APP and APLP2 provide essential functions at PNS and CNS synapses mediating neuromuscular transmission, spatial learning and synaptic plasticity

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Despite its key role in Alzheimer pathogenesis the physiological function(s) of the amyloid precursor protein APP and of its proteolytic fragments are still largely unknown. To investigate these functions we have recently generated APPsa knockin (KI) mice expressing solely the secreted APPs-alpha ectodomain from endogenous APP locus. Comparing APPsa-KI mice with APP-KO mice we could show that APPsa was sufficient to rescue the defecits of APP-KO mice and serves a key function for synaptic plasticity, learning and memory. To test whether APPsa could also rescue the lethal phenotype and neuromuscular deficits of APP/APLP2 double knockout (DKO) mice, we now crossed APPsa -KI mice onto an APLP2-deficient background. Here, we show that the majority of these APPsa-KI/APLP2-KO double mutant mice (termed APPsa-DM) survive into adulthood. This surprising viability allowed us to assess APP/APLP2 mediated functions in the adult and revealed a complex phenotype characterized by deficits both in the PNS and importantly, also severe dysfunction of adult CNS. Although in APPsa-DM mice defects in neuromuscular transmission were largely ameliorated compared to lethal APP/APLP2 DKO mice, we detected remaining impairments in neurotransmitter release including largely reduced quantal content that resulted in muscular weakness. These data suggest that secreted APPsa modulates neuromuscular transmission to a level sufficient to rescue to a large extent the postnatal lethality of DKO mice. Morphological analysis of adult neuromuscular junctions revealed pre- and postsynaptic alterations and most strikingly a high incidence of immature and fragmented postsynaptic specializations, indicating a novel function of APP/APLP2 for postnatal synaptic maturation and maintenance. Despite normal CNS morphology, APPsa-DM mice showed pronounced deficits in hippocampus-dependent learning and memory that were associated with a strong deficit in long term potentiation LTP, already present in young adults. In contrast to peripheral synapses, neither defects in basal synaptic transmission nor in presynaptic short term plasticity were detectable at glutamatergic CA3/CA1 synapses, suggesting distinct roles of APP family members at peripheral and central excitatory synapses. Collectively, our data show that both APLP2 and APP are synergistically required to mediate neuromuscular function, working memory, spatial learning and synaptic plasticity.