Matrix Metalloproteinases: Therapeutic Targets For Huntingtons Disease

https://neurodegenerationresearch.eu/survey/matrix-metalloproteinases-therapeutic-targets-for-huntingtons-disease/

Principal Investigators

ELLERBY, LISA M

Institution

BUCK INSTITUTE FOR RESEARCH ON AGING

Contact information of lead PI
Country

USA

Title of project or programme

Matrix Metalloproteinases: Therapeutic Targets For Huntingtons Disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,553,444.95

Start date of award

23/09/2013

Total duration of award in years

1

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington Disease, Matrix Metalloproteinases, stromelysin 2, MMP14 gene, therapeutic target

Research Abstract

DESCRIPTION (provided by applicant): Huntington’s disease (HD) is a fatal autosomal dominant neurodegenerative disease characterized by emotional disturbances, uncontrolled

movements and loss of intellectual abilities. As the disease progresses a massive loss of striatal and cortical neurons results from the expression of the mutant huntingtin protein containing an expanded polyglutamine tract. An important pathologic feature of HD is the production of toxic expanded polyglutamine containing N-terminal fragments that result in aggregates found in the brain. Cleavage of Htt is known to occur through caspases and calpains. However, the role of proteases in HD has not been systematically investigated. In our preliminary studies we used a genome-wide screen of protease family members to identify modifiers of huntingtin proteolysis and toxicity. We found 11 proteases that reduce the production of huntingtin fragments. Three of those proteases are members of the matrix metalloproteinase (MMP) family. We found one of these, MMP-10, cleaves huntingtin directly, and prevents cell death when knocked down in striatal HdhQ111/Q111 cells. Correspondingly, we found MMPs are activated in mouse models of HD, and loss-of- function of Drosophila homologs of MMPs suppress Ht-induced neuronal dysfunction in vivo. We have therefore identified an interesting and novel mechanism of proteolysis and toxicity for HD. In this application, we will further study the role of MMPs in the molecular pathways leading to striatal cell death. We will determine how MMPs affect the processing of Htt in brain samples of HD mouse models. Furthermore, we will investigate if pharmacological or genetic reduction of MMP-10 or MMP-14 modifies disease progression or pathogenesis in HD mouse models. By crossing MMP-10 or MMP-14 knockout mice to HD mouse models, we will determine if deficiency of MMPs in the brain can ameliorate HD-like pathologies or behavioral deficits in HD mice. We will also use MMP inhibitors to treat HD mouse models and determine if HD pathogenesis or disease progression is modified by treatment. Together, our studies will determine if MMP are valid targets for HD treatment.

Lay Summary

PUBLIC HEALTH RELEVANCE: This application seeks to determine if matrix metalloproteinase are a therapeutic target for Huntington’s disease. We will use methods to lower the levels or activity of these enzymes in mouse models of Huntington’s disease and determine if this blocks disease progression and pathogenesis.

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