Neuronal neprilysin overexpression is associated with altered locomotion, anxiety-like behavior and fear conditioning

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Due to an imbalance between its generation, degradation and clearance from the brain, abnormally high brain concentrations of amyloid-beta peptides (Abeta) is associated with the pathology of Alzheimer's disease (AD). Neprilysin is a major enzyme involved in the degradation of Abeta in vivo. We have previously shown that lower level of neprilysin leads to increased Abeta generation and cognitive impairment whereas elevation of neprilysin levels in the brain prevented accumulation of Abeta and cognitive impairment in a mouse model of amyloidosis.
To evaluate whether neprilysin upregulation could also prevent other behavioral deficits associated with amyloidosis, we crossbred transgenic mice overexpressing neprilysin (NEP) or human APP bearing the Swedish and Indiana mutations in neurons (APP). Locomotor activity and anxiety-like behavior were analyzed in their progeny at 7 months of age in Open field and elevated zero maze, respectively. Neprilysin overexpression did not prevent hyperlocomotion and decreased anxiety-like behavior observed in APP mice, but shared similar phenotype.
Because neprilysin upregulation may be a beneficial therapeutic strategy in the treatment of AD, it is important to evaluate the behavioral consequences associated with increased neprilysin activity. Compared to their wild type (WT) littermates, behavioral analysis of 7 month old neprilysin mice confirmed hyperlocomotion in emergence test and 8 arm radial maze, showed no deficit in Y maze and novel object exploration but impaired contextual fear conditioning. Since neprilysin has been shown to degrade other substrates involved in brain function such as substance P, met-enkephalin and somatostatin, we measured by quantitative radioimmunoassay their levels in the hippocampus and frontal cortex of WT, NEP, APP and NEP x APP littermates. Neprilysin overexpression did not affect levels of these proteins, suggesting that other pathways contribute to the behavioral alteration observed in NEP mice. Based on the peripheral sink hypothesis, arguing that increased peripheral degradation of Abeta may favor efflux of Abeta from the CNS, peripheral neprilysin upregulation may be an alternative approach of interest for AD.