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New Alzheimer's research suggests possible cause: The interaction of proteins in the brain

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For years, Alzheimer's researchers have focused on two proteins that accumulate in the brains of people with Alzheimer's and may contribute to the disease: plaques made up of the protein amyloid-beta, and tangles of another protein, called tau.

But for the first time, an Alzheimer's researcher has looked closely at not the two proteins independently, but at the interaction of the two proteins with each other—in the brain tissue of post-mortem Alzheimer's patients and in mouse brains with Alzheimer's disease. The research found that the interaction between the two proteins might be the key: as these interactions increased, the progression of Alzheimer's disease worsened.

The research, by Hemachandra Reddy, Ph.D., an associate scientist at the Oregon National Primate Research Center at Oregon Health & Science University, is detailed in the June 2013 edition of the *Journal of Alzheimer's Disease*.

Reddy's paper suggests that when the interaction between the phosphorylated tau and the amyloid-beta—particularly in its toxic form—happens at brain synapses, it can damage those synapses. And that can lead to cognitive decline in Alzheimer's patients.

"This complex formation between amyloid beta and tau—it is actually blocking the neural communication," Reddy said. "If we could somehow

find a molecule that could inhibit the binding of these two proteins at the synapses, that very well might be the cure to Alzheimer's disease."

To conduct the research, Reddy and his team studied three different kinds of mice, who had been bred to have some of the brain characteristics of Alzheimer's disease, including having amyloid-beta and phosphorylated tau in their brains. Reddy also analyzed postmortem brain tissue from people who had Alzheimer's disease.

Using multiple antibodies that recognize amyloid-beta and phosphorylated tau, Reddy and Maria Manczak, Ph.D., a research associate in Reddy's laboratory, specifically looked for the evidence of the amyloid beta and phosphorylated tau interactions. They found amyloid-beta/tau complexes in the human Alzheimer's brain tissue and in the Alzheimer's disease mouse brains. The Reddy team also found much more of those amyloid-beta/tau complexes in brains where Alzheimer's disease had progressed the most.

Reddy found very little or no evidence of the same interaction in the "control" subjects—mice that did not have the Alzheimer's traits and human brain tissue of people who did not have Alzheimer's.

"So much Alzheimer's research has been done to look at amyloid-beta and tau," Reddy said. "But ours is the first paper to strongly demonstrate that yes, there is an amyloid-beta/phosphorylated tau interaction. And that interaction might be causing the synaptic damage and cognitive decline in persons with Alzheimer's disease."

Reddy and his lab are already working on the next crucial questions. One is to define the binding site or sites and exactly where within the neuron the interaction of amyloid-beta and tau first occurs. The second is to find a way to inhibit that interaction—and thus maybe prevent or slow the progression of Alzheimer's.