Assemblies of glutamate receptor subunits within the excitatory synapse: new possible target in Parkinson's Disease

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Although levodopa (L-DOPA) remains the most effective drug for the symptomatic treatment of Parkinson's disease (PD), after a variable number of years abnormal involuntary movements, known as dyskinesia, emerge in response to chronic drug administration. It has been estimated that the vast majority of patients experience this problem after 10 years from initiation of L-DOPA, thus representing a serious limitation for the management of the disease in advanced patients. To date, only the NMDA receptor antagonist amantadine is used in the clinical practice to control dyskinesia severity, with variable results and side effects.

NMDA receptor subunit composition strictly commands receptor function and pharmacological responses. The identity of the GluN2 subunit regulates biophysical and pharmacological properties of the receptor and influences receptor assembly, signalling and trafficking to the postsynaptic membrane. We focused our attention on molecular and functional interactions between glutamate and dopamine receptors showing that abnormal redistribution of NMDA receptor subunits at corticostriatal synapses is associated with both experimental PD and L-DOPA-induced dyskinesia. In particular, we demonstrated that prevention of aberrant synaptic localization of GluN2A-containing NMDA receptor, by disrupting GluN2A/PSD-95 complex, is sufficient to determine a significant reduction of the onset of L-DOPA-induced dyskinesia in experimental parkinsonism in rats (Gardoni et al., Neurobiol. of Aging, 2012). A two-hybrid screening to find potential proteins interacting with the C-terminal tail of GluN2A has highlighted Rabphilin 3A (Rph3A) as a new protein partner. Rph3A interaction with GluN2A regulates GluN2A availability in the postsynaptic membrane suggesting that modulation of GluN2A/Rph3A complex could represent an innovative strategy to reduce GluN2A-containing NMDA receptors both in experimental PD and in L-DOPA-treated dyskinetic animals.