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

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Abstract:
Alzheimer's disease (AD) is associated with an increased accumulation of amyloid beta (Aβ) peptide in the brain, which is believed to lead to cognitive impairment. Neurotrophic factors, which aid neuronal growth and survival, have shown promise for treating AD symptoms. 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 and associated Aβ 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) in saline for 14 consecutive days prior to starting behavioral testing, with the researcher blind to treatment. We used a Morris water maze protocol that consisted of 6 days of place learning, 1 day of probe trials, and 3 days of cued learning. For both experiments, the transgenic mice given saline had significantly longer paths to the target platform during place learning than did all 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 ages tested. 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 of this strain 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 AD causes dysregulation of the cell cycle. Preliminary results indicate that the transgenes cause a decrease in cell proliferation within the granule cell layer and a significant increase in cell proliferation in the hilus. The drug had no effect on cell proliferation. Together, the results indicate some memory restorative effects of a neurotrophic factor mimetic that

were not associated with changes in hippocampal cell proliferation.
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