Role of Cyp46 in cholesterol metabolism and neuroprotection in Huntington’s Disease

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Role of Cyp46 in cholesterol metabolism and neuroprotection in Huntington’s Disease

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Research Abstract

Huntington’s Disease (HD) is a genetic neurodegenerative disease, due to an unstable expansion of the CAG repeat sequence, located in exon 1 of the Htt gene encoding the Huntingtin (Htt). The main clinical manifestations of this genetic disease are chorea, cognitive impairment and psychiatric disorders. The transmission of HD is autosomal dominant with a complete penetrance. The more vulnerable brain area in HD is the striatum, with a progressive extension to other brain areas. There is still no available drug therapy for slowing disease progression, which inexorably progresses until death.
One therapeutic approach in HD remains poorly investigated: the cholesterol homeostasis. Our

teams possess strong evidence that the degradation of cholesterol is altered in striatal neurons in HD. First, 24S-hydroxycholesterol, the catabolite of cholesterol, is decreased in the plasma of HD patients at early stages of the pathology. Furthermore, we recently made the observation that levels of CYP46A1, the rate-limiting enzyme for the degradation of cholesterol in neuronal cells, are decreased in the striatum of a transgenic mouse model of HD (R6/2 mice) but also in the putamen extracts of post-mortem HD patients. Furthermore, restoring CYP46A1 expression in striatal neurons in vitro significantly reduces neuronal dysfunctions induced by mHtt in primary striatal neurons in culture. It ameliorates motor behavior performance in the R6/2 HD mice in vivo.
Therefore, our aims are to propose a new therapy approach in HD. We propose to restore CYP46A1 in the striatum of HD mice, owing to a new gene therapy approach using a recombinant AAV: AAVrh10, which presents strong advantages in our perspectives. Not integrative, non immunogenic, it has a strong neuronal tropism and excellent transduction properties within the striatum. Viral injections will be performed at early stages of the pathogenic process, before the cellular and molecular dysfunctions induced by mHtt. A battery of pre-clinical behavioral tests will be performed in the HD mice infected or not with AAVrh10-CYP46A1 and their controls. We will evaluate the benefits of this therapy approach, by measuring expression levels of striatal markers, the morphology of the neurons (dendritic spines), the metabolism and the levels of cholesterol, as well as proteins of intracellular signaling in relation with lipid rafts.
We also propose to analyze in details the consequences of this gene therapy approach, and evaluate in vitro the cellular and molecular consequences of CYP46A1 overexpression. A dynamic study of the various cellular processes depending on membrane cholesterol levels will be performed: glutamatergic NMDA and BDNF receptors trafficking, formation and protein content of lipid rafts. Sophisticated and original approaches will be used: microfluidic chambers allowing the reconstitution of oriented cortico-striatal networks, fluorescent correlation spectroscopy for the study of the repartition of receptors within lipid rafts. This study will be completed by an evaluation of cellular consequences induced by depletion of CYP46A1 in the development of the pathology. ShRNAs approaches will be used in vitro and in vivo for this purpose.
Altogether, this project will give new insights into the potential application of brain cholesterol regulation as a therapeutic strategy for HD.

Further information available at:

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