Effect of long-term treatment with pramipexole or levodopa on presynaptic markers assessed by longitudinal [123I]FP-CIT SPECT and histochemistry.

A previous clinical trial studied the effect of long-term treatment with levodopa (LD) or the dopamine agonist pramipexole (PPX) on disease progression in Parkinson disease using SPECT with the dopamine transporter (DAT)-radioligand [(123)I]-CIT as surrogate marker. [(123)I]-CIT binding declined to significantly lower levels in patients receiving LD compared to PPX. However, the interpretation of this difference as LD-induced neurotoxicity, PPX-induced neuroprotection/-regeneration, or only drug-induced regulatory changes of DAT-availability remained controversial. To address this question experimentally, we induced a subtotal lesion of the substantia nigra in mice by bilateral injection of the neurotoxin 6-hydroxydopamine. After 4 weeks, mice were treated for 20 weeks orally with LD (100mg/kg/day) or PPX (3mg/kg/day), or water (vehicle) only. The integrity of nigrostriatal projections was assessed by repeated [(123)I]FP-CIT SPECT in vivo and by immunostaining for DAT and the dopamine-synthesizing enzyme tyrosine hydroxylase (TH) after sacrifice. In sham-lesioned mice, we found that both LD and PPX treatment significantly decreased the striatal FP-CIT binding (LD: -21%; PPX: -14%) and TH-immunoreactivity (LD: -42%; PPX: -45%), but increased DAT-immunoreactivity (LD: +42%);
PPX: +33%) compared to controls without dopaminergic treatment. In 6-hydroxydopamine-lesioned mice, however, neither LD nor PPX significantly influenced the stably reduced FP-CIT SPECT signal (LD: -66%; PPX: -66%; controls -66%), TH-immunoreactivity (LD: -70%; PPX: -72%; controls: -77%) and DAT-immunoreactivity (LD: -70%; PPX: -75%; controls: -75%) in the striatum or the number of TH-positive cells in the substantia nigra (LD: -88%; PPX: -88%; controls: -86%), compared to lesioned mice without dopaminergic treatment. In conclusion, chronic dopaminergic stimulation with LD or PPX induced similar adaptive presynaptic changes in healthy mice, but no discernible changes in severely lesioned mice. These findings allow to more reliably interpret the results from clinical trials using neuroimaging of DAT as surrogate parameter.