Unraveling a beneficial muscle-brain metabolic axis in healthy ageing

Ditte Finkas Damgaard

Superviser: Luc Pellerin (UPOI), Juan P Bolaños (USAL)

Introduction

- The world population in general grows older and older, but ageing is an unavoidable reaction. These two factors combined with a sedentary lifestyle makes it up for the perfect recipe for age-related cognitive impairments. Here exercising has shown promising protective effects on several tissues, here among the brain's synaptic plasticity. Where it possibly can down accelerate the ageing process.
- Exercise leads to release of lactate from the glycolytic fibers in the skeletal muscles and astrocytes in the brain. Lactate is transported out of the glycolytic fibers/astrocytes through **MCT4** and taken up by the oxidative fibers/neurons by **MCT1**. Together with the illumination of the Astrocyte-Neuron-Lactate-Shuttle have studies shown that lactate plays an important role in memory formation and maintenance.
- **The overall aim of the project** is to examine the effects of muscle derived lactate on cognitive functions in mice after a long-term training intervention. **The hypothesis** is that a knockout of MCT4 in the skeletal muscles will eliminate the major transport of lactate from the muscles to 1) The blood stream 2) The brain, and the hereby less available lactate for the brain will lead to measurable differences in behavior.

Methods and Materials (UPOI)

Step 1: Generation of a muscle-specific MCT4 knockout mice model. This will be done by a retro orbital injection of AAV8-Des-Cre-eGFP in MCT4 flox/flox mice (female, age: 2 months). Corresponding littermates will be injected with an AAV without Cre.
The AAV will have 1 month to infect the skeletal muscle cells (step 2+3).

Step 2:
Characterization of the muscle specific MCT4 knockout model

Step 3:
Long-term training with access to running wheels or sedentary behaviour with subsequent behavioural tests

Week 4:
Start of muscle physiological tests with mice which have recieved either the vehicle or AAV8-Des-Cre-eGFP.

Physiological tests
- Treadmill
- Rota rod + grip strength
- Running wheel
- Ex vivo force measurement
- Ex vivo glucose uptake

6 weeks of muscle physiological tests

6 weeks of VWR vs sedentary

2 weeks of behavioural tests

W4:
Start of long-term training protocol with mice which have recieved either the vehicle or AAV8-Des-Cre-eGFP.

W10:
Start of behavioral test for mice which have recieved vehicle or AAV8-Des-Cre-eGFP and have been subject to VWR or sedentary behaviour.

Behavioural tests
- Rota rod
- Open field
- Hole board
- Novel recognition object
- Radial maze

How the project benefits from the collaboration between UPOI and USAL

The project benefits/will benefit from the collaboration between the laboratory at University of Poitiers (UPOI) and the laboratory at University of Salamanca (USAL), in that way that each laboratory comes with their specific expertise and complementary knowledge.

The laboratory at UPOI and USAL are both labs with great interest and knowledge about neuroscience. And especially knowledge about brain metabolism in astrocytes and neurons. Next have both laboratories an interest in understanding the interaction between the brain and the skeletal muscles to understand how exercising influences the brain metabolism.

- Both the laboratory at UPOI and USAL are familiar with and use adeno associated viral vectors to produce knockout models. On behalf of this knowledge was it decide to construct the MCT4 KO model this way, which will be used in step 2+3 in the project
- Behavioural tests are also methods that both laboratories have a great knowledge about and are familiar with. This will be used in step 3 in the project.

Mail: ditte.finkas.damgaard@univ-poitiers.fr
Follow me: @dittefd
Connect with me: Ditte Finkas Damgaard

References:
- Brooks GA. The lactate shuttle during exercise and recovery. Med Sci Sports Exerc. 1986 Jun;18(3):360-8.
- Joubert R, Vignaud A, Le M, Moal C, Messaddeq N, Buj-Bello A. Site-specific Mtm1 mutagenesis by an AAV-Cre vector reveals that myotubularin is essential in adult muscle. Hum Mol Genet. 2013 May 1;22(9):1856-66.
- Pellerin L, Magistretti PJ. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc Natl Acad Sci U S A. 1994 Oct 25;91(22):10625-9.
- Suzuki A, Stern SA, Bozdagi O, Huntley GW, Walker RH, Magistretti PJ, Alberini CM. Astrocyte-neuron lactate transport is required for long-term memory formation. Cell. 2011 Mar 4;144(5):810-23.
- Tsai SF, Chen PC, Calkins MJ, Wu SY, Kuo YM. Exercise Counteracts Aging-Related Memory Impairment: A Potential Role for the Astrocytic Metabolic Shuttle. Front Aging Neurosci. 2016 Mar 22;8:57.