Loss of hippocampal synaptophysin-immunoreactive presynaptic boutons in transgenic mouse models of Alzheimer's disease

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The neuropathology of Alzheimer's disease (AD) is characterizered by ß-amyloid containing plaques, neurofibrillary tangles, and neuronal and synaptic loss. Despite intense research over the last years, however, the interrelations between these characteristics have not been elucidated. It has been proposed in the "amyloid-cascade" hypothesis of AD that ß-amyloid is the primary event in AD pathogenesis, and that neuronal and synaptic loss is the result of ß-amyloid formation. Recently, we have observed substantial age-related loss of hippocampal pyramidal cells in 17-month-old mice transgenic for mutated human amyloid precursor protein (APP) and presenilin-1 (PS-1) but not in PS-1 single transgenic mice, indicating that ß-amyloid formation can be neurotoxic. The aim of the present study was to asses whether overexpressing human mutated APP and/or PS-1 *in vivo* is also synaptotoxic. For this aim, serial sections through the hippocampus of wild type, PS-1 transgenic and APP/PS-1 transgenic mice (all female and 17 months of age) were immunohistochemically labeled for synaptophysin, i.e. a presynaptic protein. The density of synaptophysin-immunoreactive presynaptic boutons (SIPB) in plaque-free areas of the hippocampal stratum radiatum and stratum moleculare was analyzed using computer-assisted image analysis. Furthermore, the volumes of these same regions were investigated using design-based stereology. Interestingly, the density of SIPB was significantly decreased within in plaque-free areas of the hippocampal stratum radiatum and stratum moleculare of APP/PS-1 transgenic as well as in PS-1 transgenic mice as compared to wild type animals. In addition, the volumes of hippocampal stratum radiatum and stratum moleculare were reduced in the APP/PS-1 transgenic mice. Together, these data indicate that mutated human APP and PS-1 as well as mutated human PS-1 alone can be synaptotoxic *in vivo*.
Supported by the International Stichting Alzheimer Onderzoek

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Neuroscience 2 (poster)