Striatal tyrosine hydroxylase-positive neurons are associated with L-DOPA-induced dyskinesia in hemiparkinsonian mice.

Abstract:
L-3,4-Dihydroxyphenylalanine (L-DOPA) is the therapeutic gold standard in Parkinson's disease. However, long-term treatment is complicated by the induction of debilitating abnormal involuntary movements termed L-DOPA-induced dyskinesias (LIDs). Until today the underlying mechanisms of LID pathogenesis are not fully understood. The aim of this study was to reveal new factors, which may be involved in the induction of LID. We have focused on the expression of striatal tyrosine hydroxylase-positive (TH+) neurons, which are capable of producing either L-DOPA or dopamine (DA) in target areas of ventral midbrain DAergic neurons. To address this issue, a daily L-DOPA dose was administered over the course of 15 days to mice with unilateral 6-hydroxydopamine-induced lesions of the medial forebrain bundle and LIDs were evaluated. Remarkably, the number of striatal TH+ neurons strongly correlated with both induction and severity of LID as well as ?FosB expression as an established molecular marker for LID. Furthermore, dyskinetic mice showed a marked augmentation of serotonergic fiber innervation in the striatum, enabling the decarboxylation of L-DOPA to DA. Axial, limb and orolinguial dyskinesias were predominantly associated with TH+ neurons in the lateral striatum, whereas medially located TH+ neurons triggered locomotive
rotations. In contrast, identified accumbal and cortical TH+ cells did not contribute to the generation of LID. Thus, striatal TH+ cells and serotonergic terminals may cooperatively synthesize DA and subsequently contribute to supraphysiological synaptic DA concentrations, an accepted cause in LID pathogenesis.

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