HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

Drug Alcohol Depend. 2016 August 1; 165: 87–93. doi:10.1016/j.drugalcdep.2016.05.016.

Enhanced discriminative stimulus effects of Δ⁹-THC in the presence of cannabidiol and 8-OH-DPAT in rhesus monkeys

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Abstract

Background—Cannabidiol, a therapeutic with potential serotonin (5-hydroxytryptamine; 5-HT) 5-HT_{1A} receptor agonist activity, is the second most prevalent cannabinoid in *Cannabis* after Δ^9-THC. The extent to which cannabidiol modifies the effects of Δ^9-THC has not been firmly established, especially with respect to abuse-related effects in rhesus monkeys where previously antagonistic interactions have been reported for some behavioral outcomes.

Methods—Cannabidiol and the 5-HT_{1A} receptor agonist (±)-8-hydroxy-2-(dipropylamino)tetralin hydrobromide (8-OH-DPAT) were tested in two separate discrimination assays in rhesus monkeys. One group (n=6) discriminated Δ^9-tetrahydrocannabinol (Δ^9-THC; 0.1 mg/kg i.v.); a second group (n=6) discriminated the cannabinoid antagonist rimonabant (1 mg/kg i.v.) while receiving Δ^9-THC daily (1 mg/kg/12 h s.c.). Responding was maintained under a fixed ratio 5 schedule of stimulus-shock termination.

Results—Both training drugs dose-dependently increased the percentage of responses on the respective drug-associated levers. Cannabidiol (up to 17.8 mg/kg) and 8-OH-DPAT (up to 0.178 mg/kg) did not substitute for either training drug; however, both significantly increased the potency of Δ^9-THC to produce discriminative stimulus effects. Moreover, 8-OH-DPAT significantly attenuated the discriminative stimulus effects of rimonabant, whereas cannabidiol did not modify the rimonabant discriminative stimulus.

Conclusions—These results, which are consistent with cannabidiol lacking CB_1 receptor agonist or antagonist activity in vivo, demonstrate enhancement of the effects of Δ^9-THC by cannabidiol, albeit at cannabidiol amounts larger than those in *Cannabis* or cannabidiol-based therapeutics (nabiximols). In addition to showing that cannabidiol and a 5-HT_{1A} receptor agonist have overlapping behavioral effects, the current results suggest that 5-HT_{1A} agonism enhances the CB_1 receptor-mediated effects of Δ^9-THC.

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Conflict of Interest No conflict declared

Keywords

cannabinoid; rhesus monkey; drug discrimination; cannabidiol; 8-OH-DPAT; serotonin; 5-HT1A; rimonabant; dependence

1. INTRODUCTION

Among the numerous phytocannabinoids in *Cannabis sativa* (Hill et al., 2012), Δ^9-tetrahydrocannabinol (Δ^9-THC) has been the most widely studied due to its prominent psychopharmacological effects. There is increasing recognition of the contribution of other phytocannabinoids to the in vivo effects of cannabis, as well as interest in isolating phytocannabinoids for drug-like and potential therapeutic effects. Cannabidiol is the second most prevalent phytocannabinoid in *Cannabis* after Δ^9-THC and there is increasing evidence to suggest that cannabidiol has anti-inflammatory, anticonvulsant, antiemetic, and antipsychotic activity (Campos et al., 2012; Leo et al., 2016). Most recently, cannabidiol was approved in a formulation with Δ^9-THC under the generic name nabiximols for the treatment of spasticity and neuropathic pain associated with multiple sclerosis.

Δ^9-THC is a cannabinoid receptor agonist, whereas the mechanism of action of cannabidiol remains unclear. Cannabidiol lacks significant binding affinity for the prototypical cannabinoid receptors CB_1 or CB_2 (Mechoulam et al., 2002). While its mechanism of action remains poorly understood, cannabidiol exhibits a diverse pharmacology that includes activity at serotonin (5-hydroxytryptamine; 5-HT) 5-HT_{1A} receptors, G protein-coupled receptors (GPR) 55, transient receptor potential of the ankyrin type 1 (TRPA1), vanilloid type 1 (TRPV1) and vanilloid type 2 (TRPV2) channels, inhibition of synaptic uptake of norepinephrine, GABA, adenosine, and dopamine, and stimulation of $\alpha 3$ and $\alpha 1$ glycine receptors (Leo et al., 2016).

One goal of the current study was to examine cannabidiol for its capacity to modify the abuse-related effects of Δ^9-THC in two separate drug discrimination assays in rhesus monkeys. The first was a Δ^9-THC discrimination assay (McMahon, 2006b) and the second was a rimonabant discrimination assay in Δ^9-THC treated monkeys sensitive to cannabinoid antagonism (Stewart and McMahon, 2010). Whereas cannabidiol was not expected to substitute for Δ^9-THC based on published studies using pigeons (Järbe et al., 1977) and rats (Vann et al., 2008), cannabidiol was expected to modify the effects of Δ^9-THC. There are multiple reports of cannabidiol and Δ^9-THC interacting to modify each other's behavioral effects with the type of outcome, including enhancement (Karniol and Carlini, 1973; Takahashi and Karniol, 1975) and antagonism (Karniol and Carlini, 1973; Borgen and Davis, 1974; Karniol et al., 1974), depending on the endpoint of interest. In particular, antagonism was previously reported in rhesus monkeys performing operant conditioning and cognitive-based tasks (Brady and Balster, 1980; Wright et al., 2013), suggesting that cannabidiol could also attenuate the discriminative stimulus effects of Δ^9-THC in rhesus monkeys, evidenced in the current study by not only attenuation of the Δ^9-THC discriminative stimulus, but also substitution of cannabidiol for rimonabant. A second goal was to compare the effects of cannabidiol to the 5-HT_{1A} receptor agonist (±)-8-hydroxy-2-

(dipropylamino)tetralin hydrobromide (8-OH-DPAT); this was undertaken because 5-HT_{1A} agonism appears to be one of the mechanisms by which cannabidiol could produce behavioral effects (Russo et al., 2005).

2. MATERIALS AND METHODS

2.1. Subjects

The Δ^9-THC discrimination assay was conducted in six adult rhesus monkeys (*Macaca mulatta*) including two females and four males. The rimonabant discrimination assay was conducted in three adult females and three adult males. When monkeys were not in operant conditioning chambers they were housed individually on a 14-h light/10-h dark schedule. Body weights ranged from 5.6 kg to 10.1 kg and the diet consisted of fresh fruit, peanuts, and primate chow (High Protein Monkey Diet, Harlan Teklad, Madison, WI). Water was continuously available in the home cage. Monkeys had previously received non-cannabinoids and cannabinoids as described (Stewart and McMahon, 2010; Hruba et al., 2012). The experiments reported here were approved by the Institutional Animal Care and Use Committee of The University of Texas Health Science Center at San Antonio, and were conducted according to the “Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research” (National Research Council, 2011).

2.2. Surgery

A chronic indwelling catheter (heparin coated polyurethane, od = 1.68 mm, id = 1.02 mm, Instech Solomon, Plymouth Meeting, PA) was inserted into a femoral or subclavian vein while monkeys were anesthetized with ketamine (10 mg/kg i.m.) and isoflurane (1.5–3.0% inhaled via facemask). The catheter was secured in the vessel with suture silk (coated vicryl, Ethicon Inc., Somerville, New Jersey), which was also used to ligate the section of the vessel adjacent to the catheter insertion. The end of the catheter distal to the vessel was attached to a vascular access port (Mida-cbas-c50, Instech Solomon) located s.c. in the mid-scapular region of the back.

2.3. Apparatus

Monkeys were seated in chairs (Model R001, Primate Products, Miami, FL). Feet were secured in shoes containing brass electrodes to which a brief electric stimulus (3 mA, 250 ms) could be delivered from an a/c generator. Discrimination training and test sessions were performed by placing monkeys in operant conditioning chambers ventilated with blower fans. White noise was present for the duration of experimental sessions. Within the chamber was a stainless steel panel containing a left and right lever and a disc above each lever that could be illuminated red. Experimental events were controlled and recorded by an interface (MedAssociates, St. Albans, VT), a computer, and Med-PC software (MedAssociates).

2.4. Drug discrimination procedures

One group of monkeys discriminated Δ^9-THC (0.1 mg/kg i.v.) from a vehicle consisting of a mixture of absolute ethanol, Emulphor-620, and saline in a proportion of 1:1:18. The second group of monkeys discriminated rimonabant (1 mg/kg i.v.) from the same vehicle; for monkeys discriminating rimonabant, Δ^9-THC (1 mg/kg s.c.) was administered twice daily at

0600 and 1800 h and experimental sessions commenced at 1200 h. Both groups responded under a fixed ratio 5 (FR5) schedule of stimulus-shock termination. The experimental sessions were divided into multiple, consecutive cycles. For the studies with cannabidiol in combination with the training drugs, each cycle began with a 15-min timeout during which lights were not illuminated and responses on the levers resulted in no programmed consequence. The timeout was followed by a 5-min schedule of stimulus-shock termination signaled by the illumination of two red lights, one above each lever. Five consecutive responses within 40 s (Δ^9-THC discrimination) or 10 s (rimonabant discrimination) on the correct lever extinguished the red lights, prevented delivery of an electric stimulus, and initiated a 30-s timeout. Otherwise, an electric stimulus was delivered. Incorrect responses reset the response requirement on the correct lever. Determination of correct levers varied among monkeys, e.g., the right lever was associated with vehicle and the left lever was associated with the training dose, and remained the same for that monkey for the duration of the study. For studies with 8-OH-DPAT, the timeout at the beginning of each cycle was shortened to 5 min to accommodate the relatively short duration of action of 8-OH-DPAT evidenced in pilot experiments measuring disruption of operant responding; however, all other experimental parameters remained the same.

Training sessions consisted of administration of the training dose of the training drug (Δ^9-THC or rimonabant) or vehicle at the beginning of a cycle. Administration of the training dose at the beginning of a cycle was followed by 0–2 cycles during which vehicle was administered; however, the drug lever was designated as correct during every cycle following administration of the training dose during training sessions. A cycle in which the training dose was administered was preceded by 0–3 cycles, and for these preceding cycles vehicle was administered and the vehicle lever was designated correct. Training sessions in which only vehicle was administered for each cycle consisted of 3–6 cycles and the vehicle lever was designated correct throughout. Monkeys had previously satisfied the criteria for testing, defined as at least 80% of the total responses occurring on the correct lever and fewer than 5 responses occurring on the incorrect lever prior to satisfying the first FR of the cycle on the correct lever for all cycles for 5 consecutive or 6 of 7 training sessions. Tests were conducted after performance for consecutive training sessions, including both vehicle and drug training sessions, satisfied the test criteria.

Five consecutive responses on either lever postponed the shock schedule during test sessions. The control dose-response functions for each training drug were determined by administering vehicle in the first cycle followed by cumulative i.v. doses increasing by 0.5 log unit in subsequent cycles; doses larger than the rimonabant training dose were incremented in 0.25 log unit (i.e., 1.78 and 3.2 mg/kg). To examine the effects of cannabidiol and 8-OH-DPAT, a dose was administered at the beginning of the first cycle followed by cumulative doses of the training drug (Δ^9-THC or rimonabant) in subsequent cycles. Cannabidiol was studied from 0.1 mg/kg up to 17.8 mg/kg because 32 mg/kg of cannabidiol produced a convulsion. 8-OH-DPAT was studied at 0.0178, 0.056, and 0.178 mg/kg. The effects of each test drug in combination with a training drug were examined using a within-subjects design (e.g., each monkey served as its own control) in four monkeys, except for cannabidiol tests in the Δ^9-THC discrimination assay which included six monkeys. Two monkeys discriminating rimonabant contributed to tests with both

cannabidiol and 8-OH-DPAT; of the four remaining monkeys in the rimonabant discrimination assay, two were used for tests with cannabidiol and the other two were included in the tests with 8-OH-DPAT. Control dose-response data for each training drug were calculated separately for the cycle durations of 20 min (cannabidiol) and 10 min (8-OH-DPAT). The control dose-response tests were conducted non-systematically in close temporal proximity to the tests with the various doses of cannabidiol and 8-OH-DPAT.

2.5. Drugs

Rimonabant, cannabidiol, and Δ^9-THC (200 mg/ml in absolute ethanol; The Research Technology Branch of the National Institute on Drug Abuse, Rockville, MD) were dissolved in the vehicle mixture consisting of absolute ethanol, Emulphor-620 (Rhodia Inc., Cranbury, NJ), and physiological saline; each of these drugs was administered i.v. for cumulative dose-response tests. Δ^9-THC was administered s.c. for daily treatment in the group of monkeys discriminating rimonabant. (±)-8-Hydroxy-2-(dipropylamino)tetralin hydrobromide (8-OH-DPAT; Sigma Chemical Co., Saint Louis, MO) was dissolved in the same vehicle and administered s.c. Drugs were administered in a volume of 0.1–1 ml/kg. Doses were expressed as the weight of the forms listed above in milligrams per kilogram of body weight.

2.6. Data analyses

Discrimination data are expressed as a percentage; the percentage was calculated by dividing the total number responses on the drug lever by the total number of responses on both the drug and vehicle levers, for each test cycle, and multiplying each result by 100. Rate of responding on both levers (i.e., drug and vehicle) is calculated as responses per s excluding responses during timeouts. Rate of responding during a test is expressed as the percentage of the control response rate for individual animals. The control response rate is defined as the average response rate for all cycles during the five previous vehicle training sessions excluding any training sessions in which the test criteria are not satisfied. Discrimination and response rate data are averaged among subjects (± S.E.M.) and plotted as a function of dose.

The analysis of the discrimination dose-response data for each training drug includes the smallest dose tested, which is 0.0032 mg/kg for Δ^9-THC and 0.1 mg/kg for rimonabant, up to the largest dose tested as determined per individual monkey. The largest dose tested is the smallest dose producing greater than 80% drug-appropriate responding, decreasing response to less than 20% of the control response rate, or up to 0.32 mg/kg for Δ^9-THC or 3.2 mg/kg for rimonabant, whichever occurs first. Discrimination data are not included when the associated response rate is less than 20% of the control as determined per individual monkey. The individual dose-response data for each training drug in combination with various doses of a test drug are analyzed with GraphPad Prism version 6.00 (GraphPad Software, La Jolla, CA) using non-linear regression and the following equation Y=100/(1+10^((LogED-X)*slope)) with LogED calculated as $\text{LogED}_{50}\text{Control} + \log(\text{ED}_{50}\text{Ratio})$. The analysis included the common slope shared by the dose-response function of the training drug alone and in combination with the various doses of test drug. ED_{50}Control is the dose of training drug estimated to produce 50% drug-appropriate responding in the absence of test drug and ED_{50}Ratio is the ratio of the ED_{50} value of the training drug calculated in the presence of a dose of test drug divided by the ED_{50} value of the training

drug alone. A significant shift in the training drug dose-response function is evidenced by a ratio value with 95% confidence limits that do not include 1.

3. RESULTS

3.1. The effects of Δ^9-THC alone and in combination with cannabidiol or 8-OH-DPAT

The absolute rate of responding averaged over 5 vehicle training sessions for each respective monkey discriminating Δ^9-THC was 0.96, 1.06, 1.36, 1.43, 1.46, and 1.76 responses per s. Vehicle administered prior to determination of the control Δ^9-THC dose-response function resulted in 0% responses on the drug-lever (Fig. 1 top, circle above VEH). Δ^9-THC dose-dependently increased responding on the drug-lever with the training dose resulting in 97% drug-lever responding; the ED_{50} value (95% confidence limits) was 0.034 (0.018–0.068) mg/kg (Table 1 left column). Cannabidiol produced no more than 33% of the responses on the Δ^9-THC lever and this occurred at 17.8 mg/kg (Fig. 1 top left, triangle over VEH). Cannabidiol doses ranging from 0.1 to 3.2 mg/kg did not significantly modify the discriminative stimulus effects of Δ^9-THC (see Fig. 1, diamonds for 3.2 mg/kg of cannabidiol; ineffective doses less than 3.2 mg/kg not shown). In contrast, 10 and 17.8 mg/kg of cannabidiol significantly increased the potency of Δ^9-THC to produce discriminative stimulus effects (Fig. 1 top left, squares and triangles, respectively), as evidenced by dose ratios (95% confidence limits) of 0.39 (0.0077–0.78) and 0.23 (0.0030–0.46) (Table 1 left column). These represent 2.6- and 4.2-fold leftward shifts of the Δ^9-THC dose-response function. Response rate was not systematically altered following any dose of Δ^9-THC and cannabidiol, alone or in combination (Fig. 1 bottom left).

The Δ^9-THC control dose-response function determined in conjunction with the 8-OH-DPAT tests was strikingly similar to that determined for cannabidiol tests, with vehicle producing 0% drug-lever responding and the training dose (0.1 mg/kg) producing 99% drug-lever responding (Fig. 1 top right, circles). 8-OH-DPAT produced a maximum of 3% responding on the Δ^9-THC lever at 0.178 mg/kg (Fig. 1 top right, triangle above VEH). 8-OH-DPAT at a dose of 0.0178 mg/kg did not significantly modify the Δ^9-THC discrimination dose-response function (Fig. 1 top right, diamonds). In contrast, 0.056 and 0.178 mg/kg of 8-OH-DPAT significantly increased the ED_{50} value of Δ^9-THC (Fig. 1, squares and triangles, respectively), as evidenced by dose ratios (95% confidence limits) of 0.60 (0.29–0.90) and 0.078 (0.028–0.13), respectively (Table 1 right column). These represent 1.7- and 13-fold leftward shifts of the Δ^9-THC dose-response function. The largest dose of 8-OH-DPAT (0.178 mg/kg), when tested alone and in combination with Δ^9-THC, markedly decreased response rate with two of four monkeys responding less than 20% of their individual control response rate (Fig. 1 bottom right, triangles).

3.2. The effects of rimonabant alone and in combination with cannabidiol or 8-OH-DPAT in monkeys receiving Δ^9-THC (1 mg/kg/12 h)

The absolute rate of responding averaged over 5 vehicle training sessions for each respective Δ^9-THC treated monkey discriminating rimonabant was 0.85, 1.12, 1.21, 1.31, 1.41, and 1.72 responses per s. Administration of vehicle produced 0% responding on the rimonabant-associated lever (Fig. 2 top, circles above VEH). Rimonabant dose-dependently increased

drug-appropriate responding with the training dose (1 mg/kg) producing 100% responses on the drug-lever. Cannabidiol (10 and 17.8 mg/kg) alone produced no more than 7% of responses on the rimonabant lever. Cannabidiol did not significantly modify the rimonabant dose-response function for producing discriminative stimulus effects in Δ^9-THC treated monkeys (Fig. 2 top left, square and triangles, respectively). Up to 17.8 mg/kg cannabidiol did not result in marked reductions in response rate (Fig. 2 bottom left).

Determination of the control rimonabant dose-response function during shortened cycles (i.e., from 20 min for tests with cannabidiol to 10 min for tests with 8-OH-DPAT) resulted in increased potency. The ED_{50} value (95% confidence limits) of rimonabant to produce discriminative stimulus effects in these tests was 0.16 (0.12–0.25) mg/kg (Table 1). 8-OH-DPAT at a dose of 0.056 mg/kg produced 4% of responses on the rimonabant lever (Fig. 2 top right, square above VEH). This dose of 8-OH-DPAT significantly attenuated the discriminative stimulus effects of rimonabant in Δ^9-THC treated monkeys, as evidenced by a dose ratio (95% confidence limits) of 2.1 (1.1–3.1). A larger dose of 8-OH-DPAT (0.178 mg/kg) decreased responding to less than 20% of the control response rate in 3 out of 4 monkeys tested (Fig. 2 bottom right).

4. DISCUSSION

Cannabidiol did not substitute for a Δ^9-THC discriminative stimulus and did not substitute for a rimonabant discriminative stimulus in Δ^9-THC treated monkeys up to the safest dose that could be studied. This result provides strong evidence that cannabidiol does not bind appreciably to CB_1 receptors in primates. Cannabidiol significantly enhanced the potency of Δ^9-THC to produce discriminative stimulus effects, albeit at doses exceeding amounts obtained from *Cannabis* or the currently approved therapeutic nabiximols at prescribed doses. The 5-HT_{1A} agonist 8-OH-DPAT enhanced the effects of Δ^9-THC, although the greatest enhancement occurred at a dose of 8-OH-DPAT that disrupted responding in a subset of monkeys. The enhancement by 8-OH-DPAT was evidenced by not only a leftward shift of the Δ^9-THC discrimination response-response function, but also a rightward shift of the rimonabant discrimination dose-response function in Δ^9-THC treated monkeys. The same type of rightward shift in the rimonabant dose-response function is produced by increasing doses of CB_1 receptor agonists including Δ^9-THC (Ginsburg et al., 2012). Collectively, these results suggest that 5-HT_{1A} agonism can enhance the CB_1 receptor mediated in vivo effects of Δ^9-THC, and further suggest that cannabidiol and 5-HT_{1A} receptor agonists have overlapping behavioral effects.

Nabiximols, an oromucosal spray containing equal amounts of cannabidiol and Δ^9-THC, is approved for the treatment of neuropathic pain and spasticity in patients diagnosed with multiple sclerosis. Oral Δ^9-THC, prescribed under the generic name dronabinol, is an older therapeutic that has limited availability due to concerns over abuse liability. There are similar concerns over the abuse liability of cannabidiol mixed with Δ^9-THC, and questions about the extent to which cannabidiol modifies the abuse liability of Δ^9-THC. The results of clinical studies suggest that the abuse liability of nabiximols is not different from those of either *Cannabis* or Δ^9-THC (Schoedel et al., 2011). The current study had the advantage of varying cannabidiol dose across a broad range including a dose equal to the training dose of

Δ^9-THC (0.1 mg/kg) up to a dose producing a convulsion (32 mg/kg). The current study firmly demonstrates that cannabidiol exerts negligible CB_1 receptor agonist or antagonist activity across this dose range. In addition, at doses equal to or as large as 32 times greater than Δ^9-THC, cannabidiol did not modify the discriminative stimulus effects of Δ^9-THC. Only at a dose 100 times greater than Δ^9-THC did cannabidiol enhance the potency of Δ^9-THC to produce discriminative stimulus effects. Collectively, the current results suggest that cannabidiol carries negligible risk of increasing the subjective effects of Δ^9-THC, and further suggest that cannabidiol is unlikely to attenuate the subjective effects of Δ^9-THC. To the extent that subjective effects predict abuse liability, these results suggest that cannabidiol has minimal impact on the abuse liability of Δ^9-THC. Because Δ^9-THC is not unanimously self-administered in non-humans among published studies (Tanda, 2016), drug discrimination will continue to provide critical insight into mechanisms underlying the abuse-related effects of cannabinoids.

The presence and nature of the interaction between cannabidiol and Δ^9-THC appears to vary for different effects because previous studies have reported antagonism of some of the effects of Δ^9-THC by cannabidiol in rhesus monkeys. Cannabidiol administered in equal amounts with Δ^9-THC attenuated some of the disruptive effects of Δ^9-THC on some types of learning and motor behavior, but did not alter all of the effects of Δ^9-THC (Wright et al., 2013). In another study cannabidiol also attenuated the effects of Δ^9-THC on responding under a fixed interval schedule in rhesus monkeys (Brady and Balster, 1980), and in that study antagonism was obtained at a dose of cannabidiol 100 times larger than Δ^9-THC (30 and 0.3 mg/kg, respectively). The interaction in the current study was also obtained at a dose of cannabidiol 100 times greater than the Δ^9-THC dose, but the direction of the interaction was opposite to that reported previously for rate-decreasing effects. That cannabidiol enhanced the discriminative stimulus effects of Δ^9-THC in the current study and attenuated the rate-decreasing effects of Δ^9-THC in the previous study at comparable doses in the same species suggests that altered pharmacokinetics cannot explain every type of interaction. Instead, the type of interaction that occurs between cannabidiol and Δ^9-THC appears to vary for different behavioral effects, which could reflect differences in the pharmacological mechanisms that mediate the discriminative stimulus effects of Δ^9-THC versus its rate-decreasing effects, as demonstrated previously for cannabinoids under experimental conditions similar to those of the current study (Rodriguez and McMahon, 2014).

Multiple mechanisms are implicated in the pharmacological effects of cannabidiol; 5-HT_{1A} receptor agonism appears to be predominant among those mechanisms. Cannabidiol has been reported to displace [3H]8-OH-DPAT binding from cloned human 5-HT_{1A} receptors and to exert 5-HT_{1A} receptor agonist activity as evidenced by [35S]GTPgammaS binding and cyclic AMP production in vitro (Russo et al., 2005). In pre-clinical studies, serotonin 5-HT_{1A} receptors appear to mediate many of the in vivo effects of cannabidiol including anti-anxiety effects (Campos and Guimarães, 2008), anti-emetic effects (Rock et al., 2012), and antinociceptive effects (Ward et al., 2014). The current results demonstrate that the 5-HT_{1A} receptor agonist 8-OH-DPAT and cannabidiol exert qualitatively similar interactions with Δ^9-THC in rhesus monkeys. However, whereas 8-OH-DPAT attenuated the effects of rimonabant in Δ^9-THC treated monkeys, cannabidiol did not. Both discrimination assays are mediated by CB_1 receptor activity (McMahon, 2006a; 2006b). Aside from the opposing

effects on cannabinoid signaling of the training drugs, the discrimination assays also differ with respect to Δ^9-THC treatment, with the rimonabant discrimination being associated with more (i.e., daily) Δ^9-THC treatment than the Δ^9-THC discrimination assay. A parsimonious explanation of the rimonabant discrimination in Δ^9-THC treated monkeys is that the rimonabant training condition represents antagonism or decreased effectiveness of Δ^9-THC, whereas the vehicle training condition represents the presence of Δ^9-THC. That cannabidiol enhanced the effects of Δ^9-THC in the Δ^9-THC discrimination assay but not the rimonabant discrimination assay might reflect chronic Δ^9-THC induced loss of 5-HT_{1A} receptor function. However, in a previous study chronic treatment with the cannabinoid agonist WIN-55212,2 increased 5-HT_{1A} expression and enhanced sensitivity to the effects of a relatively small dose of 8-OH-DPAT that was intended to be selective for presynaptic 5-HT_{1A} autoreceptors (Moranta et al., 2009). If 5-HT_{1A} receptor agonism is the pharmacological mechanism by which cannabidiol exerts behavioral effects, however, then Δ^9-THC induced changes in 5-HT_{1A} receptor function would have been expected to impact sensitivity to the behavioral effects of both cannabidiol and 8-OH-DPAT.

In summary, cannabidiol enhanced the discriminative stimulus effects of Δ^9-THC but only at doses larger than those that would be obtained from *Cannabis* or nabiximols use. To the extent that the current results provide insight into abuse-related effects, then the potential use of nabiximols as a treatment for cannabinoid dependence and withdrawal, as tested in some clinical studies (Allsop et al., 2014), would seem to carry negligible risk of further increasing Δ^9-THC abuse liability. On the other hand, if the rimonabant discrimination assay in Δ^9-THC treated monkeys reflects Δ^9-THC withdrawal as proposed (McMahon and Stewart, 2010), then the failure of cannabidiol to modify the rimonabant discriminative stimulus suggests cannabidiol alone has limited utility as a drug therapy for cannabinoid dependence. Enhancement of the effects of Δ^9-THC and attenuation of the effects of rimonabant by 8-OH-DPAT implicates a role for 5-HT_{1A} receptor agonism in modifying the effects of cannabinoids. While the 5-HT_{1A} agonist buspirone has been reported to decrease cannabis craving, the inability of buspirone to reduce cannabis use and its potential to increase use in some individuals (McRae-Clark et al., 2015) suggests that buspirone and other potential 5-HT1A receptor based therapeutics should be prescribed with caution in *Cannabis* users.

Acknowledgments

None

Role of Funding Source Nothing declared

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Highlights

- Cannabidiol lacks CB_1 receptor agonist or antagonist activity in primates
- Cannabidiol amounts larger than those in *Cannabis* or nabiximols enhances Δ^9-THC
- Cannabidiol and a 5-HT_{1A} receptor agonist have overlapping behavioral effects
- 5-HT1A agonism enhances the CB1 receptor-mediated effects of Δ^9-THC.

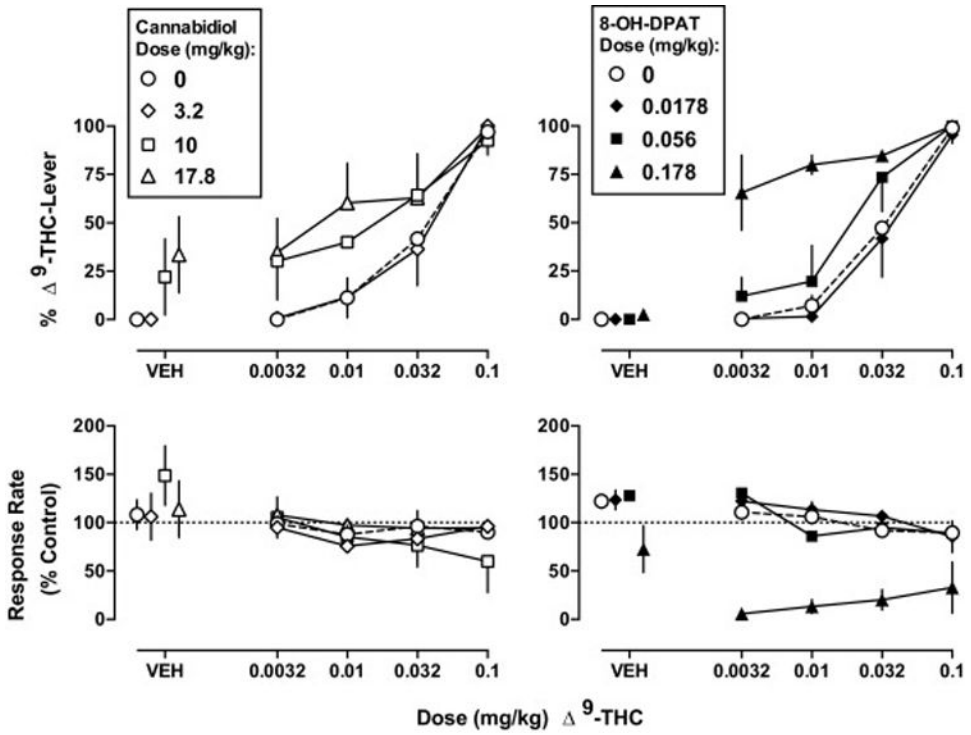

Fig. 1.

Effects of cannabidiol (left) and 8-OH-DPAT (right) following s.c. administration alone and in combination with Δ^9-THC in rhesus monkeys discriminating Δ^9-THC (0.1 mg/kg i.v.). Abscissae: vehicle (VEH) or dose of Δ^9-THC in milligram per kilogram of body weight. Ordinates: mean (± S.E.M.) percentage of responding on the Δ^9-THC lever (top) and mean (± S.E.M.) response rate expressed as a percentage of the VEH control rate (bottom). The dashed line is the dose-response function for Δ^9-THC alone. Mean data for cannabidiol are n=6, except for discrimination data at 10 and 17.8 mg/kg cannabidiol, which are 5 out of the 6 monkeys tested. Mean data for 8-OH-DPAT are n=4, except for discrimination data at 0.178 mg/kg 8-OH-DPAT, which are 2 out of the 4 monkeys tested.

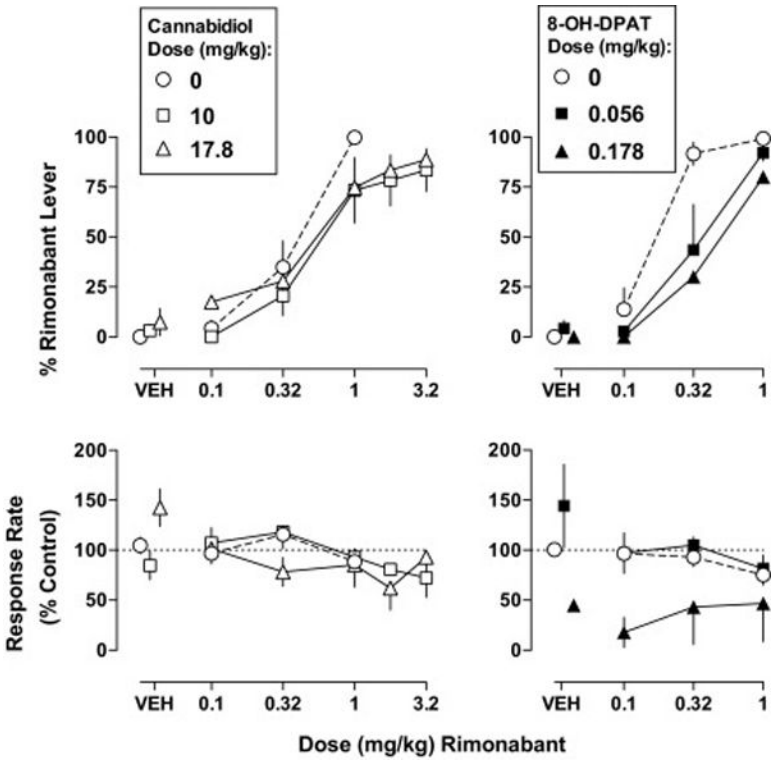

Fig. 2.

Effects of cannabidiol (left) and 8-OH-DPAT (right) following s.c. administration alone and in combination with rimonabant in rhesus monkeys discriminating rimonabant (1 mg/kg i.v.) while receiving 1 mg/kg/12 h Δ^9-THC s.c. Abscissae: vehicle (VEH) or dose of rimonabant in milligram per kilogram of body weight. Ordinates: mean (± S.E.M.) percentage of responding on the rimonabant lever (top) and mean (± S.E.M.) response rate expressed as a percentage of the VEH control rate (bottom). The dashed line is the dose-response function for rimonabant alone. Mean data for cannabidiol are n=4, except for data at 17.8 mg/kg cannabidiol in combination with 3.2 mg/kg rimonabant, which is one monkey. Mean data for 8-OH-DPAT are n=4, except for discrimination data at 0.178 mg/kg 8-OH-DPAT, which is 1 out of the 4 monkeys tested.

Table 1

ED_{50} values, dose ratios, and 95% confidence limits (95% CL) for Δ^9-THC alone, rimonabant alone, and the respective training drugs in combination with various doses of cannabidiol or 8-OH-DPAT.

	ED_{50} (95% CL)	**Dose ratio (95% CL)**
Δ^9-THC Control	0.034 (0.018–0.068)	
+ Cannabidiol (3.2 mg/kg)	0.037 (0.017–0.083)	1.0 (0.01–2.2)
+ Cannabidiol (10 mg/kg)	0.013 (0.0068–0.027)	0.39 (0.0077–0.78) *
+ Cannabidiol (17.8 mg/kg)	0.0080 (0.0039–0.016)	0.23 (0.0030–0.46) *
Δ^9-THC Control	0.032 (0.023–0.045)	
+ 8-OH-DPAT (0.0178 mg/kg)	0.036 (0.026–0.051)	1.1 (0.58–1.7)
+ 8-OH-DPAT (0.056 mg/kg)	0.019 (0.013–0.028)	0.60 (0.29–0.90) *
+ 8-OH-DPAT (0.178 mg/kg)	0.0025	0.078 (0.028–0.13) *
Rimonabant Control	0.38 (0.26–0.57)	
+ Cannabidiol (10 mg/kg)	0.61 (0.41–0.93)	1.6 (0.67–2.5)
+ Cannabidiol (17.8 mg/kg)	0.49 (0.33–0.76)	1.3 (0.55–2.0)
Rimonabant Control	0.16 (0.12–0.25)	
+ 8-OH-DPAT (0.056 mg/kg)	0.34 (0.27–0.46)	2.1 (1.1–3.0) *

* significantly different versus control ($p<0.05$)