Researchers close in on origins of main ingredient of Alzheimer's plaques

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The ability of brain cells to take in substances from their surface is essential to the production of a key ingredient in Alzheimer's brain plaques, neuroscientists at Washington University School of Medicine in St. Louis have learned.

The researchers used a drug to shut down the intake process, known as endocytosis, in a mouse model of Alzheimer's disease. The change led to a 70 percent drop in levels of amyloid beta, the protein fragment that clumps together to form Alzheimer's plaques. Importantly, they also found that endocytosis' ability to increase amyloid beta was coupled to normal nerve cell communication called synaptic activity.

"Blocking endocytosis isn't a viable option for treatment because cells throughout the body, including brain cells, need endocytosis for healthy function," says first author John Cirrito, Ph.D., research instructor in neurology. "But we are starting to understand the origins of amyloid beta in more detail now, and what we're learning is opening other options we can pursue to seek new treatments for Alzheimer's disease."

While endocytosis is necessary for normal function of brain cells, Cirrito and others believe it may accidentally be causing the cells to take in the amyloid precursor protein (APP), which breaks down into amyloid beta. If so, a drug that reduces brain cells' intake of APP may help reduce amyloid beta production.

The results appear in the April 10 issue of *Neuron*.

Other research had shown previously that endocytosis might be important for amyloid beta production, and that amyloid beta is produced inside brain cells. In 2005, Cirrito and his colleagues linked increased communication between brain cells to higher amyloid beta levels.

Cirrito decided to test both endocytosis and brain cell activity in a coordinated fashion. He used a technique known as microdialysis that he had previously adapted for Alzheimer's research to monitor the results. In addition to allowing repeated sampling of the amyloid beta levels in the brains of live mice, the approach allows him to introduce drugs that reduce endocytosis and alter communication between brain cells.

When researchers gave mice the drug that stopped endocytosis, amyloid beta levels dropped by 70 percent. To see how much normal brain activity contributed to ongoing amyloid beta production in the absence of endocytosis, they then added a second drug that reduced brain cell communication. Amyloid beta levels did not decrease further.

When they reversed the experiment, reducing brain cell communication first, amyloid beta decreased by 60 percent. Adding the drug that stops endocytosis caused an additional small reduction in amyloid beta.

The results show that amyloid beta production requires both brain cell communication and endocytosis, but endocytosis is essential for a slightly larger share of amyloid beta. Basic nerve cell physiology may explain why.

The study focused on synapses, the region where nerve cells transmit messages by releasing chemicals from small compartments near the cell surface. To replenish those compartments, the nerve cell regularly takes them back in through endocytosis. The more active a brain cell is, the more often it has to bring these compartments back into the cell and

refill them.

"Endocytosis can be messy in that it brings lots of substances into the cell from the membrane it internalizes," Cirrito says. "I think APP may be an innocent bystander in this process -- it just happens to be present on the cell surface when nerve cell communication causes more endocytosis. If there is a functional reason APP has to participate in this process, no one has found it."

Activity isn't the only cause of endocytosis in brain cells. The cells have other reasons for bringing in materials through endocytosis, and this additional intake could account for the small share of amyloid beta production that requires endocytosis but doesn't need brain cell activity.

Cirrito conducted the research in the laboratories of co-senior authors David M. Holtzman, M.D., the Andrew B. and Gretchen P. Jones Professor and chair of the Department of Neurology at the School of Medicine, and neurologist-in-chief at Barnes-Jewish Hospital, and Steven J. Mennerick, Ph.D., associate professor of neurobiology and psychiatry.

Researchers already know several proteins on the surfaces of brain cells that bind to APP. They will be conducting follow-up studies to see if blocking these interactions can block APP endocytosis and reduce amyloid beta production.

Source: Washington University