

## EFFECTS OF DIRECT AND INDIRECT CANNABINOID RECEPTOR AGONISTS ON LEVODOPA-INDUCED DYSKINESIAS IN A RAT MODEL OF PARKINSON'S DISEASE

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Levodopa is the most commonly prescribed treatment for Parkinson's disease (PD). Although levodopa improves PD symptoms in the initial stages of the disease, its long-term use results in disabling side effects, consisting of abnormal involuntary movements (dyskinesias) and psychiatric complications. Recent studies point to the endocannabinoid system as an important modulator of dopamine transmission and its pharmacologic manipulation is emerging as a promising therapy to alleviate levodopa-induced dyskinesias. Rats with 6-OHDA lesions chronically treated (11 days) with levodopa (6mg/kg, i.p.) in association with an inhibitor of aromatic aminoacid decarboxylase (benserazide, 12.5 mg/kg, i.p.), develop increasingly severe axial, limb, locomotor and orofacial abnormal involuntary movements (AIMs). Administration of the cannabinoid agonist WIN55,212-2 (WIN, 1mg/kg, i.p., Kruskal-Wallis test followed by Dunn's multiple comparison test,  $p < 0.05$ ) significantly attenuated levodopa-induced axial, limb and oral AIMs. This effect was reversed by the CB<sub>1</sub> antagonist AM251 (1mg/kg, i.p. Friedman test followed by Dunn's multiple comparison test,  $p < 0.05$ ). By contrast, systemic administration of URB597 (0.1 and 0.3mg/kg, i.p.), a potent FAAH inhibitor that increases the brain levels of the endocannabinoid anandamide by blocking its degradation, had no effect on AIMs scoring despite its ability to increase anandamide concentration throughout the basal ganglia (Two way ANOVA followed by Bonferroni's post hoc test,  $p < 0.05$ ). Unlike WIN, anandamide can also bind and activate the transient receptor potential vanilloid type-1 (TRPV1 receptors), which have been implicated in the regulation of dopaminergic transmission in the substantia nigra. Interestingly, administration of the TRPV1 antagonist capsazepine (10mg/kg, i.p., Kruskal-Wallis test followed by Dunn's multiple comparison test,  $p > 0.05$ ) had no effect on levodopa-induced AIMs, whereas co-administration of URB597 and capsazepine (0.3 and 10 mg/kg i.p., respectively, Kruskal-Wallis test followed by Dunn's multiple comparison test,  $p < 0.05$ ) significantly decreased all AIMs subtypes. Our data suggest that CB<sub>1</sub> and TRPV1 receptors play opposite roles in levodopa-induced dyskinesias.