NATURE | SCIENTIFIC AMERICAN

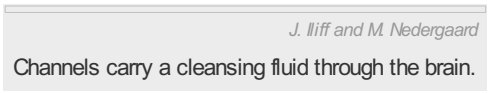
How the brain cleans itself

Fluids coursing through the nervous system could help clear the brain of toxic detritus that leads to Alzheimer's and Huntington's disorders.

Daisy Yuhas

16 August 2012

An article from Scientific American.



J. Iliff and M. Nedergaard

Channels carry a cleansing fluid through the brain.

The brain can be a messy place. Thankfully, it has good plumbing: Scientists have just discovered a cleansing river inside the brain, a fluid stream that might be enlisted to flush away the buildup of proteins associated with Alzheimer's, Huntington's and other neurodegenerative disorders.

The researchers, based at the University of Rochester (U.R.), University of Oslo and Stony Brook University, describe this new system in the journal *Science Translational Medicine*. The study adds to the evidence that the star-shaped cells called astrocytes play a leading role in keeping the nervous system in good working order.

In most of the body, a network of vessels carry lymph, a fluid that removes excess plasma, dead blood cells, debris and other waste. But the brain is different. Instead of lymph, the brain is bathed in cerebrospinal fluid. For decades, however, neuroscientists have assumed that this fluid simply carries soluble waste by slowly diffusing through tissues, then shipping its cargo out of the nervous system and eventually into the body's bloodstream. Determining what's really going on has been impossible until recently.

In this study, researchers led by U.R. neuroscientist Maiken Nedergaard have identified a second, faster brain-cleansing system. Nedergaard an expert in non-neuronal brain cells called glia, has long suspected that these cells might play a role in brain cleansing.

Nedergaard and colleagues studied live mice with holes drilled into their skulls to gain an unobstructed view. To see how waste is carried by cerebrospinal fluid in a living mouse, they injected the mice with radioactive molecules that could be traced using laser-scanning technology.

The molecules' journey began after being injected into the subarachnoid space, a cavity between membranes covering the brain and spinal cord. The researchers observed that, like a river, cerebrospinal fluid carried these molecules rapidly along specific channels. Glial cells along the outside of arteries form these channels, creating a flume for cerebrospinal fluid that follows the brain's blood vessels. In addition, the researchers found that these glial cells mediate the channel's activity, assisting the flow of fluid through the channel.

From channels alongside arteries, the tracer-bearing fluid then passes through brain tissues. At the other end of tissues, it flows into similar channels along veins. The fluid follows these veins then either returns to the subarachnoid space, enters the bloodstream or eventually drains into the body's lymphatic system. The researchers christened the network the "glymphatic" system, a nod to both glial cells and its functional similarity to the lymphatic system.

U.R. neuroscientist and lead author Jeff Iliff notes several surprises in the study: "I didn't think we would see these jets of fluid going through the brain," Iliff says. In addition, he explains that previous conception of cerebrospinal fluid's role in waste removal suggested that the process was one-way, sending particle-carrying fluid from the brain into the body. Instead, they observed a recycling, as much as 40 percent of the fluid returned to the brain.

As a test of their work, the researchers injected proteins called amyloid beta into mice's brains. In Alzheimer's, this protein—present in all healthy brains—can accumulate and clump, developing into cell-damaging plaque. The researchers compared mice with a normal glymphatic system to those with a disabled gene that prevented glial cells from assisting in the fluid flow. They found that in the normal mice, the protein rapidly cleared from the brain along these channels, but amyloid removal diminished in the gene-altered animals.

Iliff hypothesizes that a faulty glymphatic system may bear the blame for the over-accumulation of proteins seen in Alzheimer's,

amyotrophic lateral sclerosis, Huntington's and other neurodegenerative disorders—and further study may even reveal a way to dispose of these clumps.

Jaleel Miyan, a neurobiologist at the University of Manchester in England who did not participate in this research, stressed the significance of this finding by characterizing the analogy with the lymphatic system as inadequate: "What they have demonstrated is actually far more extensive and important to CSF [cerebrospinal fluid] biology." The study clarifies discrepancies in past research and may lead to a better understanding of the functioning of the glymphatic system as a possible cleanser of the neural toxins that inevitably accrete and do damage as we age.

Nature | doi:10.1038/nature.2012.11216