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5-HT_{1A} Receptors Mediate the Motor Effects of the Non-Psychotropic Phytocannabinoid Cannabidiol

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The broad presence of CB_1 receptors in the basal ganglia, mainly in GABA- or glutamate-containing neurons, as well as the presence of TRPV1 receptors in dopaminergic neurons, explain the powerful motor effects exerted by those cannabinoids able to activate/block these receptors. In contrast, cannabidiol (CBD), a phytocannabinoid with a broad therapeutic profile, is generally presented as an example of a compound with no motor effects due to its poor affinity for CB_1/CB_2 receptors, and despite its activity at the TRPV1 receptor. However, recent findings suggest that CBD may interact with the serotonin 5-HT_{1A} receptor to produce some of its beneficial effects. This may enable CBD to directly influence motor activity by modulating serotoninergic transmission in the basal ganglia. We have investigated this issue in Sprague-Dawley rats using three different pharmacological and neurochemical approaches (all approved by the ethical committee for research in laboratory animals of the Complutense University, Madrid, Spain). First, we compared the motor effects of various i.p. doses of CBD with the selective 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT; i.p.). Second, we investigated whether the motor effects of CBD are sensitive to 5-HT_{1A} receptor blockade in comparison with CB_1 receptor antagonism. Finally, we looked at possible synergies of CBD with 8-OH-DPAT. In all cases, the vehicle was saline or Tween 80-saline, as required, and the number of subjects *per* group >6. The data were assessed by one-way ANOVA followed by the Tukey test. Our results demonstrated that: (i) only high doses of CBD (20 mg/kg) altered motor behavior (34.5% reduction *versus* vehicle-treated rats, $P<0.05$) measured in a computer-aided actimeter; (ii) these alterations were restricted to vertical activity (rearing) with only modest changes in other parameters; (iii) similar effects were produced by 8-OH-DPAT (1 mg/kg), although this agonist affected exclusively vertical activity (93.4% reduction *versus* vehicle-treated rats, $P<0.0005$) and it showed always greater potency than CBD; (iv) the effects of 8-OH-DPAT (1 mg/kg) and CBD (20 mg/kg) on vertical activity were reversed ($P<0.05$) by the 5-HT_{1A} receptor antagonist WAY-100,635 (0.5 mg/kg; i.p.); (v) the effects of CBD (20 mg/kg) on vertical activity were not reversed by the CB_1 receptor antagonist rimonabant (0.1 mg/kg; i.p.); (vi) the effect of 8-OH-DPAT on vertical activity was associated with an increase in serotonin content in the basal ganglia (caudate-putamen: 6.1 ± 0.3 ng/mg protein, $P<0.05$; globus pallidus: 12.2 ± 1.5 ng/mg protein, $P<0.05$; substantia nigra: 13.2 ± 1.2 ng/mg protein, $P<0.01$) compared to vehicle-treated rats (caudate-putamen: 5.1 ± 0.2 ng/mg protein; globus pallidus: 8.5 ± 0.7 ng/mg protein; substantia nigra: 9.2 ± 0.6 ng/mg protein), a neurochemical change not produced by CBD (20 mg/kg); and (vii) the combination of CBD and 8-OH-DPAT may have produced synergistic effects, as the phytocannabinoid at a dose of 20 mg/kg was able to enhance the motor effects (77.3% reduction *versus* vehicle-treated rats, $P<0.0005$) of a sub-effective dose of 8-OH-DPAT (0.1 mg/kg; 7.0% reduction *versus* vehicle-treated rats). These results suggest that CBD may influence motor activity through an effect dependent on its ability to target the 5-HT_{1A} receptor, possibly as an allosteric modulator, a mode of action that it has been proposed might account for its anti-emetic effect.