Optogenetic and Pharmacological Control of Dopamine/Cholinergic Balance in Experimental Parkinsonism

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Résumé

The loss of striatal dopamine (DA) in Parkinson's disease (PD) models triggers increased level of striatal cholinergic (ACh) activity. How this ACh hyperactivity contributes to motor dysfunction in PD models is still not clear. To address this question, the effects of optogenetic manipulation of dorsal striatal ACh interneurons were evaluated in normal and pathophysiological conditions. To specifically express the opsins in striatal ACh interneurons, we stereotaxically injected into the striatum a Cre-inducible adeno-associated virus (AAV) vector carrying the gene encoding channelrhodopsin (ChR2) or halorhodopsin (eNpHR) in transgenic mice expressing Cre-recombinase under the choline acetyltransferase promoter. Electrophysiological recordings of ACh interneurons *in vitro* in striatal slice and *in vivo* confirmed that under laser illumination both opsins were functional: ChR2 drove spike activity while eNpHR silenced firing. We then investigated the contribution of ACh interneurons to motor control in two experimental models of PD. In the haloperidol-induced catalepsy, optogenetic inhibition of ACh interneurons reduced the akinetic symptoms, while their activation had no effect. This antiparkinsonian benefit was also confirmed in the unilateral 6-OHDA nigrostriatal lesion model of PD. Inhibition of ACh interneurons led to a reduction of postural asymmetry and turning bias in the cylinder test and cross maze. Selective muscarinic receptor antagonists (telenzepine and tropicamide, M1 and M4 receptor antagonist, respectively), systemically administered in the same rodent model of PD, decreased the postural asymmetry in the same tests and reduced amphetamine-induced circling behavior. These optogenetic and pharmacological results emphasize the critical involvement of striatal ACh interneurons activity, mediated in part by muscarinic M1 and M4 receptors, in the motor symptoms of PD.

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