Increased activity of D5R-Kv1.3 pathway in cholinergic interneurons contributes to the hypercholinergic state of parkinsonism and dyskinesias.

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Balanced actions of dopamine (DA) and acetylcholine (ACh) shape striatal function. Striatal cholinergic interneurons (ChIs) are the main striatal ACh source. In Parkinson´s disease (PD), DAergic nigrostriatal neurons degenerate, leading to a hypercholinergic state. L-dopa treatment can induce dyskinesias (LID). Previously, we found that ChIs are hyperexcitable in a mouse model of PD as result of a reduced Kv1.3 current, and, recently, that ChIs from LID mice are even more hyperexcitable. Our aim is to identify the mechanisms underlying this hyperexcitability, which are potential new therapeutic targets for Parkinson's disease and dyskinesias. Since hyperexcitability occurs in the absence of DA or L-dopa treatment, we hypothesize that physiologic activation of D5R, which results in increased excitability, reduces Kv1.3 current. Because the D5R, which has constitutive (ligand-independent) activity, excites ChIs in physiological conditions, we hypothesize that an alteration of D5R signaling causes ChIs hyperexcitability in PD. With *ex-vivo* electrophysiological recordings, we found that D5R increases ChIs excitability by reducing a Kv1.3 current through a cAMP dependent signaling cascade. Moreover, in PD and LID mouse models, elevated levels of cAMP contribute to ChIs hyperexcitability. Finally, preliminary results suggest that this pathway is overactive due to an increased constitutive activation of D5R that entails an increased cAMP production followed by a reduction in Kv1.3 current, resulting in ChIs hyperexcitability.