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Title: Parkinson's disease progression is associated with increased putaminal serotonin to dopamine transporter ratio: relevance for dyskinesias

Objective(s): To assess the role of serotonin transporter (SERT) to dopamine transporter (DAT) binding ratios in the development of levodopa-induced dyskinesias (LIDs) in Parkinson's disease (PD) patients.

Background: Serotonergic mechanisms have shown to play a key role in the development of LIDs in patients with PD. Here we hypothesised that an unfavourable serotonin to dopamine terminal ratio would be most detrimental for advanced PD patients who develop LIDs, and we sought to investigate this *in vivo* using specific serotonin and dopamine terminal markers.

Subjects/Methods: Twenty-eight patients with PD [17 with LIDs (PD duration: 11.4 ± 4.6 years); 11 stable (PD duration: 5.7 ± 2.6 years)] and 12 age- and gender-matched healthy controls were studied with [^{11}C]DASB PET and [^{123}I]FP-CIT SPECT, which are respective specific markers of DAT and SERT availability *in vivo*. We have employed a simplified reference tissue model using cerebellum as the reference tissue for the quantification of [^{11}C]DASB, whereas a semi-quantification approach was used for [^{123}I]FP-CIT data. We have estimated uptake values in the putamen.

Results: PD patients showed decreases in [^{123}I]FP-CIT binding ($p < 0.001$) compared to healthy controls, 51% in the stable and 62% in the LIDs group,. PD patients showed also decreases in [^{11}C]DASB binding ($p < 0.01$), but were no differences between the stable (37% loss) and LIDs (31% loss) groups. PD patients with LIDs had 103% increased [^{11}C]DASB to [^{123}I]FP-CIT binding ratio, whereas in the PD stable group the ratio was increased by 76%, relative to healthy controls. Higher [^{11}C]DASB to [^{123}I]FP-CIT binding ratio correlated with longer disease duration for the 28 PD patients ($r = 0.52$; $p < 0.01$).

Conclusions: SERT to DAT ratio increases as PD progresses and patients experience LIDs. Our findings further support the role of serotonin terminals within the dopaminergic denervated striatum for the development of LIDs.