Striatal Nurr1 activity facilitates the dyskinetic state: A novel therapeutic target

https://www.neurodegenerationresearch.eu/survey/striatal-nurr1-activity-facilitates-the-dyskinetic-state-a-novel-therapeutic-target/

Principal Investigators

MANFREDSSON, FREDRIC

Institution

MICHIGAN STATE UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Striatal Nurr1 activity facilitates the dyskinetic state: A novel therapeutic target

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

404624.7706

Start date of award

01/08/2016

Total duration of award in years

2

Keywords

Dyskinetic syndrome, Levodopa, Corpus striatum structure, new therapeutic target, Parkinsonian Disorders

Research Abstract

Project Summary/Abstract The standard treatment for Parkinson’s disease patients is the use of levodopa (L-DOPA), which restores dopaminergic tone to the striatum and provides subsequent symptomatic relief. However, the higher doses required with PD progression result in levodopa-induced dyskinesias (LID) which dramatically reduce the quality of life for afflicted individuals. Despite its public health importance, the etiology of LID remains unknown, thus, no uniformly

effective therapies exist. To study the molecular etiology of LID we utilized a genome array comparing mRNAs in the striata of LID+ rats to those that remained refractory to LID development. One validated protein that was induced in LID+ animals but absent in LID- animals was the orphan nuclear receptor Nurr1. We therefore hypothesized that Nurr1 is a molecular trigger of LID. To test this, we delivered adeno- associated viruses (AAV) expressing, or silencing, Nurr1 to the striatum of parkinsonian rats. Following L- DOPA treatment, Nurr1 overexpressing rats had significantly higher LID scores whereas Nurr1 silencing significantly attenuated LID scores. Moreover, we found that Nurr1 overexpression in the parkinsonian, L-DOPA naïve, striatum potentiates corticostriatal neurotransmission, identical to that seen in a LID+ parkinsonian rat. Finally, we have shown that LID is associated with changes in medium spiny neuron (MSN) dendrite distribution and morphology. Based on these findings we developed the central hypothesis of this proposal: Striatal Nurr1 activity is the key central component in developing LID by promoting structural and functional changes in the striatum. We further propose that Nurr1 facilitates the formation of this “dyskinetic state” via its well defined role in plasticity and dendrite reorganization. To test this hypothesis we propose 2 distinct Aims where we will measure the same outcomes within the striatum: MSN morphology, function, and LID behavior. (1) Following dopamine denervation and L-DOPA administration roughly 30% of Sprague- Dawley rats do not develop LID. These LID- subjects also do not express striatal Nurr1. To test our central hypothesis we will thus utilize AAV to express Nurr1 in LID- subjects and observe the effect on striatal neurons and LID behavior. (2) Finally, as we posit that induction of striatal Nurr1 activity is a core event in the development of LID we ask the critical question: Does reversing Nurr1 induction normalize striatal function, reverse structural adaptions, and thus reverse LID? Together, the aims in this proposal will provide for an extensive understanding of the molecular events that underlies the formation of the dyskinetic striatum, including the novel role for striatal Nurr1 in an array of established molecular events linked to LID. The successful identification of Nurr1 as a central factor in LID formation will open a completely unexplored area for dyskinesia treatment development whereby Nurr1 itself, or downstream Nurr1 targets, can be exploited for therapeutic development.

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