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

Duke UNIVERSITY | BASS CONNECTIONS

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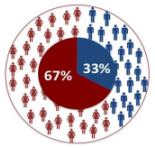
Background

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

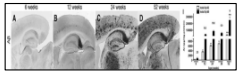
CVN-AD Mouse Model

(APPSwDI/mNos2$^{-/-}$; Cerebro-Vascular amyloid/Nos2$^{-/-}$)

Key features:
- Expresses mutated but not overexpressed APP.
- Nos2 null background creates human-like immunity.
- Established timeline of AD-like pathogenesis.

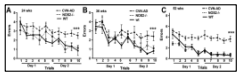
Timelines for AD-like pathogenesis

Amyloid pathology



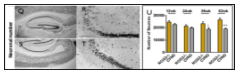
Kan et al., *Journal of Neuroscience*, 2015, 35(15):5969-5982; Colton et al., *Journal of Neuropathology & Experimental Neurology*, 2014, 73(8):752-769

Spatial memory deficits



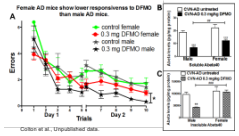
Colton et al., *Journal of Neuropathology & Experimental Neurology*, 2014, 73(8):752-769

Neuronal Loss



Kan et al., *Journal of Neuroscience*, 2015, 35(15):5969-5982; Colton et al., *Journal of Neuropathology & Experimental Neurology*, 2014, 73(8):752-769

Sex differences in pathogenesis

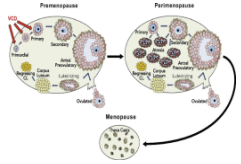


Colton et al., Unpublished data.

Transitional Menopause Mouse Model

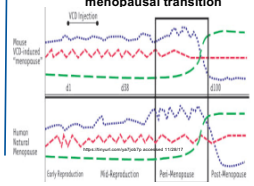
Key features:
- Produced by administering the ovotoxin 4-vinylcyclohexane (VCD) for several weeks.
- Hormonal changes caused by gradual loss of ovarian function approximates the human menopausal transition.

Accelerated ovarian failure occurs following treatment with the ovotoxin VCD



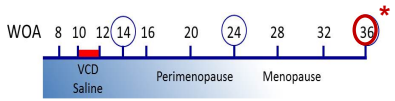
Brooks et al., *Physiology*, 2016, 31:250-257

VCD treatment of mice causes a gradual human-like menopausal transition

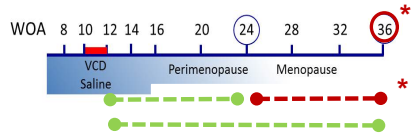


Overarching Hypotheses & Design

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

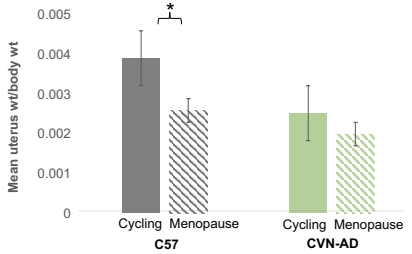


2. **Exercise will act as a neuroprotective factor to slow AD progression and prevent the decline in cognitive function seen in AD and with menopause**

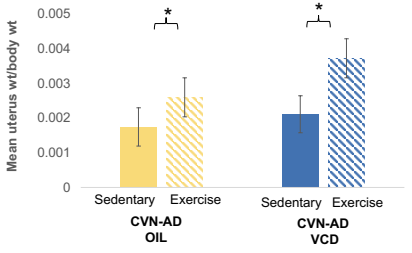


***Data presented here are the 36 wk timepoint with 12 wks of exercise starting at 24 weeks of age**

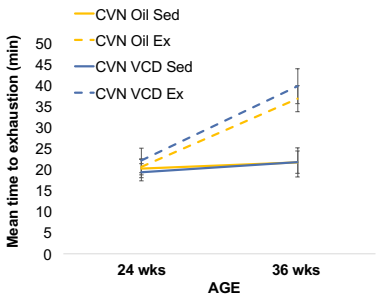
VCD reduced uterine weight of C57 and CVN-AD mice



Exercise increased uterine weight of CVN-AD mice compared to CVN-AD sedentary mice

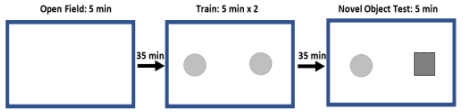


Exercise increased fitness on a treadmill stress test in CVN-AD mice

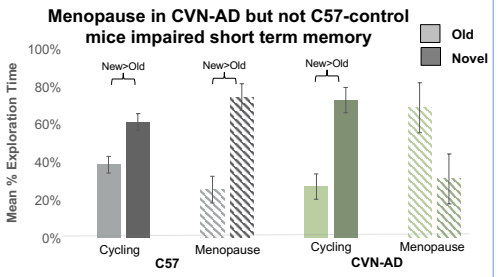


Loss of ovarian function impaired short-term memory in CVN-AD mice and exercise mitigated this loss

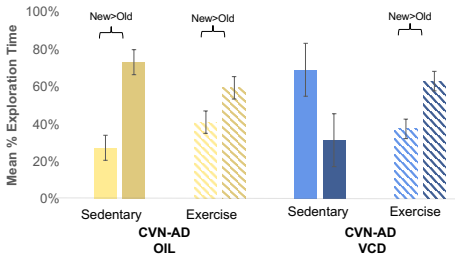
Novel Object Recognition task



Menopause in CVN-AD but not C57-control mice impaired short term memory



Exercise prevented the impairment in short-term memory induced by loss of ovarian function in CVN-AD mice

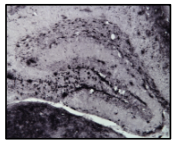


Work in Progress

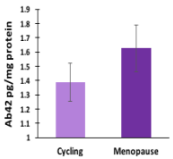
1. Behavioral analysis at 14 & 24 wk timepoints to determine if there is a sensitive period for exercise
2. Analysis of neuropathological markers of AD to determine whether VCD exacerbates and exercise mitigates decline

Preliminary results with a small sample size (n=4-5/grp) of 36-wk-old CVN-AD mice suggests that menopause may accelerate Aβ accumulation in the hippocampus

Hippocampal slice Aβ immunohistochemistry

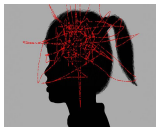


Soluble Aβ



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 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

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