Targeting GluN2A-containing NMDA receptors in Parkinson's Disease and L-DOPA-induced dyskinesia

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Parkinson's disease (PD) is characterized by degeneration of the nigrostriatal pathway, Lewy bodies pathology and motor impairment. The current therapies are symptomatic and very often cause disabling side effects known as levodopa-induced-dyskinesias (LIDs). PD pathogenesis is complex and yet unresolved. Besides dopaminergic denervation, excessive glutamatergic transmission from the cortex to the striatum and modifications of the striatal synaptic architecture play a key role in both PD and LIDs. In particular, changes in the distribution and function of N-methyl-D-aspartate glutamate receptors (NMDARs) at the dendritic spine of striatal medium spiny neurons (MSNs) have been documented in experimental models of PD and LIDs as well as in the brain of PD patients.

This work aims at: (i) characterizing NMDAR GluN2A/GluN2B subunit ratio in MSNs as a common synaptic trait in rat and primate models of LIDs as well as in dyskinetic PD patients; and (ii) validating the potential therapeutic effect of cell-permeable peptides (CPPs) interfering with GluN2A synaptic localization on the dyskinetic behavior of experimental models of LIDs.

Here we demonstrate an altered ratio of synaptic GluN2A/GluN2B-containing NMDA receptors in the striatum of levodopa-treated dyskinetic rats and monkeys as well as in post-mortem tissue from dyskinetic PD patients. The modulation of synaptic NMDA receptor composition by CPPs interfering with GluN2A subunit interaction with proteins involved in receptor retention at synapses leads to a reduction in the dyskinetic motor behavior in animal models of LIDs.

Overall, our results indicate that targeting synaptic NMDA receptor subunit composition may represent an intriguing therapeutic approach aimed at ameliorating levodopa motor side effects.