Mitochondrial SIRT3 in Huntingtons disease

https://neurodegenerationresearch.eu/survey/mitochondrial-sirt3-in-huntingtons-disease/

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Country

USA

Title of project or programme

Mitochondrial SIRT3 in Huntingtons disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

411974.3119

Start date of award

01/09/2016

Total duration of award in years

2

Keywords
Research Abstract

PROJECT SUMMARY Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder for which no disease modifying therapy exists. Clinical symptoms include progressive involuntary movement, psychiatric signs, cognitive decline, and a shortened lifespan. There is no currently available “neuroprotective” therapy to modify the disease course of HD. Although normal huntingtin (Htt) function is not fully understood, mutant HTT (mHtt) has been associated with mitochondrial dysfunction because it disrupts energetic function, leads to impaired mitochondrial protein trafficking and interruption of mitochondrial dynamics and protein import. Mitochondrial dysfunction has emerged as a key determinant of the disease progression in HD. Therefore counteracting mHtt-induced mitochondrial dysfunction is emerging as a target of treatment for this devastating condition. Proper mitochondrial function requires well-orchestrated homeostasis and careful regulation of the activity of mitochondrial enzymes. Lysine acetylation

is a highly regulated posttranslational modification in which a substantial number of mitochondrial proteins are subject to reversible lysine acetylation, and the function of these proteins is regulated by its acetylation status. SIRT3 has been demonstrated as a dominant mitochondrial deacetylase and controls acetylated levels of global mitochondrial proteins. The goal of the current application is to determine whether SIRT3 can protect against mHtt-induced mitochondrial dysfunction and neurondegeneration in vivo and reveal the underlying molecular mechanisms of SIRT3-mediated neuroprotection in HD. In pursuit of this goal, we will test the hypothesis that SIRT3 regulates mitochondrial acetylome and maintains mitochondrial metabolic homeostasis in response to mHtt through the following specific aims. In Specific Aim 1, we will determine whether overexpression of SIRT3 before or after the onset of disease will delay disease onset and slow disease progression in HD mouse models. In Specific Aim 2, we will investigate the molecular mechanisms underlying the SIRT3-medicated neuroprotection in HD by combining hypothesis-driven approach and unbiased acetylome approach. Successful completion of these specific aims will contribute to the mechanistic understanding of the role of a mitochondrial fidelity protein, SIRT3, in HD and mitochondrial dysfunction with potential identification of novel targets for pharmacologic manipulation for HD.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A