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Scientists explain underlying cause of unhealthy brain aging associated with Alzheimer's

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Doctors commonly recommend patients increase their intake of calcium as a means of combating osteoporosis for aging bones.

But calcium also plays an essential role in the neurological functioning of the brain, where it must be tightly regulated and not rise to excessive levels. A signaling molecule, calcium enables learning, cognition and the retention of memories. Calcium also facilitates communication among nerve cells and transports molecules to the many branches of the nerve cell.

Building on scientific evidence implicating disturbed calcium regulation in brain aging accumulated through the past 30 years, a research team in the University of Kentucky Department of Pharmacology and Nutritional Sciences led by principal investigator Philip Landfield has found a connection between unhealthy brain aging and a protein responsible for regulating calcium at the molecular level, called FKBP1b. The team's groundbreaking research, which was published July 29 in the *Journal of Neuroscience*, identifies a molecular mechanism occurring within the cell that appears to cause unhealthy brain aging. The research suggests the absence or addition of the FKBP1b protein is a strong determinant of functioning in the hippocampus region, a part of the brain responsible for cognition and memory retention.

Unhealthy brain aging is defined as a reduction in brain function

resulting in memory impairment. Excess calcium in brain cells appears responsible for important aspects of unhealthy brain aging, and may also increase susceptibility to diseases such as Alzheimer's, ALS, Parkinson's and vascular dementia. Until now, the precise molecular cause of the disturbed calcium regulation in brain aging has remained unknown to scientists.

After learning about the FKBP1b protein's recently uncovered role in the heart, the UK researchers wondered whether FKBP1b in the hippocampus region declines with brain aging. They then found evidence of reduced FKBP1b gene expression with aging in the hippocampus. This discovery prompted the researchers at the University of Kentucky to test whether boostingFKBP1b in the hippocampus region could reverse or prevent brain aging linked to memory loss.

"It is well-recognized that normal aging is the greatest risk factor for Alzheimer's disease, but nobody knows why," Landfield, a professor in the department, said. "It's possible this (decreased FKBP1b) is the missing link."

The team used an advanced gene therapy approach to inject harmless virus particles, which created additional copies of the FKBP1b protein, into the hippocampus of aging rats. The memory abilities of three groups of rats were tested two months after the injections. One group of young rats received a control injection, one group of aged rats received a control injection and one aged group received an injection of the FKBP1b-producing virus particles. The aged group with raised levels of FKBP1b showed restored calcium regulation and dramatically improved cognitive function, allowing them to perform the memory task as well as or better than the young rats. In addition, the researchers have repeated and extended the results in a subsequent study being prepared for publication.

The research provides evidence the manifestations of brain aging can be reversed, and cognition and memory function restored, by altering levels of FKBP1b. This finding is also significant for Alzheimer's patients as the researchers found a decline in the FKBP1b protein in the hippocampus of people who had early-stage Alzheimer's. The research has implications for preventing brain aging associated with the progression of Alzheimer's, and opens the door for pharmaceutical development aimed at sustaining levels of FKBP1b and keeping calcium in check.

"We showed FKBP1b is a master regulator of calcium in brain cells, and when we restore it, it restores the regulation of calcium and dramatically improves learning in the aged animals," Landfield said. "In all my years of doing research, I've never seen a compound this effective; it's rare that tests of a hypothesis satisfy each of the criteria that have to be met."

The UK team is the only known group studying FKBP1b in brain aging. As a next step, the researchers are interested in investigating why FKBP1b declines with age. Landfield said there is promise to regulate the protein through Vitamin D, which is known to restore calcium deficiencies in other cells.

More information: *Journal of Neuroscience*, 29 July 2015, 35(30): i; www.jneurosci.org/content/35/30/i?etoc

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