DEVELOPMENT OF EARLY CHOLINERGIC TRANSMISSION DAMAGE IN TRANSGENIC APPSWE/PS1DE9 MICE

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Invariable damage of cholinergic markers and relative sensitivity to cholinergic treatments point to an important role of cholinergic transmission in the pathogenesis of Alzheimer’s disease. It is not clear, however, whether damage of cholinergic transmission develops early in the pathogenesis or is the result of general neurodegeneration. The double transgenic mouse model APPswe/PS1dE9 closely mimics the gradual increase in soluble β-amyloid levels and amyloid plaques formation. We took advantage of these mice to determine the functional integrity of muscarinic transmission in the course of in vivo amyloid accumulation. In ex vivo experiments on brain slices from young (7-10-weeks) animals we did not find any changes in the synthesis and release of either newly synthetized or previously stored acetylcholine. In contrast, the release of newly synthetized acetylcholine was significantly reduced in cortex and hippocampus from young adult (5-6-months) animals. Presynaptic autoregulation of acetylcholine release was intact in both age groups. Carbachol-mediated G-protein activation in cerebral cortical membranes was indistinguishable between young control and transgenic animals. Activation of G-proteins by carbachol in control animals demonstrated an age-dependent decline that was significantly stronger in transgenic mice. In conclusion, we demonstrated significant impairment of muscarinic transmission at presynaptic (evoked release of acetylcholine in cortex and hippocampus) and postsynaptic (agonist-stimulated G-protein activation) level that is not present in young transgenic mice. This change develops in parallel with increase in soluble β-amyloid concentration, and precedes plaque formation and behavioral deficits. Supported by project AV0Z50110509 and grants IAA500110703, MSMT CR LC554, and EU project LipiDiDiet GA No211696.