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Scientists identify role of fatty acids in Alzheimer's disease

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Scientists at the Gladstone Institute of Neurological Disease (GIND) and the University of California have found that complete or partial removal of an enzyme that regulates fatty acid levels improves cognitive deficits in a mouse model of Alzheimer's disease (AD). Their findings, which will be published in today's issue of *Nature Neuroscience*, identified specific fatty acids that may contribute to the disease as well as a novel therapeutic strategy.

AD causes a progressive loss of cognitive functions and results in death. Over 5 million Americans are living with this condition. Although there are treatments to ease the symptoms, these treatments are not very effective and researchers have yet to discover a cure.

"Several different proteins have been implicated in Alzheimer's disease," said Lennart Mucke, M.D., GIND director and senior author of the study, "but we wanted to know more about the potential involvement of lipids and fatty acids."

Fatty acids are rapidly taken up by the brain and incorporated into phospholipids, a class of fats that form the membrane or barrier that shields the content of cells from the external environment. The scientists used a large scale profiling approach ("lipidomics") to compare many different fatty acids in the brains of normal mice with those in a mouse model of Alzheimer's disease that develops memory deficits and many pathological alterations seen in the human condition.

"The most striking change we discovered in the Alzheimer mice was an increase in arachidonic acid and related metabolites in the hippocampus, a memory center that is affected early and severely by Alzheimer's disease," said Rene Sanchez-Mejia, M.D., lead author of the study.

In the brain arachidonic acid is released from phospholipids by an enzyme called group IVA phospholipase A2 (or PLA2). The scientists lowered PLA2 levels in the Alzheimer mice by genetic engineering. Removal or even partial reduction of PLA2 prevented memory deficits and other behavioral abnormalities in the Alzheimer mice.

"Arachidonic acid likely wreaks havoc in the Alzheimer mice by causing too much excitation, which makes neurons sick. By lowering arachidonic acid levels, we are allowing neurons to function normally," said Dr. Sanchez-Mejia.

Dr. Mucke added, "in general, fatty acid levels can be regulated by diet or drugs. Our results have important therapeutic implications because they suggest that inhibition of PLA2 activity might help prevent neurological impairments in Alzheimer's disease. But a lot more work needs to be done before this novel therapeutic strategy can be tested in humans."

Source: Gladstone Institutes