M1 Muscarinic Receptor Activation Protects Neurons From ß-Amyloid Toxicity. a Role for Wnt Signaling Pathway

G. G. Farías, J. A. Godoy, F. Hernández, J. Avila, A. Fisher, N. C. Inestrosa

Abstract

Amyloid-β-peptide (Aβ) deposits are one of the hallmark features of Alzheimer's disease. Signal transduction alterations are implicate in the neuronal responses to Aβ, which include neurotransmitter systems and pathways involved in the maintenance of the nervous system. In this context, we have recently found that Aβ-neurotoxicity triggers a loss of Wnt signaling. We report here that M1-acetylcholine-muscarinic-receptor (mAChR) activation protects neurons from Aβ-toxicity. Concomitant with this effect, a modulation of the Wnt signaling was observed. M1 mAChR activation inhibits glycogen-synthase-kinase-3β (GSK-3β) activity, stabilizes cytoplasmic and nuclear β-catenin, and induces the expression of the Wnt target genes *engrailed* and *cyclin-D1*, reverting the switch off of the Wnt pathway caused by Aβ-toxicity. Neurons from mice that overexpress GSK-3β allow us to establish that M1 mAChR stimulation leads to GSK-3β inactivation. We conclude that the cross-talk between the muscarinic signaling and Wnt components underlie the neuroprotective effect of the M1 mAChR activation.