Sleep loss linked to increase in Alzheimer's plaques

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Chronic sleep deprivation in a mouse model of Alzheimer's disease makes Alzheimer's brain plaques appear earlier and more often, researchers at Washington University School of Medicine in St. Louis report online this week in *Science Express*.

They also found that orexin, a protein that helps regulate the sleep cycle, appears to be directly involved in the increase.

Neurodegenerative disorders like Alzheimer's disease and Parkinson's disease often disrupt sleep. The new findings are some of the first indications that sleep loss could play a role in the genesis of such disorders.

"Orexin or compounds it interacts with may become new drug targets for treatment of Alzheimer's disease," says senior author David M. Holtzman, M.D., the Andrew and Gretchen Jones Professor and chair of the Department of Neurology at the School of Medicine and neurologist-in-chief at Barnes-Jewish Hospital. "The results also suggest that we may need to prioritize treating sleep disorders not only for their many acute effects but also for potential long-term impacts on brain health."

Holtzman's laboratory uses a technique called in vivo microdialysis to monitor levels of amyloid beta in the brains of mice genetically engineered as a model of Alzheimer's disease. Amyloid beta is a protein fragment that is the principal component of Alzheimer's plaques.

Jae-Eun Kang, Ph.D., a post-doctoral fellow in Holtzman's lab, noticed that brain amyloid beta levels in mice rose and fell in association with sleep and wakefulness, increasing in the night, when mice are mostly awake, and decreasing during the day, when they are mostly asleep.

A separate study of amyloid beta levels in human cerebrospinal fluid led by Randall Bateman, M.D., assistant professor of neurology and a neurologist at Barnes-Jewish Hospital, also showed that amyloid beta levels were generally higher when subjects were awake and lower when they slept.

To confirm the link, Kang learned to use electroencephalography (EEG) on the mice at the Sleep and Circadian Neurobiology Laboratory at Stanford University with researchers Seiji Nishino, M.D., Ph.D., and Nobuhiro Fujiki, M.D., Ph.D. The EEG readings let researchers more definitively determine when mice were asleep or awake and validated the connection: Mice that stayed awake longer had higher amyloid beta levels.

"This makes sense in light of an earlier study in our lab where John Cirrito, Ph.D., showed that increases in synaptic activity resulted in increased levels of amyloid beta," Holtzman notes. "The brain's synapses may generally be more active when we're awake."

Depriving the mice of sleep caused a 25 percent increase in amyloid beta levels. Levels were lower when mice were allowed to sleep. Blocking a hormone previously linked to stress and amyloid beta production had no effect on these changes, suggesting that they weren't caused by the stress of sleep deprivation, according to Holtzman.

Researchers elsewhere had linked mutations in orexin to narcolepsy, a disorder that is characterized by excessive daytime sleepiness. The brain has two kinds of receptors for orexin, which is also associated with

regulation of feeding behavior.

When Holtzman's group injected orexin into the brains of the mice, mice stayed awake longer, and amyloid beta levels increased. When researchers used a drug called almorexant to block both orexin receptors, amyloid beta levels were significantly lower and animals were awake less.

Miranda M. Lim, M.D., Ph.D., a neurology resident and post-doctoral researcher in Holtzman's lab, performed long-term behavioral experiments with the mice. She found that three weeks of chronic sleep deprivation accelerated amyloid plaque deposition in the brain. In contrast, when mice were given almorexant for two months, plaque deposition significantly decreased, dropping by more than 80 percent in some brain regions.

"This suggests the possibility that a treatment like this could be tested to see if it could delay the onset of Alzheimer's disease," says Holtzman.

Holtzman notes that not only does the risk of Alzheimer's increase with age, the sleep/wake cycle also starts to break down, with older adults progressively getting less and less sleep. Investigators are considering epidemiological studies of whether chronic sleep loss in young and middle-aged adults increases risk of Alzheimer's disease later in life.

Holtzman also plans to learn more of the molecular details of how orexin affects amyloid beta.

"We would like to know if there are ways to alter orexin signaling and its effects on amyloid beta without necessarily modifying sleep," he says.

Additional studies will address the questions of whether increased amyloid beta during wakefulness is connected to increased synaptic

activity and whether some aspect of sleep lowers amyloid beta levels independent of synaptic activity.

More information: Kang J-E, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, Fujiki N, Nishino S, Holtzman DM. Amyloid beta dynamics are regulated by orexin and the sleep-wake cycle. Science Express, Sept. 24, 2009.

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