Novel approaches to modulate key targets in the pathogenesis of Huntington Disease

https://neurodegenerationresearch.eu/survey/novel-approaches-to-modulate-key-targets-in-the-pathogenesis-of-huntington-disease/

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Canada

Title of project or programme

Novel approaches to modulate key targets in the pathogenesis of Huntington Disease

Source of funding information

CIHR

Total sum awarded (Euro)

€ 528,267

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01/10/2012

Total duration of award in years

5.0

The project/programme is most relevant to:

Huntington's disease

Keywords
Research Abstract

Huntington disease (HD) is a progressive neurodegenerative disease with no way to alter the course of the illness. The underlying genetic defect is a trinucleotide expansion in the huntingtin (htt) gene. A promising therapeutic approach for HD is to selectively prevent the expression of mutant htt. We will use antisense oligonucleotides (ASOs) to test this approach in mouse models, targeting single nucleotide polymorphisms that are only present on the mutant and not

the wild-type htt gene. Additionally, cleavage of mutant htt by caspase-6, phosphorylation and excitotoxicity are implicated as crucial factors in the pathogenesis of HD. In order to further validate caspase-6 as a therapeutic target, we will ablate caspase-6 expression and test the impact on the phenotype in an HD mouse model. Methods to increase phosphorylation will also be assessed as to their impact on phenotypic features of HD. We will furthermore investigate factors that lead to the activation of caspase-6 and thus represent additional targets for therapy development. In the excitotoxic pathway, we have identified the aberrant localization of NR2B receptors as a pathogenic mechanism, and we will modulate this mislocalization through genetic and therapeutic trials in an HD mouse model. Additionally, we will test compounds that modulate the signalling pathway downstream of NR2B receptors to ameliorate excitotoxicity. The basis of this proposal is to validate novel therapeutic approaches for the treatment of HD in vivo. The end result is to provide essential information for therapeutic strategies and evaluate compounds which prevent and/or ameliorate the disease.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
Canada

Diseases:
Huntington's disease

Years:
2016

Database Categories:
N/A

Database Tags:
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