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Overlooked peptide reveals clues to causes of Alzheimer's disease

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Researchers at the RIKEN Brain Science Institute (BSI) and their collaborators have shed light on the function of a little-studied amyloid peptide in promoting Alzheimer's disease (AD). Their surprising findings reveal that the peptide is more abundant, more neurotoxic, and exhibits a higher propensity to aggregate than amyloidogenic agents studied in earlier research, suggesting a potential role in new approaches for preventing AD-causing amyloidosis.

An irreversible, progressive brain disease affecting millions worldwide, Alzheimer's disease is devastating for its victims, robbing them of their memory and cognitive skills and ultimately of their lives. Even after decades of research, however, the causes of AD remain elusive. Two features in the brain, abnormal clumps (senile plaques) and tangled bundles of fibers (neurofibrillary tangles), are known to characterize AD, but there is little consensus on the link between these features and the underlying roots of the disease.

One hypothesis that has attracted widespread support proposes that AD is caused by the buildup of the senile plaques, and in particular of their main constituent, amyloid-β peptides (Aβ). Two major forms of Aβ, Aβ40 and Aβ42, have been associated with genetic mutations causing early-onset AD, and have thus received considerable research attention. The role of longer Aβ species, in contrast, which also exist in the brains of Alzheimer's patients, has not yet been fully investigated.

In their current work, the researchers focused on Aβ43, an amyloid-β

peptide found just as often in patient brains as Aβ42, but about which relatively little is known. To study the peptide's role in AD, they generated mice with a mutation causing overproduction of Aβ43, and used a highly sensitive system to distinguish between concentrations of Aβ40, Aβ42 and Aβ43.

Their surprising results reveal that Aβ43 is even more abundant in the brains of AD patients than Aβ40, and more neurotoxic than Aβ42. Aβ43 also exhibits the highest propensity to aggregate and considerably accelerates amyloid pathology. Moreover, unlike the other two Aβ species, which exist in human and mouse brains at birth, Aβ43 levels appear to increase with age, consistent with the pattern of AD onset.

Published in the journal *Nature Neuroscience*, the findings thus reveal the possible value of Aβ43 as a biomarker for diagnosis of AD and suggest a potential role in new approaches for preventing AD-causing amyloidosis, promising hope to AD sufferers around the world.

Provided by RIKEN