A Fast-Acting Antidepressant

Glial activity reveals how sleep deprivation elevates mood

Sleep deprivation is a quick and efficient way to treat depression. It works 60 to 70 percent of the time—far better than existing drugs—but the mood boost usually lasts only until the patient falls asleep. As an ongoing treatment, sleep deprivation is impractical, but researchers have been studying the phenomenon in an effort to uncover the cellular mechanisms behind depression and remission. Now a team at Tufts University has pinpointed glia as the key players.

The researchers previously found that astrocytes, a star-shaped type of glial cell, regulate the brain chemicals involved in sleepiness. During our waking hours, astrocytes continuously release the neurotransmitter adenosine, which builds up in the brain and causes "sleep pressure," the feeling of sleepiness and its related memory and attention impairments. The neurotransmitter causes this pressure by binding to adenosine receptors on the outside of neurons like a key fitting into a lock. As more adenosine builds up, more receptors are triggered, and the urge to sleep gets stronger.

In the new study, published online January 15 in the journal *Translational Psychiatry*, the scientists investigated whether this process is responsible for the antidepressant effects of sleep deprivation. Mice with depressivelike symptoms were administered three doses of a compound that triggers adenosine receptors, thus mimicking sleep deprivation. Although the mice continued to sleep normally, after 12 hours they showed a rapid improvement in mood and behavior, which lasted for 48 hours.

The results confirm that the adenosine buildup is responsible for the antidepressant effects of a lack of sleep. This finding points to a promising target for new drug development because it suggests that mimicking sleep deprivation chemically may offer the antidepressant benefits without the unwanted side effects of actually skipping sleep. Such an intervention could offer immediate relief from depression, in stark contrast with traditional antidepressants, which take six to eight weeks to kick in.

The study may also have implications beyond depression and sleep regulation, according to Dustin Hines, lead author and a postdoctoral fellow at Tufts. "For many years neuroscientists focused almost exclusively on neurons, whereas the role of glia was neglected," Hines says. "We now know that glia play an important role in the control of brain function and have the potential to aid in the development of new treatments for many illnesses, including depression and sleep disorders."

—David Levine

SHARON DOMINICK (*Stockphoto (left)*; FROM "NEUROSCIENCE: GLIA—MORE THAN JUST BRAIN GLUE," BY NICOLA J. ALLEN AND BEN A. BARRES, IN *NATURE*, VOL. 457; FEBRUARY 5, 2009 (*right*)

Without Glia, the Brain Would Starve

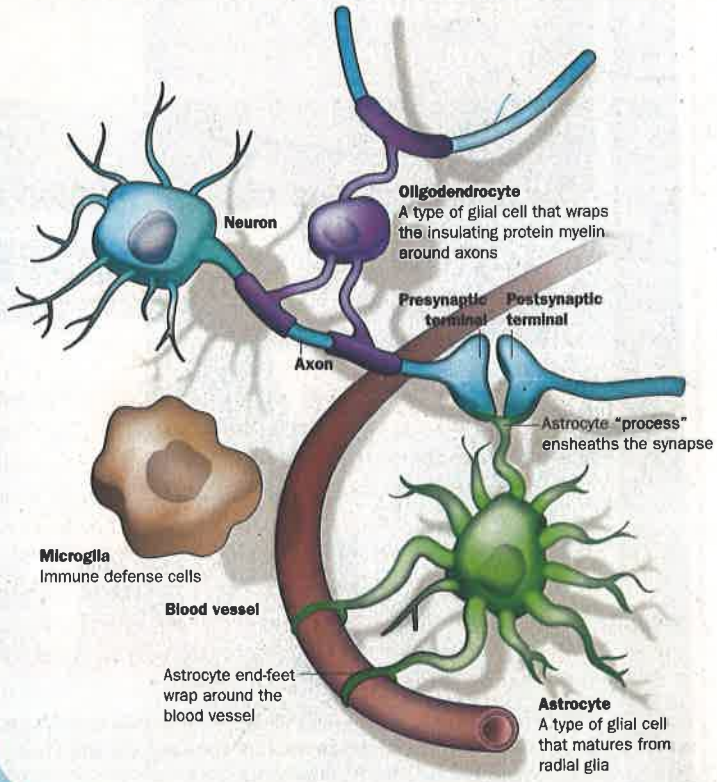
Blood vessels break down if certain glial cells are not present

The brain is voracious: compared with other organs, it consumes 10 times more oxygen and nutrients, receiving them by way of dense networks of blood vessels. Scientists know how these networks initially grow, but a surprising new study suggests that they are stabilized in early life by stem cells in the brain called radial glia. The finding could have significant implications for our understanding of Alzheimer's disease, a condition characterized in part by brainwide vascular problems.

Radial glia are stem cells that have been shown to help neurons grow and migrate throughout the brain. So when Zhen Huang, a neuroscientist at the University of Wisconsin–Madison, eliminated a gene in mice and thereby prevented radial glia from regenerating, he was "surprised to find [blood] vessels regress," he says. The mice lacking this gene not only developed fewer radial glia, blood vessel density in their cortex also dropped by 83 percent.

Huang found that the loss of glial cells caused activity in a biochemical pathway called Wnt to increase. In additional experiments, he showed that ramping up Wnt in healthy mouse embryos caused their vascular brain networks to collapse, whereas turning Wnt down preserved them. Given that the brains of people with Alzheimer's are also plagued by blood vessel problems, the findings suggest that radial glia—and their careful control over Wnt—could be important for ensuring healthy brain energy metabolism and preventing neurodegeneration.

—Melinda Wenner Moyer



antisocially. The first retinal implant was approved for use in the U.S. It required 20 years of development and more than $200 million in funding.