APP/APLP2 double-deficient mice show a behavioral phenotype reminiscent of hippocampal lesions

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The physiological function of the amyloid precursor protein (APP) is still poorly understood. While phenotypic changes in APP-knockout mice, as well as in a knockin line which expresses solely the secreted ectodomain of APP (APPsa-KI) are subtle, mice lacking both APP and amyloid precursor -like protein 2 (APLP2) die shortly after birth. APPsa-KI x APLP2-null double mutants (APPsa-DM) survive at a rate of 50% despite defective neuromuscular junctions and as adults show a deficit of hippocampal LTP (EMBO J 30:2266, 2011). We have analyzed the behavior of adult APPsa-DM mice using conventional tests and the IntelliCage. Due to their muscular weakness, APPsa-DM mice showed massive motor deficits and were unable to swim, precluding testing in the water-maze. They showed abnormal exploration and habituation in the open-field, displayed reduced alternation in the T-maze, and were unable to learn a working-memory task on the radial maze. Burrowing and nest building were strongly impaired. Behavior of APPsa-DM mice in the IntelliCage was characterized by delayed exploration followed by hyperactivity, spatial stereotypies, and poor performance in spatial reversal and patrolling tasks. Thus, beyond their neuromuscular phenotype, adult APPsa-DM mice show behavioral impairments strongly reminiscent of mice with hippocampal lesions. In conjunction with the deficit of hippocampal LTP, this demonstrates that APP and APLP2 are essential for normal CNS function, including hippocampus-dependent learning. Supp. SNF NCCR Neuro.