# Mechanism explains calcium abnormalities in Alzheimer's brain

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A new study uncovers a mechanism that directly links mutations that cause early onset Alzheimer's disease (AD) with aberrant calcium signaling. The research, published by Cell Press in the June 26th issue of the journal *Neuron*, provides exciting molecular insights into the pathology of AD and may lead to new treatment strategies.

AD is a devastating neurodegenerative disease that affects early 18 million people in the world. Most cases of AD occur spontaneously after the age of 60 but about 10% of cases are inherited and can develop decades earlier. Early onset familial AD (FAD) is caused by mutated amyloid precursor protein, which can lead to aggregation of sticky clumps of amyloid beta protein in the brain, and mutated presenilins (PS), enzymes which have been implicated in amyloid processing.

Recent research has also linked mutant PS expression with exaggerated intracellular calcium release in several model systems, including cells from FAD patients. "Accumulating evidence suggests that sustained disruption of intracellular calcium signaling may play an early role in AD pathogenesis," says study author Dr. J. Kevin Foskett from the University of Pennsylvania. Calcium plays a central role in many aspects of brain physiology including growth, plasticity and learning and memory as well as cell death and degeneration.

Dr. Foskett and colleagues found that biochemical interactions of FAD mutant PS with an intracellular calcium release channel, called inositol trisphosphate receptor (InsP3R), profoundly increased channel activity in a manner that could account for exaggerated calcium responses in cells exposed to normal stimulation and caused low level calcium signaling in unstimulated cells. The researchers went on to show that this enhancement of channel activity was directly involved in mutant PS-mediated amyloid beta generation, a hallmark of AD.

"We have discovered a mechanism that can account for altered calcium signaling in AD cells that involves a biochemical and functional interaction of FAD mutant PS with the InsP3R calcium release channel. These observations provide unique molecular insights into the calcium dysregulation hypothesis of AD pathogenesis and they suggest novel targets for therapeutic intervention," concludes Dr. Foskett.

In a related finding, published in the June 27th issue of the journal *Cell*, abnormal calcium signaling was also linked to the more common spontaneously occurring form of AD. In this study, Dr. Fabien Campagne from Weill Medical College, Dr. Philippe Marambaud from Albert Einstein College of Medicine and their colleagues discovered a mutation associated with late onset, sporadic AD that disrupted a previously uncharacterized brain calcium channel and led to subsequent accumulation of amyloid beta protein. Therefore, dysregulation of intracellular calcium levels appears to play a role in both sporadic and hereditary AD.

Source: Cell Press