The Role of Physical Activity in the Treatment of Type 2 Diabetes-Induced Vascular Cognitive Impairment

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ABSTRACT

Type 2 Diabetes (T2D) carriers are at increased risk for vascular cognitive impairment (VCI). Our laboratory has focused on the development and progression of VCI in Otsuka Long Evans Tokushima Fatty (OLETF) rats, a model of T2D. We have previously found that physical activity attenuates age-related declines in middle cerebral artery (MCA) vasomotor function, but the underlying mechanisms remain to be elucidated. The purpose of our study is to examine the relationship between cerebrovascular function, T2D and PA. We hypothesize that working memory (Barnes maze) and middle cerebral artery vasomotor function (pressure myography) will be impaired in T2D. Further, that spontaneous PA, initiated after the onset of T2D, will attenuate age-related declines in memory and MCA vasomotor function. Forty Otsuka Long Evans Tokushima fatty rats (hypertensive model of T2D) will be divided into three groups: food restricted (FR; n=16; do not develop T2D as we restrict food intake), T2D (n=16) and T2D+PA (n=8; PA begins at 20 wk). Memory and MCA vasomotor function will be examined at eight FR and T2D rats at 20 wk (onset of T2D) and in all remaining rats at 40 wk. We anticipate that working memory and MCA endothelial-mediated vasodilation (acetylcholine dose response curve) will be reduced in T2D vs. FR rats at 20 wk of age. Between 20-40 wk, age-related declines in working memory, endothelial vasodilation and myogenic responsiveness (pressure curves) will be accelerated in the T2D group. However, between 20-40 wk, T2D+PA rats will preserve working memory and vasomotor responses, suggesting PA attenuates age-related decline in cognition and cerebrovascular function. Potentially, chronic PA improves cerebral endothelial function and cerebrovascular autoregulation, and as a result helps preserve working memory in T2D. Supported by CVM faculty research grant (PI: Laughlin)

INTRODUCTION

Type 2 Diabetes (T2D) is implicated in Vascular Cognitive Impairment (VCI). Physical activity (PA) is known to have many benefits, including the improvement of vascular function and cognition. However, whether PA-induced improvements in cerebral vascular function mediate improvements in cognition remains to be elucidated fully.

HYPOTHESIS

• Middle Cerebral Artery (MCA) vasomotor function and working memory will be impaired in T2D
• Physical activity attenuates age-related declines in MCA and cognitive function in rats with T2D

METHODS

EXPERIMENTAL DESIGN

At 4 weeks: OLETF T2D
At 20 weeks: FR
At 40 weeks: FR

Otsuka Long Evans Tokushima Fatty rats (hypertensive model of T2D) will be divided into three groups: food restricted (FR; n=16; do not develop T2D as we restrict food intake), T2D (n=16) and T2D+PA (n=8; PA begins at 20 wk). Memory and MCA vasomotor function will be examined at eight FR and T2D rats at 20 wk (onset of T2D) and in all remaining rats at 40 wk. We anticipate that working memory and MCA endothelial-mediated vasodilation (acetylcholine dose response curve) will be reduced in T2D vs. FR rats at 20 wk of age. Between 20-40 wk, age-related declines in working memory, endothelial vasodilation and myogenic responsiveness (pressure curves) will be accelerated in the T2D group. However, between 20-40 wk, T2D+PA rats will preserve working memory and vasomotor responses, suggesting PA attenuates age-related decline in cognition and cerebrovascular function. Potentially, chronic PA improves cerebral endothelial function and cerebrovascular autoregulation, and as a result helps preserve working memory in T2D. Supported by CVM faculty research grant (PI: Laughlin)

METHODS

ANIMAL MODEL of T2D

Otsuka Long Evans Tokushima Fatty (OLETF) rats lack functional cholecystokinin receptors in the brain, as a result they are hyperphagic and develop T2D. As a control group we food restrict (FR) OLETFT rats by 30%

Cerebral vascular function:
• MCA will be harvested, mounted on two glass pipettes and pressurized to 80 mmHg with PSS to mimic physiological environment and a dose response curve for Acetylcholine (ACh) will be conducted
• ACh-induced dilation functions through the release of endothelial- Nitric Oxide. Therefore, ACh-induced dilation is an indicator of endothelial function
• Previously, we observed that T2D OLETF rats exhibit impaired endothelial function, indicated by reduced ACh-induced dilation in skeletal muscle arteries
• We want to extend on these findings and determine if endothelial function is impaired in the MCA

ALTERNATIVE APPROACH

If our hypothesis is false, we plan to investigate:
• Insulin-Like Growth Factor (IGF-1) and Brain-Derived Neurotrophic Factor (BDNF)
• BDNF and IGF-1 are hormones that are secreted in response to intense PA and known to work together to maintain cognitive function by stimulating neurogenesis in the hippocampus
• The hippocampus is involved in consolidation of short to long term memory and spatial navigation
• Thus, we plan to measure the circulating concentrations of these hormones in the setting of T2D with and without concurrent PA

ACKNOWLEDGEMENTS

CVM Faculty Research Grant: Laughlin, PI