Preventing Experience Dependent Aberrant Plasticity Under Dopamine Deficiency

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Preventing Experience Dependent Aberrant Plasticity Under Dopamine Deficiency

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The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract

The therapeutic effects of L-DOPA are remarkable in early stage Parkinson's disease (PD). However, with chronic dopamine replacement therapy, motor side effects such as dyskinesia become a severe problem in advanced PD. Mechanisms underlying PD symptoms and therapy are still poorly understood. Our recent studies in animal models have for the first time demonstrated that experience-dependent aberrant motor learning (learned motor inhibition)

under low dopamine conditions may play a major role in PD motor symptoms, which was supported by recent studies on PD patients and by computational models. Moreover, we have demonstrated that glutamatergic inputs in combination with dopamine signaling through the adenylyl cyclase type 5 (AC5) and the cAMP pathway contributes to corticostriatal long-term potentiation and depression (LTP and LTD) in the dopamine D2 receptor-expressing striatal medium spiny neurons (MSNs). More importantly, we have found that aberrant LTP is associated with aberrant motor learning while prevention of such aberrant LTP is associated with prevention of aberrant motor learning. Our behavioral and electrophysiological advances have set the stage for identifying and testing potential PD therapies based on preventing and/or reversing aberrant corticostriatal LTP. In this application, we propose to test the precise conditions/parameters for induction of corticostriatal LTP/LTD in D2-expressing MSNs. We then aim to establish a causal link between aberrant corticostriatal LTP and aberrant motor learning as well as to test treatments that can prevent such aberrant corticostriatal LTP and aberrant motor learning. Finally, we will test the therapeutic effects of preventing and reversing aberrant LTP in PD models.

Lay Summary
Project Narrative We will test in animal models potential novel Parkinson's disease therapies based on preventing and/or reversing aberrant corticostriatal plasticity.

Further information available at:

Types:
Investments > €500k

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United States of America

Diseases:
Parkinson's disease & PD-related disorders

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