The secreted APPs-alpha domain is sufficient to rescue the anatomical, behavioral, and electrophysiological abnormalities of APP deficient mice

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It is well established that the proteolytic processing of the beta-amyloid precursor protein (APP) generates beta-amyloid (A-beta) which plays a central role in the pathogenesis of Alzheimer's disease (AD). In contrast, the physiological role of APP and of its numerous proteolytic fragments and the question of whether a loss of these functions contributes to AD are still unknown. To address this question, we replaced the endogenous APP locus by gene targeted alleles and generated two lines of knockin mice that exclusively express APP deletion variants corresponding either to the secreted APP ectodomain (APPs-alpha) or to a C-terminal truncation lacking the YENPTY interaction motif (APP-deltaCT15). Interestingly, the deltaCT15-deletion resulted in reduced turnover of holoAPP, increased cell surface expression and largely reduced A-beta levels in brain, likely due to reduced processing in the endocytic pathway. Most importantly, we demonstrate that in both APP knockin lines the expression of APP N-terminal domains either largely attenuated or completely rescued the prominent deficits of APP knockout mice, such as reductions in brain and body weight, grip strength deficits, alterations in circadian locomotor activity, exploratory activity, and the impairment in spatial learning and LTP. Taken together our data suggest that the APP C-terminus is dispensable and that APPs-alpha is sufficient to mediate the physiological functions of APP assessed by these tests.

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