l-DOPA-induced dyskinesia is associated with a deficient numerical downregulation of striatal tyrosine hydroxylase mRNA-expressing neurons.

Abstract:

L-3,4-Dihydroxyphenylalanine (L-DOPA) is the therapeutic gold standard in Parkinson's disease. However, most patients develop debilitating abnormal involuntary movements termed L-DOPA-induced dyskinesia (LID) as therapy-complicating side effects. The underlying mechanisms of LID pathogenesis are still not fully understood. Recent evidence suggests an involvement of striatal tyrosine hydroxylase (TH) protein-expressing neurons, as they are capable of endogenously producing L-DOPA and possibly dopamine. The aim of this study was to elucidate changes of TH transcription in the striatum and nucleus accumbens that occur under experimental conditions of LID. Mice with a unilateral 6-hydroxydopamine-induced lesion of the medial forebrain bundle were treated daily with L-DOPA for 15 days to provoke dyskinesia. In situ hybridization analysis revealed a significant numerical decrease of TH mRNA-positive neurons in the striatum and nucleus accumbens of mice not exhibiting LID, whereas dyskinetic animals failed to show this reduction of TH transcription. Interestingly, similar changes were observed in intact non-deafferentiated striata, demonstrating an L-DOPA-responsive
transcriptional TH regulation independently from nigrostriatal lesion severity. Consolidation with our previous study on TH protein level (Keber et al., 2015) impressively highlights that LID is associated with both a deficient downregulation of TH transcription and an excessive translation of TH protein in intrastriatal neurons. As TH protein levels in comparison to mRNA levels showed a stronger correlation with development and severity of LID, antidyskinetic treatment strategies should focus on translational and posttranslational modulations of TH as a promising target.