Deranged calcium signaling and polyglutamine expansion disorders

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Country

USA

Title of project or programme

Deranged calcium signaling and polyglutamine expansion disorders

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,592,486.24

Start date of award

15/12/2007

Total duration of award in years

5

The project/programme is most relevant to:

Huntington's disease

Keywords

sigma-1 receptor, polyglutamine, Calcium Signaling, Huntington Disease, ITPR1 gene

Research Abstract

? DESCRIPTION (provided by applicant): The broad, long-term objective of the project is to understand the causes of neurodegeneration in Huntington’s disease (HD). In HD polyglutamine-

expanded Huntingtin (Httexp) causes early synaptic dysfunction and eventual neurodegeneration through poorly understood mechanisms. We previously discovered that Httexp binds to and sensitizes inositol 1,4,5-triphosphate receptor 1 (InsP3R1) to InsP3. We also demonstrated that a novel inhibitor of neuronal store-operated calcium entry (nSOC) improved motor symptoms in transgenic HD flies and inhibited and neurodegeneration in YAC128 HD mouse medium spiny neurons (MSNs), the primary cell type affected in HD. Based on these results, we propose that excessive activation of InsP3R1 causes a persistent reduction in endoplasmic reticulum (ER) calcium levels, elevated nSOC and neuronal and dendritic spine loss in HD-afflicted MSNs. To test this hypothesis, we will focus on the following aims: 1. To evaluate the causes and importance of supranormal nSOC in synaptic loss in HD MSNs To test the role of InsP3R1, we will use antisense oligonucleotides (ASOs) to knockdown InsP3R1 expression in YAC128 MSNs. We will also reduce levels of InsP3 by overexpressing a 5PP-RA phosphatase that metabolizes InsP3. To test the role of nSOC more directly we will use genetic strategies to knockout or knockdown STIM2, a regulator of synaptic nSOC. The effects of suppression of InsP3R1- and STIM2- mediated signaling will be evaluated in vitro and in vivo in experiments with the YAC128 HD mouse model. 2. To investigate the role of sigma 1 receptor (S1R) in HD and to evaluate S1R as a potential therapeutic target. Sigma 1 receptor (S1R) is an ER-resident protein that is activated in response to ER stress and ER calcium depletion. Activated S1R is thought to promote neuroprotection and stabilize InsP3R function, which may protect MSNs and their synaptic connections. Our preliminary data indicates upregulation of S1R in the striatum of both aged YAC128 mice and human HD patients. We will study changes in S1R- mediated signaling in the HD-afflicted striatum and investigate the potential relationship between S1R and ER Ca2+ signaling in HD MSN spines. We will also use a variety of pharmacological and molecular tools to validate S1R as a novel therapeutic target for HD. In these studies we will evaluate potential roles of dysregulated ER Ca2+ signaling, nSOC and S1R in synaptic loss in HD MSNs. We will also appraise InsP3R1, STIM2 and S1R as potential therapeutic targets for HD.

Lay Summary
PUBLIC HEALTH RELEVANCE: The proposed project will have direct and immediate relevance for public health. Huntington’s disease (HD) is a major cause of dementia in the elderly and an enormous health problem. The experiments described in the grant are aimed at testing specific hypothesis regarding pathogenesis of HD and will provide information critical for eventual development of the cure.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

Database Categories:
N/A

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