Potential memory restorative effects of a neurotrophic factor mimetic in an aged, transgenic mouse model of Alzheimer’s disease.

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Alzheimer’s disease (AD) is associated with an increase accumulation of amyloid beta (Aβ) peptide in the brain, which is believed to lead to cognitive impairment. Neurotrophic factors have shown promise in the treatment of AD symptoms, and we tested the effectiveness of a growth factor mimetic (BTX-1039) in the treatment of spatial memory deficits. The transgenic mice used in this study have three mutations that lead to over-production of the 770 isoform of the human amyloid beta-precursor protein in a C57BL/6J background strain. We conducted separate experiments with 6-month-old and 9-month-old mice. Our four treatment groups were: AD mouse/drug, AD mouse/vehicle, wild type mouse/drug, and wild type mouse/vehicle. Mice received daily i.p. injections of 0.20 ml saline or BTX-1039 (60mg/kg) for 14 consecutive days prior to starting behavioral testing. [Say something about blindedness?] We used a Morris water maze protocol that consisted of 6 days of place learning, 1 day of probe trials, followed by 3 days of cued learning. For both experiments, the transgenic mice injected with saline had significantly longer paths to the target platform during place learning than did all the other groups, indicating that the drug restored some memory function. The groups showed no differences in learning during the cued trials, indicating no effect of the transgenes or the drug on stimulus-response learning. For the probe trials, we observed significant impairment in memory retention in the transgenic mice relative to the wild type mice at 6 months of age, but we observed no differences between the strains at 9 months of age and no effects of the drug in either age class. This indicates that mice under 9 months of age should be used to test memory retention, but also suggests that our drug mainly impacts spatial learning rather than memory retention. In a pilot study, we tested mice of an intermediate age (8 months) using a higher dose of the drug (100 mg/kg), and these results suggest even stronger effectiveness for the drug in restoring spatial learning. We also quantified cell proliferation (Ki67 expression) within the dentate gyrus of the 9-month-old mice, as some studies indicate that AD causes a dysregulation of the cell cycle. Preliminary analyses indicate that the transgenes cause a small decrease in cell proliferation within the granule cell layer and a significant increase in cell proliferation in the hilus. No effects of the drug on cell proliferation were observed. Together, the results indicate some memory restorative effects of a neurotrophic factor mimetic that were not associated with changes in cell proliferation in the hippocampus.