nih record

Vol. LXVII, No. 8 April 10, 2015

Welcome to the Glymphatic System

Nedergaard Explores Why We Need Sleep

By Rich McManus

On the front page...

We all know why that guy over there needs sleep—phew, did you get a whiff of him?—but Dr. Maiken Nedergaard thinks she knows why the rest of mankind needs sleep, and why without it, we die.

In a recent Wednesday Afternoon Lecture titled “The Nightlife of the Brain”—who can resist that?—she showed painstaking scientific evidence that the brain has its own public works system. Yes, a subdural network of utilities—okay, a sewer system—much like what undergirds New York and Washington (but perhaps more aromatic).

And the odd thing about it is that it has what you might call the discretion to function mainly while a person is asleep. That’s right, it goes to work when you lay down for a bit of kip. It’s like the housekeeping staff that descends on a midtown office building after hours.

Dr. Maiken Nedergaard at NIH

Nedergaard, who is Frank P. Smith professor of neurosurgery and co-director of the Center for Translational Neuromedicine at the University of Rochester Medical Center, has long been fascinated by glia, a unique cell type found only in the brain.

In her view, the brain may indeed be a nest of connections, but it is not a computer. It’s an organ, just like lungs and kidneys. The same things that make lungs and kidneys happy—exercise, food and rest—make brains happy.

Nedergaard, who is not trained in sleep studies, asked a simple question: What keeps a brain healthy? “A nice night of sleep is best to keep it in shape,” she said. But more than that, sleep is an essential phenomenon. Flies, rats and humans all die if their brains don’t experience sleep. There is a part of the brain—the locus ceruleus—in which dendrites die if sleep is withheld.

She reviewed a number of theories about what makes sleep a biological imperative, including benefits to memory, the immune system and the sheer preservation of human energy, given that a sleeping person’s metabolism slows by 15 percent vs. waking hours.

Sleep’s importance is further underscored by circadian rhythm, which keeps us in sync with the day/night cycle and is regulated by a sophisticated network of clock genes. Work late a few evenings and you begin to experience “sleep pressure,” which builds up in no other organ in the body except brain. “What drives that?” Nedergaard wondered.

She and her colleagues noted that the brain and spinal cord lack a lymphatic system, which plays a key role in the immune system. “Why does the brain not have it?” they asked, especially when brain tissue has 10 times the energy demand of other human tissues and would likely need a way to dispose of excess proteins and fluids.

Nedergaard and her team realized that a number of neurological disorders—including Alzheimer’s disease and other dementias—are characterized by an accumulation of proteins. Could such illnesses boil down to something like a sewage backup?

The scientists found that cerebrospinal fluid (CSF) can act as a sink for waste—the brain can actually export molecules to the liver. Studies in rodents showed that glia in the brain are the headwaters of tiny rivers that end up in the lymph nodes of the neck. This partnership—a macroscopic pathway in the central nervous system—they dubbed “the glymphatic system.” It facilitates the clearance of interstitial waste products from neuronal metabolism, she said.

They discovered a phenomenon they called CSF pulsation—the brain, which gets a disproportionate amount of the body’s blood supply (Nedergaard said the brain pumps more fluid than the kidney)—actually throbs like a beating heart.

The photo of the brain that seems to hover over Nedergaard was part of her presentation on a waste-removal system in the brain known as the glymphatic system.

Photos: Bill Branson

According to her lecture summary, “The glymphatic clearance of macromolecules is driven by CSF that flows along para-arterial spaces and through the brain parenchyma via support from astroglial aquaporin-4 water channels. The glymphatic circulation constitutes a complete anatomical pathway: para-arterial CSF exchanges with the interstitial fluid, solutes collect along para-venous spaces and then drain into the vessels of the lymphatic system for ultimate excretion from the kidney or degradation in the liver.

“The peri-vascular space is very unique,” said Nedergaard, describing a loose fibrous matrix around such vessels as pial arteries that act as a highway for fluid flow. She credited NINR director Dr. Patricia Grady with making a key observation about this system, years ago, in a paper on para-vascular fluid circulation in the mammalian central nervous system. “It created a lot of excitement in the field,” said Nedergaard.

The recent paper “Go With the Flow,” published by Nedergaard’s team in *Science* in 2013 and named one of its top 10 reports that year, describes the intricate micro-plumbing that clears the brain of debris such as amyloid.

Further work in mice has demonstrated that, while the glymphatic system is always functioning, it is much more active when the animal is asleep. The difference “is like turning a faucet on and off,” Nedergaard reported.

Somehow—the work is still ongoing—the volume of interstitial space in mammalian brain expands during sleep. The pipes fly open. Deprive an animal of sleep and the diffusion of fluid is reduced, with potentially drastic consequences.

Nedergaard noted that her team’s work has immediate implications for clinical care of patients with traumatic brain injury.

“Stop waking them up every 10 minutes to take vital signs,” she counseled. That sleep they are getting is actually healing them.

Also, TBI patients often have portions of their skulls removed temporarily, to relieve swelling. Nedergaard says it’s important to patch these holes up quickly because it restores convective flow of CSF. “Patients get better faster,” she said.

Nedergaard’s talk can be viewed at http://videocast.nih.gov/summary.asp?Live=15718&bhcp=1.