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Targeting fyn by localized RNA therapy to reduce levodopa induced dyskinesias in Parkinson's disease

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PLevodopa is the gold standard treatment for Parkinson's disease (PD) despite after its necessary and prolonged use most patients often develop side effects, known as levodopa-induced dyskinesia (LID). The management of LID usually requires therapeutic intervention, and the only available alternative is the use of the NMDA receptor antagonist amantadine, which provides limited efficacy. LID is currently one of the major challenges in PD research and the NMDA receptor is indeed the most plausible target to its management. In this context, we postulated the kinase Fyn, a key NMDA receptor regulator, as a new putative molecular target against LID. Our group developed an experimental therapeutic strategy to knock down Fyn expression to alleviate LID in 6-OHDA-lesioned mice treated with levodopa. To such a goal we performed intra-striatal delivery of a designed micro-RNA against Fyn (miRNA-Fyn), which was delivered either before or after levodopa exposure to assess its ability to prevent or revert dyskinesia. Pre-administration of miRNA-Fyn reduced LID with a concomitant reduction of FosB-ΔFosB protein levels –a marker of LID– as well as decreased phosphorylation of the NR2B-NMDA subunit, which is a main target of Fyn. On the other hand, post L-DOPA delivery of miRNA-Fyn was less effective to revert already established dyskinesia, suggesting that early blocking of Fyn activity might be a more efficient therapeutic approach. Our results provide proof of concept about Fyn as a plausible therapeutic target to manage LID, and validate RNA silencing as a potential approach to locally reduce striatal Fyn, rising new perspectives for RNA therapy interventions in PD.

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