ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER

Releasing the Brakes on Post-Injury Nerve Growth

Winter 2006
Vol. 12, No. 1

Unlike peripheral nerves that help us feel sensations and move, cells in the central nervous system (CNS) – the brain, spinal cord, retina and optic nerve – are unable to heal themselves after an injury. If you cut the tip of your finger, new nerves are able to sprout and make connections with other nerves (in a process called nerve regeneration), restoring feeling to your fingertip. With a spinal cord injury, useful function below the level of the injury is often permanently eliminated because new, healthy nerve cells are unable to grow.

For many years, scientists have been searching for ways to stimulate the growth of new nerve cells following injury to the CNS. A number of things conspire to prevent this nerve growth from occurring, however, including proteins in the nerves' protective myelin sheath and molecules released by scar tissue that forms around the site of the nerve injury.

Zhigang He, Ph.D., an assistant professor of neurology at Harvard Medical School (HMS), and his colleagues at Children's Hospital Boston recently discovered one of what may be many molecular compounds that act as brakes on the regrowth of nerves after an injury. The compound they discovered is called "epidermal growth factor receptor," or EGFR, which until now was thought to signal nerve cells to divide. Their findings indicate possible new therapies for restoring post-injury function to a damaged central nervous system.

After screening hundreds of molecular compounds to identify those capable of reversing the action of myelin proteins that prevent nerves from growing, He reported in the October 7 issue of *Science* that his team found, to their surprise, that blocking EGFR could spur the growth of axons, the long nerve fibers that conduct electrical signals away from nerve cells.

He and his colleagues found that the protein molecules in myelin activate EGFR, possibly by rushing calcium into the cells to stimulate the receptor. The researchers say that if the protein activity of myelin can be hindered by blocking the activation of EGFR, then nerve re-growth might be possible. They also say that inhibiting the action of EGFR can lead to axon growth on scar tissue cells (called proteoglycans) at the site of the CNS injury.

To test their hypothesis, He's team worked closely with Dong Feng Chen, Ph.D., M.D., an HMS assistant professor of ophthalmology at Schepens Eye Research Institute, to determine if blocking EGFR could aid in the regrowth of the optic nerve in mice. The researchers injured the optic nerves of adult mice and soaked the injury site with a solution containing substances that prevent EGFR activity. After two weeks, the mice had a ninefold increase in the growth of nerve cells compared to untreated mice.

In studies published in 2002, He's team identified a new blocker of axon growth and found that it, along with two other already-identified blockers, function by binding to the same cell receptor. This discovery is crucial to understanding the signaling events that occur to prevent axon regeneration.

Scientists say it is encouraging that both blocking mechanisms identified by He work through a common signal. The Food and Drug Administration has already approved drugs that jam this signaling pathway for the treatment of certain cancers.

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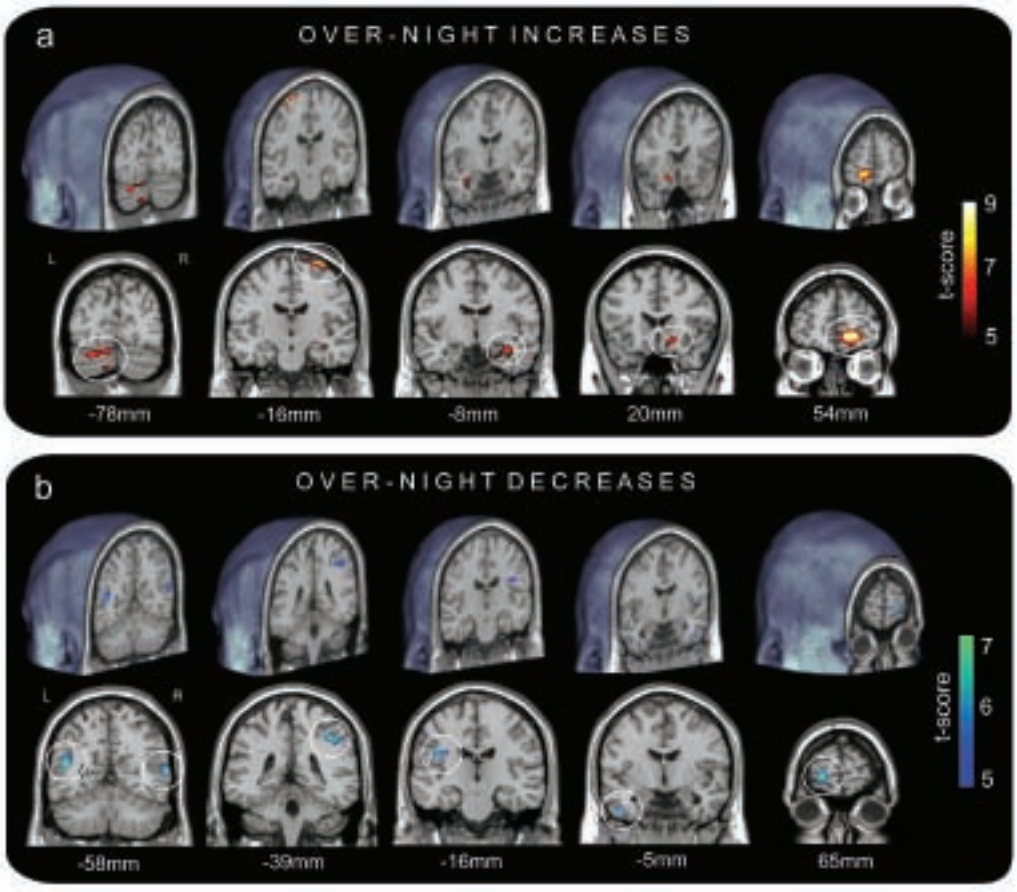
Practice – Plus Sleep – Makes Perfect

Like the characters in the Holiday Inn commercials on television, most of us know the value of a good night's sleep. Studies have shown that we need, on average, about eight hours of sleep per night to perform at our peak the next day and to maintain optimal health. Now, researchers at Harvard Medical School (HMS) have found that sleep also helps us solidify and improve long-term memory of skills and procedures, and master new skills.

In a study that sought to determine if sleep could trigger the brain's ability to adapt its behavior and circuitry, researchers at Beth Israel Deaconess Medical Center's Sleep and Neuroimaging Laboratory taught 12 healthy college-aged subjects a finger-tapping test similar to playing piano keys. The subjects were tested in the morning or evening and then retested after either 12 hours containing sleep or 12 hours of awake time. During the retest a functional MRI (fMRI) scan measured brain activity, enabling the researchers to see which parts of the brain were active and which were inactive while the subjects were being tested.

"A night of sleep," says Matthew Walker, Ph.D., an assistant professor of psychiatry at HMS and the study's lead author, "reorganizes the representation of a memory within the human brain, making the memory more efficient. After sleep, you improve your performance by about 20 percent to 30 percent. Without sleep, there is no improvement. So, practice with a good night sleep makes perfect."

Using fMRI, the researchers discovered significant differences in the patterns of brain activity of subjects who slept prior to the test compared to those who remained awake. After a night of sleep, the primary motor cortex and cerebellum, which



Sleep-dependent motor memory reorganization in the human brain. **Subjects were trained on a sleep-dependent motor skill task and then tested 12 hours later, either following a night of sleep or following intervening wake, during a functional magnetic resonance imaging (fMRI) brain-scanning session. Scans after sleep and wake were compared (subtracted), resulting in regions showing increased fMRI activity post-sleep (in red/yellow; or decreased signal activity postsleep, relative to postwake. Activation patterns are displayed on three-dimensional rendered brains (top panel of each graphic), together with corresponding two-dimensional sections (bottom panel of each graphic). Following sleep, regions of increased activation were identified in the right primary motor cortex, the left cerebellum, the right hippocampus, and the right medial prefrontal cortex. Regions of decreased activity postsleep were expressed bilaterally in the parietal lobes, together with the left insula cortex, left temporal pole, and left frontopolar area, all regions of the extended limbic system. In total, these results suggest that sleep-dependent motor learning is associated with a large-scale plastic reorganization of memory throughout several brain regions, allowing skilled motor movements to be executed more quickly, more accurately, and more automatically following sleep. These findings hold important implications for understanding the brain basis of perfecting real-life skills and may signify a potential role for sleep in clinical rehabilitation following brain damage.**

are the main motor control areas of the brain and are responsible for speed and accuracy, expressed greater activity, as did the right frontal and right temporal lobes. These two areas of the brain help construct memory sequences. The parietal cortex, which is responsible for unconscious motor control, showed reduced activity following a night of sleep. The brains of those who stayed awake showed no such changes.

During learning and memory formation, our brains undergo both physical and chemical changes. In order to learn or memorize a fact or a skill, there must be persistent functional changes in the brain that represent new knowledge. This process is called neuroplasticity, the ability of the brain to reorganize how neurons connect to one another based on new experiences. At first, new memories can be easily disrupted. But, over time and through a series of molecular processes, they are crystallized into long-term memory. This process, called memory consolidation, solidifies memories into the neural architecture, making them more permanent. Many scientists now believe that processes of memory consolidation occur when we are asleep.

Walker says that a certain type of sleep is required to consolidate motor skill memories. One of his previous studies showed a "strong correlation" between Stage 2, non-REM sleep and memory consolidation. This stage of sleep is characterized by unique brain waves that contain quick bursts of electrical activity and a slowing down of such bodily functions as blood pressure, cardiac activity and metabolism.

While acknowledging that his team does not know exactly how or why this happens, Walker says "people show the most dramatic improvement [on memory tasks] if they have had significant amounts of this stage of sleep. Bizarre electrical bursts occur around the motor cortex that may trigger plastic changes in the brain and a cascade of events that form memories. While we only have indirect evidence of this, we believe that these electrical bursts trigger these changes in plasticity."

Modern society's increasing erosion of sleep time, says Walker, is cause for concern. Many people believe they can accumulate sleep by "bingeing" on weekends, thus making up for lost sleep time. Walker says people can't learn effectively if they short-change their brains of sleep.

"If you practice a task in the evening, stay up all night and through the next day, and then have a recovery night of sleep, you will fail to show improvement on the re-test," says Walker. "If you don't sleep within 24 hours of learning a memory, you lose the ability to consolidate it."

The findings show that procedural skills such as learning to walk or coordinating limb movements become more automatic with sleep, which may explain why babies require so much sleep and why children and adolescents need more sleep than adults. Walker says that sleep plays a critical role in human development. Infants are in a constant state of motor learning and have "an immense amount of new material to consolidate. Consequently, this intensive period of learning may demand a great deal of sleep."

His findings also have implications for the real-life learning of motor skills for sports, playing a musical instrument, even for acquiring surgical skills – all of which are based on motor skill memory processing – as well as clinical significance for people who have suffered a stroke or brain injury.

"A good night of sleep may be able to help re-establish connections in the brains of stroke victims," he says. "Since the brain undergoes these plastic changes, patients can take on new tasks and learn new ways of doing things they did prior to their stroke. Sleep may incrementally assist their recovery." The next step is to test this theory with clinical stroke patients and track their improvement with sleep.

Walker and his colleagues also plan to examine sleep and learning disorders that occur in depression, schizophrenia and Alzheimer's disease to determine if any relationship exists between the two.

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