

The Role of the Glymphatic System in Neurological Health

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Glymphatic system is the name given to the anatomical and functional pathways by which soluble waste proteins and metabolic products are drained away from cerebral interstitial fluid. The terms “glial” and “lymphatic” were combined to describe this complex system because perivascular astroglial cells are intrinsic to the waste-removal process in the CNS, and the mechanism appears to resemble the lymphatic system in the periphery. The brain’s drainage system is critical for maintaining homeostasis of intracranial fluid volume. It is also key to CNS immune response and surveillance.¹ In addition to removing waste, the glymphatic system aids in distribution throughout the brain of glucose, lipids, and signaling molecules.²

The anatomy and function of the brain’s waste-removal pathways are still being defined but involve the glymphatic system for cerebrospinal fluid (CSF) transport, which in turn is interconnected with the meningeal lymphatic network.^{3,4} It is likely that the changes in vascular pulsatility observed in cerebrovascular disorders adversely affect glymphatic function. Suboptimal glymphatic function is also evident in the changes in brain function related to aging, possibly because the stiffening of vessel walls that occurs with aging causes reduced vascular pulsation.²

The removal of potentially neurotoxic waste from the CNS is crucial for health across the lifespan, especially given that protein aggregation is a feature of most neurodegenerative conditions. Glymphatic system impairment is thought to contribute to the pathogenesis and pathophysiology of several neurodegenerative, neuroinflammatory, and neurovascular disorders, as well as to the effects of traumatic brain injuries (TBIs).^{5,6} Several preclinical studies show that the glymphatic system removes beta-amyloid and tau proteins from the brain, and that the activity of the glymphatic system, along with CSF outflow, markedly decreases with age.^{7,8}

The glymphatic system and the blood-brain barrier clear neurotoxic proteins from the extracellular space, interstitial fluid, and CSF. The intracellular removal of neurotoxic proteins is mostly accomplished by autophagy, the process by which surplus or harmful cytoplasmic material is transported to a lysosomal degradation system. Reduction in glymphatic flow raises protein concentration thereby increasing the likelihood of protein aggregation, which in turn reduces the capacity for autophagy.^{9,10}

The Role of Sleep in Brain Health

The biological necessity of sleep is corroborated by the fact that the glymphatic system mostly disengages during the waking state and predominantly functions during sleep, in particular during NREM sleep, which is characterized by slow waves (also known as delta waves).^{11,12} Sleep deprivation for only one night is associated with increased beta-amyloid levels in human brains.¹³ Intriguingly, animal studies have shown that during sleep (either natural or induced by anesthesia), the volume of interstitial space in the brain increases,

which lowers resistance to fluid flow, allowing for greater exchange between the CSF and interstitial fluid to support the removal of metabolic waste products.^{14,15}

Glymphatic dysfunction induced by sleep disturbance results in protein aggregation and is associated with increased risk of neurological disorders including Alzheimer's disease¹⁶ and Parkinson's disease.¹⁷

Therapeutic Considerations

Along with a healthy diet and prioritizing sleep, clinicians may wish to recommend the following to their patients to support the optimal health of brain detoxification mechanisms:

Exercise

Young mice allowed to run on a wheel displayed twice the glymphatic activity as mice prevented from exercising.¹⁸ A similar experiment in aged mice found a significant increase in glymphatic function in mice allowed to exercise, along with decreased beta-amyloid concentration. Mice allowed to exercise showed significantly better spatial memory as well.¹⁹

Melatonin Supplementation

Daily supplementation of 3-12 mg of melatonin at bedtime was shown to enhance the glymphatic clearance of pathological proteins as well as to preserve the slow-wave sleep cycle.²⁰

N-Acetylglucosamine (NAG)

N-acetylglucosamine(NAG) is a glycosaminoglycan that may be useful in maintaining the integrity of the blood-brain barrier by preserving or helping to rebuild the endothelial glycocalyx, which creates a barrier between circulating blood and the blood vessel wall.²¹

References

1. <https://www.frontiersin.org/articles/10.3389/fnins.2021.639140/full>
2. <https://portlandpress.com/clinsci/article-abstract/131/17/2257/71552/Perivascular-spaces-glymphatic-dysfunction-and?redirectedFrom=fulltext>
3. <https://www.nature.com/articles/nature14432?mobile>
4. <https://rupress.org/jem/article/212/7/991/41853/A-dural-lymphatic-vascular-system-that-drains>
5. <https://www.sciencedirect.com/science/article/pii/S030100821730062X>
6. <https://www.karger.com/Article/FullText/490349>
7. <https://pubmed.ncbi.nlm.nih.gov/22896675/>
8. <https://pubmed.ncbi.nlm.nih.gov/29127332/>
9. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6456907/>
10. <https://www.frontiersin.org/articles/10.3389/fpsyt.2021.658340/full>
11. <https://www.sciencedirect.com/science/article/pii/S2468867319301609>
12. <https://pubmed.ncbi.nlm.nih.gov/30820460/>
13. <https://pubmed.ncbi.nlm.nih.gov/29632177/>
14. <https://www.sciencedirect.com/science/article/abs/pii/S1474442218303181>
15. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3880190/>
16. <https://www.science.org/doi/abs/10.1126/scitranslmed.3004291>
17. <https://www.sciencedirect.com/science/article/abs/pii/S0149763419300284>

18. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5696653/>
19. <https://www.frontiersin.org/articles/10.3389/fnmol.2017.00144/full>
20. <https://onlinelibrary.wiley.com/doi/abs/10.1002/mus.27168>
21. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3997148/>

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