Mitochondrial fission in Huntingtons Disease

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Country

USA

Title of project or programme

Mitochondrial fission in Huntingtons Disease

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NIH (NINDS)

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01/04/2006

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2

The project/programme is most relevant to:

Huntington's disease

Keywords

Dynamin, Huntington Disease, Mitochondria, Huntington gene, Guanosine Triphosphate Phosphohydrolases

Research Abstract

DESCRIPTION (provided by applicant): Huntington’s disease (HD) is a neurodegenerative disease caused by an abnormal expansion of a poly- glutamine (poly-Q) repeats in huntingtin (Htt), a 350 kDa protein. People with HD experience chorea, dementia, and psychiatric disturbances. In HD, long projection neurons of the cortex and striatum degenerate by an

unknown mechanism. There is currently no cure or effective treatment for this devastating disease. Neurons depend on mitochondria to provide energy to fuel specialized processes, e.g., synaptic transmission, channel activity, and axonal transport. To meet the constantly changing energy needs of neurons, mitochondria undergo frequent fission and fusion. These dynamic processes stimulate ATP synthesis, maintain Ca2+ homeostasis, and mediate cell survival. However, excessive fission without counterbalancing fusion causes fragmented mitochondrial morphology, neuronal injury, and apoptosis. Fission and fusion is regulated by large conserved GTPases of the dynamin super-family. Dynamin-related protein 1 (DRP1) is required for mitochondrial fission. Under physiological conditions, DRP1 GTPase activity is kept in check. Posttranslational modifications (PTMs) including phosphorylation can activate DRP1. For example, transient DRP1 Ser616 phosphorylation by Cdk1-CyclinB activates mitochondrial fission. There is strong evidence that mitochondrial dysfunction occurs early and plays a causal role in HD. For example, mitochondria from HD patients and HD mice exhibit fragmented morphology, respiratory complex inhibition, diminished Ca2+ buffering capacity, and a sensitized induction towards cytochrome c release and apoptosis. In addition, mutant Htt (mHtt) localizes to mitochondrial fission sites, directly binds DRP1, activates DRP1 GTPase activity, and alters its oligomeric ring-like structure. We have shown that decreasing DRP1 GTPase activity rescues cultured neurons from mHtt-induced excessive mitochondrial fission, axonal transport defects, synaptic injury, and cell death. Persistent Cdk5 activation by p25 and aberrant Cdk5 subcellular localization and substrate specificity also contribute to neurodegeneration. Whether Cdk5-p25 aberrantly phosphorylates DRP1 at Ser616, thereby promoting excessive mitochondrial fission in HD, is unknown. Therefore, the specific questions that will be addressed here are: (1) Does Cdk5-p25 cause DRP1 Ser616 hyperphosphorylation and mitochondrial fission in HD? (2) Does DRP1 Ser616 hyperphosphorylation play a causal role in mHtt-mediated neuronal cell death? (3) By which mechanism does mHtt interaction and Ser616 phosphorylation stimulate DRP1 activity? Results obtained here may provide a mechanistic explanation for DRP1 hyperactivity in neurodegeneration and form the basis for new therapies.

Lay Summary
PUBLIC HEALTH RELEVANCE: Huntington’s disease (HD) is an inherited neurodegenerative disorder affecting one in 10,000 Americans. People with HD gradually lose their normal motor function, cognitive abilities, and emotional health. The course of the disease typically lasts from 15-20 years. There is currently no effective treatment or cure for HD. An early event in HD is the breakdown of energy metabolism resulting from defective mitochondria. We identified hyperactivity of dynamin-related protein 1 (DRP1) as one of the main culprits in this mitochondrial dysfunction. Therefore, the goal of this project is to unravel the detailed mechanisms by which DRP1 becomes overactive in HD. Insights gained here might lead to new therapies that can slow neuronal loss in HD, thereby improving patient’s lives and lowering care-giving costs.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Huntington's disease

Years:
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