REVERSING EPHB2 DEPLETION RESCUES COGNITIVE FUNCTIONS IN ALZHEIMER MODEL


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Background: Amyloid-β (Aβ) oligomers may cause cognitive deficits in Alzheimer’s disease (AD) by impairing neuronal NMDA-type glutamate receptors, whose function is regulated by the EphB2 receptor tyrosine kinase. EphB2 is decreased in the dentate gyrus (DG) of human amyloid precursor protein (hAPP) transgenic mice and of humans with AD. We hypothesized that reductions in EphB2 contribute to Aβ-induced deficits in synaptic plasticity and cognitive functions.

Objective: To evaluate the potential importance of neuronal EphB2 depletion in the pathogenesis of AD.

Methods: We engineered lentiviral vectors to direct neuronal expression of EphB2 (Lenti-EphB2), an shRNA directed against EphB2 (Lenti-shEphB2R), or controls. For knockdown experiments, wildtype mice received bilateral injections of Lenti-shEphB2 or control into the DG at 4-5 months of age. Knockdown of EphB2 was confirmed by qRT-PCR and western blotting. For rescue experiments, hAPP mice and nontransgenic controls received bilateral injections of Lenti-EphB2 or control into the DG at 2 months of age. LTP recordings and behavioral tests were used to assess the effects of EphB2 modulations.

Results: In wildtype mice, shRNA-mediated knockdown of EphB2 reduced NMDA receptor currents and impaired long-term potentiation (LTP) in the DG, which are important for memory formation. These deficits closely resembled those seen in untreated hAPP mice. Normalizing EphB2 levels in the DG of hAPP mice reversed their deficits in NMDA receptor dependent LTP and their memory impairments.

Conclusion: These data suggest that increasing the level or function of EphB2 could be of therapeutic benefit in AD.