Role of microtubule acetylation in Parkinson’s disease

https://neurodegenerationresearch.eu/survey/role-of-microtubule-acetylation-in-parkinsons-disease/

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Country

United Kingdom

Title of project or programme

Role of microtubule acetylation in Parkinson's disease

Source of funding information

MRC

Total sum awarded (Euro)

€ 645,187

Start date of award

27/07/2015

Total duration of award in years

3.0

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract
Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most common genetic cause of Parkinson’s disease (PD). LRRK2 is a multifunctional protein comprising GTPase and kinase activities that affects many cellular processes. How mutations in LRRK2 cause PD is not known. We have found that pathogenic mutations in the LRRK2 Ras of complex proteins (Roc) GTPase domain (R1441C) and the carboxy-terminal of Roc (COR) domain (Y1699C) domain

preferentially associate with deacetylated microtubules, and inhibit axonal transport in vitro in primary neurones and in vivo in transgenic Drosophila larvae. Moreover these LRRK2 Roc-COR domain mutants caused locomotor deficits in vivo in adult transgenic Drosophila. Treating neurones with the histone deacetylase inhibitor Trichostatin A (TSA) to increase microtubule acetylation restored axonal transport in vitro and systemic administration of TSA to transgenic mutant LRRK2 flies was able to restore axonal transport in vivo. Furthermore post hoc administration of TSA reversed the locomotor deficits in adult LRRK2 Roc-COR mutant transgenic flies. Thus, our findings reveal a novel pathogenic mechanism for mutant LRRK2 and a potential therapeutic intervention for PD. In this project we will test the hypothesis that disruption of MT acetylation by mutant LRRK2 is a neurotoxic event in PD that leads to neuron death by disrupting axonal transport. Our aims are to investigate: (1) the therapeutic potential of MT acetylation and the (de)acetylase pathways involved in LRRK2 Roc-COR mutant associated familial PD; (2) how LRRK2 regulates MT acetylation; (3) the involvement of MT acetylation and LRRK2 in models of a-synuclein-related familial PD and sporadic PD In summary, this study aims to investigate how LRRK2 regulates MT acetylation and its involvement in PD pathogenesis. This will allow us to pinpoint and test more precise drug targets and to determine the therapeutic potential of MT acetylation drugs in PD.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

Database Tags:
N/A