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## RA improves cognitive function of Alzheimer's disease mouse model through inhibition of BACE1 expression and neuroinflammation

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Alzheimer's disease (AD) is the most common dementing illness, and the peptide amyloid- $\beta$  ( $A\beta$ ) has a chief function in the pathogenesis of AD. Sequential proteolysis of amyloid precursor protein (APP) by BACE1 and  $\gamma$ -secretase produces  $A\beta$  which drives cerebral neuroinflammation. Recent findings have provided insight into a newly discovered inflammatory mechanism that contributes to the pathogenesis of Alzheimer's disease mediated by multi-protein complexes called NLRP inflammasomes. In the present study, we orally administered the brain penetrant, natural compound isolated from compound RA to the transgenic APP/PS1 (bearing mutant human APP and presenilin-1 transgenes) and 3xTg-AD (bearing mutant human APP, presenilin-1, and tau transgenes) mice models of Alzheimer's disease. Oral treatment of natural compound reversed transgene-associated behavioral deficits, but did not alter wild-type mouse behaviors. Furthermore, brain  $A\beta$  depositions as well as abundance of various  $A\beta$  species were decreased in natural compound-treated AD mice. These effects occurred with decreased cleavage of  $\beta$ -carboxy-terminal APP fragment, reduced BACE1 expression, attenuated neuroinflammation, and reduced expression of NLRP inflammasome proteins. As *in vitro* validation, we treated neuronal and microglial cells with this compound and found that the levels of NLRP inflammasome proteins,  $A\beta$  production, BACE1 expression, and oxidative stress were significantly decreased. Collectively, our findings reveal this compound as a potential therapeutic modality for targeting  $A\beta$  production and  $A\beta$ -induced NLRP inflammasomes.

### Biography

Gun Young has completed his B.S. from Sungkyunkwan University School of Pharmacy in 2015. He is doing his master's degree at Sungkyunkwan University School of Pharmacy. His major expertise is molecular cell biology.

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