

The effect of 5-HT1A agonists and NMDA antagonists in Parkinson's Disease and Dyskinesia in a Unilateral 6-OHDA Rat Model

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Parkinson's disease (PD) is the result of a lack of dopamine (DA) in the striatum. Treatment of PD with DA agonists such as apomorphine and L-DOPA often leads to dyskinetic motor complications caused by raising DA levels in the striatum too highly. However, there are two classes of drugs, serotonin (5-HT1A) agonists and glutamate (NMDA) antagonists that appear to ameliorate both symptoms. In Experiment 1, it was found that 0.2 mg/kg (but not others) of the 5HT1A agonist 8-OH-DPAT produced an 8.3% increase in contralateral forepaw stepping in rats with unilateral 6-OHDA lesions of the medial forebrain bundle, whereas 8 mg/kg L-DOPA improved forepaw stepping by 29.4%. In Experiment 2, 2 weeks of daily 0.05 mg/kg injections of the D2/D3 agonist apomorphine, sufficient to produce dyskinesia in half of the rats, increased contralateral stepping by 12.2%, but decreased ipsilateral by 30.7%. In these animals, 0.2 mg/kg 8-OH-DPAT increased contralateral stepping by 4.7% and 0.2 mg/kg of the NMDA receptor antagonist MK-801 increased stepping by 13.0%, in all rats, and by 23.1% and 41.1% respectively in rats that did not demonstrate an anti-PD effect of apomorphine. 0.3 mg/kg 8-OH-DPAT and 0.1 mg/kg MK-801 did not have an effect. 0.2 mg/kg 8-OH-DPAT also reduced the apomorphine-induced dyskinesia (measured by AIMs) by 21.9%, whereas 0.2 mg/kg MK-801 reduced AIMs by 39.1%. I argue that both of these drugs act to reduce PD and dyskinesia, by decreasing striatal glutamatergic transmission. 5-HT1A agonists likely act to reduce glutamate release from corticostriatal glutamate neurons, whereas NMDA antagonists antagonize postsynaptic NMDA receptors of medium spiny GABAergic neurons.