Levodopa remains the mainstay of treatment for Parkinson disease (PD), but its use is associated with dyskinesias (LID) in many patients. LID likely reflect dysregulated release of dopamine combined with altered postsynaptic mechanisms due to pulsatile dopamine receptor stimulation. Dopamine D<sub>3</sub> receptors are increased in animal models of LID, and experimental LID is attenuated by suppression of D<sub>3</sub> signaling, but the relevance to LID in humans is uncertain. Payer et al. used PET with the D<sub>3</sub>-preferring dopamine receptor agonist [<sup>11</sup>C]PHNO. Compared to patients with PD without LID, those with LID had increased binding in the globus pallidus and decreased binding in the ventral striatum. In the dorsal striatum, PHNO binding was increased in both PD groups, but the difference between PD-stable and PD-LID was not significant. However, [<sup>11</sup>C]raclopride binding to D<sub>2</sub> and D<sub>3</sub> receptors was increased in patients with LID when controlling for levodopa dose.

The findings support the importance of D<sub>3</sub> receptor upregulation in pallidum and possibly dorsal striatum in the pathogenesis of LID in humans. At least 4 issues prompt caution: (1) PHNO binds preferentially but not selectively to D<sub>3</sub> receptors; (2) the proportion of PHNO binding to D<sub>3</sub> receptors varies from one region to another, but could be affected by disease and treatment; (3) PHNO binding is susceptible to competition from endogenous (levodopa-derived) dopamine; and (4) the low doses of PHNO injected are not trace, further complicating the interpretation of the imaging data. In ventral striatum, patients with PD-LID had more severe disease and higher daily levodopa requirements than those without LID; thus reduced PHNO binding may reflect more severe dopamine denervation. Finally, there was considerable variability in pallidal PHNO binding, suggesting that the effect seen could have been driven by outliers or that D<sub>3</sub> receptor upregulation alone may be neither necessary nor sufficient to result in LID.


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