Manipulating mitochondrial dynamics as a potential therapeutic strategy for Parkinson’s disease

https://neurodegenerationresearch.eu/survey/manipulating-mitochondrial-dynamics-as-a-potential-therapeutic-strategy-for-parkinsons-disease/

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Country

United Kingdom

Title of project or programme

Manipulating mitochondrial dynamics as a potential therapeutic strategy for Parkinson's disease

Source of funding information

MRC

Total sum awarded (Euro)

€ 693,125

Start date of award

01/06/2014

Total duration of award in years

3.0

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract
Mitochondria are dynamic organelles that can be controlled by fission (Drp1 and hFis1) and fusion (OPA1 and Mfn1/2) proteins. Imbalances in fission/fusion can result in synaptic dysfunction and neurodegeneration. This research will use two novel animal models of

Parkinson’s disease to evaluate the therapeutic effects of promoting mitochondrial fusion. The virally-transduced alpha-synuclein rats represent a human relevant genetic model with neurodegeneration. Because regular wild type mice do not display striatal damage, the novel Oct3-knockout mice will be used to model paraquat neurotoxicity. We hypothesize that blocking Drp1 or promoting OPA1 function will attenuate neurodegeneration and synaptic deficits in these animal models. To test these hypotheses in vivo, we will use rigorous state-of-the art techniques such as: 1) in vivo microdialysis in freely moving mice followed by HPLC to quantify evoked striatal dopamine release; 2) Electrophysiology performed in acute slices to further investigate synaptic activities in these animals; 3) The Seahorse XF24 extracellular flux analyzer to measure striatal synaptosomal mitochondrial respiration; 4) Laser capture microdissection followed by single cell RT-PCR to quantify mitochondrial DNA mutations in nigral dopaminergic neurons; 5) rAAV-mediated gene transfer to inhibit Drp1 function or promote mitochondrial fusion. To complement our genetic approach, we will systemically inject a Drp1 inhibitor. 6) Animal locomotor activities (using the highly sensitive force-plate actometer) and neuropathology (stereological cell counting, striatal DA terminal density and total striatal DA content as well as protein aggregation) will be assessed.

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