AMPK, metabolism and ALS

https://neurodegenerationresearch.eu/survey/ampk-metabolism-and-als/

Principal Investigators

KALB, ROBERT G

Institution

CHILDREN'S HOSP OF PHILADELPHIA

Contact information of lead PI
Country

USA

Title of project or programme

AMPK, metabolism and ALS

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,137,224.77

Start date of award

15/03/2016

Total duration of award in years

5

The project/programme is most relevant to:

Motor neurone diseases

Keywords

5'-AMP-activated protein kinase, Amyotrophic Lateral Sclerosis, Metabolism, Glycolysis, Hexosamines

Research Abstract

? DESCRIPTION (provided by applicant): All neurodegenerative diseases (NDG) display mitochondrial dysfunction and this can lead to activation of AMP activated protein kinase (AMPK) either through a reduced cellular AMP/ATP ratio or via the production of reactive oxygen species. Active AMPK re-wires cellular metabolism by inhibiting catabolic and

stimulating anabolic processes. While intuitively activated AMPK ought to be healthful for neurons, in several NDG models AMPK activation has been shown to be noxious to neurons. This proposal aims to identify the mechanism by which activated AMPK in neurons is injurious in cellular models of Amyotrophic Lateral Sclerosis (ALS). Neurons expressing mutant SOD or TDP43 (to model ALS) have enhanced glycolysis as a function of AMPK activation. Experiments in Specific Aim #1 test the hypothesis that by diverting glycolytic substrates away from the hexosamine biosynthetic and the pentose phosphate pathways – key pathways for maintaining healthy redox state and suppressing the unfolded protein response – activated AMPK is noxious to neurons. To translate these observations into a potential therapy for ALS patients we need to be able to manipulate glycolysis in neurons specifically – since inhibition of glycolysis in glial cells could have adverse effects. In Specific Aim #2, we will use genetically modified mice to isolate ribosomes from neurons and glial cells separately and interrogate the associated mRNA for cell type specific variants of glycolytic enzymes. Rewiring metabolism in the setting of toxic proteins may be reporter for a subgroup of ALS patients that could respond to metabolism-targeted intervention. In Specific Aim #3, we will determine the prevalence of metabolic re-wiring in fibroblasts re-programmed into neurons from ALS patients and controls. Understanding the neuron-specific adaptation to metabolic stress in NDG has the potential to uncover new targets for therapeutic intervention.

Lay Summary

PUBLIC HEALTH RELEVANCE: Normal neurons and neurons experiencing neurodegenerative insults utilize fuel in distinct ways. This proposal investigates how metabolic adaptations in specific cells types influence survival of insulted neurons. Identifying the enzymes in neurons specifically that mediate these metabolic adaptations will lead to new therapeutic opportunities.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Motor neurone diseases

Years:
2016

Database Categories:
N/A

Database Tags:
N/A