Calcium may be the key to understanding Alzheimer's disease

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Researchers at the University of Pennsylvania School of Medicine have shown that mutations in two proteins associated with familial Alzheimer's disease disrupt the flow of calcium ions within neurons. The two proteins, called PS1 and PS2 (presenilin 1 and 2), interact with a calcium release channel in an intracellular cell compartment.

"The 'calcium dysregulation' hypothesis for inherited, early onset familial Alzheimer's disease has been suggested by previous research findings, but our current study identifies a molecular mechanism that makes this hypothesis very compelling," says lead author J. Kevin Foskett, PhD, Professor of Physiology. "Mutated PS1 and PS2 caused exaggerated cellular calcium signaling in cells through a calcium channel in the endoplasmic reticulum called the inositol trisphosphate receptor [InsP3R], suggesting that it or other proteins in this calcium signaling pathway could be targets for new Alzheimer's disease therapies." The study appeared in the June 26 issue of *Neuron*.

Alzheimer's disease affects as many as 5 million Americans, 5 percent of whom have the familial form. The hallmark of the disease is the accumulation of tangles and plaques of amyloid beta protein in the brain. "The amyloid hypothesis has long been invoked to explain the cause of Alzheimer's" says Foskett. In the Neuron study, cells that carried the disease-causing mutated form of PS1 showed increased processing of amyloid beta that depended on the interaction of the PS proteins with the InsP3R. This observation links mis-regulation of calcium inside cells with the production of amyloid, a characteristic feature in the brains of

people with Alzheimer's disease.

Current therapies for Alzheimer's include drugs that treat the symptoms of cognitive loss and dementia. Drugs that address the pathology of Alzheimer's are only experimental. For example, a vaccine that stimulates antibodies to amyloid beta is currently being investigated. But these new observations suggest that new approaches could be explored. The next steps are to find out if other mutations in PS1 and PS2 that cause Alzheimer's disease have a similar effect on calcium signaling in the brain, and to identify drugs that might inhibit the interaction between InsP3R and PS1 or PS2 specifically in the brain.

"The significance of identifying the molecular mechanism and pathway of disrupted calcium signaling is that a number of novel treatment targets can now be developed and tested," says Foskett.

The central role of calcium signaling disruptions in Alzheimer's is strengthened by another study in which the Foskett laboratory was involved. This research was published in the June 27 issue of Cell. Investigators discovered a new gene that influences calcium regulation and amyloid beta levels in the brain. In this genetic study, a polymorphism in the gene CALHM1 significantly increased the risk of sporadic, late-onset Alzheimer's, the more common form of disease. The Foskett lab was responsible for showing that the Alzheimer's disease-associated polymorphism disrupts the gene's function in cellular calcium regulation. These investigations were led by a group from The Feinstein Institute for Medical Research, North Shore in Manhasset, NY and the Albert Einstein College of Medicine, Bronx, NY.

"Calcium is the common denominator in our two studies, strongly suggesting that it plays an important role in the development of Alzheimer's disease," notes Foskett. "However, our experiments have identified calcium inside cells as the important feature. No one should

consider modifying their dietary intake of calcium as a strategy to limit the risk of developing Alzheimer's disease, because the body very effectively regulates the amount of calcium absorbed from food and the levels in the blood and brain. And it is also very important for people who take calcium channel blockers, for cardiovascular problems for example, not to alter their medication regime as a response to our studies"

Source: University of Pennsylvania