Study shows antibody therapy clears Alzheimer's plaques in mice

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Antibodies against amyloid beta (A?) protein deposits that are thought to play a role in Alzheimer's disease have shown some success in preventing the buildup of deposits in animals, but they have not been effective at removing preexisting deposits. Now researchers reporting in the December issue of the Cell Press journal *Neuron* show that a modified antibody was able to clear preexisting A? deposits in a mouse model of Alzheimer's disease.

"These findings have important implications for current and future development of antibodies for the treatment of Alzheimer's disease," says first author Ronald DeMattos, PhD, of Eli Lilly and Company.

One of the hallmarks of Alzheimer's disease is the accumulation between nerve cells of hard, insoluble protein fragments called amyloid plaques (or deposits). These plaques consist of A? fragments that are normally broken down and eliminated in the healthy brain. Emerging literature suggests that extensive plaque deposition occurs in Alzheimer's disease patients some 10 years prior to first memory complaint, and by the time of diagnosis, plaque deposition is already reported to be at or near maximal levels.

Immunotherapy for Alzheimer's disease is a promising therapeutic approach that uses antibodies to target and clear A? that exists as a soluble peptide or within insoluble deposits. Thus far, many investigators have utilized antibodies that can bind both soluble and insoluble forms of A?. These antibodies are effective in reducing amyloid deposition in mice prone to developing plaques, when given as a preventative measure; however, when given to aged mice with preexisting plaques, they have little or no effect and often cause severe side effects.

Dr. DeMattos and his colleagues hypothesized that these antibodies are unable to remove existing plaques because they become saturated with soluble A? when they enter the brain, and as such they are not able to bind to their intended target. To test this hypothesis, they developed a genetically engineered antibody that selectively targets the plaques.

The Lilly researchers found that their plaque-specific antibody crossed the blood-brain barrier, bound to deposited beta amyloid, and caused robust clearance of preexisting plaques in mice without causing microhemorrhage. A comparator antibody that bound to both soluble and insoluble A? did not effectively lower existing plaques yet caused an increase in microhemorrhage. "The data suggest that an antibody that binds to only insoluble amyloid beta is likely critical for plaque removal without the associated adverse event of microhemorrhage," says Dr. DeMattos.

The Lilly researchers believe these results are consistent with their original hypothesis. "Target engagement is fundamental for the clearance of deposited plaques, and these results highlight that approaches aimed at increasing antibody binding, or target engagement, will result in significant plaque clearance," says Dr. DeMattos.

The findings may help explain why the Alzheimer's drug bapineuzumab was no better than placebo in two recent late-stage trials in patients who had mild to moderate Alzheimer's disease. Bapineuzumab binds to both soluble and insoluble beta amyloid.

More information: DeMattos et al.: "A plaque-specific antibody clears existing ?-amyloid plaques in Alzheimer's disease mice." DOI: 10.1016/j.neuron.2012.10.029

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