Calpain inhibition improves synaptic function and memory in a mouse model of Alzheimer's disease

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Alzheimer's Disease (AD) is a devastating disorder that affects a large percentage of the senile population. The disease is thought to start with subtle synaptic changes leading to memory loss, probably due to amyloid-beta (Aβ) species, a group of peptides that is elevated in AD. Activation of the calpain system is likely to contribute to these changes [1-3]. Calpains regulate the function of many proteins by limited proteolysis and initiate the degradation of other proteins. In particular, they modulate processes that control the function and metabolism of proteins key to the pathogenesis of AD, including tau [4, 5] and Aβ precursor protein [6-8]. During the last 10 years we have investigated whether and how Aβ interferes with both memory formation and the regulation of hippocampal synaptic function. I will now present data showing that inhibition of calpains rescues the defect of synaptic transmission both in mouse models of amyloid elevation such as the APP/PS1 mouse and the APP mouse as well as after elevation of Aβ. I will also discuss our studies on the beneficial effect of calpain inhibition against the reduction of spatial-working memory and associative fear memory both in double transgenic APP/PS1 mice and single transgenic APP animals. Finally, I will present data showing that Aβ-induced down-regulation of phosphorylation of the memory-related molecule CREB is rescued by calpain inhibition. Taken together, these findings suggest that calpain inhibitors may prove useful in the alleviation of memory loss in AD.

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