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Alzheimer's patients can't effectively clear sticky plaque component

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(PhysOrg.com) -- Neurologists finally have an answer to one of the most important questions about Alzheimer's disease: Do rising brain levels of a plaque-forming substance mean patients are making more of it or that they can no longer clear it from their brains as effectively?

"Clearance is impaired in Alzheimer's disease," says Randall Bateman, MD, assistant professor of neurology at Washington University School of Medicine in St. Louis. "We compared a group of 12 patients with early Alzheimer's disease to 12 age-matched and cognitively normal subjects. Both groups produced amyloid-beta (a-beta) at the same average rate, but there's an average drop of about 30 percent in the clearance rates of the group with Alzheimer's."

Scientists calculate this week in Science Express that it would take 10 years for this decrease in clearance to cause a build-up of a-beta equal to those seen in the brains of Alzheimer's patients.

The results have important implications for both diagnosis and treatment, according to the authors. Scientists are now interested in learning how a-beta, a byproduct of normal metabolism, is moved out of the brain for breakdown and disposal. As these details come in, they will be essential for physicians working to diagnose the disease before symptoms develop and for drug developers, who can target the problems with pharmaceuticals.

A-beta was recognized long ago as a key component of the brain plaques

found during autopsies of Alzheimer's patients. One of the ways the brain clears away the a-beta normally produced by brain cell activity is by moving it to the spinal fluid for disposal. Studies have suggested that a drop in spinal fluid levels of a-beta may be a presymptomatic indicator of Alzheimer's disease, possibly because a-beta is getting stuck in the brain and starting to accumulate there.

Recent failures of therapies designed to clear a-beta from the brain have led some neurologists to speculate that a-beta may not be causatively linked to Alzheimer's. According to Bateman, though, the new data show that Alzheimer's is associated with disruption of the brain's ability to handle a-beta normally.

"These findings support the idea that impaired a-beta clearance is fundamentally linked to Alzheimer's disease," Bateman says.

For the new study, scientists used stable isotope-linked kinetics (SILK), a process Bateman and his colleagues developed, to assess a-beta clearance and production rates.

During SILK, researchers give test subjects an intravenous drip of the amino acid leucine that has been very slightly altered to label it.

Over the course of hours, cells in the brain pick up the labeled leucine and incorporate it into the new copies they make of a-beta and other proteins. Scientists take periodic samples of the subjects' cerebrospinal fluid through a lumbar catheter, purify the a-beta from the samples and determine how much of the a-beta includes labeled leucine.

Tracking the rise of a-beta with labeled leucine over time gives scientists the subject's a-beta production rate. When the percentage of a-beta containing labeled leucine plateaus, researchers stop introducing labeled leucine. Periodic sampling of the patients' CSF continues, allowing

scientists to get a measurement of how quickly the nervous system clears out the labeled a-beta.

Average clearance rate for a-beta differed significantly between the 12 normal subjects and the 12 with early Alzheimer's, but some normal subjects had lower clearance rates close to or slightly within the range seen in Alzheimer's patients.

"Cognitive tests show no signs of dementia in these participants now, but we'll be interested to see if a lower clearance rate is a predictive marker for future diagnosis of Alzheimer's disease," Bateman says.

More information: Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, Yarasheski KE, Bateman RJ. Decreased clearance of CNS amyloid-beta in Alzheimer's disease. *Science Express*, Dec. 9, 2010.

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