VIEWPOINT

Does Sleep Flush Wastes From the Brain?

Anthony L. Komaroff, MD
Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Why do humans sleep? Most people spend one-third of their lives asleep. For most of human history, individuals have been much more vulnerable to enemies and predators when sleeping. But still, everyone sleeps and cannot help but do it. So, there must be a good reason for sleep, an evolutionary advantage.

Some Benefits of Sleep

One reason for sleeping may be to rest the brain and body. Nevertheless, most organs continue to work during sleep. In particular, the brain is highly active during sleep.[1] Sigmund Freud thought one purpose of sleep was to grapple with negative thoughts buried in the unconscious through dreams. Sleep definitely helps to consolidate memories and learning. Some have speculated that during sleep unused synapses are pruned, strengthening the rest of the synapses in the same way that pruning dead branches enhances the health of a rose bush. Together, these all might seem reason enough to sleep.

Within the past decade, however, new discoveries have suggested another important role for sleep: a type of "waste management." Neurons and glia have high metabolic rates and produce a lot of waste. The waste includes toxic substances including 2 molecules (amyloid-β [Aβ] and tau) central to the pathology of Alzheimer disease (AD). Neurons and glia are easily injured by such waste and therefore have a great need to efficiently eliminate waste.

> Why do people sleep? How does the brain eliminate waste products? Increasingly, it appears that the answers to these questions may be linked.

The brain has a variety of ways of eliminating waste products, including local proteolytic degradation, phagocytosis by microglial cells, and passage across a porous blood-brain barrier into the circulation. However, several centuries of anatomical studies had found no lymphatic system in the brain.[2] That was puzzling because the lymphatic system drains waste products from other organs.

Thus, the brain, an organ composed of cells easily injured by toxins and an organ that produces large amounts of toxins, appeared to be deprived of a critical part of its waste management system. Yet, to remain functional an organ needs a good waste management system.

Discovery of Brain Waste Management Systems

Meningeal Lymphatic System

In 2015, lymphatic vessels were discovered in the meninges of rodents, nonhuman primates, and humans.[3] These vessels carry both fluid and immune cells to deep cervical lymph nodes, and ultimately into the systemic circulation.

Glymphatic System

A bigger surprise was the discovery of the glymphatic system—first suggested in the 1980s[4] and identified definitively by Iliff and colleagues[2] in 2012. The glymphatic system is a drainage system that mingles "fresh" cerebrospinal fluid (CSF) with waste product–rich brain interstitial fluid (ISF) and flushes the fluid and waste products out of the brain and into the systemic circulation.

How the Glymphatic System Works to Flush Out the Brain

Fresh CSF, produced largely by the choroid plexus, travels to the subarachnoid space. Then the CSF enters the periarterial part of the glymphatic system (a tube that is wider than the artery, like a collar around the artery through which fresh CSF flows). Thus, the outer wall of the artery also is the inner wall of the periarterial glymphatic vessel.

The outer wall of a glymphatic vessel is a truly novel structure. It is composed of the flat end feet of specialized astrocytes, which are densely studded with water channels (aquaporins). The water channels are like pores in a sieve.[1] The CSF within periarterial glymphatic vessel passes through the water channels in the outer wall of the vessel and out into a large space (the neuropil). The neuropil is filled with waste product–rich ISF and with neurons and glial cells, packed together as densely as passengers on a subway car at rush hour before the pandemic.

Several forces (arterial pressure, diffusion, pressures generated by respiration) move the mixture of CSF and ISF toward the perivenous part of the glymphatic system. When it reaches the perivenous glymphatic system, the fluid moves through the water channels on the outer wall of that system and into the perivenous glymphatic vessels. The fluid travels down to the lymphatic system in the neck, and then into the systemic circulation.

In short, fresh CSF travels from the choroid plexuses into the subarachnoid space, then into the periarterial glymphatic systems, then mixes with waste product–rich ISF that surrounds the neurons and glial cells, then passes into the perivenous glymphatic system, then into the lymphatic system, and finally into the systemic circulation. The brain has been flushed.

At least in animals, there is evidence that glymphatic pathways also may be associated with cranial nerves. It is not known whether fluid and solutes travel outside or within the nerve—between its fascicles—nor how important these neural routes are to waste removal.

Sleep and the Glymphatic System

Glymphatic Flow During Sleep

The flow of fluid through the glymphatic system is greatest during sleep, particularly during non–rapid eye

Corresponding Author: Anthony L. Komaroff, MD, Brigham and Women's Hospital, 1620 Tremont St, Boston, MA 02120 (komaroff@hms.harvard.edu).

movement, slow-wave sleep.[5] That is true even during daytime sleep. Certain anesthetic agents (such as ketamine) also produce the same effect in animals.[6]

During sleep, substantial changes occur to increase glymphatic flow. Most important, the ISF increases by 60%.[6] How does this happen? During sleep, intracellular fluid from neurons and glial cells rushes through water channels in these cells and into the interstitial space; intracellular volume shrinks and the ISF expands. With more fluid, there is more flushing.

Up to 60% of large proteins and solutes are removed via the glymphatic pathway.[2] Removal of Aβ and tau[2,7] mitigates the formation and growth of Aβ-rich plaques and prevents the seeding and spreading of tau filaments[7]—2 key features of AD. Perhaps more important, the glymphatic system flushes out the small, soluble forms of Aβ and tau that may be neurotoxic.

Disorders That Impair the Glymphatic System

The function of the glymphatic system appears to be compromised by aging. One reason that glymphatic function is decreased with aging is that the number of water channels diminishes.

Glymphatic system function also is reduced in people with circadian misalignment (eg, shift work) and in people with a sedentary lifestyle. It also is reduced following traumatic brain injury, in conditions characterized by elevated intracranial pressure, and in patients with sleep apnea, obesity, hypertension, type 2 diabetes, cerebrovascular atherosclerosis, cerebrovascular hemorrhage, ischemic stroke, AD, and sleep disruption or deprivation.[1]

Are the Health Consequences of Sleep Deprivation Secondary to Glymphatic Dysfunction?

Chronic sleep loss is associated with a variety of neurological disorders, including AD, Parkinson disease, multiple sclerosis, stroke, Huntington disease, epilepsy, glioma, autism spectrum disorders, and neuropathic pain. Sleep deprivation also reduces glymphatic system function. Could the latter explain the former?

The possibility is clearest with AD. In fruit flies, rodents, and humans with normal cognitive function, sleep deprivation appears to increase the accumulation of Aβ.[8] Animal studies indicate it does so by impairing the function of glymphatic water channels. For example, mice with impaired water channels (compared with mice with intact water channels) have reduced glymphatic function, an accumulation of Aβ and tau proteins in the brain, neuroinflammation, loss of synapses, and decreased working memory. Similarly, when the glymphatic vessels of mice are experimentally ablated, Aβ deposits build up, and when the glymphatic vessels are experimentally expanded, monoclonal antibodies targeting Aβ (like those used in human AD trials) are much more effective in clearing the Aβ.[9] Adverse outcomes from impaired water channels or glymphatic vessels become much more likely when the mice are sleep-deprived.

Human studies are consistent with the animal studies. Inherited polymorphisms in the water channels that reduce glymphatic flow are associated with cognitive decline in prospective studies of people with AD.[1] In humans, total sleep deprivation for even 1 night causes an increase in the Aβ burden in the hippocampus and thalamus.[8] The pattern of spread of Aβ and tau in AD (and of α-synuclein in Parkinson disease) mirrors the pattern of glymphatic flow revealed by magnetic resonance imaging.[1]

Conclusions

The discovery of the glymphatic system and of the meningeal lymphatic system expands current understanding of how the brain eliminates waste products. The previously noted correlation between chronic sleep deprivation and several major diseases is plausibly explained by the resulting impairment in glymphatic system function, given its link to sleep. More human studies are needed, particularly in adolescents and children in whom sleep disruption is common. One obvious focus of the research should be on therapies that improve glymphatic system function.

Why do people sleep? How does the brain eliminate waste products? Increasingly, it appears that the answers to these questions may be linked: a principal reason for sleep may be to activate the newly discovered glymphatic system to flush waste products from the brain.

ARTICLE INFORMATION

Published Online: May 17, 2021. doi:10.1001/jama.2021.5631

Correction: This article was corrected on June 4, 2021, to remove the words "lactate and" from the third sentence in the third paragraph and to add the word "of" to the last sentence in the paragraph right before the "Conclusions" paragraph.

Conflict of Interest Disclosures: Dr Komaroff reported receiving personal fees from Serimmune Inc, Ono Pharma, and Deallus and receiving grants from the National Institutes of Health.

Additional Contributions: I thank Clifford B. Saper, MD, PhD (James Jackson Putnam Professor of Neurology and Neuroscience, Harvard Medical School, and Chair, Department of Neurology, Beth Israel Deaconess Medical Center), for his review and editorial suggestions on the manuscript and Jill Mazzetta for helping gather the literature. Neither received compensation for their contributions.

REFERENCES

1. Nedergaard M, Goldman SA. Glymphatic failure as a final common pathway to dementia. *Science*. 2020;370(6512):50-56. doi:10.1126/science.abb8739

2. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci Transl Med*. 2012;4(147):147ra111. doi:10.1126/scitranslmed.3003748

3. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature*. 2015;523(7560):337-341. doi:10.1038/nature14432

4. Rennels ML, Gregory TF, Blaumanis OR, Fujimoto K, Grady PA. Evidence for a 'paravascular' fluid circulation in the mammalian central nervous system, provided by the rapid distribution of tracer protein throughout the brain from the subarachnoid space. *Brain Res*. 1985;326(1):47-63. doi:10.1016/0006-8993(85)91383-6

5. Fultz NE, Bonmassar G, Setsompop K, et al. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science*. 2019;366(6465):628-631. doi:10.1126/science.aax5440

6. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science*. 2013;342(6156):373-377. doi:10.1126/science.1241224

7. Holth JK, Fritschi SK, Wang C, et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science*. 2019;363(6429):880-884. doi:10.1126/science.aav2546

8. Shokri-Kojori E, Wang G-J, Wiers CE, et al. β-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci U S A*. 2018;115(17):4483-4488. doi:10.1073/pnas.1721694115

9. Da Mesquita S, Papadopoulos Z, Dykstra T, et al. Meningeal lymphatics affect microglia responses and anti-Aβ immunotherapy. *Nature*. 2021;593:255-260. doi:10.1038/s41586-021-03489-0