Menopause exacerbates and exercise mitigates cognitive decline in a female mouse model of Alzheimer’s disease

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Background

Alzheimer’s Disease (AD)
- AD is a progressive, age-related neurodegenerative disease which causes neuronal damage and death and leads to profound impairments of memory and other cognitive functions.

Higher AD risk and incidence in women
- More than 2/3 of people with AD are women.
- Women have an earlier onset, faster progression, and greater severity of AD than men of the same age.

The gradual loss of ovarian hormones during the menopausal transition is thought to be a key factor in the higher female risk for AD, with cognitive and neuropathological changes likely accelerating during this 5-10 year period.

Neuroprotective effects of Exercise
- Lack of physical activity is a predisposing factor for AD.
- Long-term physical exercise has been associated with a reduction in the rates of cognitive decline, dementia and neurodegenerative diseases.

Developing a mouse model of female physiology in AD

CVN-AD Mouse Model

Transitional Menopause Mouse Model

Key features:
- Females raised but not ovariectomized (FROVX) model.
- Male and female inbred mice.
- Established timeline of AD-like pathologies.

Hormonal changes during the transition to menopause accelerate/exacerbate cognitive decline and the onset and progression of AD

1. VCD reduced uterine weight of C57 and CVN-AD mice

2. Exercise will act as a neuroprotective factor to slow AD progression and prevent the decline in cognitive function seen in AD and with menopause

Overarching Hypotheses & Design

Exercise increased fitness on a treadmill stress test in CVN-AD mice

1. Behavioral analysis at 14 & 24 wk timepoints to determine if there is a sensitive period for exercise

Work in Progress

Loss of ovarian function impaired short-term memory in CVN-AD mice and exercise mitigated this loss

Future Direction

To investigate the effects of chronic early life stress on cognitive function, depression-like behavior and AD-like neuropathogenesis in cycling and menopausal female CVN-AD.

- Stress caused by maternal neglect, separation, or maltreatment during early development increases the likelihood of cognitive decline, and stress vulnerability.
- The two prevalent co-morbidities in Alzheimer’s disease are cognitive loss and depression.
- Our female mouse model of Alzheimer’s disease will allow us to determine the relationship between these two symptoms of AD as they develop and to examine how these symptoms related to the neuropathogenesis that underlies this progressive disease.

Acknowledgements
- Funding: Duke University Bass Connections program, the Charies Lafitte Foundation, Duke BioCore.
- Many thanks to the Williams lab members: Irene Koc, Ameen Ahmad, Ahbiji Suhag, & Leila Boyle.
- Technical assistance: Thanks to Joan Wilson and Stuart Sundet.