Glial uptake of dopamine after L-DOPA medication

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Country

USA

Title of project or programme

Glial uptake of dopamine after L-DOPA medication

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

370187.156

Start date of award

01/05/2016

Total duration of award in years

3

Keywords

Levodopa, Dopamine, Astrocytes, uptake, monoamine

Research Abstract
? DESCRIPTION (provided by applicant): Parkinson's disease (PD) affects more than a million persons in the U.S. and is the 2nd most common progressive, neurodegenerative disease. Early on, the movement deficits (tremor, rigidity, slowed movement, altered gait), usually respond to oral levodopa (L-DOPA) and other medications. However, with disease progression, L-DOPA's effectiveness gradually diminishes and dyskinesia and motor fluctuations emerge. Most symptoms of PD are due to a reduction of dopamine (DA)-secreting cells in the substantia nigra.

In PD, L-DOPA restores function by replacing lost DA. Endogenous L-DOPA and DA concentrations are largely regulated by astrocytes, which maintain extracellular homeostasis. Although astrocytes have several transporter systems for monoamine uptake, including DA, we have shown that astrocytes take up excess of DA via low-affinity, high-capacity Uptake2 transporters. We also demonstrated that astrocytes wrapping around blood vessels take up L-DOPA and contain monoamine oxidase (MAO) type B which oxidizes DA taken up by the cell. We hypothesize that astrocytes take up and oxidize the vast majority of DA converted from L-DOPA, especially when DA neurons are severely degenerated due to PD. Reducing the ability of astrocytes to take up DA through use of specific transporter blockers may permit the use of lower doses of L-DOPA, thereby diminishing DA pulsatility and motor fluctuations. This hypothesis will be tested here in 3 Aims. Aim 1. Identify the specific transporter molecules involved in dopamine reuptake by astrocytes using brain slice and cell culture models. Aim 2. Identify which specific transporter blockers can slow DA reuptake using an astrocyte brain slice model. Aim 3. Identify which Uptake2 blockers are effective in reducing therapeutic L-DOPA concentrations in a whole animal model of PD. The results will greatly enhance the understanding of the role of astrocytes in PD etiology and pave the way to the development of preventive measures for L-DOPA-induced dyskinesia.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A