

Effects of intracranial rAAV.Neu3 on dementia and neuropathology

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Research Abstract

A valid assessment of memory is perhaps the most important component of an endeavor to develop a novel treatment for Alzheimer's disease. However, memory is only one of the

behavioral impairments that Alzheimer's patients exhibit. They also have affective and sensorimotor deficits, and problems with social behavior. The 5xFAD transgenic mouse bears five mutations known to cause familial Alzheimer's disease (FAD). Like other Alzheimer models, they exhibit profound cognitive deficits on tests of spatial learning and memory. Unlike other APP-overexpressing mice, the 5xFAD transgenics exhibit robust neurodegeneration by 9 months of age. However, the 5xFAD mice also show a host of other behavioral anomalies. For example, they exhibit abnormal social behavior toward their cage-mates and do not exhibit the barbering phenomenon characteristic of wild-type mice of the same strain. Although a published report shows that 5xFAD mice spend more time on open arms of a plus maze, indicative of decreased anxiety, we have shown that this is attributable to impaired habituation and degeneration of inhibitory interneurons in layer IV whisker barrels (putatively making closed arms aversive). All indices of anxiety in the 5xFAD transgenics were normal in our hands. In the studies proposed herein we will determine whether the ganglioside-specific murine sialidase Neu3 can enhance cognition, normalize social behavior, and prevent neuronal loss and amyloid-related neuropathology in the 5xFAD mice. We have shown previously that intraventricular infusion of sialidase from *V. cholerae* (VCS) protects against kainate-induced hippocampal damage. VCS hydrolyzes gangliosides and produces a brain ganglioside profile that is similar to that of GD3 synthase (GD3S) inhibition, which we have shown to be neuroprotective, reduce plaque, and improve memory in APP-overexpressing transgenics. Our preliminary data show that infusion of VCS for 8 weeks is neuroprotective and reduces plaque in 12-month-old 5xFAD mice, but complications with chronic infusion over months and the need for multiple surgeries to exchange pumps make this approach impractical. Instead, we developed a recombinant adeno-associated viral vector (rAAV) that produces neuraminidase 3 (Neu3) indefinitely. In the present study mice will be injected with rAAV.Neu3 or rAAV.eGFP control in the dorsal hippocampus at 4 months of age, when A β expression and memory impairments are already evident in 5xFAD transgenics. Social behavior, social cognition, and spatial memory will be assessed from 7 to 9 months, as well as control tests for anxiety and sensorimotor function. Post-mortem analyses will assess Alzheimer-related neuropathology and neurodegeneration. Successfully reducing amyloid burden, cell death, and memory impairments in the transgenic mice may provide insight into new treatment strategies for Alzheimer's disease—treatments that could reduce or prevent dementia and associated behavioral symptoms in Alzheimer patients.

Further information available at:

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