Mechanisms of Huntingtin-induced Neurodegeneration

https://neurodegenerationresearch.eu/survey/mechanisms-of-huntingtin-induced-neurodegeneration/

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Country

USA

Title of project or programme

Mechanisms of Huntingtin-induced Neurodegeneration

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,836,076.15

Start date of award

01/07/2000

Total duration of award in years

2

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington gene, Huntington Disease, Nerve Degeneration, protein misfolding, polyglutamine

Research Abstract

DESCRIPTION (provided by applicant): Huntington’s disease (HD) is an untreatable inherited adult onset neurodegenerative disease caused by an abnormal expansion in the polyglutamine (polyQ) tract in the Huntington (Htt) protein. The polyQ expansion makes mutant Htt (mHtt)

prone to aggregate, but the relationship between aggregation and neurodegeneration has been difficult to understand. In the previous funding period, we invented a new imaging platform to study a neuron model of HD and discovered that the aggregation of mHtt into visible deposits called inclusion bodies (IBs) appears to be a coping response. Recently, we developed new methods to study neuronal protein homeostasis in the context of mHtt in live neurons. Surprisingly, we showed that neurons recognize and target mHtt for accelerated degradation in vitro and in vivo. Remarkably, we found that the protein homeostasis and clearance capacity of different types of neurons varies and significantly predicts their susceptibility to mHtt. We discovered that a major protein clearance pathway called autophagy is differentially regulated in neurons. We found small molecules that stimulate neuronal autophagy and showed that they lower mHtt levels and protect them from neurodegeneration. These findings have led to the overarching hypothesis that motivates this proposal: the demand made by aggregation-prone mHtt on the protein homeostasis network of susceptible neurons exceeds their capacity leading to neurodegeneration. In the first Aim, we will investigate how neurons recognize and respond to misfolded protein. The highly conserved heat shock response mediates responses to misfolded proteins in most cells, but it seems different and ineffective in neurons. In Aim 2, we will test two major hypotheses about how protein dyshomeostasis leads to neurodegeneration- that inadequate capacity created by the demands of mHtt (1) leads to cell-wide protein misfolding and deleterious loss-of-function of metastable proteins or (2) a competition for flux through critical clearance pathways such as mitochondria and accumulation of substrates, such as dysfunctional mitochondria. In Aim 3, we propose to adapt our powerful in vitro single cell longitudinal methods to study neuronal protein homeostasis and Htt metabolism in vivo. The results could help validate the protein dyshomeostasis model of HD and lead to new therapies.

Lay Summary

PUBLIC HEALTH RELEVANCE: This is a competing renewal of a highly productive research program on Huntington’s disease, which led to the development of a novel imaging platform for cell biology. With it, we made the surprising discovery that neurons with mutant huntingtin (mHtt) that form inclusion bodies (IB) live longer than those that don’t form an IB. We also discovered that neurons regulate protein homeostasis differently than non-neuronal cells in key ways that could be relevant to neurodegenerative disease. In this proposal, we will dig deeper to understand the homeostatic mechanisms neurons have for responding to protein misfolding and test two key ideas for how protein dyshomeostasis causes neurodegeneration. During the previous funding period, we discovered compounds that stimulate an important component of the protein homeostasis system, a clearance pathway called autophagy. We showed that they protect neurons from mHtt-induced degeneration in vitro and in this proposal we will develop ways to adapt our powerful in vitro single cell methods for studying protein homeostasis in vivo.

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