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Unlocking The Link: Exploring The Interplay Between Sleep Deprivation, Insomnia, And Alzheimer's Disease Pathogenesis.

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Abstract: sleep deprivation refers to the condition of not having enough sleep, either due to lack of opportunity to sleep or difficulty in falling asleep. It can lead to various cognitive, emotional, and physical impairments, impacting overall health and well-being. Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline, memory loss, and impaired daily functioning. AD represents a significant global health concern, yet despite extensive scientific endeavors, effectively treating AD remains an ongoing challenge. Sleep plays crucial roles in the processes of learning and consolidating memories. Research indicates that sleep deprivation and insomnia have been linked to the Pathogenesis of Alzheimer's Disease. Sleep deprivation has been found to increase Amyloid beta deposition and tau hyperphosphorylation, both of which are implicated as risk factors in the pathogenesis and progression of Alzheimer's Disease. Understanding the molecular mechanisms linking sleep deprivation to AD is imperative, as it could pave the way for the development of preventive and therapeutic interventions for the disease. This review explores the intricate relationship between sleep disruption, insomnia, and the pathogenesis of Alzheimer's Disease. It delves into the bidirectional influence of sleep disturbances and AD pathology, highlighting the potential mechanisms linking these phenomena. Understanding these connections is crucial for developing preventive and therapeutic strategies for AD.

Keywords: Sleep deprivation, Insomnia, Alzheimer's Disease, Amyloid beta, Tau protein, Inflammatory mechanisms

1. INTRODUCTION

Alzheimer's disease (AD) is the utmost common form of dementia, a usual term for memory defect and other cognitive impairments that seriously affect daily life [(2)]. AD negatively impacts both life quality and expectancy [(1)]. Based on WHO reports, nearly 50 million people have dementia worldwide. There are about 10 million new cases annually and Alzheimer's Disease (AD) may contribute to 60-70 % of the cases [(4)]. AD is a progressive neurodegenerative condition characterized by a range of cognitive and non-cognitive impairments [(5)]. Symptoms can vary depending on the extent of neuronal damage in different brain regions. Common signs include memory loss, particularly recent information, difficulties with recall, tracking time, problem solving, language, and recognition [(6)]. The accumulation of extracellular amyloid-beta(Aβ) plaques is a significant pathological feature of AD, along with increased intraneuronal tau expression and the age-related formation of intracellular tau tangles, which often coincide with Aβ deposition and worsen the condition [(7-8)]. Neuroinflammation also plays a crucial role in AD progression, triggered by and exacerbating both Aβ and tau buildup. This inflammatory response involves various processes, including the recruitment of peripheral immune cells like leukocytes and T cells, activation of glial cells, activation of intracellular signaling pathways, and the release of inflammatory molecules including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-18 (IL-18), tumor necrosis factor-α (TNF-α), interferons (IFN) and interleukin-12 (IL-12). These cytokines are upregulated in signature AD regions and result in neuronal dysfunction or can be fatal.

Sleep, constituting approximately one-third of human life, plays a pivotal role in growth, emotional regulation, and memory consolidation, while also facilitating the clearance of metabolic waste and minimizing energy loss [11-13]. Despite its importance, approximately one third of the global population experiences sleep deprivation (SD) [14], characterized by intentional or unintentional reduction in sleep duration due to various factors such as work demands, academic pressure, or underlying sleep disorders [14-15]. SD is prevalent across diverse occupational sectors, including health care professionals, military personnel, shift workers, and the elderly population, often exacerbated by conditions like Parkinson's disease or sleep apnea syndrome. The association between SD and age-related diseases like dementia and stroke, particularly AD, is well-documented, with research highlighting the profound negative effects of even a single night of inadequate sleep. These effects range from emotional stress and impaired cognitive function to increased risk of cardiovascular diseases. Obesity, and diabetes [12-16]. Moreover, SD contributes to industrial, traffic, and medical accidents, underscoring the urgent need for effective interventions to mitigate its societal impacts. Recent advancements in research have shed light on the relationship between the sleep deprivation (SD) and neurodegenerative diseases, garnering significant attention. Extensive studies have revealed the detrimental impact of SD on learning and memory, with a well-documented bidirectional relationship between SD and Alzheimer's disease observed in both human and animal research. Further investigations have elucidated how SD contributes the deposition of Amyloid-β and the hyperphosphorylation of tau, pivotal pathological mechanisms underlying AD. Consequently, SD has emerged as a recognized risk factor for the onset of AD.

Insomnia, a common sleep disorder, characterized by persistent difficulty falling asleep, staying asleep, or experiencing non-restorative sleep, leading to impairment in daytime functioning. Based on the studies, the major pathological agent in AD is Aβ. It has been reported that insomnia can cause a rise in the CSF levels of Aβ [4]. This review will primarily focus on examining the complex interplay between sleep deprivation (SD), Insomnia, and Alzheimer's disease (AD), while also investigating the underlying mechanisms by which SD impacts the development

2. Disturbances in sleep-wake cycle and AD pathology

Understanding the interplay between Alzheimer's disease (AD) and sleep disturbances require familiarity with the two primary sleep stages: Rapid eye movement (REM) and Non-rapid eye movement (NREM). NREM sleep encompasses three stages: N1, N2, and N3, characterized by EEG patterns evolving from low amplitude/high frequency to high voltage/low frequency waves, with N3 also known as slow wave sleep (SWS). NREM sleep is associated with reduced synaptic activity and behavioral quiescence, while REM sleep mirrors waking EEG patterns, earning it the moniker "paradoxical sleep" [1]. Despite many AD patients perceiving their sleep as satisfactory, a substantial portion experience sleep-impairments, including prolonged sleep onset latency, increased nocturnal awakenings, and daytime sleepiness. Even in early AD stages, both REM and NREM sleep durations decline, with alterations in slow-wave sleep and activity potentially serving as early biomarkers. Sleep disorders like insomnia and sleep apnea are prevalent in AD patients. Research into mechanisms behind these sleep disturbances faces challenges, yet studies utilizing actigraphy, a non-invasive method to assess rest and activity cycles, suggest that individuals with Amyloid-β deposition, a precursor to AD, exhibit altered sleep patterns and indicative of preclinical AD. Animal models, particularly genetically modified mice, have elucidated a direct connection between AD pathology and sleep disruptions. For instance, mice expressing Amyloid plaques in key sleep-regulating brain regions exhibit sleep abnormalities, underscoring the role of AD pathology in sleep disturbances. Similarly, Platt and colleagues engineered triple knock-in mice by introducing human amyloid and tau transgenes into an existing presenilin mutant mouse line. These triple transgenic mice developed intraneuronal amyloid deposits and hyperphosphorylated tau in the hippocampus and cortex by 6 months of age. Consistent with other models, these mice exhibited heightened wakefulness, decreased NREM sleep, increased sleep fragmentation, and elevated delta power during wakefulness and REM sleep. These sleep disturbances preceded deficits in hippocampal synaptic plasticity and memory formation, manifesting around 12 months of age. Another AD mouse model, featuring mutations in APP, PS1, and tau, demonstrated age-related loss of noradrenergic neurons in the locus coeruleus, a key region for regulating wakefulness. Collectively, these findings highlight the association between Alzheimer pathologies in mouse models and disruptions in wakefulness, sleep duration, and sleep quality, including alterations in sleep architecture and homeostasis. Both clinical studies in AD patients and animal models emphasize the impact of Aβ deposition on sleep patterns and animal suggest that specific sleep disturbances could serve as early biomarkers for AD [1].

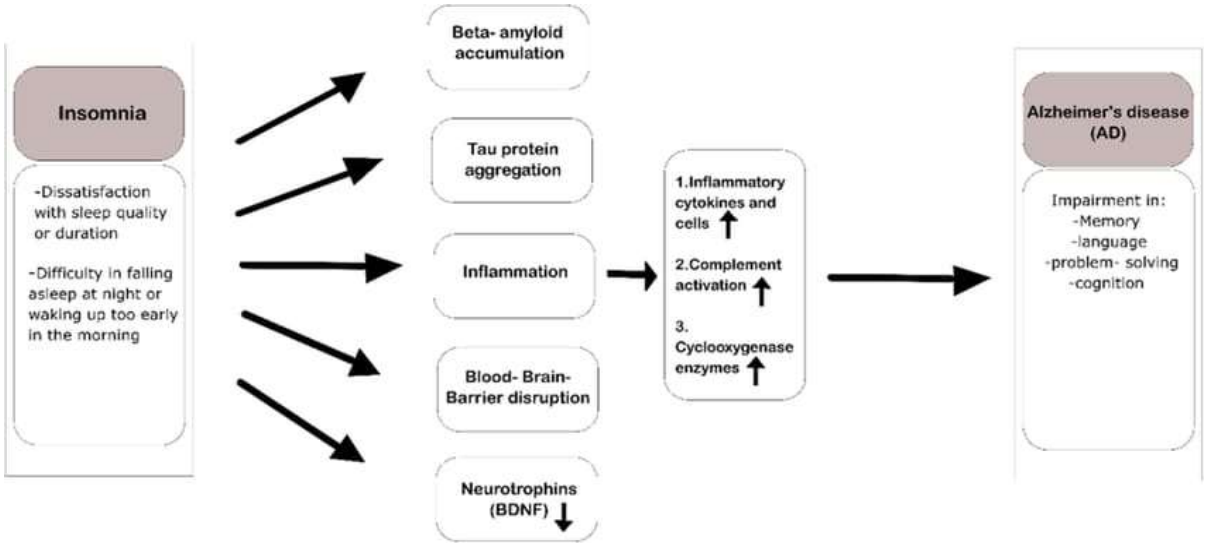

Fig. 1 Mechanisms that can link insomnia to the pathogenesis and progression of AD pathology.

3. Senile plaques (SPs) of Amyloid-β

The 39 to 40 residue amyloid peptides, known as Aβ, arise from the proteolytic cleavage of amyloid precursor protein (APP) by β and γ-secretases. In Alzheimer's disease, the accumulation of Aβ is a significant factor leading to synaptic dysfunction and neurotransmission impairment. This accumulation results from an imbalance between Aβ production and its clearance. Intraneuronal buildup of Aβ is an early event in AD, initiated by APP cleavage at the beta sire. BACE1, also known as β-site APP-cleaving enzyme 1, plays a pivotal role in Aβ accumulation. APP is widely distributed in cellular membranes, including the plasma membrane, synaptic terminals, Golgi network, (ER), and various organelles, contributing to cell adhesion and movement. Initially produced as monomers, Aβ peptides aggregate into multimeric complexes predominantly at the plasma membrane, where β and γ-secretases are highly concentrated. These oligomeric Aβ species are particularly pathological, contributing to hippocampal synaptic loss and impaired long-term potentiation in rodent models. The neurotoxic effects of amyloid-β peptides include degeneration of cholinergic neurons, alterations in glutamatergic synaptic transmission, and crucially, synaptic loss, dendritic spine loss, and cell death. Intracerebral injection of synthetic Aβ, comprising fibrils, protofibrils, oligomers, and monomers, has been shown to impair learning behaviour in rats. Amyloidosis, a clinical disorder characterized by the deposition of insoluble pathogenic amyloid composed of misfolded proteins, can occur extracellularly and/or intracellularly. While cells possess sophisticated systems, including chaperones and the proteasome, to regulate protein folding and degradation, amyloid species can evade quality control mechanisms, leading to aggregation into fibrillar structures. Inhibition of proteasome pathways, Aβ-degrading enzymes like β- and γ-secretases, or uptake mechanisms by lysosomes or brain vasculature can exacerbate the accumulation of misfolded amyloidogenic proteins and peptides. Various cell types in the brain parenchyma and vasculature participate in the clearance of Aβ, mediated by cell surface Aβ-binding receptors and regulated by apolipoprotein E (apoE).

Studies have linked sleep disturbance and insomnia to a higher incidence of dementia. Animal models have shown increased levels of brain Aβ peptides in response to sleep deprivation, attributed to elevated BACE1 and β-secretase levels. Chronic sleep restriction has also been associated with increased Aβ plaque formation in transgenic mice. Human studies have corroborated these findings, with primary insomnia patients exhibiting a higher risk of subsequent dementia diagnosis. Long-term poor sleep quality has been linked to increased brain Aβ42 levels. Wakefulness promotes neuronal activity and Aβ production, while sleep facilitates Aβ clearance, potentially through mechanisms like the glymphatic system, which operates more efficiently during sleep [(4).]

Collectively, evidence from animal and human studies suggests that elevated amyloid peptides during sleep deprivation may contribute to the progression of AD. However, further research is needed to fully elucidate this potential pathogenic mechanism.

4. Neurofibrillary tangles of tau protein

Tau, the major microtubule-associated protein in neurons, is encoded by the MAPT gene situated on chromosome 17. Within the human central nervous system, particularly in the brain, tau protein is translated from mRNA transcripts yielding six isoforms, whose abundance varies across different brain regions. Notably, the 0N3R tau isoform is less abundant in the cerebellum compared to other regions, while 4R tau isoforms show an increase in the Globus pallidus. Tau plays a pivotal role in maintaining neuronal morphology and integrity by participating in microtubule assembly and reducing their dynamic instability. Additionally, it has been implicated in interfering with the binding of kinesin and kinesin-like motors to microtubules, thereby affecting axonal transport. Tau exhibits interactions with various cellular components including mitochondria, plasma membrane, and nucleic acids, acting as a mediator between microtubules and these organelles. Phosphorylation plays a critical role in regulating tau's function, with hyperphosphorylation leading to detachment from microtubules, aggregation, impaired axonal transport, and ultimately neuronal cell death. Accumulation of misfolded tau can lead to protein aggregation and secretion, contributing to the spread of tau pathology, a characteristic feature of Alzheimer's disease (AD). Neurofibrillary tangles (NFTs), composed of hyperphosphorylated tau aggregates, are associated with the severity of dementia in AD patients.

"Therefore, the deposition of Aβ and hyperphosphorylation of tau proteins are the key pathological processes underlying the pathogenesis of AD. "[3]

Studies in transgenic mice expressing human tau isoforms have demonstrated neurodegeneration, suggesting a neurotoxic role for hyperphosphorylated tau. Mechanistically, tau has been implicated in microtubule disassembly, compromising stability and function, disrupting intracellular compartments, and altering the distribution of organelles crucial for normal metabolism. Furthermore, tau interacts with amyloid-beta (Aβ), and both contribute synergistically to synaptic toxicity and neurodegeneration. Evidence suggests that Aβ immunization may mitigate tau pathology to some extent, while tau is essential for Aβ-mediated pathology in animal models. Decreasing endogenous tau levels appears to be protective against synapse loss in the context of plaque deposition [4].

5. The mechanisms underlying Aβ deposition and hyperphosphorylation of tau proteins induced by SD

Sleep deprivation (SD) indeed poses a significant risk factor for various neurological disorders, including Alzheimer's disease (AD), Parkinson's disease, and stroke. Identifying and addressing sleep problems may potentially mitigate these risks. The detrimental effects of SD on neurological health are well-documented, particularly its role in promoting the aggregation of amyloid-beta (Aβ) and tau proteins, which are central to the pathogenesis of AD.

Research into why SD promotes Aβ deposition and tau aggregation, as well as why it leads to cognitive decline, primarily focuses on several key mechanisms:

Activation of Glial Cells: Glial cells, particularly microglia and astrocytes, play crucial roles in the clearance of Aβ and tau proteins. SD can activate these cells, altering their function and potentially impairing their ability to effectively clear protein aggregates.

Glial Lymphatic System: The glymphatic system, which is responsible for clearing waste products from the brain, including Aβ and tau, may be impacted by SD. Disruptions to this system could lead to the accumulation of protein aggregates.

Circadian Rhythms: Sleep is intricately tied to circadian rhythms, which regulate various physiological processes, including protein clearance mechanisms in the brain. SD can disrupt circadian rhythms, potentially impairing the brain's ability to clear Aβ and tau efficiently.

Orexin: Orexin, a neuropeptide involved in regulating wakefulness and arousal, may also play a role. Disruptions to the orexin system due to SD could contribute to Aβ deposition and tau aggregation.

Synaptic Plasticity: SD has been shown to negatively impact synaptic plasticity, the brain's ability to adapt and form new connections. This impairment can lead to deficits in learning and memory functions.

Inflammation: SD can induce neuroinflammation, characterized by the activation of immune cells in the brain. Chronic inflammation may exacerbate Aβ deposition and tau aggregation, contributing to cognitive decline.

Neurotrophic Factors: Sleep is crucial for the production and release of neurotrophic factors, which support the survival and function of neurons. SD-induced deficits in neurotrophic factors may impair neuronal health and contribute to cognitive decline.

Gut Microbiota: Emerging research suggests a link between gut microbiota and brain health. Disruptions to the gut microbiota due to factors like SD could influence neurological function, potentially impacting Aβ and tau pathology. Understanding these mechanisms is essential for developing strategies to mitigate the adverse effects of SD on neurological health and to potentially uncover new therapeutic targets for neurological disorders associated with sleep disturbances [(3)].

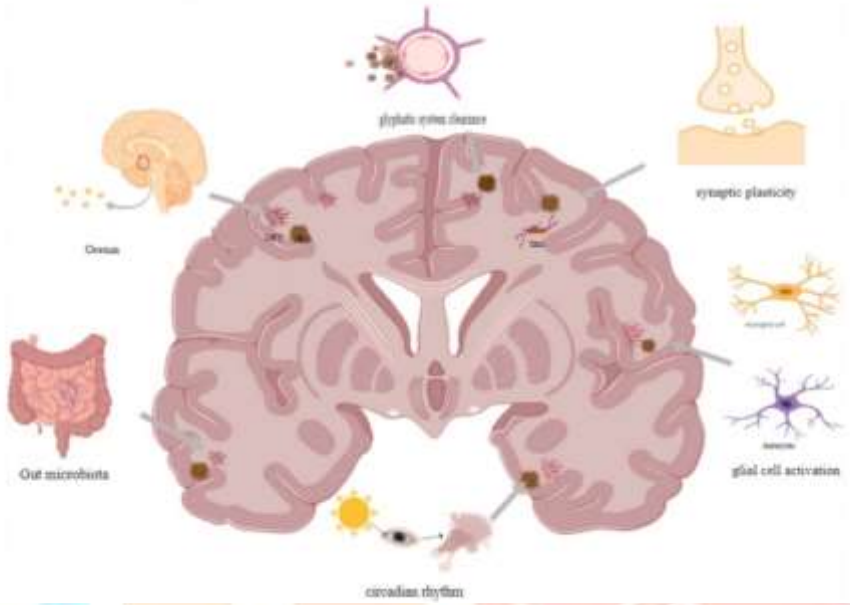

Fig 2. Illustrates a potential pathway linking SD to the onset and progression of AD. SD emerges as a notable risk factor for both the initiation and advancement of AD, implicating mechanisms such as glial cell activation, glymphatic system function, orexin system activity, circadian disruption, synaptic plasticity alterations, and gut microbiota involvement.

6. Existing treatment modalities

Currently, therapeutic options for Alzheimer's disease (AD) patients experiencing disruptions in their sleep-wake cycle are notably limited [(18)]. Approaches centered on optimizing sleep hygiene hold promise for slowing the progression of AD, underscoring the importance of further investigating the intricate relationship between AD and sleep quality to inform novel therapeutic strategies [(19)]. Longitudinal sleep studies should encompass individuals with preclinical AD or familial AD-associated genetic mutations to fully grasp the therapeutic potential of sleep interventions. Nonpharmacological interventions, such as optimizing sleep habits, reducing caffeine and alcohol intake, maintaining regular sleep schedules, and minimizing nighttime light exposure, are recommended for managing sleep disturbances in AD patients [(22-23)]. Institutionalized patients often face inadequate daytime light exposure, which can exacerbate sleep issues. Pharmacological strategies targeting sleep quality enhancement in AD remain limited, with medications like melatonin, trazodone, and ramelteon showing mixed results in improving sleep parameters[(1)]. Type 4 phosphodiesterase inhibitors (PDE4 inhibitors) present a promising avenue for both AD and sleep therapy. Clinical and preclinical evidence suggests that PDE4 inhibitors may enhance cognition and promote synaptic resilience against AD pathology, potentially mitigating the detrimental effects of sleep deprivation on memory function. Future therapeutic development targeting PDE4-cofilin signalling holds promise for addressing sleep disturbances in AD patients [(20)].

Understanding these mechanisms is essential for developing strategies to mitigate the adverse effects of SD on neurological health and to potentially uncover new therapeutic targets for neurological disorders associated with sleep disturbances.

7. Conclusion

In conclusion, the intricate interplay between sleep deprivation, insomnia, and Alzheimer's disease (AD) pathogenesis underscores the importance of further exploration in both clinical and preclinical settings. This

review has highlighted the multifaceted relationship between disrupted sleep patterns and the onset and progression of AD, shedding light on potential therapeutic avenues. From elucidating the mechanistic underpinnings linking sleep disturbances to AD pathology to evaluating existing treatment modalities, this comprehensive examination offers insights into promising strategies for managing sleep-related symptoms in AD patients. Moving forward, continued research efforts are imperative to unlock the full therapeutic potential of addressing sleep disruptions in the context of AD, ultimately aiming to improve patient outcomes and enhance quality of life for individuals affected by this devastating neurodegenerative disorder.

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