The Regulation of Synaptic Connectivity and Homeostasis by Huntingtin

https://neurodegenerationresearch.eu/survey/the-regulation-of-synaptic-connectivity-and-homeostasis-by-huntingtin/

Principal Investigators

EROGLU, CAGLA

Institution

DUKE UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

The Regulation of Synaptic Connectivity and Homeostasis by Huntingtin

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,558,727.52

Start date of award

01/02/2016

Total duration of award in years

5

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington gene, Synapses, Homeostasis, Huntington Disease, Corpus striatum structure

Research Abstract

? DESCRIPTION (provided by applicant): Huntington’s disease (HD) is a fatal neurodegenerative disease caused by mutations introducing an extended stretch of poly-

glutamines (poly-Q) at the N-terminus of huntingtin (Htt). A widely accepted, yet unproven, hypothesis is that HD is caused by gain-of-function, toxic effects of mutant Htt protein. In recent years, dominant negative loss-of-function effects of poly-Q mutations have also emerged as drivers of disease pathophysiology. However, despite what is known about pathophysiology of mutant Htt, the functions of wildtype (WT) Htt are still largely unknown. Astrocytes, the major glial cells of the brain, secrete synaptogenic thrombospondin family proteins to initiate synapse formation. Thrombospondin induces synaptogenesis by binding to a neuronal receptor, the gabapentin receptor ??-1. In our preliminary experiments, we found that ??-1 interacts with huntingtin and this interaction is impaired in the presence of poly-Q expansions. Early synaptic problems in the excitatory cortical and striatal connections have been reported in HD, but whether huntingtin played a role in synaptic connectivity was unknown. By conditionally silencing Htt in the mouse cortex we showed that huntingtin controls synapse formation and maturation within cortical and striatal circuits. Moreover, by using an HD mouse model, we found that this function of huntingtin is lost when the pathogenic poly-glutamine mutation is present. Based on these findings, here we will test the hypotheses that huntingtin controls synaptic connectivity through its interaction with ??-1, and that the impairment of this interaction in the presence of the disease-causing poly-Q mutations leads to detrimental errors in synaptic connectivity. The loss-of-function effects of mutant Htt during development may be important for driving the disease onset and could underlie prodromal neurological symptoms of HD. Therefore, understanding the function of WT Htt in synaptic development may enable us to find ways to correct the developmental errors in the cortical and striatal circuits of mutant Huntingtin carriers. This approach could therefore lead to the prevention of disease onset or greatly diminished disease progression, allowing HD patients to live full, healthy lives.

Lay Summary
PUBLIC HEALTH RELEVANCE: Huntington’s Disease (HD) is the most common genetic disorder that causes abnormal involuntary writhing movements due to progressive neurodegeneration that takes place in the striatum of the affected individuals. Uncovering the cellular and molecular mechanisms governed by Htt is crucial to understand the pathophysiology of HD. By elucidating the roles of Htt in the formation and function of synaptic connections, we will gain the much-needed new insight into the progressive synaptic dysfunction seen in HD. Such an understanding has the potential to lead to the development of innovative approaches to cure HD.

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