High brain levels of neprilysin ameliorate Alzheimer pathology and rescue Aβ-dependent cognitive deficits

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Abnormal accumulation of β-amyloid (Aβ) peptide in the brain is considered as the first pathological key event leading to Alzheimer's disease (AD). Therefore, reduction of Aβ production, or its accelerated clearance from the brain, were proposed as therapeutic targets for drug development to ameliorate AD pathology and related cognitive deficits.

Activation of enzymes that degrade Aβ in vivo may be a valuable tool for AD therapy. We show here that neuronal upregulation of endogenous neprilysin in young transgenic mice expressing the AD-causing APP mutations led to reduction of brain Aβ levels and delayed amyloid plaque deposition. Moreover, neuronal expression of neprilysin rescued, in the Morris water maze, the Aβ-dependent memory deficit of an AD mouse model. Our results suggest neprilysin upregulation/activation as a therapeutic approach to prevent Aβ-related cognitive deficits in AD.

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