Vorschlag für ein Promotionsprojekt im Rahmen des VorSPrUNG-Programms

Hauptbetreuer (↗ VorSPrUNG-Konzept):

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Titel des Projektes:

Investigating the role of the cerebellum in Levodopa-induced dyskinesia in Parkinson´s disease

Abstract:

Levodopa is the most efficacious drug in the symptomatic therapy of motor symptoms in Parkinson´s disease (PD). The long-term treatment with levodopa is often complicated by the occurrence of troublesome involuntary hyperkinesia, so called levodopa-induced dyskinesia (LID), which severely affect the quality of life of patient. The main known risk factors for the development of LID are the severity and duration of the disease, as well as the dose and length of treatment with Levodopa. It has been demonstrated that ten years after the start of levodopa, 89% of patients suffer from this side-effect of the therapy. Despite considerable advances in the pharmacotherapy of PD, it is notoriously difficult to suppress LID once they have occurred.
Cumulative evidence suggests that the pathogenesis of LID is based on a complex interplay of various pre – and postsynaptic mechanisms in the brain that are triggered by the non-physiological synthesis, release and reuptake of dopamine metabolized from high dosages of exogenously administered Levodopa. However, the exact pathophysiological mechanisms in the generation of LID remain incompletely understood. A number of different theories exist, on where LID are generated in the brain.
Until now, studies have mainly focused on the role of dysfunctional basal ganglia activity in the generation of LID. Major findings were that chronic Levodopa therapy leads to aberrant synaptic plasticity at the cortico-striatal synapse and to hyperactivity of direct pathway projection neurons in the striatum. Moreover, the primary motor cortex has been implicated in theories on the pathophysiology of LID in PD.
Only recently preliminary evidence has been published that the cerebellum could be of major importance in the pathophysiology of LID. This assumption is mainly based on two crucial observations. First, it has been repeatedly demonstrated that LID scores can be persistently decreased by inhibitory cerebellar transcranial magnetic stimulation. This amelioration of LID severity was not only associated with a reduction in the metabolic activity of the cerebellum but also with a partial normalization of cortical synaptic plasticity. Second, an increased binding capacity of sigma receptors in the cerebellum correlated with the magnitude of LIDs but not with the motor symptoms of PD. Successful pallidal neurosurgery reduces the severity of LID and normalizes the binding of sigma ligands in the cerebellum.
In conclusion, the generation of LID is associated with a dysfunction in the motor network including the BG, motor cortex and cerebellum. However, so far it has never been assessed, if the basal ganglia and the cerebellum independently contribute to the development of LID, and if a pathological reciprocal interaction of the two motor systems could be a main factor. The possibility of such a pathophysiological mechanism is supported by the recent finding of a direct subcortical interaction of the cortico-basal ganglia-thalamo-cortical and the cerebellar-thalamo–cortical loop, that enables a fast

dynamic interaction of the basal ganglia and the cerebellum bypassing the cortex. Derived from the dimmer-switch model of tremor in PD, a hypothesis has recently been formulated of a combined dysfunction of the basal ganglia and the cerebellum. According to this model, the basal ganglia propagate a pathological signal via the subthalamic nucleus to the cerebellum. Inside the cerebellum this signal gets further amplified and is finally transmitted via the thalamus to the striatum and the motor cortex thereby mediating the dyskinesia. However, this theoretical model has never been tested experimentally.

The primary goal of the project is to define the influence of the cerebellum in the generation of LID. Specifically, we will characterize the oscillatory pattern in the basal ganglia and the cerebellum during the generation of LID. To reach that aim we will simultaneously investigate oscillatory network activity in the basal ganglia and the cerebellum by multiple parallel in-vivo electrophysiological recordings in two animal models of LID in PD. Thus, we will be able to distinguish the differential contribution of the two subcortical motor systems and their interactions to the generation of LID.