Dynamin-related protein 1, neurodegeneration and Huntingtons disease

https://neurodegenerationresearch.eu/survey/dynamin-related-protein-1-neurodegeneration-and-huntingtons-disease/

Principal Investigators

QI, XIN

Institution

CASE WESTERN RESERVE UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Dynamin-related protein 1, neurodegeneration and Huntingtons disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,590,454.13

Start date of award

01/06/2014

Total duration of award in years

3

The project/programme is most relevant to:

Huntington's disease

Keywords

Dynamin, Huntington Disease, Nerve Degeneration, Mitochondria, MAPK1 gene

Research Abstract

DESCRIPTION (provided by applicant): Huntington’s disease (HD) is a fatal, autosomal dominant, neurodegenerative disorder caused by a glutamine-coding CAG expansion within

exon 1 of the huntingtin gene. Although the genetic mutation associated with the disease has been identified, the molecular and cellular basis of HD is not yet understood and successful treatment for this disease remains elusive. Basic research and clinical studies indicate that mitochondrial dysfunction plays an important role in the pathogenesis of HD. Mitochondria are organized in a highly dynamic tubular network that is continuously reshaped by opposing processes of fusion and fission. Dynamin-related protein 1 (Drp1) is a large GTPase and a key protein governing mitochondrial fission. Recent studies have highlighted the causal role of Drp1-mediated excessive mitochondrial fission in neuronal death in HD cell culture models. However, how Drp1 hyperactivation mediates mitochondrial damage and neurodegeneration in HD and whether pharmacological inhibition of Drp1 activation is sufficient to reduce mutant Htt (mtHtt)-induced neurotoxicity and neurodegeneration are not known. Our recent work showed that Drp1 is translocated to the mitochondria and hyper-activated in both HD cell cultures and in vivo in the HD R6/2 transgenic mouse brain. Importantly, using a novel and selective peptide inhibitor of Drp1, P110, recently developed in our group, we found that inhibition of Drp1-dependent mitochondrial impairment corrected mitochondrial dysfunction and neuronal cell death in HD cell cultures, and reduced behavioral deficits and loss of striatal neurons in HD R6/2 transgenic mice. Moreover, treatment with P110 corrected mitochondrial morphology and reduced neurite loss and cell death in GABAergic striatal neurons derived from HD patient- induced pluripotent stem cells (HD-iPS cells). Further, using unbiased proteomic analysis, we recently profiled the interactome of Drp1 in neuronal cultures derived from HD patient-iPS cells. Our preliminary studies identified two mechanistically distinct candidate proteins (ATADA3, a member of mitochondrial AAA-ATPase family, and MAPK1, a serine/threonine kinase) that are involved in Drp1-mediated neuronal damage. These lines of evidence indicate that Drp1 hyperactivation is a predominant cause of neurodegeneration in HD. Thus, we hypothesize that inhibition of Drp1-mediated mitochondrial damage is a novel approach for reducing neuropathology in HD models in vitro and in vivo. Using biochemical, imaging, bio-energetic, proteomic and pharmacological approaches ranging from animals to patient neurons, our goal in this application is to unravel the complexity of Drp1-mediated mitochondrial dysfunction in neurodegeneration in both mechanistic and therapeutic detail. The proposed study will produce novel information on the role of Drp1-mediated mitochondrial fission in the pathogenesis of HD and provide a useful model system in which to study mitochondrial pathology in striatal neurons. We will also generate pharmacological tools to inhibit HD pathogenesis as a first step towards the development of novel therapeutics for HD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Huntington’s disease (HD) is fatal autosomal dominant neurodegenerative disorder. The exact causes of neuronal damage are unknown and effective treatment is not available. Basic research and clinical studies indicate that mitochondrial dysfunction plays an important role in the underlying mechanisms of striatal neuronal cell death both in HD patients and HD animal models. The data gained in this project will be directly applicable to developing novel therapeutic interventions in treating HD through the manipulation of the mitochondrial fission.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:
Huntington's disease

Years:
2016

Database Categories:
N/A

Database Tags:
N/A