Effects of modified erythropoietin on cognition and neuropathology

https://neurodegenerationresearch.eu/survey/effects-of-modified-erythropoietin-on-cognition-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. Unlike other APP-overexpressing mice, the 5xFAD transgenics exhibit robust neurodegeneration by 9 months of age. Like other Alzheimer models, they exhibit profound cognitive deficits on tests of spatial learning and memory. However, the 5xFAD mice show a host of other behavioral anomalies. For example, they exhibit much more social behavior toward their cage-mates as do wild-type mice, but do not exhibit the barbering phenomenon characteristic of some strains of laboratory mice, including wild-types of the same strain. Although published reports show 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 (i.e., making closed arms aversive). We have shown previously that a mutant, non-erythropoietic erythropoietin (Epo) is neuroprotective in models of glaucoma, macular degeneration, and MPTP neurotoxicity, without raising hematocrit. This modified Epo, EpoR76E, is generated indefinitely by a recombinant adeno-associated viral (rAAV) vector injected into the gastrocnemius (leg) muscle. Our preliminary data show that amyloid plaque is nearly completely cleared 2 months after a single intramuscular injection of rAAV.EpoR76E, in 12-month-old 5xFAD transgenics that started with extensive plaque in the cortex and hippocampus. The objective of this application is to determine whether rAAV.EpoR76E is neuroprotective and able to prevent or reverse the cognitive deficits and abnormal social behaviors exhibited by 5xFAD mice. The general hypothesis of the proposed research is that the Epo variant will successfully reduce plaque formation and prevent neurodegeneration and memory impairments in the mutant mice. We also expect the social behavior phenotype to be normalized in 5xFAD mice receiving rAAV.EpoR76E, on the expectation that it is an effect of neurodegeneration. In the proposed experiments, mice will be injected at 4 or 13 months of age with EpoR76E or rAAV.eGFP control construct. Social behavior and memory will be assessed, as well as control tests for anxiety and sensorimotor function. Post-mortem analyses will assess Alzheimer-related neuropathology and cell death. Finally, we will examine factors known to be involved in the production and clearance of A?, such as BACE1, IDE, and neprilysin, to determine the reason why A? is being cleared from 5xFAD brain by rAAV.EpoR76E. Cell culture work in primary neurons from 5xFAD and wild-type mice will determine how the mutant Epo construct affects APP processing. Successfully reducing amyloid burden, cell death, and memory impairments in the transgenic mice may provide insight into new treatment strategies that could reduce or prevent dementia in Alzheimer patients.

Lay Summary
The proposed experiments will test the effects of novel modified erythropoietin (Epo) variants on memory, social behavior, and Alzheimer-related neurodegeneration and neuropathology. The use of modified Epo represents not only a novel treatment strategy, but a novel therapeutic target for Alzheimer’s disease. These experiments are consistent with the stated goals of National Institute on Aging and National Institute of Neurological Disorders and Stroke.

Further information available at:

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