Impairment of cholinergic neurotransmission in adult and aged transgenic Tg2576 mouse brain expressing the Swedish mutation of human beta-amyloid precursor protein.

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Abstract: To address the question of whether beta-amyloid peptides also affect cholinergic neurotransmission in vivo, brain tissue from transgenic Tg2576 mice with Alzheimer plaque pathology at ages ranging from 7 to 24 months were examined by immuno- and histochemical staining for choline acetyltransferase (ChAT) and acetycholinesterase (AChE), by assaying cholinergic enzyme activities and high-affinity choline uptake as well muscarinic and nicotinic cholinergic receptor binding levels by quantitative autoradiography. Cortical and hippocampal activities of AChE and ChAT were not different between transgenic mice and non-transgenic littermates regardless of the postnatal ages examined. However, high-affinity choline uptake was reduced in the hippocampus of 21-month-old transgenic mice. In brains of 8-month-old transgenic mice which do not yet demonstrate cortical beta-amyloids, reduced binding levels of cortical and hippocampal M1-muscarinic cholinergic receptors were observed, which were still reduced in 17-month-old transgenic mouse brains with high plaque load as compared to non-transgenic littermates. M2-muscarinic cholinergic receptor binding was hardly affected in brains from 8-month-old transgenic mice, but in 17-month-old transgenic mice reduced cortical and hippocampal binding levels were observed as compared to non-transgenic controls. Decreased cortical nicotinic cholinergic receptor binding was detected in 17-month-old transgenic mice. The development of changes in cholinergic synaptic markers in transgenic Tg2576 mouse brain before the onset of progressive plaque deposition provides in vivo evidence of a modulatory role of soluble beta-amyloid on cholinergic neurotransmission and may be referred to the deficits in learning and memory also observed in these mice before significant plaque load.

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