Overexpression of human APP and neprilysin deficiency counteract to influence exploration and memory in mice

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Alzheimer's disease (AD), responsible for vast majority of dementia cases in elderly population, is caused by accumulation of high levels of Abeta in the brain. Neprilysin is the major enzyme responsible for the degradation of Abeta in vivo. We showed that elevation of neprilysin levels in the brain delayed the deposition of Abeta-plaques in a mouse model of amyloidosis and lack of neprilysin leads to increased Abeta generation and deposition of amyloid plaques in mouse brains [Poirer et al., 2006; Madani et al., 2006]. This study was designed to test whether low brain levels of neprilysin may affect the amyloid pathology or behavioral characteristics of aged mice. To this aim, we employed the J20 transgenic mice, overexpressing mutated human amyloid precursor protein (APP) in neurons, and mice with targeted depletion of one allele of Mme, the gene encoding neprilysin (NEP+/-), as well as J20.NEP+/- doubly-mutated littermates. Biochemical analysis, utilizing murine Abeta Elisa and immune histochemistry revealed weak amyloid phenotype in the J20 mice. Surprisingly, and mirroring these biochemical findings, behavioral analysis indicated a better performance of the J20 mice overexpressing hAPP in exploratory and memory paradigms, with neprilysin deficiency alone ranging from impairing to neutral, and often interacting with the hAPP effect. In the open field, neprilysin deficiency slightly decreased exploration, which was rescued in J20.NEP+/- doubly-mutated mice. In Y-maze hAPP overexpression improved working memory in both J20 and double-transgenic mice, whereas NEP+/- mice were indistinguishable form wild type controls. Finally, hAPP overexpressing mice were superior in solving the cognitive task in the in burrowing "plug puzzle" paradigm, while neprilysin deficiency suppressed the beneficial APP effect. These data suggest that, (1) overexpression of moderate levels of APP-transgene in neurons positively effects the exploration and memory, and (2) a partial neprilysin deficiency as is found during aging, exacerbate amyloid pathology and impair some cognitive functions.

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