Distinct in vivo role of APPsα versus APPsβ for spine density, synaptic plasticity and cognition

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APP is key to Alzheimer's disease (AD) pathogenesis as APP processing gives rise to the Aβ peptide, that is found in AD patients' brains. To elucidate its physiological functions and to circumvent compensation by the close homologue APLP2 we had previously generated conditional double knockout (cDKO) mice lacking both APP and APLP2 in excitatory forebrain neurons. These cDKO mice showed a pronounced synaptic phenotype with deficits in neuronal morphology, spine density, synaptic plasticity (LTP) and hippocampus dependent learning and memory (Hick et al, 2015).

There is increasing evidence that the synaptic functions of APP may be carried out by its secreted fragments. Therefore, we re-expressed the secreted ectodomains APPsα and APPsβ in the hippocampus of adult cDKO mice using AAV9 based vectors. Here, we demonstrate that acute expression of APPsα, but not APPsβ, in the adult brain of cDKO mice is sufficient to fully rescue spine density of CA1 pyramidal neurons and to restore LTP recorded at CA3-CA1 synapses. Moreover, we observed a partial rescue of spatial memory in the Morris water maze. We also showed that the C-terminal 16 amino acids of APPsα (lacking in APPsβ) proved sufficient to facilitate LTP in a mechanism that depends on functional nicotinic α7-nAChRs. Collectively, we identified α7-nAChRs as a crucial physiological receptor specific for APPsα and show distinct in vivo roles for APPsα versus APPsβ. Our findings support therapeutic approaches aimed at directly or indirectly increasing APPsα expression in the brain to ameliorate synaptic deficits in AD or other neurodegenerative diseases.