Modulation of tyrosine hydroxylase activity to control catecholamine synthesis and its effect on cellular metabolism – CORE

https://neurodegenerationresearch.eu/survey/modulation-of-tyrosine-hydroxylase-activity-to-control-catecholamine-synthesis-and-its-effect-on-cellular-metabolism-core/

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Country

Luxembourg

Title of project or programme

Modulation of tyrosine hydroxylase activity to control catecholamine synthesis and its effect on cellular metabolism - CORE

Source of funding information

FNR

Total sum awarded (Euro)

€ 584,000

Start date of award

01/05/2014

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3.0

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract

Tyrosine hydroxylase (TH) is the rate limiting step for catecholamine (CA) biosynthesis including dopamine (DA). Decreased striatal DA levels caused by a loss of dopaminergic neurons in the

substantia nigra are directly linked to Parkinson’s disease. We hypothesize that only modest increases in TH activity could compensate for the loss of many dopaminergic neurons (e.g. a 20% increase in activity may overcome a critical threshold of DA and may therefore compensate for a loss of dopaminergic neurons). On the other hand, CA intermediates and their degradation products are highly toxic to the cell. This is one of the reasons why TH is strictly regulated on several levels including transcription, protein stability, phosphorylation of specific residues in its regulatory domain and feedback inhibition by CAs. With the proposed research project, we intent to study how a modulation of TH can result in an increase in CA and DA production in whole human neuronal cells in culture. Moreover, we intend to determine the capacity limits of the metabolic flux through TH. By targeted profiling of CA metabolism and non-targeted profiling of central carbon metabolism, we will determine cellular effects caused by elevated TH activity. To reach our aims, we propose to express various defined variants of TH (differences on amino acid sequence level) in a human cellular neuronal cell culture system under the same genetic and regulatory background. Using this system, we will study CA metabolism and central carbon metabolism to investigate effects related to altered TH activity. Finally, the proposed system will allow for screening the activities of patient specific TH variants.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
Luxembourg

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

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