# Striatal CaV1.3 Calcium Channels: An Overlooked Antidyskinetic Target for PD

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**Country**

USA

**Title of project or programme**

Striatal CaV1.3 Calcium Channels: An Overlooked Antidyskinetic Target for PD

**Source of funding information**

NIH (NINDS)

**Total sum awarded (Euro)**

352064.2202

**Start date of award**

15/09/2015

**Total duration of award in years**

1

**Keywords**

Levodopa, Calcium Channel, Dyskinetic syndrome, Corpus striatum structure, Dihydropyridines

**Research Abstract**

? DESCRIPTION (provided by applicant): Previous studies, including those in our lab have shown that subcutaneous, slow release pellets containing CaV1.2/1.3 channel antagonists can reduce the expression of levodopa-induced dyskinesias (LID) produced by low dose (6 mg/kg) and high dose levodopa (12.5 mg/kg), however, this effect is partial and lost over time. These data suggest that the CaV1.3 channel is a potential antidyskinetic target, yet whether the limitation in scope and loss of protection over time are related to pharmacological limitation

remains unknown. There are several issues that limit validating the involvement of CaV1.3 channel antagonism for any use in Parkinson’s disease (PD) with pharmacological agents, which includes: 1) there is no currently available pharmacological agent that can selectively silence CaV1.3 channels without impacting the CaV1.2 channels that are important in cardiovascular function; 2) CaV1.3 channels are incompletely inhibited even by high concentrations of currently available dihydropyridine (DHP) drugs ; and 3) pharmacological blockade traditionally employed results in non-continuous channel blockade, which we propose contributes to the variable or partial protective outcome of all previous clinical and preclinical studies. We posit that the previous studies provide strong and necessary rationale that the CaV1.3 channel is a potential antidyskinetic target and that development of an innovative approach to confirm its possible clinical utility is warranted. To provide unequivocal proof-of-principle evidence, devoid of pharmacological limitations, we propose three Specific Aims (SA) that will allow examination of the impact of continuous, high potency and target-selective, mRNA-level silencing of striatal CaV1.3 channel on LIDs, using the R21 mechanisms to assist in developing and executing these important studies. In SA 1, we will determine the time course of striatal CaV1.3 gene and protein silencing achieved with our recombinant adeno-associated virus (rAAV)-mediated expression of a short hairpin RNA (shRNA) designed against the CaV1.3 mRNA, which will guide the timing of interventions in SA 2 and 3. In SA 2, we will test the hypothesis that constitutive silencing of striatal CaV1.3 channels prior to levodopa exposure will provide potent and enduring amelioration of LIDs. In SA 3, we will test the hypothesis that constitutive silencing of striatal CaV1.3 channels in subjects already expressing LIDs will significantly decrease severity of established LIDs.

**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