RESEARCH HIGHLIGHT

The night shift: norepinephrine drives glymphatics

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The glymphatic system clears waste most efficiently during non-rapid eye movement sleep, driven by rhythmic norepinephrine oscillations that regulate slow vasomotion. This discovery sheds light on the interplay between disruptions in sleep architecture and neurodegenerative diseases and highlights the need for therapies that preserve or restore physiologic sleep patterns to enhance brain clearance.

The glymphatic system is a pathway whereby clean subarachnoid cerebrospinal fluid (CSF) is able to perfuse the brain's interstitial spaces for a variety of functions including waste clearance, fluid balance, neuronal–immune cell crosstalk, and antigen presentation.[1–3] Characterization of this fluid exchange pathway has found that CSF enters the central nervous system (CNS) parenchyma within the perivascular spaces of arteries, largely driven by arterial pulsations.[1,4] Once within the extracellular space, CSF then mixes with interstitial fluid (ISF) to carry solute, including waste, toward perivenous spaces that ultimately drain directly to the dura via arachnoid cuff exit points.[5] Fluid and solute deposited in the dura can then be cleared from the CNS via meningeal lymphatic vessels that drain to the cervical lymph system.[6] The glymphatic system has been implicated as a critical driver of pathologically relevant solutes such as amyloid-β, as well as in conditions of dysregulated fluid homeostasis including post-ischemic cerebral edema.[1,7] Since the identification of the glymphatic system over a decade ago, perhaps the most exciting and impactful discovery is that the brain-cleaning activity of this pathway is enhanced during sleep.[8] This has led to an important follow-up discovery suggesting that glymphatic activity is closely linked to neuronal activity, specifically synchronous neuronal activity during natural sleep.[9] However, the mechanistic link between synchronous neuronal firing during sleep and heightened glymphatic clearance has remained elusive. New research from Hauglund et al.,[10] for the first time makes the connection between sleep and glymphatic performance, demonstrating that norepinephrine (NE)-mediated slow vasomotion is the primary driving force for glymphatic clearance during non-rapid eye movement (NREM) sleep. Further, they suggest that physiologic sleep architecture, rather than pharmacologically suppressed consciousness, is critical for optimal glymphatic function.

NE, a centrally produced catecholamine released from the brainstem nucleus locus coeruleus, acts on vascular smooth muscle within the CNS to cause arterial vasoconstriction. Hauglund and colleagues hypothesized that rhythmic release of NE during sleep would lead to alternating arterial constriction and dilatation, with concomitant increase and decrease in periarterial space size, respectively, and that if synchronized, this could be a strong driver of CSF flow and brain clearance.[10] To answer this relatively simple question requires the capability to study electrical activity, neurotransmitter levels, blood flow, and CSF dynamics in the naturally sleeping murine brain. While there are well-established techniques to study each of these physiologic processes in isolation in either in vitro or anesthetized in vivo model systems, the present study represents a major technological leap forward by combining electroencephalogram (EEG) with fiber photometric imaging of genetically encoded NE sensors and fluorescently labeled albumin, as well as exogenously delivered CSF-based fluorescent tracers in unrestrained naturally behaving mice.[10]

Using this elegant technique, the authors found that the locus coeruleus releases NE in an infraslow (~0.02 Hz) oscillatory pattern during NREM sleep, resulting in strong anti-correlated changes in cerebral blood volume and CSF flow, which acts as a pump to drive CSF and ISF through the glymphatic pathway (Fig. 1). Further, through optogenetic stimulation of the locus coeruleus, they were able to demonstrate a dose-dependent relationship between NE release, slow vasomotion, and glymphatic CSF transport. Interrogating sleep architecture, the authors found that EEG sigma power during NREM sleep was tightly phase-locked with NE, blood volume, and CSF volume oscillations. Interestingly, they also observed that micro-arousals were directly correlated with glymphatic clearance, however, this appeared to be co-incidental rather than mechanistically upstream of CSF flow. Highlighting how exquisitely sensitive this entire process is to physiologic sleep architecture, when the commonly prescribed sleep aid zolpidem was given to the mice, despite promoting sleep onset, there was a suppression of infraslow NE oscillations with downstream disrupted slow vasomotion and glymphatic CSF flow[10] (Fig. 1).

These findings have major clinical implications not only for neurodegenerative diseases like Alzheimer's disease and Parkinson's disease but also for normal aging, neurovascular conditions, and sleep disorders. The next crucial step is translating this research to human conditions by examining the relationship between sleep architecture, NE oscillations, glymphatic flow, and waste clearance in both healthy individuals and those with neurological diseases. Many neurodegenerative conditions are marked by the accumulation of pathological proteins such as amyloid-β and tau, which may stem from impaired clearance of these naturally occurring solutes. Notably, these diseases have also been associated with poor sleep quality and disrupted sleep

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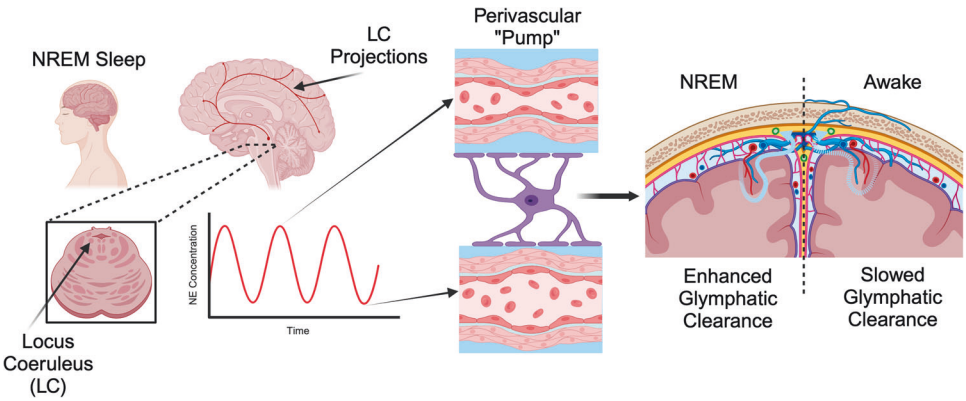

Fig. 1 Infraslow NE oscillations drive slow vasomotion to control CSF and brain waste clearance. During NREM sleep, synchronous activity from the locus coeruleus generates infraslow (0.2 Hz) NE oscillations, which results in alternating arterial contraction and dilatation. This NE-dependent slow vasomotor activity drives a "perivascular pump", enhancing glymphatic brain perfusion during NREM sleep and reducing brain clearance during wakefulness.

architecture. This study provides the first direct evidence that disrupted NE oscillations and impaired slow vasomotion may be the missing link between sleep disturbances and reduced brain waste removal in aging and neurodegeneration.[10] Furthermore, findings by Hauglund et al., on the effects of sleep aids like zolpidem highlight the need for therapies that preserve or restore physiological sleep architecture, maintain NE oscillatory activity, and enhance glymphatic clearance to slow or even reverse neurodegenerative disease progression. Additionally, conditions involving vascular stiffening, such as cerebral amyloid angiopathy and intracranial atherosclerosis, may impair glymphatic perfusion even when NE oscillations remain intact. Therefore, an alternative therapeutic approach should focus on enhancing intrinsic vascular vasomotor activity rather than solely restoring normal sleep patterns and NE dynamics.

The discovery of NE-driven slow vasomotion as a key mediator of glymphatic clearance during NREM sleep marks a major leap forward in our understanding of the link between sleep, its architecture, and brain waste removal. These findings highlight the centrality of normal sleep physiology in maintaining brain health and propose new therapeutic targets in natural aging, neurodegenerative diseases, and neurovascular conditions. Future research should focus on translating these insights to humans, exploring interventions that preserve or restore sleep architecture and NE oscillatory activity, and enhance glymphatic function. Ultimately, targeting both sleep-dependent and vascular-intrinsic clearance mechanisms may open new avenues for preventing and treating neurological disorders linked to impaired waste clearance.

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ADDITIONAL INFORMATION

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