit appears to be modulated through multiple molecular pathways of neuronal injury in addition to the effect on Aβ accumulation. Two-month sleep deprivation in mice not only altered the Aβ protein precursor processing but also raised the phosphorylated tau (p-Tau) level and resulted in impairment in cognitive performance compared to non-sleep deprived controls. In addition to increased $A\beta_{42}$ production and more senile plaques in the cortex and hippocampus, sleep deprivation also caused neuronal mitochondrial damage, caspase cascade activation, and mediated neuronal apoptosis. These changes were long-lasting and were irreversible during a 3-month follow-up under normal conditions [56]. Transgenic mice that were sleep deprived showed significant increase in the insoluble fraction of tau, lower levels of postsynaptic density protein 95, and increased glial fibrillary acidic protein levels [57]. Sleep-deprived mice displayed increased Aβ and p-Tau levels in the cortex and higher circulating levels of the hormone corticosterone, responsible for energy, immune, and stress response regulation, compared to controls [58]. Other animal models of chronic sleep deprivation have shown depletion of glycogen stores and increase in oxidative stress and free radical formation [59], thus emphasizing that multiple molecular pathways are involved in neurodegeneration in response to chronic sleep deficit.

Orexin

Orexin, the neuropeptide that promotes wakefulness, appears to play a significant role in Aβ-mediated neurodegeneration. APP/PS1 transgenic mice, in which the orexin gene was knocked out, display a marked decrease in the amount of Aβ pathology in the brain with an associated increase in sleep time. In contrast, sleep deprivation or increasing wakefulness by rescue of orexinergic neurons in APP/PS1 mice lacking orexin increase the amount of Aβ pathology in the brain [60]. Orexin activation has also been shown to play a role in behavioral fear expression in an animal model [61]. Similarly, another animal study showed that orexin administration impaired fear extinction [62]. These studies

suggest that inappropriate excitation of this pathway may account for the fear generalization observed in PTSD. Additionally, altered orexin signaling may lead to sleep disturbance and changes in Aβ pathology.

Alzheimer's disease, sleep, and the immune system

Sleep deprivation is associated with increased risk of cardiovascular disease, diabetes, hypertension, and obesity with a 45% increase in the risk of a fatal heart attack. These consequences of sleep loss are characterized, in part, by inflammatory processes [63]. Sleep deficit-induced proinflammatory response is considered a risk factor for neurodegenerative diseases such as AD [64]. Sleep appears to have a bidirectional relationship with the immune system and over the past few decades it has become increasingly apparent that sleep is closely intertwined with the immune system. In 1975, Pappenheimer et al. [65] reported isolating a substance which they termed sleep-promoting factor (factor S) and later research identified this substance as a bacterial cell wall peptidoglycan fragment known as muramyl peptide, a pyrogenic cytokine. This substance was shown to induce sleep in non-sleep deprived animals and it also induced inflammatory cytokines [66]. These findings led to further research to delineate the role of sleep, in immune responsiveness and the findings have confirmed a bidirectional relationship between sleep and immune function. It has been found that through neuro–immune interactions, sleep loss alters immune function and immune challenges alter sleep pattern. As more became known about the sleep response to infectious challenge, it became clear that IL-1β and TNF-α are among the inflammatory markers that are involved in the central nervous system regulation of physiological sleep [67].

SUMMARY

Individuals diagnosed with PTSD are at least twice as likely to develop AD than those without PTSD. Sleep deprivation is the most commonly reported consequence of PTSD and has been reported as a major accelerant of AD pathology in patients and in AD animal models. Sleep deprivation appears to affect multiple molecular pathways leading to higher risk for neurodegeneration and therefore interventions aimed at improving sleep patterns will have a much broader impact than medications targeting any single molecular mechanisms. It has been established that neurodegeneration in AD begins years before symptom manifestation presenting an opportunity for intervention prior to onset of symptoms.

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