Project 3:

Environmental Enrichment in Alzheimer’s Transgenic mice

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The specific aims of Project 3 are to:

1) Dissect out the components of “complete” environmental enrichment (EE) in Alzheimer’s transgenic (Tg) mice

2) Elucidate the cellular and molecular mechanisms through which EE and its component activities may protect, as well as improve, cognitive function in AD Tg mice

3) Determine the inter-relationships between behavioral, neurohistologic, and neurochemical measures taken from the same animals and to relate cognitive benefits of EE in Tg mice to similar studies being done in AD patients within Florida ADRC Project 2.

Accomplishments of Project 3:

This project has been intimately involved with studies investigating the potential of environmental activities (cognitive, physical, social) to protect against AD. The project was designed to investigate protective and treatment effects of “environmental enrichment” in Alzheimer’s Tg mice. Lifelong “cognitive activity/stimulation” in humans has been associated with a lower risk of AD, but causality is difficult to prove. In an initial study during this grant period (Costa et al., 2007), we placed adolescent AD transgenic mice into either an enriched or standard housing environment. Behavioral testing at 4.5-6 months showed that environmentally enriched Tg mice outperformed mice in standard housing; indeed, they performed at the level of non-transgenic mice in multiple cognitive-based tasks. Microarray analysis revealed large enrichment-induced changes in hippocampal expression of genes/proteins related to Aβ sequestration and synaptic plasticity.

Although social, physical, and cognitive activities have each been suggested to reduce the risk of AD, epidemiologic studies cannot determine which activity or combination of activities is most important. To address this question, we did a comprehensive study (Cracchiolo et al., 2007) in which AD transgenic mice were reared long-term in one of four housing conditions (impoverished, social, social+physical, or complete enrichment) from 1.5 through 9 months of age. Thus, a stepwise layering of social, physical, and enhanced cognitive activity was created. Behavioral evaluation in a full battery of sensorimotor, anxiety, and cognitive tasks was carried out during the final 5 weeks of housing. Only AD mice raised in complete enrichment (i.e., enhanced cognitive activity) showed: (1) protection against cognitive impairment, (2) decreased brain Aβ deposition, and (3) increased hippocampal synaptic immunoreactivity. The protection provided by enhanced cognitive activity spanned multiple cognitive domains (working memory, reference learning, and recognition/identification). These results indicate that the enhanced cognitive activity of complete enrichment is required for cognitive and neurologic benefit to AD mice — physical and/or social activity are insufficient. This study predicts that enhanced physical activity will not protect against AD in humans.
To determine if a selective increase in neurogenesis occurs in cognitively-protected Tg mice raised in an enriched (cognitive) environment compared to those reared in physical activity housing, we analyzed the hippocampal subgranular zone for BrdU-positive cells in Sanchez-Ramos et al. (2009). A significant increase in cellular proliferation was evident for Tg mice raised with cognitive or physical activity compared to Tg mice reared in standard housing. However, counts of BrdU birth-dated cells two weeks after labeling revealed no differences among the three groups, indicating decreased survival of cells in the cognitive and physical activity groups. In view of our prior study showing that enhanced cognitive activity (but not enhanced physical activity) protects Alzheimer’s Tg mice against cognitive impairment, this neurogenesis study indicates that increased generation and survival of new neurons in the hippocampal dentate gyrus is not involved with the cognitive protective effects of complete (cognitive) environment in Alzheimer's transgenic mice.

Our most recent studies (unpublished) continue to underscore that enhanced cognitive activity is more effective than social and/or physical activity for cognitive protection against AD. Although there is evidence that physical activity protects against “general” cognitive decline during aging in humans and some animal studies, there have been essentially no controlled clinical studies showing beneficial protective or treatment effects of physical activity against Alzheimer’s disease.

References:

