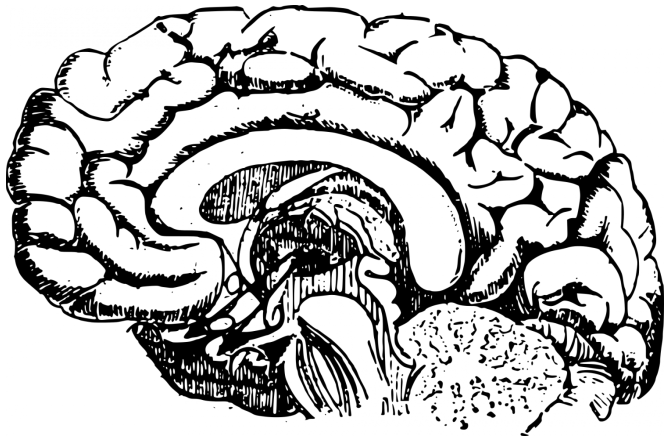
Redefined Alzheimer's biology has implications for drug design

7 February 2018



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Despite the 25-year focus on the build-up in brain tissues of one protein, amyloid beta, as the purported origin of Alzheimer's disease (AD), a new study argues that it is likely triggered instead by the failure of a system that clears wastes from the brain - and actually begins decades before memories fade.

Based on findings published online February 7 in the journal *PLOS ONE*, researchers at the NYU School of Medicine demonstrate that the current biological understanding of AD is incomplete. The new evidence suggests that standard diagnostic tools fail to catch future AD in many patients younger than age 70, say the study authors.

In the commonly held definition of Alzheimer's disease, one type of amyloid-beta (A?42) starts to form clumps between nerve cells, injuring them. Worsening injury is then marked by the release and toxic buildup of a second protein called tau. Together, changes in A?42 and tau levels represent the standard international measure of a patient's risk for future cognitive decline.

The new study found that the build-up in the brain of amyloid beta cannot be the sole trigger of subsequent nerve damage because many relatively younger people who develop disease later do not show signs of the buildup.

"Once you stop assuming that the starting point of Alzheimer disease is marked by the buildup of A?42 in brain cells, a different picture emerges," says lead study author Mony de Leon, EdD, a professor in the Department of Psychiatry, and director of the Center for Brain Health, at NYU Langone Heath. "By recognizing an earlier disease phase, we may be able to start treating earlier and in tailored ways based on a better understanding of disease biology."

For many years, neuroscientists have sought to predict AD risk by tracking protein levels in the cerebrospinal fluid (CSF) that fills the spaces around brain tissue, and which can be sampled by lumbar puncture as part of a spinal tap. In 1999, de Leon and colleagues started collecting clinical and CSF protein level data from healthy normal subjects every two years. Combining this NYU database with two others, the current study is the largest of its kind to date, including roughly 700 patients.

Specifically, the study found that the best predictor of future AD risk was not, as currently thought, decreased CSF A?42 levels with elevated tau. Elevated CSF A?42 levels were also found to confer future AD risk.

By including in AD risk prediction models patients with either rising or falling CSF A?42, along with steadily rising tau, the team increased the accuracy of future risk prediction by nearly 20 percent over current models, which only consider falling levels. The improved accuracy was even more pronounced in those aged younger than 70 years, de Leon says. In mathematical terms, the relationship between A?42 and tau is best

described by a quadratic equation rather than the current linear one, which attempts to make a curve "fit" onto a straight line.

The results add to the evidence that an increase in CSF tau over a lifetime may be the more relevant, early feature of AD than a drop in CSF A?42 (taken as evidence of a buildup in brain cells), researchers say.

While the actual mechanism behind Alzheimer's disease and the trajectory of A?42 and tau levels remains obscure, say the authors, the results provide evidence in support of the "clearance theory." It holds that the pumping of the heart, along with constriction of blood vessels, pushes cerebrospinal fluid through the spaces between brain cells, clearing potentially toxic proteins into the bloodstream. Mid-life cardiovascular changes that bring on heart failure and hypertension may lessen the CSF flow needed to clear tau, and perhaps disease-causing proteins yet to be identified.

Aside from A?42 which is readily deposited into the brain, the team found that CSF levels of two other common forms of amyloid beta that are less able to build up, A?38 and A?40, increase in proportion to rising tau throughout the normal older adult lifespan, even after CSF A?42 starts to decrease. This is further evidence of a decline in clearance with age, researchers say.

"Future CSF studies need to follow normal subjects, starting at age 40, for decades to get an unbiased look at the trajectory of CSF proteins and the likelihood of developing cognitive impairment decades later," says de Leon.

Provided by NYU Langone Health