NAD, PGC-1alpha and SIRT3 as Therapeutics Targets for Huntingtons Disease

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Contact information of lead PI
Country

USA

Title of project or programme

NAD, PGC-1alpha and SIRT3 as Therapeutics Targets for Huntingtons Disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,666,812.84

Start date of award

15/02/2015

Total duration of award in years

4

The project/programme is most relevant to:

Huntington's disease

Keywords

nicotinamide-beta-riboside, Bexarotene, Fenofibrate, Huntington Disease, therapeutic target

Research Abstract

? DESCRIPTION (provided by applicant): Huntington’s disease (HD) is an autosomal dominant progressive neurodegenerative disease leading to both cognitive as well as motor deficits, and

severe disability. The disease is caused by an unstable CAG repeat expansion which leads to a polyglutamine stretch within the protein huntingtin. The toxic effects of mutant huntingtin result in transcriptional dysregulation as well as mitochondrial dysfunction and oxidative damage. There is a deficiency of PGC-1alpha, a transcriptional coactivator which controls mitochondrial biogenesis and expression of antioxidant enzymes. There is also a deficiency of SIRT3, which is a protein deacetylase whose expression within mitochondria is dependent on PGC-1alpha. We propose validating both PGC-1alpha and SIRT3 as therapeutic targets for the treatment of HD. We will determine whether crossing both R6/2 and KI-zQ175 mice with SIRT3 overexpressing mice will produce neuroprotective effects. We will administer nicotinamide riboside (NR) in the diet as a means of activating SIRT1 and SIRT3, and determine whether this produces neuroprotective effects in both the R6/2 and the BACHD transgenic mouse models of HD. Lastly we will determine whether administration of the panPPAR agonist fenofibrate, or the RXR agonist bexarotene either alone or in combination will increase PGC-1alpha expression and exert neuroprotective effects in R6/2 and BACHD transgenic mice. These studies will validate PGC-1alpha and SIRT3 as therapeutic targets, and will determine whether NR, fenofibrate and bexarotene are suitable for further preclinical development, and ultimately for clinical trials to establish efficacy as neuroprotective therapies for HD.

Lay Summary
PUBLIC HEALTH RELEVANCE: The proposed studies will determine whether increasing the activity of PGC-1alpha, SIRT1 and SIRT3 will exert neuroprotective effects in transgenic mouse models of Huntington’s disease (HD). We will determine whether genetically increasing SIRT3, or administration of nicotinamide riboside (NR) to increase brain and mitochondrial levels of NAD+, and activate SIRT1 and SIRT3 are valid therapeutic strategies for HD. Lastly we will examine the effects of fenofibrate and bexarotene as means of pharmacologically increasing expression of PGC-1alpha, and thereby producing neuroprotective effects in transgenic mouse models of HD.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Huntington's disease

Years:
2016

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