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Oxidative modification of γ-secretase enhances amyloidogenic pathway

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The cause of elevated level of amyloid beta-peptide (Aβ42) in common late-onset sporadic Alzheimer's disease (AD] has not been established. Here, we show that the membrane lipid peroxidation product 4-hydroxynonenal (HNE) is associated with amyloid and neurodegenerative pathologies in AD and that it enhances gamma-secretase activity and Aβ42 production in neurons. The gamma-secretase substrate receptor, nicastrin, was found to be modified by HNE in cultured neurons and in brain specimens from patients with AD, in which HNE–nicastrin levels were found to be correlated with increased gamma-secretase activity and Abeta plaque burden. Furthermore, HNE modification of nicastrin enhanced its binding to the gamma-secretase substrate, amyloid precursor protein (APP) C99. In addition, the stimulation of gamma-secretase activity and Aβ42 production by HNE were blocked by an HNE-scavenging histidine analog in a 3xTg-AD mouse model of AD. These findings suggest a specific molecular mechanism by which oxidative stress increases Aβ42 production in AD and identify HNE as a novel therapeutic target upstream of the gamma-secretase cleavage of APP.

Biography

Harkkyun Kim has completed his BS degree at the age of 26 years and is studying Molecular Cellular Biology from Sungkyunkwan University School of Pharmacy. Now he is Ph.D candidiate studying molecular pathogenesis of Alzheimer's disease, especially about the relationship between adiponectin and Alzheimer's disease.

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