Support cells, not neurons, lull the brain to sleep

January 28 2009

Brain cells called astrocytes help to cause the urge to sleep that comes with prolonged wakefulness, according to a study in mice, funded by the National Institutes of Health. The cells release adenosine, a chemical known to have sleep-inducing effects that are inhibited by caffeine.

"Millions of Americans suffer from disorders that prevent a full night's sleep, and others - from pilots to combat soldiers - have jobs where sleepiness is a hazard. This research could lead to better drugs for inducing sleep when it is needed, and for staving off sleep when it is dangerous," says Merrill Mitler, Ph.D., a program director with the NIH's National Institute of Neurological Disorders and Stroke (NINDS).

The study appears Jan. 29, 2009 in *Neuron*, and was funded by NINDS, the National Institute of Mental Health (NIMH) and the National Institute on Aging (NIA), all part of NIH. It is the result of a collaboration among Michael Halassa, M.D., and Philip Haydon, Ph.D., at Tufts University School of Medicine in Boston and Marcos Frank, Ph.D., and Ted Abel, Ph.D. at the University of Pennsylvania School of Medicine in Philadelphia.

Although the exact purpose of sleep is unknown, everyone seems to need it, and some research suggests that it strengthens memories by adjusting the connections between neurons. As the waking hours tick by, all animals experience an increasing urge to sleep, known as sleep pressure. If sleep is delayed, a deep, long sleep usually follows as the body's means of compensating.

Prior studies pointed to adenosine as a trigger for sleep pressure. The chemical accumulates in the brain during waking hours, eventually helping to stimulate the unique patterns of brain activity that occur during sleep.

Dr. Halassa says that the results of the new study show that "adenosine from astrocytes clearly regulates sleep pressure." He notes that this is the first time a non-neuronal cell within the brain has been shown to influence behavior. Unlike neurons, astrocytes do not fire electrical spikes, and they are often described as support cells.

In experiments on mice, Dr. Halassa and his colleagues used a genetic switch, called the dnSNARE transgene, to block the release of adenosine and other chemicals from astrocytes. The researchers then deprived the mice of sleep for short periods, and evaluated them with behavioral tests and with electroencephalography (EEG), a means of recording brain activity.

Mice subjected to the genetic blockade exhibited less sleep pressure than control mice. Following sleep deprivation, they did not need as much compensatory sleep, and during the early phases of sleep, they had patterns of brain activity consistent with low sleep pressure. When they were evaluated with a memory test, they performed as if their sleep had been undisturbed.

The researchers observed similar results when they used certain compounds to block the effects of adenosine on neurons. Neurons have several types of cell-surface receptors that enable them to respond to adenosine, but only pharmacological blockade of the A1 type of receptor was effective. That result shows that adenosine acts through the A1 receptor to produce sleep pressure.

Taken together, the results hint at the possibility of new drugs that could

increase or decrease sleep pressure as necessary. The best available sleep aids tend to be effective at inducing sleep, but not effective at keeping it steady throughout the night. Meanwhile, the most commonly used stimulant, caffeine, acts on multiple types of adenosine receptors, and can affect sleep patterns even when it is consumed in the morning. Drugs that target astrocytes or the A1 receptors on neurons might be more effective at fine-tuning the urge to sleep, the study authors say.

The dnSNARE mice also will prove useful for answering some long-standing questions about sleep, experts say. For instance, since the dnSNARE mice are resistant to sleep deprivation, they might help explain why some people need less sleep than others. Further studies of the dnSNARE mice could help reveal why people need sleep at all.

This research "puts astrocytes at the heart of why we sleep," says Dr. Halassa.

Reference: Halassa MM, Florian C, Fellin T, Munoz JR, Lee S-Y, Abel T, Haydon P and Frank MG. "Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss." *Neuron*, January 29, 2009.

Source: NIH/National Institute of Neurological Disorders and Stroke