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Analysis of the Influence Between Glymphatic System and Sleep Disorder

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Abstract. The glymphatic system, first described in 2012 by Iliff and Nedergaard's team, is a macroscopic waste clearance pathway in the central nervous system, and plays an essential role in maintaining brain homeostasis by facilitating the convective exchange of cerebrospinal fluid (CSF) with interstitial fluid (ISF) to remove neurotoxic solutes. Its functionality is inseparably linked to the physiological state of sleep, with clearance rates dramatically upregulated during non-rapid eye movement (NREM) sleep. Conversely, sleep disturbances, including sleep fragmentation, chronic insomnia, and obstructive sleep apnea (OSA), impair glymphatic function, leading to the accumulation of neurotoxic proteins such as amyloid-beta (Aβ), tau, and α-synuclein. The aging process further compounds this vulnerability through reduced sleep efficiency, diminished slow-wave sleep, and aquaporin-4 (AQP4) depolarization. This review synthesizes current evidence on the bidirectional relationship between the glymphatic system, sleep, and aging, examining the structural components, sleep-dependent activation mechanisms, and the pathological consequences of glymphatic dysfunction. This study proposes that the glymphatic system serves as a crucial biological link connecting sleep disorders, aging and neurodegenerative disease, positioning it as a promising therapeutic target for cognitive decline.

Keywords: glymphatic system, aquaporin-4, obstructive sleep apnea, neurodegenerative disease, cognitive impairment

1. Introduction

The brain is one of the most active organs in the human body. It uses a lot of energy and produces many waste products. Unlike other parts of the body, the brain does not have a lymphatic system to remove waste. For a long time, scientists did not know how the brain cleaned itself. In 2012, researchers discovered a system called the glymphatic system, which acts like a built-in cleaning system for the brain [1].

The name "glymphatic" comes from combining the words "glial" (a type of brain cell) and "lymphatic" (the body's waste removal system). This system uses channels around blood vessels to move cerebrospinal fluid (CSF) through the brain. The fluid washes away harmful proteins, including amyloid-beta and tau, which are linked to Alzheimer's disease [2].

The glymphatic system is most active during sleep. Studies have shown that the system clears waste twice as fast during sleep compared to being awake [3]. When people do not get enough sleep,

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harmful proteins can build up in the brain. This may explain why poor sleep is linked to a higher risk of dementia [1].

Aging also affects the glymphatic system. As people get older, their sleep quality often decreases. They spend less time in deep sleep, and they wake up more often during the night. The water channels in the brain that help move fluid also start to work less effectively. This means that older people may not clear waste from their brains as well as younger people [4].

This review explains how the glymphatic system works, how sleep affects it, and what happens when the system stops working properly. It also discusses why aging makes the system less effective and what can be done to protect brain health.

2. Structure of the glymphatic system and sleep-dependent activation mechanisms

2.1. Anatomical architecture of the glymphatic system

The glymphatic system is made up of several parts that work together to clean the brain.

The glymphatic system is a cerebrospinal fluid (CSF)-interstitial fluid exchange network mediated by aquaporin-4 (AQP4) channels expressed on astrocytic endfeet. Specialized for rapid clearance of cerebral metabolites and maintenance of central nervous system (CNS) homeostasis, this system is increasingly recognized as a critical component of central immune surveillance [3]. Acting as a bidirectional interface between the CNS and peripheral circulation, its primary roles include removing metabolic waste products from brain tissue and facilitating nutrient delivery. Key characteristics of the glymphatic system include:

Directional fluid transport: CSF enters the brain via perivascular spaces surrounding arteries, and exits alongside veins carrying "waste-laden" interstitial fluid

Pathological waste clearance: Amyloid-beta and other metabolic byproducts are eliminated through glymphatic pathways

AQP4-dependent mechanism: Fluid movement relies on polarized localization of AQP4 channels on astrocytic endfeet adjacent to vasculature

Sleep-dependent enhancement: Glymphatic flux and CSF penetration into the neuropil are significantly upregulated during sleep, correlating with increased clearance of metabolic waste [3].

2.2. The glymphatic convective flow process

Step 1: Influx. Cerebrospinal fluid from the space around the brain enters along the outside of the arteries. The movement is driven by arterial pulsation, which is the rhythmic expansion and contraction of blood vessels with each heartbeat [5].

Step 2: Exchange. The fluid crosses through AQP4 water channels on astrocytes into the brain tissue. Here, it mixes with interstitial fluid (the fluid that surrounds brain cells). This mixture helps wash away waste products [2].

Step 3: Clearance. The fluid carries waste products like amyloid-beta and tau through the brain tissue towards the veins. This is the actual "cleaning" step [2].

Step 4: Efflux. The dirty fluid leaves the brain along the veins, drains into the meningeal lymphatic vessels, and finally reaches the cervical lymph nodes in the neck. At this point, the waste has been removed from the brain [2].

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2.3. Sleep as a master regulator of glymphatic function

Studies have shown that during the awake state, the glymphatic system is promoted. On the other hand, the system is enhanced in the sleep state [5]. Glymphatic clearance is predominantly active during slow-wave sleep, clinically classified as the N3 stage of non-rapid eye movement (NREM) sleep. Accumulating evidence links slow-wave sleep to both glymphatic system function and the pathogenesis of dementia [1]. A study based on mice has demonstrated that glymphatic activity is dramatically increased during sleep, with the rate of metabolites such as Aβ doubling compared to the awake state [5]. In both naturally sleeping and anesthetized mice, glymphatic clearance efficiency was doubled compared to their awake counterparts [3]. This correlation indicates that two of sleep's most critical physiological functions are the activation of the glymphatic system and the clearance of neurotoxic waste products from the central nervous system [1]. Consequently, there could be a bidirectional relationship between OSA and asthma, as OSA has been linked to poor asthma control as shown in studies [1]. Meanwhile, this interdependency indicates that two of sleep's most critical physiological functions are the activation of glymphatic pathways and the elimination of neurotoxic waste products from the central nervous system [1].

2.4. Interplay with circadian rhythms

The glymphatic system is also affected by the body's internal clock, known as the circadian rhythm. Research shows that glymphatic activity follows a daily pattern, being most active during the time when animals normally sleep [2]. AQP4 polarization also changes with the time of day [5]. This means that even if you sleep during the day, your body's internal clock may still affect how well your brain cleans itself. This may explain why shift work and disrupted sleep schedules are linked to higher rates of neurological disease [2].

3. Sleep disorders and glymphatic dysfunction

3.1. Obstructive sleep apnea (OSA)

Obstructive sleep apnea (OSA) is a prevalent sleep-related disorder characterized by recurrent upper airway collapse, apnea, hypoxia, and frequent arousals, often accompanied by cognitive decline [6]. Multiple mechanisms underlie cerebrospinal fluid (CSF) drainage impairment in OSA:

Sleep architecture disruption: Fragmented sleep or circadian rhythm disturbances can impair glymphatic system function and accelerate organismal aging [3].

Hypoxic stress: Intermittent hypoxia alters glial metabolism and disrupts the vascular components of the glymphatic clearance system [6].

Hemodynamic alterations: Abnormal respiratory patterns in OSA increase intrathoracic negative pressure, reducing venous return and elevating intracranial venous pressure, which impairs perivenous CSF outflow and CSF-interstitial fluid (ISF) exchange [5].

Neuroimaging studies reveal significantly enlarged perivascular spaces (PVSs) in the bilateral frontal cortex and basal ganglia of OSA patients compared to healthy controls [6]. Cognitive assessment demonstrates moderate positive correlations between MMSE/MoCA scores and glymphatic clearance rates (measured via type I CTC wash-out), directly linking OSA-related cognitive impairment to glymphatic dysfunction [6]. Continuous positive airway pressure (CPAP) therapy has been shown to improve glymphatic clearance efficiency and mitigate OSA-related pathological changes [6].

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3.2. Sleep deprivation and insomnia

Sleep loss activities directly impair glymphatic function through multiple pathways. Firstly, sleep deprivation alters the expression of AQP4 [1]. Secondly, it promotes inflammation, BBB disruption, and glymphatic dysfunction, all of which have direct consequences on neurodegeneration [1]. Lastly, the reduction of cytokine clearance due to glymphatic impairment when undergoing sleep deprivation amplifies neuroinflammation [1].

3.3. Sleep disorders and neurodegenerative disease risk

Sleep disorders are linked to a higher risk of neurodegenerative diseases like Alzheimer's and Parkinson's [1]. The link could be explained by glymphatic dysfunction.

In Alzheimer's disease, AQP4 becomes depolarized, and amyloid-beta clearance is reduced by 55%-65% when AQP4 is missing [5]. In Parkinson's disease, alpha-synuclein buildup is linked to reduced AQP4 expression [5]. These findings suggest that sleep disorders may contribute to neurodegeneration by impairing the glymphatic system.

4. Aging and glymphatic decline

4.1. Age-related changes in sleep

Typically, aging is characterized by significant alterations in sleep patterns that directly impair glymphatic function: diminished slow-wave sleep (SWS), reduced sleep efficiency, increased sleep fragmentation, and advanced sleep phase syndrome [1].

4.2. Age-related AQP4 changes

Aging exerts a detrimental impact on aquaporin-4 (AQP4) channel regulation. Specifically, quantitative analyses have demonstrated reduced polarized localization of AQP4 on astrocytic processes surrounding cortical-penetrating arterioles in the brains of older individuals compared to younger subjects [1]. Studies also suggest that AQP4 overexpression on astrocytic parenchymal processes [7] may represent a compensatory mechanism in the aging brain.

4.3. Reduced glymphatic clearance efficiency with age

Many studies show that glymphatic function declines with age. One study based on mice demonstrates a significant age-related decline in glymphatic function that CSF-ISF exchange decreases markedly with age. The experiment resulted in Aβ clearance impaired by up to 40% in aged mice relative to young mice and arterial pulsatility is reduced by 27% in small intracortical arterioles [3].

4.4. Aging, glymphatic dysfunction, and neurodegeneration

Dysfunction of the glymphatic system—the primary pathway for clearing metabolic waste products from the central nervous system—results in the accumulation of neurotoxic byproducts. These waste deposits induce structural and functional damage to neurons and glial cells, trigger or amplify neuroinflammatory responses, promote oxidative stress cascades, and ultimately drive neuronal loss and neurodegeneration, culminating in cognitive impairment [3].

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5. Mechanisms connecting glymphatic dysfunction, sleep, and aging

5.1. Oxidative stress and mitochondrial dysfunction

Oxidative stress (damage caused by free radicals) and mitochondrial dysfunction (when the cell's powerhouses stop working well) are common in both sleep disruption and aging [7]. Glymphatic dysfunction can cause oxidative stress, which in turn damages the glymphatic system [8].

5.2. Neuroinflammation and immunosenescence

When the glymphatic system fails, waste products and inflammatory chemicals build up in the brain. This creates a cycle: inflammation damages the glymphatic system, which causes more inflammation. Aging is also linked to immunosenescence (weakening of the immune system), which adds to this cycle [8].

5.3. Circadian rhythm disruption

The body's internal clock is disrupted in aging and metabolic disorders [7]. Since glymphatic function follows a daily rhythm, circadian disruption can directly impair brain cleaning [2]. This may explain why shift work and irregular schedules are linked to higher rates of cognitive decline.

6. Therapeutic implications and future directions

6.1. Sleep-based interventions

First and most important, getting a good sleep. The simplest and most effective way to maintain glymphatic function is to get good-quality sleep. In addition, CPAP treatment, the standard therapy for OSA, used for sleep apnea improves glymphatic function and may slow cognitive decline [9]. Finally, sleeping on your side may help glymphatic clearance better than sleeping on your back or stomach [7].

6.2. Exercise

Exercise has been shown to improve glymphatic function. Studies in elderly rodents found that voluntary exercise increased waste clearance, lowered amyloid-beta levels, improved synaptic integrity, and enhanced spatial memory [1].

6.3. AQP4 as a therapeutic target

Because AQP4 is so important for glymphatic function, researchers are exploring it as a drug target [7]. One compound, 5-caffeoylquinic acid (5-CQA), has been shown to normalize AQP4 location and increase amyloid-beta clearance in animal models [7].

6.4. Imaging and future research

AI has potential for predicting metabolic disorders and assessing glymphatic function through imaging analysis [7]. But of course, more studies are needed to understand how the glymphatic system works, to develop better imaging techniques, and to test new treatments.

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7. Conclusion

This review synthesizes current evidence on the bidirectional relationship between the glymphatic system, sleep and aging, examining the structural components, sleep-dependent activation mechanisms, and the pathological consequences of glymphatic dysfunction. This study proposes that the glymphatic system serves as a crucial biological link connecting sleep disorders, aging and neurodegenerative disease, positioning it as a promising therapeutic target for cognitive decline.

The glymphatic system is a crucial cleaning system for the brain. It is most active during deep sleep, when it washes away toxic proteins like amyloid-beta and tau. Sleep disorders, especially obstructive sleep apnea (OSA), harm the glymphatic system by fragmenting sleep and causing oxygen drops. Aging also damages the system by reducing sleep quality, depolarizing AQP4 and decreasing arterial pulsatility. The result is a vicious cycle: sleep disorders cause glymphatic dysfunction, which leads to protein buildup and inflammation, which causes more sleep problems, and the cycle repeats [1]. However, this cycle can be broken. Getting good quality sleep, treating sleep apnea with CPAP, exercising regularly, and possibly targeting AQP4 with drugs are all promising strategies for protecting brain health [9]. Sustaining consistent, high-quality sleep represents the most evidence-based strategy for preserving optimal glymphatic clearance efficiency [1]. In conclusion, the glymphatic system is a fundamental part of brain health. Understanding it may help us find new ways to prevent cognitive decline and neurodegenerative diseases.

References

[1] Voumvourakis, K. I., Sideri, E., et al. (2023). The dynamic relationship between the glymphatic system, aging, memory, and sleep. *Biomedicines, 11*(8), 2092.

[2] Yi, T., Gao, P., Zhu, T., Yin, H., & Jin, S. (2022). Glymphatic system dysfunction: A novel mediator of sleep disorders and headaches. *Frontiers in Neurology, 13*, 885020.

[3] Xie, L., Kang, H., et al. (2013). Sleep drives metabolite clearance from the adult brain. *Science, 342*(6156), 373-377.

[4] Kress, B. T., Iliff, J. J., Xia, M., Wang, M., Wei, H. S., Zeppenfeld, D., ... & Nedergaard, M. (2014). Impairment of paravascular clearance pathways in the aging brain. *Annals of Neurology, 76*(6), 845-861.

[5] Zhang, D., Li, X., & Li, B. (2022). Glymphatic system dysfunction in central nervous system diseases and mood disorders. *Frontiers in Aging Neuroscience, 14*, 873697.

[6] Khatana, J., Thavamani, A., Umapathi, K. K., Sankararaman, S., & Roy, A. (2024). Obstructive sleep apnea is associated with worsened hospital outcomes in children hospitalized with asthma. *Children, 11*(8), 1029.

[7] Maiese, K. (2025). Diabetes mellitus and glymphatic dysfunction: Roles for oxidative stress, mitochondria, circadian rhythm, artificial intelligence, and imaging. *World Journal of Diabetes, 16*(1), 98948.

[8] Silva, I., Silva, J., Ferreira, R., & Trigo, D. (2021). Glymphatic system, AQP4, and their implications in Alzheimer's disease. *Neurological Research and Practice, 3*(1), 5.

[9] Wang, J., Tian, Y., Qin, C., Meng, L., Feng, R., Xu, S., ... & Wang, X. (2023). Impaired glymphatic drainage underlying obstructive sleep apnea is associated with cognitive dysfunction. *Journal of Neurology, 270*, 2204-2216.