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Brain Drain

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Abstract

An internal plumbing system rids the brain of toxic wastes. Sleep is when this cleanup ritual occurs.

The human brain weighs only about three pounds, or roughly 2 percent of the average adult body mass. Yet its cells consume 20 to 25 percent of the body's total energy. In the process, inordinate amounts of potentially toxic protein wastes and biological debris are generated. Each day, the adult brain eliminates a quarter of an ounce of worn-out proteins that must be replaced with newly made ones, a figure that translates into the replacement of half a pound of detritus a month and three pounds, the brain's own weight, over the course of a year.

To survive, the brain must have some way of flushing out debris. It is inconceivable that an organ so finely tuned to producing thoughts and actions would lack an efficient waste disposal system. But until quite recently, the brain's plumbing system remained mysterious in several ways. Questions persisted as to what extent brain cells processed their own wastes or whether they might be transported out of the nervous system for disposal. And why is it that evolution did not seem to have made brains adept at delivering wastes to other organs in the body that are more specialized for removing debris? The liver, after all, is a powerhouse for disposing of or recycling waste products.

About five years ago we began trying to clarify how the brain eliminates proteins and other wastes. We also began to explore how interference with that process might cause the cognitive problems encountered in neurodegenerative disease. We thought that disturbances in waste clearance could contribute to such disorders because the disruption would be expected to lead to the accumulation of protein debris in and around cells.

This idea intrigued us because it was already known that such protein clumps, or aggregates, do indeed form in brain cells, most often in association with neurodegenerative disorders. What is more, it was known that the aggregates could impede the transmission of electrical and chemical signals in the brain and cause irreparable harm. In fact, the pathology of Alzheimer's, Parkinson's and other neurodegenerative diseases of aging can be reproduced in animal models by the forced overproduction of these protein aggregates.

In our research, we found an undiscovered system for clearing proteins and other wastes from the brain—and learned that this system is most active during sleep. The need to remove potentially toxic wastes from the brain may, in fact, help explain the mystery of why we sleep and hence retreat from wakefulness for a third of our lives. We fully expect that an understanding of what happens when this system malfunctions will lead us to both new diagnostic techniques and treatments for a host of neurological illnesses.

The Glymphatic System

In most regions of the body, a network of intricate fluid-carrying vessels, known as the lymphatic system, eliminates protein waste from tissues. Waste-carrying fluid moves throughout this network between cells. The fluid collects into small ducts that then lead to larger ones and eventually into blood vessels. This duct structure also provides a path for immune defense, because lymph nodes, a repository of infection-fighting white blood cells, populate ducts at key points throughout the network. Yet for a century neuroscientists had believed that the lymphatic system did not exist in the brain or spinal cord. The prevailing view held that the brain eliminated wastes on its own. Our research suggests that this is not the complete story.

The brain's blood vessels are surrounded by what are called perivascular spaces. They are doughnut-shaped tunnels that surround every vessel. The inner wall of each space is made of the surface of vascular cells, mostly endothelial cells and smooth muscle cells. But the outer wall is unique to the brain and spinal cord and consists of extensions branching out from a specialized cell type called the astrocyte.

Astrocytes are support cells that perform a multitude of functions for the interconnected network of neurons that relay signals throughout the brain. The astrocytes' extensions—astrocytic end feet—completely surround the arteries, capillaries and veins in the brain and spinal cord. The hollow, tubelike cavity that forms between the feet and the vessels remains largely free of obstructions, creating a spillway that allows for the rapid transport of fluid through the brain.

Scientists knew about the existence of the perivascular space but until very recently had not identified any specific function for it. Thirty years ago Patricia Grady, then at the University of Maryland, described perivascular fluid flows, but the significance of this finding was not recognized until much later. She reported that large proteins injected into the cerebrospinal fluid (CSF) could later be found in the perivascular spaces of both dogs and cats. At the time, other groups could not replicate her findings, and not knowing the meaning of what such an observation might be, research did not proceed any further.

When we began our investigations into the waste-disposal system of the brain just a few years ago, we focused on prior discoveries that water channels built from a protein called aquaporin-4 were embedded in the astrocytic end feet. In fact, the density of the water channels was comparable to that of those in the kidney, an organ whose primary job is to transport water.

We were immediately interested in the multiplicity of the astrocytic water channels and their positions facing the blood vessel walls. Our interest only grew when we looked more closely because we found that the vascular endothelial cells bordering the perivascular space lacked these channels. Thus, fluid could not be moving directly from the bloodstream into brain tissue. Rather the liquid had to be flowing between the perivascular space and into the astrocytes, thereby gaining access to the brain tissue.

We asked whether the perivascular space might constitute a neural lymphatic system. Could it perhaps provide a conduit for cerebrospinal fluid? Arterial pulsations might drive the CSF through the perivascular space. From there, some of it could enter astrocytes through their end feet. It could then move into the area between cells and finally to the perivascular space around veins to clear waste products from the brain.

Along with our laboratory members Jeff Iliff and Rashid Deane, we went on to confirm this hypothesis. Using chemical dyes that stained the fluid, combined with microscopic techniques that allowed us to image deep inside live brain tissue, we could directly observe that the pumping of blood propelled large quantities of CSF into the perivascular space surrounding arteries. Using astrocytes as conduits, the CSF then moved through the brain tissue, where it left the astrocytes and picked up discarded proteins.

The fluids exited the brain through the perivascular space that surrounded small veins draining the brain, and these veins in turn merged into larger ones that continued into the neck. The waste liquids went on to enter the lymph system, from which they flowed back into the general blood circulation. They combined there with protein waste products from other organs that were ultimately destined for filtering by the kidneys or processing by the liver.

When we began our research, we had no idea that astrocytes played such a critical role in the brain's counterpart of a lymphatic system. Additional proof came when we used genetically engineered mice that lacked the aquaporin-4 protein that makes up the astrocytes' water channels. The rate of CSF flow entering the astrocytes dropped by 60 percent, greatly slowing fluid transport through their brain.

We had now traced a complete pathway within the brain for these cleansing fluids to effectively sweep away waste products. We named our discovery the glymphatic system. The newly coined word combined the words “glia”—a type of brain cell of which the astrocyte is one example—and “lymphatic,” thus referencing this newly discovered function of the brain's glial cells.

As we came to recognize the important role of the glymphatic system, we immediately wondered whether proteins that build up in the brain in neurodegenerative diseases might, in the healthy brain, be typically washed out along with other, more mundane cellular waste. In particular, we focused on a protein linked to Alzheimer's called beta-amyloid, which had previously been thought to be cleared under normal circumstances by degradation or recycling processes that take place within all brain cells. In Alzheimer's, aggregates of beta-amyloid form amyloid plaques between cells that may contribute to the disease process. We found that in a healthy brain, beta-amyloid is cleared by the glymphatic system. Other proteins implicated in neurodegenerative diseases, such as the synuclein proteins that turn up in Parkinson's, Lewy body disease and multisystem atrophy, might also be carried away and could build up abnormally if the glymphatic system were to malfunction.

A symptom that accompanies Alzheimer's and other neurodegenerative diseases provided a hint of how to proceed. Many patients with Alzheimer's experience sleep disturbances long before their dementia becomes apparent. In older individuals, sleep becomes more

fragmented and shallow and lasts a shorter time. Epidemiological studies have shown that patients who reported poor sleep in middle age were at greater risk for cognitive decline than control subjects when tested 25 years later.

Even healthy individuals who are forced to stay awake exhibit symptoms more typical of neurological disease and mental illness—poor concentration, memory lapses, fatigue, irritability, and emotional ups and downs. Profound sleep deprivation may produce confusion and hallucinations, potentially leading to epileptic seizures and even death. Indeed, lab animals may die when deprived of sleep for as little as several days, and humans are no more resilient. In humans, fatal familial insomnia is an inherited disease that causes patients to sleep progressively less until they die, usually within 18 months of diagnosis.

Knowing all this, we speculated that the sleep difficulties of dementia might not just be a side effect of the disorder but might contribute to the disease process itself. Moreover, if the glymphatic system cleared beta-amyloid during sleep at a higher rate than when awake, perhaps the poor sleeping patterns of patients with neurodegenerative disorders might contribute to a worsening of the disease. Because our initial experiments had been performed in anesthetized mice, we further speculated that the fast fluid flows that we noted were not necessarily what we might anticipate in an awake and active brain, which would be subject to other demands in its typical functioning.

To test the idea, Lulu Xie and Hongyi Kang, both in the Nedergaard Laboratory, trained mice to sit still underneath a microscope to capture images of a tracer chemical in the CSF using a novel imaging technique called two-photon microscopy. We compared how the tracer moved through the glymphatic system in awake versus sleeping mice. Because imaging is neither invasive nor painful, the mice remain quiet and compliant, so much so that animals often fall asleep while being imaged. We were thus able to image inflows of CSF in a particular area of the same mouse brain during both sleep and wakefulness.

CSF in the glymphatic system, it turned out, fell dramatically while the study mice were awake. Within minutes after the onset of sleep or the effects of anesthesia, however, influxes of the fluid increased significantly. In a collaboration with Charles Nicholson of New York University, we found that the brain's interstitial space—the area between cells through which glymphatic fluid flows on its way to perivascular spaces around veins—rose by more than 60 percent when mice fell asleep. We now believe that the flow of glymphatic fluid increases during sleep because the space between the cells expands, which helps to push fluid through the brain tissue.

Our research also revealed how the rate of fluid flow is controlled. A neurotransmitter, or signaling molecule, called norepinephrine appeared to regulate the volume of the interstitial area and consequently the pace of glymphatic flow. Levels of norepinephrine rose when mice were awake and were scarce during sleep, implying that transient, sleep-related dips in norepinephrine availability led to enhanced glymphatic flow.

The Power of Sleep

Having demonstrated that the expansion and contraction of the interstitial space during sleep were important to both brain function and protein-waste clearance, we then wanted to test a corollary to this observation: Could sleep deprivation precipitate neurodegenerative disease? Experiments that we conducted in mice showed that during sleep, the glymphatic system did indeed remove beta-amyloid from the brain with remarkable efficiency: its clearance rate more than doubled with sleep. On the other hand, mice genetically engineered so that they lacked aquaporin-4 water channels in astrocytes demonstrated markedly impaired glymphatic function, clearing 40 percent less beta-amyloid than control animals.

The remarkably high percentage of beta-amyloid removed challenged the widely held idea that brain cells break down all their own wastes internally (through degradation processes called ubiquitination and autophagy); now we know that the brain removes a good deal of unwanted proteins whole, sweeping them out for later degradation. These new findings, moreover, seemed to confirm that the sleeping brain exports protein waste, including beta-amyloid, through the glymphatic transport system. Additional support for this thesis came from David M. Holtzman's group at Washington University in St. Louis, which demonstrated that beta-amyloid concentration in the interstitial space is higher during wakefulness than in sleep and that sleep deprivation aggravates amyloid-plaque formation in mice genetically engineered to accumulate it in excess.

So far these investigations have not moved beyond basic research labs. Drug companies have yet to consider antidementia therapies that would physically remove amyloid and other toxic proteins by washing out the brain with glymphatic fluids. But maybe they should. New strategies are desperately needed for a disease that costs the U.S. health care system $226 billion annually. A number of clinical trials for Alzheimer's are under way, although no drug in development has yet demonstrated a clear-cut benefit. Stimulating glymphatic flows offers a new approach that is worth investigating.

A pharmaceutical that regulates the glymphatic system by increasing the rate of CSF flow during sleep could literally flush amyloid out of the brain. A treatment used for a well-known neurological syndrome provides a clue that this approach might work. Normal-pressure hydrocephalus, an illness typically seen in the elderly, is a form of dementia in which excessive CSF accumulates in the hollow central brain cavities, the cerebral ventricles. When a procedure called lumbar puncture removes the fluid by draining it out, patients often exhibit remarkable improvements in their cognitive abilities. The basis for this observation has long been a mystery. Our research suggests that restoring fluid flows through the glymphatic system might mediate the restoration of cognition in these patients.

Even if a new drug is not imminent, knowledge of the glymphatic systems suggests fresh ideas for diagnosing Alzheimer's and other neurological conditions. A recent study by Helene Benveniste of the Stony Brook School of Medicine has shown that standard magnetic resonance imaging can visualize and quantify the activity of the glymphatic system. The technology may allow tests of glymphatic flow designed to predict disease progression in patients suffering from Alzheimer's or related dementias or normal-pressure

hydrocephalus. It might even foretell the ability of patients with traumatic brain injuries to recover. Most of our studies of the glymphatic system to date have focused on the removal of protein wastes. Yet the glymphatic system may also prove to be a fertile area for gaining a basic understanding of how the brain works.

Intriguingly, fluids moving through the glymphatic system may do more than remove wastes; they may deliver various nutrients and other cargo to brain tissue. A new study showed that glymphatic channels deliver glucose to neurons to provide energy. Further studies are now investigating whether white matter, the insulationlike sheathing around neurons' wirelike extensions, called axons, may rely on the glymphatic system for delivery of both nutrients and materials needed for maintaining the cells' structural integrity. Such studies promise to elucidate the many unexpected roles of the glymphatic system in the daily life—and nightlife—of the brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

In Brief

- Where do these wastes go if the brain lacks the elaborate network of lymph vessels that transports wastes outside the nervous system? New research has recently found detritus-carrying passages in the brain that are most active during sleep.
- The glymphatic system, as these fluid vessels are known, may become a critical target for the treatment of neurological diseases such as Alzheimer's or Parkinson's that result from the buildup of toxic proteins that are not cleared from the brain.