Early hippocampal neuron loss in a novel transgenic/knock-in mouse model of AD

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Despite intense research over the last years, transgenic animal models of Alzheimer's disease (AD) showing age-related neuron loss (a hallmark of AD) were not available. We have recently shown substantial hippocampal neuron loss in 17-month-old transgenic mice expressing human mutant APP (Thy1 promotor) and human mutant PS-1 (HMG-coreductase promotor) (Am J Pathol 164 [2004] 1495-1502). Here we present a novel mouse model of AD, carrying M233T/L235P knocked-in mutations in human PS-1 (PS1KI) and/or overexpressing human APP_{751} carrying the London (V717I) and Swedish (K670N/M671L) mutations (APPhe). In the APPhe/PS1KI mice substantial volume loss was observed in the hippocampal CA1/2 pyramidal cell layer and in the hippocampal white matter already at 10 months of age. Additionally, substantial neuron loss was observed in the hippocampus of these mice at 10 months, particular in the CA1/2 pyramidal cell layer. The lack of volume and neuron loss in the hippocampal cell layers of both PS1KI mice and APP single transgenic mice indicated that a combination of both genes was necessary to cause hippocampal volume and neuron loss seen in this mouse model of AD. To determine the contribution of extracellular Aβ deposits to the observed volume and neuron loss, the hippocampal plaqueburden was determined by point counting methods. The results were consistent with our previous observations in the 17 months-old APP/PS1 transgenic mice, indicating that only part of the observed neuron loss could be explained by the accumulation of extracellular amyloid. This implicated the existence of additional mechanisms of neuron death in the brain of these mice, which remain to be determined. In conclusion, this is the first animal model of AD showing substantial neuron loss already at 10 months of age. It is to expect that this animal model will play a major role in the development of new therapeutics for AD.
Supported by ISAO (Internationale Stichting Alzheimer Onderzoek

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Neuroscience 2 (poster)