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Sleep And Neurodegenerative Disorders

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ABSTRACT

Sleep is a physiological process mediated by homeostatic components that are activated during wakefulness and suppressed during sleep. It performs several physiological functions necessary to maintain brain homeostasis. Neurodegenerative disorders are disorders of progressive loss of neurons of the central nervous system and they include Parkinson's disease, Alzheimer's disease, Huntington's disease and amyotrophic lateral sclerosis, and are usually associated with sleep disturbances. This review discusses the links between sleep and neurodegenerative disorders with highlights on the relationship of sleep deprivation and progression of neurodegeneration. Understanding this interplay provides the knowledge necessary for the prevention and treatment of these diseases. It also aids in the exploration of sleep-targeted therapies and non-pharmacological interventions.

Keywords: Sleep, Neurodegenerative disorders

INTRODUCTION

Sleep is a complex reversible state of the mind and body indicated by reduced body movements, diminished response to external stimuli and slower breathing rate, essential for the well-being of the mind and body(1). Sleep is a physiological process mediated by homeostatic components that are activated during wakefulness and suppressed during sleep(2). It is initiated and established by the activation of inhibitory neurons of the Ventrolateral Preoptic Area (VLPO) on the Ascending Reticular Activating System (ARAS) that sustains wakefulness(2,3). The accumulation of extracellular adenosine molecules in the basal forebrain during wakefulness activates the inhibitory neurons of the VLPO area via adenosine receptors resulting in the initiation of sleep(2,4) Also, the suppression of neurotransmitters of the ARAS such as dopamine, serotonin, acetylcholine, histamine and orexin have been found to induce sleep(2).

Sleep is important in multiple physiological processes such as in cognitive development (5), memory and consolidation(6), behavioral and mental health(7), and clearance of metabolic waste of the brain via the glymphatic system(8). Furthermore, the importance of sleep is evident in sleep deprived individuals who exhibit impaired cognition and coherence, irritability, and lethargy(9).

Sleep is more qualitative when it advances through the appropriate physiological sequences in alignment with the circadian rhythm, that is, the body's 24-hour clock that controls the sleep-wake cycle(4,10). This physiological clock is controlled by the suprachiasmatic nucleus located in the hypothalamus and the hormone melatonin which is secreted from the pineal gland(11). The secretion of this hormone is suppressed during the day and on exposure to blue light. Sleep disorders such as insomnia, narcolepsy and obstructive sleep apnea have been shown to disrupt the circadian rhythm which may progressively lead to neurodegenerative disorders(10,11).

Neurodegeneration can be defined as the progressive loss of neurons and their processes with corresponding progressive impairment in neuronal function(12,13). Neurodegenerative disorders (NDDs) are characterized by the accumulation and deposition of protein aggregates leading to a condition where the neurons of the central nervous system gradually stop working or die (12,14). These proteins aggregates include amyloid-β, tau, prion, Tar-DNA-binding Protein-43(TDP-43) and α-synuclein(15). Common neurodegenerative disorders are Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis (ALS) and motor neuron disease(4,15).

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SLEEP PHYSIOLOGY AND BIOPHYSIOLOGY

Sleep is characterized by two stages: the NREM (Non-Rapid Eye Movement) and REM (Rapid Eye Movement)(2). While asleep, one cycles between episodes of NREMs and REMs about every 90 minutes with the NREM sleep coming before the REM sleep(1,6). NREM sleep occurs in the first half of the night and REM towards the morning(16). NREM, also referred to as slow wave sleep, is associated with strong brain waves and a synchronous electroencephalogram (EEG); it is further divided into three stages based on depth of sleep and brain wave patterns(2,6). The REM stage is characterized by rapid movements of the eyes, muscle atonia, dreaming and desynchronized EEG(6).

Electrical brain waves are the summation of rhythmic and spontaneous cortical oscillations(1).The changes in brain activity that bring about these brain waves are mediated by potassium and calcium ions and their channels which are detected on the surface of the scalp using an electroencephalograph and are used to determine the state of the brain(1). Based on their ranges of frequency, brain waves can be classified as alpha, beta, theta and delta waves, deviations from which can be indicative of a neurological disorder (1,2).

ROLE OF SLEEP IN BRAIN HEALTH

Sleep is important for the overall wellbeing of the body system and has been shown to enhance- cognitive development, mental health, synaptic plasticity, clearance of metabolic waste from the CNS via the glymphatic system, consolidation of short-term memory into long-term memory and the maintenance of the brain homeostasis(17,18). The NREM sleep is important for facilitation of cognition and declarative memory while REM sleep has been shown to aid neural development in neonates and it is involved in procedural memory(1). Also, sleep enhances the nervous system's regenerative trait which includes changes in the strength, numbers, size and structures of synapses, that is, the brian's synaptic plasticity to promote learning and memory consolidation(19,20). Synaptic plasticity is triggered by events that occur during wakefulness and further strengthened during sleep(20).

The glymphatic system is a pathway that circulates cerebrospinal fluid (CSF) within the brain tissue to facilitate exchange of material between the CSF and interstitial fluid, leading to the clearance of metabolic waste from the brain(8). During sleep, there is a marked increase in production and circulation of the cerebrospinal fluid which is associated with clearance of molecular wastes (8,18). Sleep disturbances lead to disruptions in this glymphatic system which causes accumulation of protein aggregates that cause neurodegenerative disorders(12).

Sleep is necessary to recover from physical and mental stress and to maintain alertness during the course of the day (2). Loss or decreased hours of sleep is associated with feelings of irritability, negativity, and detachment(18). Deprivation of sleep leads to disruptions in learning, molecular signaling and neurological changes(10).

NEURODEGENERATIVE DISORDERS

Neurodegeneration refers to the progressive loss and death of neurons in the central nervous system caused by accumulation of misfolded protein aggregates within the brain tissue(15). Another common occurrence in neurodegenerative diseases is oxidative stress resulting from overproduction of reactive oxygen species (ROS) which are involved in the process of aging and accelerate deterioration of neurons leading to their dysfunction and death(21,22). Neurodegeneration may also be caused by neuroinflammation which occurs due to microglia activation of immune response components recruited in response to imbalances caused by trauma, stress or pathology in the central nervous system(21,23). Deterioration of neurons in a region of the brain may coincide with areas responsible for physiologic processes that affect the sleep-wake process(21,22). Also, sleep disturbances may cause neurodegeneration through defects in the clearance system of the CNS, causing formation and accumulation of protein aggregates (22). The common neurodegenerative disorders include Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis.

Alzheimer's disease, a common neurodegenerative disorder, is associated with a gradual decline in cognitive functions, memory, learning and thinking capacity of patients(23,24). Progressively, individuals with Alzheimer's disease develop dementia, develop personality changes and become dependent on others(24). The neuropathology of this disease is characterized by aggregates of neurofibrillary tangles of amyloid-β peptide and neuronal tau inclusions in the basal forebrain, limbic structures, and cortices of frontal and

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temporal lobes(15). Also, atrophy of the temporofrontal cortex causes neuroinflammation leading to the deposition of amyloid plaques and increased presence of monocytes, macrophages, and activation of microglial cells(23).

Parkinson's disease is a disease caused by neurodegeneration of mostly motor neurons majorly in the basal ganglia and substantia nigra(15,25). Clinical features of Parkinson's disease include bradykinesia, tremors, rigidity and gait abnormalities. It is associated with the deposition of large amounts of **α**-synuclein, a 140 amino acid, in the cytoplasm of cells in the substantia nigra, forming Lewy bodies (15,25). These protein aggregates over time spread into the brainstem and regions of the higher brain(25) They are also found in synaptic terminals where they bind to the lipid membrane of neurons in the central nervous system (15). Parkinson's disease may also be inherited, caused by a genetic variant in the Gaucher disease causing gene, a lysosomal dysfunction that impairs the degradation of **α**-synuclein leading to its accumulation (25).

Huntington's disease is an inherited neurodegenerative disorder characterized by chorea, difficulty with speech and swallowing, impaired memory and attention deficit, loss of motivation and a high risk of depression (26). Huntington's disease is caused by neurodegeneration of neurons in the corpus striatum, cortical pyramidal neurons in the frontal and occipital cortices and the hypothalamus (27,28). This disease affects exon 1 of the huntingtin gene on chromosome 4 causing it to have longer than normal (>35) repeats of the trinucleotide, CAG (26).

Amyotrophic lateral sclerosis which is characterized by muscle weakness and wasting that starts from the limbs and spreads with progression of the disease. This disease affects upper and lower motor neurons, but may spread into extra motor sites like hippocampus and amygdala leading to dementia (29). It is associated with the deposition of TDP-43 aggregates in areas of the brain such as the motor cortex and neurons(15).

SLEEP DISTURBANCE IN NEURODEGERATIVE DISORDERS

Sleep patterns are profoundly altered in neurodegenerative diseases (30,31). Common disturbances include sleep fragmentation, insomnia, hypersomnia, and REM sleep behavior disorder (RBD) (32). Patients with Alzheimer's Disease (AD) experience reduced slow-wave sleep and fragmented NREM (33). They wake up intermittently from their sleep due to hippocampal atrophy affecting memory-related sleep spindles (34). A notable observation in patients with Parkinson's Disease (PD) is REM sleep behavior disorder (RBD). Patients with this condition progressively develop muscle atonia and often act out their vivid dreams while sleeping (35). This sleep behavior usually appears a few years before they eventually develop the motor symptoms of the disease (35,36). In Huntington's Disease (HD) however, there is prolonged sleep latency and reduced REM. Studies have linked this dynamic to the progressive breakdown of cells in the striatum which is a common feature of the disease (37). Amyotrophic Lateral Sclerosis (ALS) is another neurodegenerative condition with its own sleep-related challenges. Patients with ALS often experience sleep apnea causing them to have fragmented sleep; the apnea experienced by these patients can be linked to the respiratory muscle weakness seen in the natural progression of the disease (38).

According to Jung-Won Shin, melatonin levels in the brain have a direct impact on sleep by acting as an important mediator of circadian regulation(39). Suprachiasmatic nucleus degeneration in AD and PD usually results in reduced secretion of melatonin. The effect of this reduction is seen as a disruption occurring in circadian rhythms. People affected by these conditions show symptoms like sundowning which involves late-day confusion, agitation, and mood disturbances; and irregular circadian rhythms (39). Similarly in HD, there are delayed melatonin peaks. Patients with this disease have demonstrated persistent insomnia according to recent investigations.Due to increasing immobility in these patients, they experience a misalignment in circadian rhythm with the same sleep symptoms as in AD and PD (40, 41).

LINKS BETWEEN SLEEP AND NEURODEGENERATION

Sleep deprivation plays a significant role in neurodegenerative processes, particularly in AD. Patients deprived of sleep have a buildup of beta-amyloid proteins in interstitial spaces (42). Normally, clearance of these proteins occurs during NREM sleep (43). In support of this, cohort studies suggest that chronic sleep loss raises interstitial beta-amyloid levels, promoting plaque formation, and accelerates tau hyperphosphorylation through stress kinases like GSK-3β.(44) Several animal models have also shown that acute

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deprivation of sleep induces the protein pathology described above (45).

In the case of PD, sleep regulates dopamine through circadian influences on striatal receptors (46). When this system is disrupted, especially in conditions such as RBD, it correlates with alpha-synuclein spread, progressively impairing motor function (47). It has also been reported that sleep loss worsens the loss of dopaminergic neurons, which is the fundamental pathogenesis of PD (48). The after effect of the loss of these neurons is an increase in oxidative stress and inflammation. HD and ALS also have a similar relationship with sleep deprivation as demonstrated in a study by Lulu Xie and colleagues (49). Patients with fragmented sleep were discovered to have accumulated proteins and neuronal excitotoxicity (50).

Sleep disturbances are early biomarkers of neurodegeneration; RBD is a strong pointer to PD with high specificity, and reduced REM in AD often signals progression of the disease (51). These associations help highlight the role of sleep in mitigating neurodegeneration through the clearance of waste and repair of neurons.

THERAPEUTICS APPROACHES AND MANAGEMENT OF SLEEP DISTURBANCE

In managing sleep disturbances in neurodegenerative disorders, a bidirectional strategy is adopted: To improve sleep so as to slow down the progression of the disease and also to treat the neurodegeneration to improve sleep.

This can be broadly categorized into two: pharmacological and non-pharmacological interventions. While pharmacological treatments use medications to target specific neurochemical pathways and sleep mechanisms, non-pharmacological treatments emphasize behavioral modifications and lifestyle adjustments. Both of these are practical methods that provide a solid way to deal with sleep-related problems in neurodegenerative conditions.

Pharmacological interventions offer several promising avenues, though they require thoughtful consideration of each patient's unique circumstances. One common pharmacological option is exogenous melatonin. The drug helps to make up for the disruption in pineal gland's ability to secrete melatonin as discussed earlier. It not only helps regulate circadian rhythms but also provides neuroprotective antioxidant effects (52). A study by Zhang W, et al demonstrated that melatonin in doses between 2 and 10 mg can improve sleep onset and overall quality in conditions like Alzheimer's disease (AD) and Parkinson's disease (PD) (53).

Other than melatonin, sedatives like benzodiazepines (e.g., lorazepam) or non-benzodiazepines (e.g., zolpidem) also help improve insomnia, but they must be used with caution due to potential risks of falls and cognitive worsening (54). Shorter-acting drugs have been demonstrated in studies to minimize the suppression of REM (55). Studies have shown that dopamine agonists like pramipexole have biphasic effects; in low doses they promote sleep in patients that have PD, while higher doses may have a contrary effect on the patients (56). Non-pharmacological treatments are the more preferred method for the treatment of sleep disturbances due to their inherent safety.

Cognitive behavioral therapy for insomnia (CBT-I) is one of the commonest non-pharmacological treatments (57). It integrates aspects like sleep hygiene, stimulus control, and relaxation strategies, all of which have been shown to significantly reduce sleep fragmentation in patients with AD and PD (58).

Light therapy is another non-pharmacological option. The procedure involves exposure to bright morning light, which can help to reset circadian rhythms (59). According to a study, light therapy helps in mitigating issues like sundowning (60). Cohort studies have also shown that lifestyle modifications such as regular physical activity and making dietary adjustments can greatly improve sleep quality (61).

FUTURE DIRECTIONS AND RESEARCH GAPS

Despite significant progress in studies, important gaps still exist in our understanding of how sleep is linked to neurodegeneration. Longitudinal studies are vital to elucidate the bi-directional relationships between sleep and neurodegeneration.

Exciting developments in biomarkers and imaging techniques like measuring neurofilament, light in cerebrospinal fluid, orexin levels, PET scans for amyloid/tau, and DTI to assess glymphatic flow, hold key promise of identifying markers of neurodegeneration at an early stage (62, 63). Also, analyzing EEG microstructure can further enhance our understanding of these changes.

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Finally, sleep-targeted therapies should also be studied in at-risk populations. There is the need for further population-based research on non-pharmacological interventions like CBT-I, light therapy, and emerging orexin modulators. Multidisciplinary collaboration between neurology and sleep medicine specialists, engineers and the use of artificial intelligence are necessary to develop truly effective preventive strategies.

CONCLUSION

This review explores the complex relationship between sleep and neurodegenerative disorders. It has examined everything from physiological underpinnings to novel therapeutic possibilities. Key findings reveal that sleep plays a key role in homeostasis via mechanisms like the glymphatic system and its disruptions in neurodegenerative disorders such as AD and PD. It also scrutinizes the bidirectional mechanistic links between sleep and neurodegenerative diseases. Therapeutic options which include combining pharmacological and non-pharmacological approaches offer promising hope for symptom management and possibly altering the course of these diseases.

Sleep is increasingly recognized in studies for its neuroprotection. Optimizing it could potentially help delay the onset of neurodegenerative diseases and slow down their progression. Nevertheless, gaps in longitudinal data and biomarkers underscore the need for further research on sleep-based interventions to help shape preventive healthcare. By making sleep health a priority, we could significantly enhance the quality of life for older adults and those living with neurodegenerative disorders.

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