Exploring the contribution of astrocytes to Huntington disease

https://www.neurodegenerationresearch.eu/survey/exploring-the-contribution-of-astrocytes-to-huntington-disease/

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Country

USA

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Exploring the contribution of astrocytes to Huntington disease

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NIH (NINDS)

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4

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington Disease, Astrocytes, Huntington gene, Glutamates, Length

Research Abstract
? DESCRIPTION (provided by applicant): Huntington’s disease (HD) is an adult-onset autosomal dominant neurodegenerative disorder characterized clinically by cognitive, psychiatric and motor deficits which progress to severe disability and death. To date there are

no affective treatments for HD. The mutated huntingtin (mHTT) protein is widely expressed in neuronal and non-neuronal cells, yet neurodegeneration critically affects a few subsets of neuronal cell types in the brain. Understanding the toxicity produced by mhtt in non-neuronal cell types and the basis for this selective neurodegeneration are likely to be critical in the desin of effective therapies for the disease. The goal of this proposal is to expand our knowledge of the contribution of full length-mHTT (fl-mHTT) expressing astrocytes to neurodegeneration in HD. Astrocytes are critical to the proper function and development of the nervous system. They are involved in modulating synaptic activity and neurotransmission. Studies from our laboratory have uncovered increased SNARE-dependent glutamate release from astrocytes in culture taken from the conditional fl-mHTT expressing BACHD mouse model. This is a new found disruption caused by fl-mHTT expression in the astrocytes, which further implicates these cells in HD pathogenesis. Furthermore, we demonstrate that reducing fl-mHTT expression in astrocytes in vivo, contributes to the behavioral and neuropathological phenotypes observed in the conditional BACHD mouse model. The studies proposed here will further our understanding of astrocyte contribution to HD and determine if targeting this cell type for therapeutic intervention is worthwhile. We will use conditional genetic mouse models in these studies and propose three aims: 1) To determine if fl-mHTT expressing astrocytes contribute to HD pathogenesis by increasing glutamate levels in BACHD mice through exocytosis of glutamate; 2) To determine if expression of mutant huntingtin in astrocytes contributes to the abnormal medium spiny neuron physiology observed in BACHD mice; and 3) To determine if decreasing fl-mHTT expression in astrocytes after disease onset in BACHD mice is sufficient to alleviate HD symptoms and whether astrocyte specific expression in a new mouse model is sufficient to cause HD-like phenotypes in mice. Together these studies will help to define the role of fl-mHTT within astrocytes in HD pathogenesis, and may lead to novel therapeutic approaches for treatment of HD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Huntington’s disease (HD) is a devastating progressive adult-onset neurodegenerative disease. Currently, there is no treatment or a cure for HD. HD is one of the most common familial neurodegenerative disorders, with 30,000 clinically diagnosed HD patients and another 150,000-200,000 at risk for HD in the US.

Further information available at:

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Investments > €500k

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United States of America

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Huntington's disease

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