Glial huntingtin and neurodegeneration

https://neurodegenerationresearch.eu/survey/glial-huntingtin-and-neurodegeneration/

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Country

USA

Title of project or programme

Glial huntingtin and neurodegeneration

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,565,366.97

Start date of award

15/09/2015

Total duration of award in years

4

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington gene, Huntington Disease, Neuroglia, Nerve Degeneration, Oligodendroglia

Research Abstract

? DESCRIPTION (provided by applicant): Huntington’s disease (HD) represents an age-dependent neurodegenerative disease family including Alzheimer’s (AD) and Parkinson’s (PD) diseases. These diseases are characterized by selective neurodegeneration that is caused by misfolded proteins in an age-dependent manner. In HD, the disease protein huntingtin (htt) carries an expanded polyglutamine repeat, accumulates in the brain, forms aggregates as

patients become old, and causes progressive neurological symptoms. Given the known genetic mutation in HD and its well-characterized neuropathology, HD makes an ideal model for investigating how selective neuropathology occurs in an age-dependent manner. Most previous studies focused on the effect of mutant htt on neuronal cells and revealed that N-terminal fragments of mutant htt are misfolded and cause cell-autonomous and non-cell-autonomous pathological events in a variety of animal models. In the brain, the majority of cells are non-neuronal cells that provide essential support to the survival and function of neuronal cells. These non-neuronal cells mainly consist of three types of glial cells: astrocytes, microglial cells and oligodendrocytes. It is known that oligodendrocytes produce myelin proteins for myelination of axons, and astrocytes can release neurotrophins to support neuronal survival and function. However, whether mutant htt in glial cells affects these important functions remains to be investigated. We have established transgenic mouse models that express mutant htt specifically in astrocytes (GFAP-160Q) or oligodendrocytes (PLP-150Q). Both HD mouse models develop age-dependent neurological phenotypes, suggesting that mutant htt in glial cells affects glial function during aging and critically contribute to the age-dependent clinical phenotypes. We also found that in our GFAP-160Q HD transgenic mice, mutant htt can reduce BDNF release from astrocytes and cause demyelination or neuronal death reminiscent the pathological events in previous HD mouse models and human HD patient’s brains. In this application, we propose three aims to investigate how expression of mutant htt in glial cells causes neuronal dysfunction and neurological phenotypes in HD transgenic mice. Aim 1 is to examine the effect of mutant htt on secretion of neurotrophic factors from glial cells. Aim 2 is to explore how mutant htt in glial cells causes age-dependent neurological phenotypes and neuropathology. Aim 3 is to investigate the protective effects of reducing htt in glial cells or improving glial function in HD mouse brains. These studies will help understand the mechanisms for age-dependent neuropathology in HD and the contribution of glial htt to HD pathology. Because glial cells are a desirable transplant population for therapy, the findings from our study may also provide a new therapeutic target for treating HD.

Lay Summary

PUBLIC HEALTH RELEVANCE: We generated Huntington disease transgenic mice, which express mutant huntingtin in glial cells, and will use these mice to investigate how mutant huntingtin in glial cells causes age-dependent neuropathology and neurological phenotypes in mice. We will also explore the protective effect of knocking down mutant huntingtin specifically in glial cell on the HD neuropathology and phenotypes.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

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N/A

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