

Summary

Impairment of the cholinergic neurotransmission system is regularly detected in animal models of Alzheimer's disease as well as in human patients suffering from this serious disease. Moreover, there is increasing amount of evidence suggesting that activation of individual mAChR subtypes specifically influences the cleavage of APP, the precursor for β -amyloid. APP can be processed in an amyloidogenic or non-amyloidogenic pathway and a relative abundance of these pathways contributes to establishing the final concentration of neurotoxic β -amyloid in the brain. In this work, I have studied the acute and chronic effects of A β 1-42 on binding and functional characteristics of mAChR. I have demonstrated that A β 1-42 present in cell culture expressing the individual subtypes of mAChR negatively and specifically influences the function of the M1 mAChR subtype. I have also detected a decline in muscarinic receptor-mediated signal transduction in brain tissue of young adult APP^{swe}/PS1^{dE9} mice, a commonly used animal model of Alzheimer's disease. Demonstration of the impairment of muscarinic transmission in transgenic mice by soluble β -amyloid that occurs earlier than amyloid pathology and behavioral deficit, and its imitation by soluble A β 1-42 in vitro lend strong support to the notion of the early involvement of muscarinic transmission in pathogenesis of Alzheimer's disease. Mechanisms underlying the negative effects of A β 1-42 on mAChR are not yet clear. Some results suggest that structural changes of cell membrane and successive changes in receptor/G-protein interaction may be involved.