ABETA FROM APP/PS1 ALZHEIMER MICE HIPPOCAMPUS INDUCED SYNAPTIC DAMAGE IN VIVO AND IN VITRO

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We aim to investigate the effects of Abeta from young APP/PS1 mouse model of Alzheimer`s disease (AD) on the synaptic integrity, as the loss of synapses strongly correlates with cognitive deficits in patients. Plaque-associated abnormal swellings of neuronal processes represent the first indicator of disease development and might compromise neuronal integrity and synaptic function. Here, we examined the synaptic nature of dystrophic neurites, and the reduction of both synapses and vesicles density in presynaptic terminals along with the progressive accumulation of autophagic structures and Abeta within hippocampal synaptosomes during the aging. We analysed both the direct synaptotoxic effect of plaques in the hippocampus of this model and also the repercussion of the soluble (S1) fraction in neuronal cultures.

Hippocampal synapses were observed under both optic and electron microscopy. Synapses and vesicle density were quantified in periplaque and control (plaque-free) areas by electron microscopy. Primary neuronal cultures were incubated for 48 hours with 6-month-old APP/PS1 and wild-type S1 fractions. In addition, Abeta immunodepletion was carried out with different anti-Abeta antibodies and the levels of synaptic proteins were measured by Western-blot (WB).

Both synapse number and synaptic-vesicles density were significantly decreased in young APP/PS1 mice, close to the Abeta deposits, in several hippocampal layers. Importantly, there was a correlation between the synaptic deficiencies and the distance to plaques, which presented oligomeric forms in their periphery. Some presynaptic elements were abnormally swollen, containing autophagic vesicles. In addition, we found by WB a decrease in several hippocampal synaptic markers as early as 4 months of age in this model, and also in neuronal cultures incubated with S1 fractions. Significantly, the neuronal reduction in VGLUT was reversed after Abeta immunodepletion.

Plaque-associated oligomeric Abeta induced an early deleterious effect on synapses that correlates with memory deficits in young APP/PS1 mice. Moreover, soluble Abeta derived from these transgenic mice reduced synaptic protein content *in vitro*, which was restored after immunodepletion of Abeta species. Therefore, this model produced synaptotoxic Abeta and may represent a valuable tool to test novel treatments to protect synapses as an early therapeutic approach for AD.

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