Travis Blaze McMurphy
PhD Candidate

“Environmental and gene therapy approaches to improve glycemic control and promote healthy aging”

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06.23.1985 . . . . . . . . . . . . . . . . . . . . . . . . . . . Born– Rome, OH

2009 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . Bachelor of Science, Marketing, Edinboro University of PA

2011 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . Bachelor of Science, Biology, Edinboro University of PA

2012-Present . . . . . . . . . . . . . . . . . . . . . . . . . Graduate Research Associate, Biomedical Sciences Graduate Program, The Ohio State University

COMMITTEE MEMBERS

Dr. Lei Cao Ph.D., Advisor

Dr. A. Courtney DeVries Ph.D.

Dr. Denis C. Guttridge Ph.D.

Dr. F. Kay Huebner Ph.D.
ABSTRACT

The epidemic of obesity and associated complications comprising metabolic syndrome exact a monumental burden on global public health in both morbidity and cost of treatment. Stressful, sedentary lifestyles coupled with excessive caloric intake contribute to increasing rates of obesity and type II diabetes mellitus worldwide. Additionally, the likelihood of excess visceral adiposity progressing into metabolic syndrome grows dramatically with age. Obesity-associated insulin resistance commonly precedes the onset of type II diabetes and most treatments for the resulting hyperglycemia mimic, sensitize, or enhance secretion of insulin. Therefore, interventions that improve glycemic control independently of insulin signaling are appealing alternatives. The overall objective of this dissertation is to evaluate the efficacy of environmental enrichment and gene therapy models to improve glycemic control and promote healthy aging.

The ability of pathogenic viruses to alter host metabolism has been recently characterized. Infection by the human adenovirus serotype 36 (AD36) promotes obesity in animal models and correlates to increased adiposity in humans, yet improves glycemic control. Based on in vitro studies, the E4ORF1 protein is responsible for both the adipogenic and insulin sparing properties of AD36 infection via insulin independent Akt activation. We generated a recombinant adeno-associated viral (rAAV) vector to express AD36E4ORF1. Through intravenous delivery we expressed AD36E4ORF1 in the livers of diabetic, insulin resistant, and wild-type mice. Hepatic AD36E4ORF1 improved glucose tolerance and attenuated hyperglycemia in obese diabetic Db-/- mice without improving insulin sensitivity. AD36E4ORF1 also reduced hyperinsulinemia and improved glucose tolerance in insulin resistant mice with diet induced obesity (DIO). Liver specific glucose uptake was increased without improving insulin sensitivity. Confirming the findings of previous in vitro studies, Akt activity was not only increased but also required for AD36E4ORF1 mediated glucose uptake. AD36E4ORF1 expression is a model of insulin independent AKT activation and
provides a novel therapeutic mechanism to improve glycemic control in cases of insulin resistance.

Next, we looked at how environmental factors might contribute to healthy aging and prevention of metabolic syndrome. Animals housed in a larger, more complex enriched environment (EE) are provided with increased somatosensory stimulation, physical exercise, and enhanced social interactions. Together, these stimuli increase expression of brain derived neurotrophic factor (BDNF) in the hypothalamus, activating a hypothalamic sympathoneural-adipocyte axis (HSA). In young animals, HSA activation has been shown to improve glycemic control and overall health but its impact in older animals has not been previously characterized.

Middle-aged 10 month old female mice were housed in EE for 6 weeks and displayed HSA activation, improved glycemic control, and decreased adiposity without a reduction in overall body weight. In a long term study of middle-aged mice housed in EE for 12 months, we observed a metabolic phenotype characteristic of healthy aging and improved glycemic control. The animals housed in EE exhibited improved glucose tolerance, enhanced motor skills, reduced adiposity, increased mitochondrial biogenesis, remodeling and browning of the white adipose tissue, and prevention of age-associated decline in the brown adipose tissue. Remodeling of the adipose tissue was accompanied by an adipose-specific upregulation of the tumor suppressor phosphatase tensin homologue deleted on chromosome ten (PTEN). Activation of the HSA axis was necessary and sufficient to upregulate PTEN in the adipose tissue. Moreover, sympathetic activation of type 1 and 2 β-adrenergic receptors was responsible for increasing PTEN expression. This study is the first to identify a novel physiological mechanism of PTEN upregulation through sympathetic stimulation of the adipose tissue. EE initiated in middle-aged female mice provides a model of improved glycemic control, healthy aging, and physiologically induced PTEN expression in the adipose tissue. Based on these findings, living in enriched environments with increased social and physical interactions promotes healthy aging through activation of a brain-adipocyte connection which reduces risk factors contributing to age-associated pathologies.
McMurphy, T. B., Huang, W., Liu, X., Widstrom, K., Queen, N., Siu, J., & Cao, L. Environmental Activation of a Hypothalamic-Adipocyte Axis Promotes Healthy Aging. *Manuscript in Preparation*


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FUTURE PLANS

After graduation I will move on to a postdoctoral research position. I am currently pursuing opportunities in the United States and Grenada. My long term goal is a career in academia focused on translational research in the areas of aging and regenerative medicine.
Biomedical Sciences Graduate Program
1170 Graves Hall
333 W. 10th Avenue
Columbus, Ohio 43210