2018

Genetic manipulation of lactate metabolism to regulate memory and Alzheimer's disease pathogenesis

BrainsCAN , Western University

Robert Cumming

Robert Bartha

Tim Scholl

Western BrainsCAN
Transforming brain research.

Project **Summary**

KNOWLEDGE MOBILIZATION & IMPACT

Genetic manipulation of lactate metabolism to regulate memory and Alzheimer's disease pathogenesis

Background

Neurons have very high-energy needs as they transmit signals in the brain. It has long been accepted that glucose fuels the brain via a process called 'mitochondrial oxidative phosphorylation'. This form of metabolism uses certain enzymes to oxidize glucose while releasing large amounts of energy.

However, another process, termed 'aerobic glycolysis', has been found to play a key role with respect to memory. Aerobic glycolysis is an alternative form of metabolism that breaks glucose down into lactate.

The brain consists primarily of two main cell types; neurons and astrocytes. Neurons are cells that process and transmit information via electrical and chemical signals; an energetically demanding process that is critical for the formation of memories. Astrocytes are star-shaped cells that provide nutrients to neurons and maintain the extracellular ion balance within the brain. Astrocytes are believed to use aerobic glycolysis to produce lactate, which is then transported to neurons and used as a fuel source for memory processes.

We have recently found an age-related decline in a key enzyme responsible for the production of lactate within the brain. The decline in this enzyme was also associated with decreased lactate levels and poorer memory performance in aged mice. Interestingly, we discovered that lactate generating enzymes were found mostly in neurons and, to a lesser extent, in astrocytes. Therefore, neurons may be capable of directly generating lactate for memory purposes.

Surprisingly, we found that brain lactate levels remained elevated with age and increased expression of lactate generating enzymes correlated with poorer memory performance in a mouse model of Alzheimer's disease (AD). Our highly novel findings suggest that **while lactate production within the brain is beneficial in healthy aging, increased lactate metabolism may contribute to cognitive decline in AD.** In support of our theory, recent clinical studies have shown that elevated lactate levels correlate negatively with memory performance in AD patients.

Funding Program

BrainsCAN Accelerator Grant: Stimulus
Awarded: $53,684

Additional BrainsCAN Support

Imaging Core
Rodent Cognition Core

Western Faculty, Group or Institution

Department of Biology, Faculty of Science

Keywords

Alzheimer's disease, memory

Related

none

Share this page

Tweet Share

The Problem

While we know that lactate production in the brain is beneficial for memory in healthy aging, dysfunctional production seems to contribute to a decline in memory function. No study to date has tried to determine which cell type produces lactate and if cell-type specific lactate production in the brain is important for normal memory function.

We aim to understand the processes of production and utilization of lactate and its effect on memory and cognition in health and in disease across the lifespan. This can open up new clinical approaches to treating cognitive and neurodegenerative diseases such as AD by altering lactate metabolism.

The Project

Our project will attempt to determine the relative importance of astrocyte or neuronal directed lactate generation on memory by modifying mouse models to either suppress or overexpress the lactate producing enzyme in either cell type. Using these newly created transgenic mouse models, we aim to understand the processes of production and utilization of lactate and its effect on memory and cognition in health and in AD across the lifespan. The outcome of our study may lead to entirely new clinical approaches to treating cognitive and neurodegenerative disorders via drugs which alter lactate metabolism.

Western Researchers

Robert Cumming
Robert Bartha
Tim Scholl