Low levels of brain protein may lead to Alzheimer's

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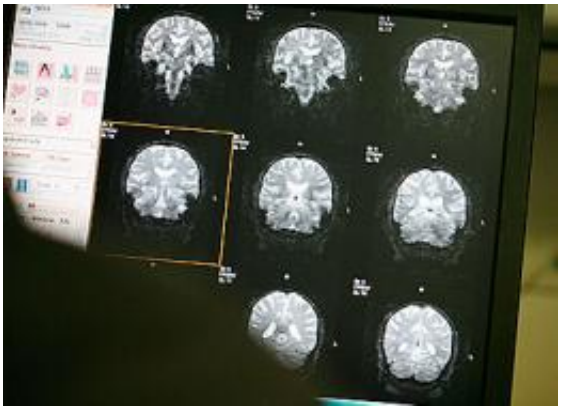

In Alzheimer’s disease, short, toxic amyloid beta peptides build up inside the brain, erasing memories, altering behavior, and ultimately destroying lives.

Scientists have a good idea how toxic amyloid beta is created, but what’s not clear is why excessive amounts of amyloid beta accumulate in people who develop Alzheimer’s. After all, each of us produces some degree of the toxic protein throughout our lives.

Now findings suggest that amyloid beta may accumulate in some patients because of a flaw in their neurons’ internal transportation system, according to a new study from researchers in the Taub Institute at

Columbia University College of Physicians and Surgeons and the University of Toronto. The study was led by Christiane Reitz, MD, assistant professor of neurology, and Richard Mayeux, MD, the Sergievsky Professor of Neurology, Psychiatry, and Epidemiology and co-director of the Taub Institute of Research on Alzheimer's Disease and the Aging Brain at P&S, and was published in the Jan. issue of the Annals of Neurology.

Like all cells, neurons use transport proteins to ship cellular components from one region of the cell to another. The shipping process is critical to the production of amyloid beta: transport proteins must carry the amyloid precursor protein (APP) to certain regions of the cell where the protein is processed into soluble forms of amyloid beta.

The new research reveals that a different transport protein, called SORCS1, appears to ferry APP to safe destinations within the cell where it's sliced into non-toxic pieces instead of amyloid beta.

Alzheimer's patients appear to express reduced levels of SORCS1 in their brains, Reitz and Mayeux also found, suggesting that APP in patients is more likely to be shipped to cellular compartments that process the protein into toxic amyloid.

Genetic studies included in the paper also show that people who carry certain variants of the SORCS1 gene have a 15 percent greater risk of developing Alzheimer's.
Taken together, Mayeux says the results show that APP transport proteins are key players in the development of Alzheimer's disease, especially when considered with similar findings for a related transport protein called SORL1. (The same Columbia and Toronto research group discovered the SORL1 link four years ago).

Increasing SORCS1 or SORL1 activity could potentially reduce the

amount of amyloid beta in the brain and slow or prevent Alzheimer's. SORCS1 and SORL1 may be hard to target directly, but other proteins in the SORCS1-SORL1 network could provide better opportunities, Mayeux says.

The researchers are now collaborating with Columbia's Initiative in Systems Biology and Center for the Multiscale Analysis of Genetic Networks to map the entire network and identify promising targets.

Provided by Columbia University