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MUSCARINIC ACETYLCHOLINE RECEPTOR REGULATION OF AMYLOIDOGENESIS

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of amyloid plaques, neurofibrillary tangles, and deficits in cholinergic neurotransmission. In addition to improving clinical symptoms, accumulating evidence suggests that cholinergic-based therapeutics may modify disease progression in AD. However, the molecular mechanisms of this effect, particularly the role that muscarinic acetylcholine receptor (mAChR) subtypes play in regulating amyloidogenesis, remain poorly understood. In order to investigate this question at the genetic level, we have used mice deficient in individual mAChR subtypes to study their respective roles in amyloidogenesis. Primary neuron cultures from wildtype mice demonstrated that amyloid precursor protein (APP) processing is regulated in a mAChR atropine-sensitive manner. Cultures derived from mice deficient in M1 and M2/M4 receptors demonstrate that these mAChR subtypes differentially regulate the shedding of APP α and the production of the A β peptide. To further investigate the potential in vivo role of M1 in amyloid deposition, mice deficient in M1 were bred into an AD transgenic mouse model. Complementary studies took advantage of recent progress in drug discovery to address these questions with a pharmacological approach. We recently reported that the novel M1-selective agonist TBPB regulates non-amyloidogenic APP processing in PC12 cells, and we now show that a novel M1-selective positive allosteric modulator potentiates carbachol-mediated APP α release. Taken together, these data suggest that therapies designed to modulate cholinergic function may not only alleviate AD symptoms, but may also alter the course of the disease.