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# Divergent effects of cannabidiol on the discriminative stimulus and place conditioning effects of $\Delta^9$-tetrahydrocannabinol

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**Abstract**

*Cannabis sativa* (marijuana plant) contains myriad cannabinoid compounds; yet, investigative attention has focused almost exclusively on $\Delta^9$-tetrahydrocannabinol (THC), its primary psychoactive substituent. Interest in modulation of THC's effects by these other cannabinoids (e.g., cannabidiol (CBD)) has been stimulated anew by recent approval by Canada of Sativex (a 1:1 dose ratio combination of CBD:THC) for the treatment of multiple sclerosis. The goal of this study was to determine the degree to which THC's abuse-related effects were altered by co-administration of CBD. To this end, CBD and THC were assessed alone and in combination in a two-lever THC discrimination procedure in Long-Evans rats and in a conditioned place preference/aversion (CPP/A) model in ICR mice. CBD did not alter the discriminative stimulus effects of THC at any CBD:THC dose ratio tested. In contrast, CBD, at CBD:THC dose ratios of 1:1 and 1:10, reversed CPA produced by acute injection with 10 mg/kg THC. When administered alone, CBD did not produce effects in either procedure. These results suggest that CBD, when administered with THC at therapeutically relevant ratios, may ameliorate aversive effects (e.g., dysphoria) often associated with initial use of THC alone. While this effect may be beneficial for therapeutic usage of a CBD:THC combination medication, our discrimination results showing that CBD did not alter THC's discriminative stimulus effects suggest that CBD:THC combination medications may also produce THC-like subjective effects at these dose ratios. Published by Elsevier Ireland Ltd.

*Keywords:* $\Delta^9$-Tetrahydrocannabinol; Cannabidiol; Marijuana; Drug discrimination; Conditioned place aversion

## 1. Introduction

The medicinal and recreational properties of *Cannabis sativa* (marijuana plant) have been recognized for thousands of years. Nearly 70 cannabinoids have been found in marijuana, including $\Delta^9$-tetrahydrocannabinol (THC) (its primary psychoactive constituent), cannabidiol (CBD), cannabinol, cannibigerol, and cannabichromene (see review Elsohly and Slade, 2005). Yet, until recently, only THC had been formulated in an oral form for medical use. THC and nabilone, a synthetic derivative of THC, have been marketed as appetite stimulants and antiemetics in chronic diseases such as AIDS and cancer; however, therapeutic success of these drugs has been hampered by adverse side effects, including reports of negative subjective effects such as dysphoria (see review Ben Amar, 2006). Recent findings with CBD, a cannabinoid without THC-like psychoactivity, have suggested that it may have potential therapeutically useful effects when administered alone (e.g., as an antipsychotic, see Zuardi et al., 2006). In addition, it has been proposed that CBD may complement or attenuate various effects of THC (see Russo and McPartland, 2003).

### 1.1. Preclinical and clinical interactions between THC and CBD

Preclinical research has yielded inconsistent results regarding the influence of CBD on a battery of four pharmacological effects in mice that are characteristic of THC and other THC-like cannabinoids (Martin et al., 1991): suppression of spontaneous activity, antinociception, hypothermia, and catalepsy. For example, some investigators report that high doses of CBD increased the antinociceptive, cataleptic, and hypothermic effects of THC

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in mice (Fernandes et al., 1974; Karniol and Carlini, 1973), while other investigations reported CBD antagonized them (Welburn et al., 1976; Karniol and Carlini, 1973; Borgen and Davis, 1974) or had no effect (Sanders et al., 1979; Jones and Pertwee, 1972; Ham and De Jong, 1975). Recently, Varvel et al. (2006) demonstrated that equivalent doses of CBD did not substantially modify the effects of THC on locomotor activity, nociception (tail flick), rectal temperature, and catalepsy.

The putative beneficial effects of combined THC and CBD also have been investigated recently in several clinical trials for multiple sclerosis, neuropathic pain, and varied neurogenic symptoms (Berman et al., 2004; Brady et al., 2004; Rog et al., 2005; Wade et al., 2004, 2003). In addition, Sativex®, a 1:1 THC: CBD ratio oromucosal spray formulation, is currently marketed in Canada for treatment of neuropathic pain associated with multiple sclerosis. Indeed, separate clinical studies have demonstrated that dronabinol (oral THC) (Svendsen et al., 2004), GW-2000-02 (oromucosal spray containing primarily THC), and GW-1000-02 (Sativex) (Berman et al., 2004) were marginally, yet significantly, effective against pain symptoms associated with multiple sclerosis, although each drug produced greater adverse events than placebo treatment. In that study, comparisons were only made to placebo treatment. Thus inferences regarding therapeutic differences between administration of THC alone (GW-2000-02) and THC combined with CBD (GW-1000-02) can be made. Nevertheless, anecdotal reports that smoked marijuana is considered more favorably as a medication by some patients than is synthetic oral THC persist. While the conflicting body of scientific literature has not clearly demonstrated that CBD markedly alters the characteristic, but non-selective (Wiley and Martin, 2003), preclinical effects of THC in mice nor that it enhances therapeutic effects of THC in the clinic, modulation of the selective subjective effects of THC by CBD and/or other similar cannabinoids might affect patient perception.

### 1.2. CBD and THC interactions in drug discrimination

THC's discriminative stimulus effects are mediated via CB1 cannabinoid receptors (Wiley et al., 1995) and are pharmacologically selective for cannabinoids that possess THC-like psychoactivity, including plant-derived cannabinoids, classical tricyclic analogs, and other non-structurally related synthetic cannabinoids (Wiley, 1999). Further, these effects serve as an animal model of the subjective effects of marijuana in humans (Balster and Prescott, 1992). In drug discrimination studies, combined administration of THC and CBD has resulted in varied effects including no effect, lack of antagonism, or time course potentiation. For example, co-administration of 17.5 mg/kg CBD and several doses of THC (0.1, 0.3, and 0.56 mg/kg) produced no change in THC appropriate responding in pigeons compared to that of THC alone (Hiltunen and Jarbe, 1986a). The time course of THC's stimulus effects was unchanged as well. Additionally, CBD failed to substitute for THC in pigeons trained to discriminate THC from vehicle (Jarbe et al., 1977). On the contrary, in rats, CBD 30 mg/kg potentiated the time course effects of low doses of THC (0.3 and 1.0 mg/kg) (Hiltunen and Jarbe, 1986a). Metabolic interference is one possible explanation for this prolongation of THC' s time course effects by CBD (Bornheim et al., 1993, 1995; Jones and Pertwee, 1972). Since all of these results were obtained with doses of CBD that were 30-fold and 100-fold higher than the co-administered THC doses, these effects, or lack of effects, may be associated with high ratios of CBD to THC, only.

### 1.3. Purpose of study

To this end, the first objective of this study was to determine the effects of CBD on THC drug discrimination over a greater range of CBD to THC ratios. Secondly, the effects of CBD alone and in combination with THC were evaluated using the place conditioning paradigm. Place conditioning is a learning paradigm that can be used to investigate associations between preference/aversive properties of psychoactive drugs and contextual cues (see review, Tzschentke, 1998). Together, these experiments will assess CBD's ability to produce marijuana-like discriminative stimulus effects in rats and its effectiveness as a rewarding or aversive stimulus in a place conditioning procedure in mice in THC to CBD ratios similar to those found in marijuana and Sativex. In addition, the ability of CBD to modulate the effects of THC in these mice and rat models will be evaluated.

## 2. Methods

### 2.1. Subjects

Male ICR mice (25–32 g), used in the place conditioning experiments, were purchased from Harlan (Dublin, VA) and were housed in groups of four. All mice were kept in a temperature-controlled (20–22 °C) environment with a 14:10-h light/dark cycle and received food and water ad libitum. Male Long-Evans rats (Harlan) were used in the drug discrimination experiments. They were individually housed in a temperature-controlled (20–22 °C) vivarium with a 12-h light/dark cycle. During the drug discrimination studies, rats were maintained within the indicated weight range (400–450 g) by restricted post-session feeding and had ad libitum water in their home cages. All animals used in this study were cared for in accordance with the guidelines of the Institutional Animal Care and Use Committee of the Virginia Commonwealth University and the 'Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, National Academy Press, 1996).

### 2.2. Apparatus

Place conditioning chambers (ENV-3013), interface, and software were purchased from Med Associates, Inc. (St. Albans, VT). The overall inside dimensions of the conditioning apparatus were 47 cm × 13 cm × 18 cm ($L \times W \times H$) and consisted of three distinct compartments (separated by manual doors). The center compartment 11 cm long was gray with a smooth PVC floor. The choice compartments each measured 18 cm long. One compartment was all black with a stainless steel grid rod floor consisting of 3 mm rods placed on 8 mm centers. The other compartment was all white with a stainless steel mesh floor. All chambers had hinged clear polycarbonate lids for animal loading. Data were collected by a PC, which was interfaced to infrared photobeam strips that were located within each chamber.

For the drug discrimination studies, rats were trained and tested in standard operant conditioning chambers (BRS/LVE Inc., Laurel, MD or Lafayette Instruments Co., Lafayette, IN) housed in sound-attenuated cubicles. Pellet dispensers delivered 45-mg BIO SERV (Frenchtown, NJ) food pellets to a food cup on the front wall of the chamber between two response levers. Fan motors provided