

Pathophysiology of Transgenic Mouse Models of Huntingtons Disease

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USA

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Pathophysiology of Transgenic Mouse Models of Huntingtons Disease

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1

The project/programme is most relevant to:

Huntington's disease

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Huntington Disease, Corpus striatum structure, Huntington gene, Transgenic Mice, Substantia nigra structure

Research Abstract

DESCRIPTION (provided by applicant): The fatal mutation in Huntington's disease (HD) leads

to an expanded glutamine repeat within the huntingtin protein which causes neuronal dysfunction typically followed by selective neurodegeneration especially within the striatum and cortex. These dysfunctions in neurons and circuits occur during the development of the disease phenotype, well before there is significant cell loss. The experiments in this application are designed to understand the functional changes that occur in specific populations of neurons during the progression of the HD phenotype and to uncover new targets and approaches for therapies. Our working hypothesis is that the most conspicuous cellular dysfunctions leading to pathology in HD result from a combination of cell- autonomous changes and cell-cell interactions. This two-hit hypothesis implies that mutation of the gene in the cell alone may not be sufficient to cause significant dysfunction; other changes have to occur to cause symptoms of the disease, and some of these include altered intercellular synaptic interactions. Previously, we examined changes in the striatum, the cortex and corticostriatal interactions, as the cortical input is one of the two major excitatory inputs to the striatum. However, the excitatory thalamic input to the striatum may be as important as the cortical input in the HD phenotype. It is presently unclear if both thalamostriatal and corticostriatal pathways contribute equally or differentially to alterations in striatal neurons. Aim 1 will use optogenetics to specifically and separately activate striatal glutamatergic inputs to identified subpopulations of striatal neurons and determine their relative contribution to cellular alterations. Medium-sized spiny neurons of the direct and indirect striatal output pathways also display unique, selective and complex alterations as the HD phenotype progresses. These will affect their targets in globus pallidus and substantia nigra. To our knowledge, striatal outputs in HD have not been studied in any detail, especially in mouse models, yet they are extremely important because they determine how the basal ganglia influence the thalamus and cortex. Aim 2 will specifically examine alterations in striatal output target structures while Aim 3 will manipulate striatal output pathways differentially in an attempt to counter the imbalance of direct and indirect pathways as the disease progresses. Our studies use state-of-the-art optogenetic techniques to specifically activate or inhibit subclasses of neurons as well as genetic techniques to remove expression of the mutant huntingtin gene in subclasses of neurons. Together, the studies will provide the basis for novel and rational treatments for HD by delineating more restricted targets spatially and temporally and will be relevant for understanding other CAG triplet repeat diseases and neurodegenerative disorders.

Lay Summary

Huntington's disease is a fatal, genetic neurodegenerative disorder characterized by motor dysfunction, cognitive impairments and psychiatric disturbances for which no successful treatments exist. Genetic mouse models have been instrumental in understanding the dysfunctions underlying behavioral phenotypes, neuronal abnormalities and neurodegeneration and they permit examination of the progression of the disease, the discovery of cause-effect relationships and evaluation of potential therapies. This proposal uses state-of-the-art techniques to examine mechanisms that lead to dysfunction in specific neuronal populations during the progression of the phenotype and will uncover new targets for therapies to alleviate symptoms and slow the progression of this devastating genetic disorder.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:

Huntington's disease

Years:

2016

Database Categories:

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