Neuronal upregulation of neprilysin as a potential therapeutic approach in Alzheimer's disease: A behavioral study

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Increased levels of beta-amyloid peptide (Abeta) and its subsequent accumulation in Alzheimer's disease (AD) brains are linked to an imbalance between its production, clearance and degradation. Therefore, upregulation of enzymes capable of degrading Abeta in vivo, such as neprilysin (NEP), represents a potential therapeutic approach to lower Abeta levels, prevent or inhibit its associated pathology and the impairment of brain functions, including memory.

It was recently shown, by gene transfer and transgenic overexpression, that NEP could significantly reduce brain Abeta levels, amyloid plaque formation and the associated cytopathology. However, the consequences of a sustained upregulation of neprilysin have not been yet investigated at the behavioral level.

In the aim to evaluate the behavioral effects of NEP overexpression and the potential benefits for AD, we generated mice with a neuronal overexpression of NEP. One of several transgenic lines, which shows a high NEP protein level and enzyme activity in the brain, was bred with amyloid precursor protein (APP) transgenic mice (J20). We show that brain Abeta levels are significantly reduced in the doubly NEPxJ20 transgenic mice and compare the performances of NEP overexpressing mice and NEPxJ20 doubly transgenic mice to their respective controls in motor and cognitive tasks.

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