RA improves cognitive function of Alzheimer’s disease mouse model through inhibition of BACE1 expression and neuroinfammation

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Alzheimer's disease (AD) is the most common dementing illness, and the peptide amyloid-β (Aβ) has a chief function in the pathogenesis of AD. Sequential proteolysis of amyloid precursor protein (APP) by BACE1 and -secretase produces Aβ which drives cerebral neuroin ammation. Recent ndings have provided insight into a newly discovered in ammatory mechanism that contributes to the pathogenesis of Alzheimer's disease mediated by multi-protein complexes called NLRP in ammasomes. 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 de cits, but did not alter wild-type mouse behaviors. Furthermore, brain Aβ depositions as well as abundance of various Aβ species were decreased in natural compound-treated AD mice. ese e ects occurred with decreased cleavage of β-carboxy-terminal APP fragment, reduced BACE1 expression, attenuated neuroin ammation, and reduced expression of NLRP in ammasome proteins. As *in vitro* validation, we treated neuronal and microglial cells with this compound and found that the levels of NLRP in ammasome proteins, Aβ production, BACE1 expression, and oxidative stress were signi cantly decreased. Collectively, our ndings reveal this compound as a potential therapeutic modality for targeting Aβ production and Aβ-induced NLRP in ammasomes.

Biography

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