APP/Go protein Gb gamma-complex signaling mediates A beta degeneration and cognitive impairment in Alzheimer's disease models

Anahi Bignante, Elena; Eric Ponce, Nicolas; Heredia, Florencia; Musso, Juliana; Krawczyk, Maria C.; Millan, Julieta; Pigino, Gustavo F.; Inestrosa, Nibaldo C.; Boccia, Mariano M.; Lorenzo, Alfredo

Abstract

Deposition of amyloid-β (Aβ), the proteolytic product of the amyloid precursor protein (APP), might cause neurodegeneration and cognitive decline in Alzheimer's disease (AD). However, the direct involvement of APP in the mechanism of Aβ-induced degeneration in AD remains on debate. Here, we analyzed the interaction of APP with heterotrimeric Go protein in primary hippocampal cultures and found that Aβ deposition dramatically enhanced APP-Go protein interaction in dystrophic neurites. APP overexpression rendered neurons vulnerable to Aβ toxicity by a mechanism that required Go-Gβγ complex signaling and p38–mitogen-activated protein kinase activation. Gallein, a selective pharmacological inhibitor of Gβγ complex, inhibited Aβ-induced dendritic and axonal dystrophy, abnormal tau phosphorylation, synaptic loss, and neuronal cell death in hippocampal neurons expressing endogenous protein levels. In the 3xTg-AD mice, intrahippocampal application of gallein reversed memory impairment associated with early Aβ pathology. Our data provide further evidence for the involvement of APP/Go protein in Aβ-induced degeneration and reveal that Gβγ complex is a signaling target potentially relevant for developing therapies for halting Aβ degeneration in AD.

Keywords

Alzheimer, Amyloid β (Aβ), Amyloid precursor protein (APP), Go protein, Gβγ complex, Degeneration, 3xTg-AD mice.