To Sleep, Perchance to Clean

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By Mark Michaud

Study reveals brain ‘takes out the trash’ while we sleep

In findings that give fresh meaning to the old adage that a good night’s sleep clears the mind, a new study shows that a recently discovered system that flushes waste from the brain is primarily active during sleep. This revelation could transform scientists’ understanding of the biological purpose of sleep and point to new ways to treat neurological disorders.

“This study shows that the brain has different functional states when asleep and when awake,” said Maiken Nedergaard, M.D., D.M.Sc., co-director of the University of Rochester Medical Center (URMC) Center for Translational Neuromedicine and lead author of the article. “In fact, the restorative nature of sleep appears to be the result of the active clearance of the by-products of neural activity that accumulate during wakefulness.”

The study, which was published today in the journal *Science*, reveals that the brain’s unique method of waste removal – dubbed the glymphatic system – is highly active during sleep, clearing away toxins responsible for Alzheimer’s disease and other neurological disorders. Furthermore, the researchers found that during sleep the brain’s cells reduce in size, allowing waste to be removed more effectively.

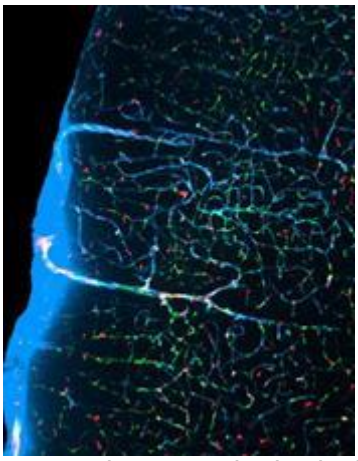

Image shows cerebral spinal fluid (in blue) entering the brain via a "plumbing system" that piggybacks on the brain's blood vessels.

The purpose of sleep is a question that has captivated both philosophers and scientists since the time of the ancient Greeks. When considered from a practical standpoint, sleep is a puzzling biological state. Practically every species of animal from the fruit fly to the right whale is known to sleep in some fashion. But this period of dormancy has significant drawbacks, particularly when predators lurk about. This has led to the observation that if sleep does not perform a vital biological function then it is perhaps one of evolution's biggest mistakes.

While recent findings have shown that sleep can help store and consolidate memories, these benefits do not appear to outweigh the accompanying vulnerability, leading scientists to speculate that there must be a more essential function to the sleep-wake cycle.

The new findings hinge on the discovery last year by Nedergaard and her colleagues of a previously unknown system of waste removal that is unique to the brain. The system responsible for disposing cellular waste in the rest of the body, the lymphatic system, does not extend to the brain. This is because the brain maintains its own closed "ecosystem" and is protected by a complex system molecular gateways – called the blood-brain barrier – that tightly control what enters and exits the brain.

The brain's process of clearing waste had long eluded scientists for the simple fact that it could only be observed in the living brain, something that was not possible before the advent of new imaging technologies, namely two-photon microscopy. Using these techniques, researchers were able to observe in mice – whose brains are remarkably similar to humans – what amounts to a plumbing system that piggybacks on the brain's blood vessels and pumps cerebral spinal fluid (CSF) through the

brain’s tissue, flushing waste back into the circulatory system where it eventually makes its way to the general blood circulation system and, ultimately, the liver.

The timely removal of waste from the brain is essential where the unchecked accumulation of toxic proteins such as amyloid-beta can lead to Alzheimer’s disease. In fact, almost every neurodegenerative disease is associated with the accumulation of cellular waste products.

One of the clues hinting that the glymphatic system may be more active during sleep was the fact that the amount of energy consumed by the brain does not decrease dramatically while we sleep. Because pumping CSF demands a great deal of energy, researchers speculated that the process of cleaning may not be compatible with the functions the brain must perform when we are awake and actively processing information.

Through a series of experiments in mice, the researchers observed that the glymphatic system was almost 10-fold more active during sleep and that the sleeping brain removed significantly more amyloid-beta.

“The brain only has limited energy at its disposal and it appears that it must choice between two different functional states – awake and aware or asleep and cleaning up,” said Nedergaard. “You can think of it like having a house party. You can either entertain the guests or clean up the house, but you can’t really do both at the same time.”

Another startling finding was that the cells in the brain “shrink” by 60 percent during sleep. This contraction creates more space between the cells and allows CSF to wash more freely through the brain tissue. In contrast, when awake the brain’s cells are closer together, restricting the flow of CSF.

The researchers observed that a hormone called noradrenaline is less active in sleep. This neurotransmitter is known to be released in bursts when brain needs to become alert, typically in response to fear or other external stimulus. The researchers speculate that noradrenaline may serve as a “master regulator” controlling the contraction and expansion of the brain’s cells during sleep-wake cycles.

“These findings have significant implications for treating ‘dirty brain’ disease like Alzheimer’s,” said Nedergaard. “Understanding precisely how and when the brain activates the glymphatic system and clears waste is a

critical first step in efforts to potentially modulate this system and make it work more efficiently."

Additional co-authors of the study include Lulu Xie, Hongyi Kang, Qiwu Xu, Michael Chen, Yonghong Liao, Thiyagarajan Meenakshisundaram, John O'Donnell, Daniel Christensen, Takahiro Takano, and Rashid Deane with URMC, Jeffrey Iliff with Oregon Health and Science University, and Charles Nicholson with New York University. The study was supported by the National Institute of Neurological Disorders and Stroke.