Brains flush toxic waste in sleep, including Alzheimer's-linked protein, study of mice finds

By Meeri Kim, The Washington Post

While we are asleep, our bodies may be resting, but our brains are busy taking out the trash.

A new study has found that the cleanup system in the brain, responsible for flushing out toxic waste products that cells produce with daily use, goes into overdrive in mice that are asleep. The cells even shrink in size to make for easier cleaning of the spaces around them.

Scientists say this nightly self-clean by the brain provides a compelling biological reason for the restorative power of sleep.

"Sleep puts the brain in another state where we clean out all the byproducts of activity during the daytime," said study author and University of Rochester neurosurgeon Maiken Nedergaard. Those byproducts include beta-amyloid protein, clumps of which form plaques found in the brains of Alzheimer's patients.

Staying up all night could prevent the brain from getting rid of these toxins as efficiently, and explain why sleep deprivation has such strong and immediate consequences. Too little sleep causes mental fog, crankiness, and increased risks of migraine and seizure. Rats deprived of all sleep die within weeks.

Although as essential and universal to the animal kingdom as air and water, sleep is a riddle that has baffled scientists and philosophers for centuries. Drifting off into a reduced consciousness seems evolutionarily foolish, particularly for those creatures in danger of getting eaten or attacked.

One line of thinking was that sleep helps animals to conserve energy by forcing a period of rest. But this theory seems unlikely since the sleeping brain uses up almost as much energy as the awake brain, Nedergaard said.

Another puzzle involves why different animals require different amounts of sleep per night. For instance, cats sleep more than 12 hours a day, while elephants need only about three hours. Based on this newfound purpose of sleep, neuroscientist Suzana Herculano-Houzel speculates in a commentary that the varying sleep needs across species might be related to brain size. Larger brains should have a relatively larger volume of space between cells, and may need less time to clean since they have more room for waste to accumulate throughout the day.

Sleep does play a key role in memory formation — mentally going through the events of the day and stamping certain memories into the brain. But sleeping for eight hours or more just to consolidate memories seems excessive, Nedergaard said, especially for an animal such as a mouse.

Last year, Nedergaard and her colleagues discovered a network that drains waste from the brain, which they dubbed the glymphatic system. It works by circulating

cerebrospinal fluid throughout the brain tissue and flushing any resulting waste into the bloodstream, which then carries it to the liver for detoxification.

She then became curious about how the glymphatic system behaves during the sleep-wake cycle.

An imaging technique called two-photon microscopy enabled the scientists to watch the movement of cerebrospinal fluid through a live mouse brain in real time. After soothing the creature until it was sound asleep, study author Lulu Xie tagged the fluid with a special fluorescent dye.

“During sleep, the cerebrospinal fluid flushed through the brain very quickly and broadly,” said Rochester neuropharmacologist Xie. As another experiment revealed, sleep causes the space between cells to increase by 60 percent, allowing the flow to increase.

Xie then gently touched the mouse’s tail until it woke up from its nap, and she again injected it with dye. This time, with the mouse awake, flow in the brain was greatly constrained.

“Brain cells shrink when we sleep, allowing fluid to enter and flush out the brain,” Nedergaard said. “It’s like opening and closing a faucet.”

They also found that the harmful beta-amyloid protein clears out of the brain twice as fast in a sleeping rodent as in an up-and-about one. The study was published in the journal Science on Thursday.

New York University cell biologist and Alzheimer’s specialist Ralph A. Nixon, who was not involved in the study, said the findings could be of great interest to the Alzheimer’s research community. For instance, the overproduction of beta-amyloid could be linked to the development of the disease, but he said these new findings hint that the lack of clearing it out might be the bigger problem.

Other neurodegenerative disorders, such as Parkinson’s disease or chronic traumatic encephalopathy, are also associated with a backup of too much cell waste in the brain. “Clearance mechanisms may be very relevant to keeping these proteins at a level that isn’t disease-causing,” Nixon said.

An MRI diagnostic test for glymphatic clearance is in the works by Nedergaard and her colleagues. She also believes that a drug could be developed to force a cleanup if necessary, perhaps by mimicking the sleep-wake cycle.

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