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Intrinsic aerobic capacity, sex, and brain aging: Determinants of Alzheimer's disease risk

Edziu M Franczak[1] | Julia A. Stopperan[1] | Julie A. Allen[1] | Fu-Chen Jane Yang[1] | Natalie S. Swerdlow[1] | Kartik M Shankar[2] | John A Stanford[1] | Lauren Gerard Koch[3] | Steven L. Britton[4] | John P Thyfault[1] | **Heather M Wilkins[5]**

[1] University of Kansas Medical Center, Kansas City, KS, USA

[2] University of Colorado School of Medicine, Denver, CO, USA

[3] The University of Toledo, Toledo, OH, USA

[4] University of Michigan, Department of Anesthesiology, Functional Genomics Laboratory, Ann Arbor, MI, USA

[5] University of Kansas Alzheimer's Disease Center, Fairway, KS, USA

Correspondence
Heather M Wilkins, University of Kansas Alzheimer's Disease Center, Fairway, KS, USA.
Email: hwilkins@kumc.edu

Abstract

Background: Low aerobic capacity (or cardiorespiratory fitness) is strongly associated with all-cause mortality and risk for Alzheimer's disease (AD). Individuals with early dementia and AD have lower aerobic capacity compared to age-matched controls. The mechanism by which low aerobic capacity influences AD are unknown but are suggestive of an impairment in mitochondrial energetics.

Method: Here we used rats selectively bred over several generations to have intrinsic low or high exercise capacity. Rats were bred based on low or high capacity to complete an aerobic treadmill running test resulting in rats with robustly different intrinsic aerobic capacity despite being maintained sedentary. We examined mitochondrial function, RNA sequencing, and markers of AD in brain tissue from 18-month-old male and female Low Capacity Runners (LCR) and High Capacity Runners (HCR) from generation 43 of selection.

Result: We found lower mitochondrial respiration in brains of female LCR rats for complex I-, ADP-, uncoupled-, and complex II-driven flux when compared to LCR males. Brain Complex I driven respiratory flux was reduced in LCR females when compared to HCR females. No differences were observed in complex I or citrate synthase (CS) Vmax but complex IV Vmax was lower in LCR males versus HCR males. Female LCR rats had higher $A\beta_{42}$ while both male and female LCR rats had higher phosphorylated tau at threonine 181 in whole brain homogenates. RNAseq revealed a greater effect of sex on gene expression than strain (HCR vs. LCR). However, FOXO signaling, axonal guidance, ubiquitination, and protein phosphorylation pathways were greater in male LCR versus male HCR rats. Glutamate NMDA receptor subunit 3A (Grin3a) and Transcription factor 7-like 2 (TCF7L2) were identified as coordinating numerous downstream targets with IPA analysis in male LCR rats. RNA sequencing outcomes suggest downregulation of AMPK signaling in female LCR rats.

Conclusion: These data support a strong relationship between intrinsic aerobic capacity, sex, and markers of brain mitochondrial function and AD in late-middle aged HCR and LCR rats.