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Research on the bidirectional relationships between sleep and parkinson's disease

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Abstract. Parkinson's disease (PD) is the second most prevalent neurodegenerative disease in the world, and among its most common symptoms is sleep disruption. Due to the glymphatic system's role in removing alpha-synuclein and other substances related to PD pathogenesis, glymphatic dysfunction has been established as a risk factor for PD. Though sleep disturbance is often a symptom of PD, its role in increasing glymphatic clearance has led some researchers to believe that sleep disturbance could also be a risk factor for PD. This review will examine the scientific literature that suggests links between sleep disruption, PD pathology, or glymphatic dysfunction, as well as address some of the limitations in affirming such relationships. According to current research, sleep disruption is a common nonmotor symptom of PD but can also lead to reduced glymphatic function, which in turn reduces alpha-synuclein clearance and advances PD pathogenesis. However, PD development could also impair glymphatic clearance by depolarizing AQP4 channels or reducing sleep duration and quality.

Keywords: sleep, glymphatic system, Parkinson's disease, alpha-synuclein.

1. Introduction

This review summarizes previous literature on the relationships between sleep disruption, PD pathology, and glymphatic dysfunction, and discusses their limitations accordingly. Parkinson's disease is an age-related disorder and the second most common neurodegenerative condition in the world, with its prevalence only predicted to rise to upwards of 12 million by 2040 [1]. PD causes the degeneration of dopaminergic neurons in the substantia nigra (SN) in the midbrain, which is the underlying cause of the prominent motor and non-motor symptoms of PD [2]. Bradykinesia, tremor, rigidity, postural instability, dystonia, and hypomimia are examples of motor symptoms. Depression, anxiety, sleep issues, digestive issues, discomfort, exhaustion, urinary issues, and impaired memory are examples of non-motor symptoms [3].

PD is marked by Lewy bodies containing misfolded alpha-synuclein, which can be brought on by mitochondrial dysfunction, oxidative stress, neuroinflammation, and glymphatic system impairment [4, 5, 6].

The glymphatic system is a perivascular network spanning the brain that supplies it with nutrients while removing potentially neurotoxic substances [7]. Glymphatic clearance has a marked increase during sleep due to an increase in interstitial volume [8,9].

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The intimate link between sleep and the glymphatic system has led researchers to suggest bidirectional relationships between alpha-synuclein aggregation, glymphatic system dysfunction, and sleep [10, 11].

2. PD pathology/sleep

Sleep disruption has been observed to be a prevailing nonmotor symptom (NMS) in PD patients. In a study that investigated the rate of nonmotor symptoms in PD patients, sleep problems and psychiatric symptoms were determined to be the most prevalent NMS in motor fluctuating PD patients in all Hoehn and Yahr stages [12]. In a study that monitored the hormone and clock gene expression of PD patients, it was found that PD patients exhibited a lack of time-dependent variation in Bmal1 expression, reduced melatonin levels, and elevated cortisol [13]. This was accompanied by reduced REM sleep and sleep efficiency, as well as an increase in sleep latency [13]. PD patients have also shown diminished levels of Bmal2, a functional paralog of Bmal1 [14]. Additionally, a study found that the number of insomnia complaints tended to increase alongside the severity of PD [15]. PD has also been found to damage important neurotransmitter mechanisms regulating sleep, like serotonin, dopamine, GABA, and others [16].

Meanwhile, sleep disruption has also been found to be a risk factor in the diagnosis of PD. Firstly, REM sleep behavioral disorder (RBD) – a parasomnia characterized by physical dream-enactment behaviors during a loss of REM sleep atonia – is one of the strongest clinical predictors of future PD risk (as well as a prodromal state to PD) [17]. To support this, a study using video-supported polysomnography to investigate 457 sleep-disturbed PD patients found that 46% of the subjects had RBD. Patients with PD and RBD had longer disease duration, higher Hoehn & Yahr stages, as well as a higher dose of levodopa [18]. Apart from motor manifestations, RBD also accelerates autonomic manifestations in PD patients, as shown by a study using polysomnogram recordings and MIBG scintigrams to monitor the 123I-labeled meta-iodobenzylguanidine (MIBG) uptake of 49 PD patients [19]. The absorption of 123I-MIBG was found to be considerably reduced in non-demented PD patients with RBD compared to PD patients with subclinical RBD [19]. The study concluded that the decreased 123I-MIBG uptake could be a sign that PD patients with symptomatic RBD had a broader alpha-synuclein pathology [19]. In addition, a cohort study involving 91,273 Taiwanese patients without signs of PD but with non-apneic sleep disorders revealed the presence of sleep disorders to be an independent risk factor for incident PD [20]. Patients with persistent insomnia (lasting over 3 months) were most at risk [20]. Additionally, an in vitro study found that melatonin inhibits alpha-synuclein assembly and destabilizes fibrils – thereby preventing alpha-synuclein cytotoxicity and thus neurodegeneration [21]. Consequently, the study concluded that reduced melatonin levels would therefore worsen alpha-synuclein pathogenicity [21]. Since melatonin is also involved with the promotion of sleep and the timing of other circadian functions, this strongly reinforces the connection between sleep and PD pathology [22].

3. Glymphatic system/PD pathology

In PD, apart from disrupting sleep, dopaminergic deterioration may also impair glymphatic flow. In a study, 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine (MPTP) was administered to different groups of mice (control group and mutated group lacking in AQP4) to simulate PD-related dopaminergic deterioration in the substantia nigra [23]. As a result, it was found that the mice lacking AQP4 demonstrated a notable increase in MPTP-induced neurotoxicity compared to control groups [23]. In another study involving MPTP-induced PD symptoms in mice, mice with AQP4 deficiencies demonstrated notable increases in dopaminergic neurodegeneration compared to wild-type control subjects, as well as heightened microglial inflammation [24]. Moreover, animal studies have found that amyloid beta clearance decreased by 40% in healthy aged mice compared to younger ones [25]. Extensive AQP4 depolarization was also observed in the older mice, explaining the impaired glymphatic clearance and suggesting that glymphatic function worsens with age [25]. Since PD also exacerbates with age, one of the factors driving PD pathogenesis may be the reduced glymphatic function observed

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when aging. Furthermore, there have been studies linking dilated perivascular spaces to glymphatic impairment [26, 27]. Research has found that dilated perivascular spaces in the substantia nigra are indicative of dopaminergic neurodegeneration and the accumulation of neurotoxic substances like alpha-synuclein [26]. To support this, a different study used MRI to determine that PD patients with enlarged perivascular spaces in the basal ganglia were prone to cognitive decline, lacked dopamine, and had noticeably elevated levels of CSF toxic proteins [27].

Altogether, these studies provide strong evidence that glymphatic system impairment (through reduced AQP4 function) accelerates PD pathogenesis to a considerable degree. However, the relationship between glymphatic impairment and PD pathogenesis does not solely act in one direction.

Dopamine has been observed to inhibit striatal glial cell proliferation and AQP4 expression in glial cells, suggesting that it plays a role in the regulation of AQP4 [28]. These results suggest that dopamine may mediate AQP4 function, and while AQP4 deficiency can exacerbate dopaminergic neurodegeneration, the cycle caused by the bidirectional nature of both processes may impair glymphatic clearance, causing diminished alpha-synuclein clearance [29]. Also, astrocytes are susceptible to mitochondrial oxidative phosphorylation defects during PD, providing another avenue for reduced glymphatic function [30]. These conclusions are further supported by a study investigating the relationships between several PD pathogenesis markers and AQP4 impairment brought on by increased alpha-synuclein accumulation. In a study, the glymphatic clearance of A53T mice (overexpressing alpha-synuclein) was impaired via ligation of deep cervical lymph nodes, and common PD phenotypes were monitored [31]. Afterward, perivascular alpha-synuclein aggregation and reduced AQP4 polarization were seen in the substantia nigra [31]. The cervical lymphatic ligation also led to various PD phenotypes manifesting in A53T mice, like glial activation, inflammation, dopaminergic neuronal loss, and motor deficits. Since the overexpression of alpha-synuclein can cause AQP4 depolarization–impairing the glymphatic system and in turn causing even more alpha-synuclein aggregation, this suggests the existence of a bidirectional relationship between glymphatic dysfunction and PD pathology and how it can lead to a vicious cycle of alpha-synuclein accumulation.

4. Sleep/glymphatic system

Several studies have demonstrated the role of sleep in the glymphatic clearance of metabolites from the brain. In one such study, the iontophoretic tetramethyl-ammonium (TMA) method was used in the brains of sleeping and awake mice, with the dilution of the TMA being used to determine interstitial space volume. It was found that interstitial space volume increases by >60% during sleep, greatly aiding glymphatic clearance [8]. These findings could be replicated even when the mice were anesthetized during waking hours, demonstrating that this increase in interstitial volume is related to the state of arousal instead of circadian rhythms [8]. Moreover, both amyloid beta and an inert tracer were cleared twice as fast in sleeping and anesthetized mice compared to awake mice [8].

To further support this, a study involving 22 participants aged 35–65 years studied how amyloid beta clearance was affected by conditions of sleep such as slow wave activity [32]. A strong correlation between slow wave activity disruption and amyloid beta clearance was discovered, where increased slow wave activity disruption resulted in greater increases in amyloid beta [32]. In addition, a study monitoring RBD patients found that the index of diffusion tensor imaging analysis along the perivascular space was significantly decreased compared to healthy controls (during the REM phase), suggesting glymphatic dysfunction [33].

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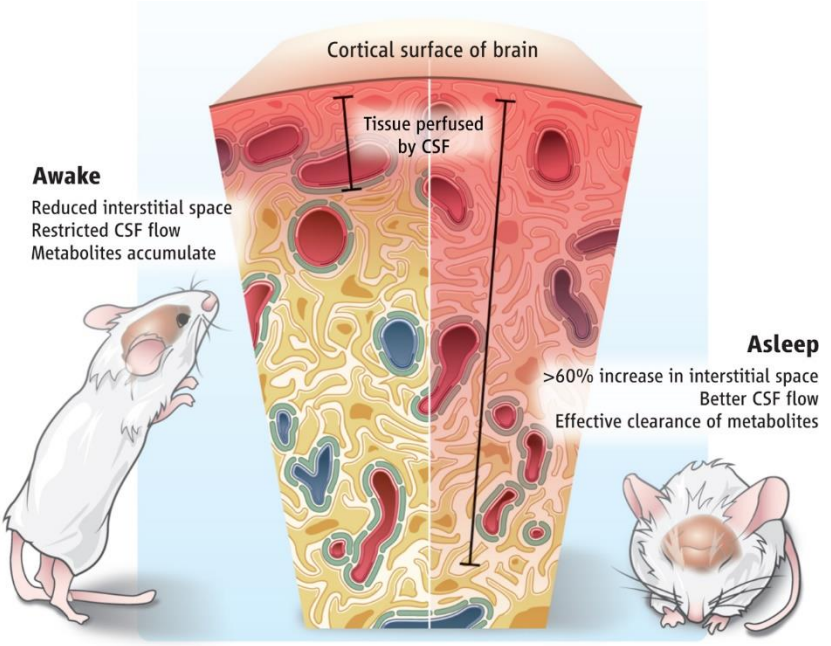

Figure 1. Glymphatic function when asleep and awake.

When awake, metabolites accumulate throughout the brain. These metabolites are cleared during sleep, when interstitial volume increases by >60%, allowing for more CSF flow and effective clearance of metabolites [34].

The idea that sleep drives glymphatic clearance was further supported by a study that monitored the EEG patterns of awake, sleeping, and anesthetized mice. According to the results, glymphatic influx has a positive correlation with delta power and a negative correlation with beta power [35]. Delta activity is a biomarker of the homeostatic sleep drive — often indicative of greater sleep duration and intensity. Conversely, beta waves — involved in conscious thought and logical thinking — are commonly observed when awake. Aging has been linked with decreased EEG delta power, which could cause decreased glymphatic clearance [35, 36]. As previously mentioned, PD is known to worsen with age, so this further strengthens the postulation that decreased glymphatic function exacerbates PD.

Also supporting the link between sleep and glymphatic clearance is the finding that the slow waves during NREM sleep are followed by hemodynamic oscillations coupled to CSF flow [37]. This demonstrates how fluctuations in slow wave activity mediate CSF influx in the brain [37].

4.1. Implications for Mitigating PD

If the correlation between impaired glymphatic flow, sleep disruption, and PD development can be definitively established, it may provide insight into the approaches that can be taken to mitigate PD. If sleep is indeed a neuroprotective factor in PD, then this may lend credence to treatments like U-133 – the administration of increased deep sleep and slow-wave activity in the preclinical PD stages of aged rats [38]. If increased glymphatic clearance is a neuroprotective factor in PD, then certain lifestyle choices like sleeping in a right lateral position (which leads to more CSF clearance compared to supine or prone positions [39]) can be used to increase glymphatic flow and therefore reduce the risk of developing PD.

4.2. Limitations

Several limitations stand in the way of ascertaining links between sleep, Parkinson's disease, and the glymphatic system. Firstly, ethical issues prevent easy analysis of live human brain tissue, leading scientists to utilize murine models. Using murine models may pose issues of reliability, as the fundamental differences in genetics and neurophysiology mean that rodents cannot serve as fully

analogous representations of neurological disease in humans. Additionally, another popular method to monitor glymphatic flow is MRI, which is limited by its inability to account for other pulsations potentially affecting the arterial pulsation driving glymphatic flow [40]. This may require difficult methodological adjustments due to the other pulsations causing motion during neuroimaging [40]. Also, much of the data collected for the NMS of PD patients was obtained through questionnaire-based studies, which may be affected by the patients' inaccurate judgement. Furthermore, it is important to note that the glymphatic system is still a relatively recent discovery, its links with sleep and PD are still being researched. Many studies stress the need for further research and new information may still come to light that disproves these findings.

5. Conclusion

In conclusion, there is evidence to suggest bidirectional relationships between sleep disturbance, the glymphatic system, and PD pathology. Due to the activity of the glymphatic system being strongly reliant on sleep, sleep disruption can therefore lead to impaired glymphatic function, in turn causing alpha-synuclein to accumulate in the parenchyma. These alpha-synuclein aggregates can cause aggressive neuroinflammation and AQP4 deficiency, further exacerbating the glymphatic impairment and causing common PD characteristics, like dopaminergic degeneration in the SN.

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