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# Pharmacological specificity of $\Delta^9$-tetrahydrocannabinol discrimination in rats

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**Abstract** While many previous studies have shown that a variety of cannabinoids substitute and cross-substitute for $\Delta^9$-tetrahydrocannabinol (THC) in drug discrimination procedures, few have systematically examined potential THC-like effects of non-cannabinoid compounds. The purpose of the present study was to delineate further the pharmacological specificity of THC discrimination. Rats were trained to discriminate THC (3.0 mg/kg) from vehicle. Following determination of a dose-effect curve with THC, substitution tests with selected compounds from a variety of pharmacological classes, including *l*-phenylisopropyl adenosine, dizocilpine, dextromethorphan, clozapine, buspirone, MDL 72222, muscimol, midazolam and chlordiazepoxide, were performed. Whereas THC produced full dose-dependent substitution, substitution tests with non-cannabinoid drugs resulted in less than chance (50%) levels of responding on the THC-appropriate lever, with the exception of (+)-MDMA (2.5 mg/kg, 50%) and diazepam (3.0 mg/kg, 67%). These results are consistent with those of previous studies and suggest that the discriminative stimulus effects of THC exhibit pharmacological specificity.

**Key words** $\Delta^9$-THC · Drug discrimination · Benzodiazepines · Specificity

## Introduction

$\Delta^9$-Tetrahydrocannabinol (THC), the psychoactive constituent in *Cannabis sativa L.*, produces a wide spectrum of pharmacological effects in animals (Pertwee 1988); however, not all of these effects are unique to cannabinoid drugs. Effects such as catalepsy, hypokinesia, hypothermia, and antinociception are also produced by drugs that do not produce marijuana-like effects in humans. In contrast, the discriminative stimulus effects of THC appear to be specific for marijuana-like cannabinoids (Browne and Weissman 1981; Balster and Prescott 1992). A large number of studies have shown that compounds that bind to the cannabinoid receptor, including various 11-hydroxy metabolites of THC (Balster and Ford 1978; Järbe and McMillan 1979), CP 55,940 {(−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl) cyclohexanol} (Gold et al. 1992), (+)-WIN 55,212 (Compton et al. 1992), cannabinol (Järbe and Hiltunen 1987), and $\Delta^8$-tetrahydrocannabinol (Järbe and McMillan 1979), produce full substitution for THC, and, where tested, cross-substitution for other THC-like compounds (Balster and Ford 1978; Wiley J.L. et al., 1995), in drug discrimination studies with animals. Further, all of these cannabinoids that have been tested in humans also produced marijuana-like subjective effects (see Balster and Prescott 1992). Thus, it is well established that psychoactive cannabinoids substitute for THC in THC discrimination studies.

Although the conclusion that cannabinoids produce THC-like effects in drug discrimination procedures in rats is well supported, few studies have systematically examined the pharmacological specificity of THC discrimination. In fact, much of the previous information available on the pharmacological specificity of THC discrimination in rats comes from a single study (Browne and Weissman 1981) and two review articles (Balster and Ford 1978; Balster and Prescott 1992). Although all of the non-cannabinoid compounds tested failed to substitute completely for THC (with the majority of the compounds yielding less than 35% THC-lever responding), the effects of most of the drugs were examined over a limited range of doses. Further,

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a number of classes of non-cannabinoid drugs were not systematically studied. The primary goal of the present study was to expand our knowledge of the specificity of THC discrimination by evaluating representative compounds from drug classes which have not been well studied or which have shown evidence of partial substitution in previous studies.

Eleven non-cannabinoid compounds from a variety of pharmacological classes were evaluated for their ability to substitute for the THC (3.0 mg/kg) discriminative stimulus. Drugs that were tested included an adenosine agonist (*l*-PIA), an atypical neuroleptic with 5-$HT_2$ antagonist effects (clozapine), a 5-$HT_3$ antagonist (MDL-72222), a 5-$HT_{1A}$ agonist/antagonist (buspirone), a substituted phenethylamine stimulant/hallucinogen [(+)-MDMA], a noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist (dizocilpine), and an antitussive/sigma agonist/NMDA antagonist (dextromethorphan). We chose to examine these drugs because they represented drug classes that had not been studied extensively in the THC discrimination model. In addition, selected benzodiazepines and GABAergic compounds were studied because partial substitution with benzodiazepines had been observed in previous studies (Mokler et al. 1986; Järbe and Hiltunen 1988).

## Materials and methods

### Subjects

Eight male Sprague-Dawley rats (COBS CD, Charles River Farms, Wilmington, Mass.), weighing 290–300 g upon arrival, were used in this study. They were housed individually in wire cages in a temperature-controlled environment (20–22°C) with water available ad libitum. The animals were reduced to 85% of their initial weight and continued on restricted post-session feeding throughout the study. Sessions were conducted during the light period (6:30 a.m.–8:30 p.m.) of a light/dark cycle.

### Apparatus

Eight standard two-lever operant conditioning chambers were contained within sound-attenuated boxes (Models 80200 and 80015, Lafayette Instrument Company, Lafayette, Ind.). Levers were located on one wall of the chamber equidistant from the food dispenser which could dispense 45-mg pellets (Dustless Precision Pellets, Bioserv, Frenchtown, N.J.). White house lights were used to illuminate the chambers during the experimental session and to signal its beginning and end. Ventilation fans provided white noise.

### Procedure

Subjects initially received an injection of vehicle (VEH) 30 min prior to each session and were trained to press a lever during daily 60-min sessions under a fixed-ratio 1 (FR-1) schedule of food reinforcement. Half of the rats were trained to respond on the right lever; the other half, on the left lever. When the rats were responding reliably on the VEH lever, they began receiving injections of THC (3.0 mg/kg, IP, 30 min pre-session), alternating every third session with VEH injections (i.e., THC, THC, VEH, VEH, THC, etc.). On days that THC was administered, responding was reinforced on the non-VEH (drug) lever. Gradually, the value of the fixed ratio was increased on each lever to a terminal value of FR-10 and the session length was shortened to 10 min. Discrimination training continued until the following criteria were achieved: each rat was required to complete the first FR on the correct lever, respond at least 80% (session mean) on the correct lever, and produce a rate of $> 0.05$ responses/s across the duration of the session. The response rate criterion was chosen, based on previous work in this area (Gold et al. 1992; Wiley et al. 1993), such that a rat that met the criterion would have the opportunity to earn three reinforcers if responding was on the correct lever.

Following acquisition, 2-min test sessions were typically conducted on Tuesdays and Fridays, with the double alternation sequence of VEH and THC training days continuing on Mondays, Wednesdays, and Thursdays. A dose-effect curve for THC was determined in all subjects before evaluation of any of the other drugs. Noncannabinoid drugs were tested in random order with a minimum of seven rats. Doses were selected so that at least one dose of each drug decreased rates of responding. A dose-effect curve for each drug was typically completed before the dose-effect curve for the next drug was initiated. Following evaluation of all test drugs, a dose-effect curve for THC was redetermined in the remaining seven subjects.

### Data analysis

Data are presented as the mean (± SEM) percentage of THC-lever responding and mean (± SEM) responses/s. (Data on percentage THC-lever responding for rats that failed to meet the response rate criterion of 0.05 responses/s were excluded.) In addition, data for rats that failed to meet the discriminative stimulus control criteria (listed in the procedure section) on the previous training day were not included in the group averages for either measure.

Factorial repeated measures analyses of variance (ANOVAs) were performed using general linear model procedures (SAS Institute, Cary, N.C.) on percentage of THC-lever responding and response rate during the two THC dose-effect curves (factors = time of testing and dose). Single factor repeated measures ANOVAs were performed on both dependent variables for drugs that produced partial substitution (defined as $\geq 50\%$ THC-lever responding). Tukey post hoc tests were used to specify differences revealed by significant ANOVAs.

### Drugs

THC (National Institute on Drug Abuse, Rockville, MD.) was dissolved in absolute ethanol and diluted with an equal concentration of Emulphor-620 (Rhone-Poulenc, Paris, France) in order to make a solution of 100 mg/ml. Saline was added to this solution to form a clear homogeneous suspension which consisted of emulphor-ethanol-saline in a final ratio of 1:1:18. Appropriate dilutions were made to the 10 mg/ml THC stock solution with the emulphor-ethanol-saline (1:1:18) solution, which also served as vehicle for VEH sessions. Fresh solutions of the training drug were made a minimum of once per week. Diazepam (Elkins-Sinn, Cherry Hill, N.J.) was diluted in deionized water, propylene glycol, absolute ethanol, benzyl alcohol, and benzoic acid in a ratio of 50:20:5:2.5:22.5. Midazolam hydrochloride (Hoffman-LaRoche, Nutley, N.J.) was diluted in 0.8% NaCl, 0.01% disodium edatate, and 1% benzyl alcohol, and the pH was adjusted with HCl. Buspirone hydrochloride, *l*-phenylisopropyl adenosine (*l*-PIA), MDL-72222 (3-tropanyl-3,5-dichlorobenzoate), (+)-MDMA HCl [S(+)-3, 4-methylenedioxymethamphetamine hydrochloride], and dizocilpine hydrogen maleate, obtained from Research Biochemicals (Natick, Mass.), were dissolved in saline (0.9% NaCl). MDL-72222 also required a few drops of lactic acid. Clozapine (Sandoz Research Institute, East Hanover, N.J.), chlordiazepoxide

HCl, dextromethorphan HBr, and muscimol HBr obtained from Sigma (St Louis, Mo.), were dissolved in saline. All doses refer to the forms listed above. All injections were given intraperitoneally (IP) at the times indicated in Table 1.

## Results

All rats acquired the THC discrimination in 25–30 sessions. Figure 1 shows the dose-effect curves for THC at the beginning and end of the study, as well as the results of control tests with VEH and 3.0 mg/kg THC conducted before each dose-effect determination. During VEH and THC control tests, rats responded predominantly (≥ 90%) on the injection-appropriate lever. THC produced a dose-dependent increase [$F(3, 21) = 25.1$, $P = 0.0001$] in responding on the THC lever (compared to the 0.3 mg/kg dose) during both dose-effect curves with a maximum of 100% or 93%

**Table 1** Results of substitution tests in rats trained to discriminate 3.0 mg/kg $\Delta^9$-THC from vehicle

| Compound | Time[a] | Dose[b] | %THC[c] | Rate[d] | (*n*/*N*)[e] |
|---|---|---|---|---|---|
| Buspirone | 15 | 0.03 | 1 (1) | 0.85 (0.11) | 6/6 |
| | | 0.10 | 7 (4) | 0.62 (0.09) | 8/8 |
| | | 0.30 | 19 (10) | 0.55 (0.15) | 6/6 |
| | | 1.0 | 0 (0) | 0.06 (0.05) | 1/7 |
| Chlordiazepoxide | 30 | 1.0 | 11 (10) | 0.58 (0.13) | 7/7 |
| | | 3.0 | 16 (12) | 0.61 (0.1) | 8/8 |
| | | 10.0 | 35 (12) | 0.59 (0.08) | 7/7 |
| | | 30.0 | – – | 0.02 (0.01) | 0/7 |
| Clozapine | 30 | 1.0 | 0 (0) | 0.31 (0.11) | 5/5 |
| | | 3.0 | 37 (14) | 0.31 (0.08) | 6/7 |
| | | 10.0 | – – | 0.01 (0) | 0/8 |
| Dextromethorphan | 30 | 3.0 | 4 (3) | 0.60 (0.09) | 7/7 |
| | | 10.0 | 2 (2) | 0.48 (0.09) | 7/7 |
| | | 15.6 | 6 (4) | 0.50 (0.06) | 7/7 |
| | | 30.0 | 3 (0) | 0.08 (0.08) | 1/7 |
| Diazepam | 30 | 0.5 | 6 (6) | 0.56 (0.07) | 8/8 |
| | | 1.0 | 33 (15) | 0.39 (0.08) | 8/8 |
| | | 3.0 | 67 (10) | 0.31 (0.07) | 6/7 |
| | | 10.0 | 48 (13) | 0.28 (0.06) | 7/8 |
| Dizocilpine | 30 | 0.03 | 3 (3) | 0.65 (0.14) | 7/7 |
| | | 0.10 | 15 (11) | 0.12 (0.08) | 5/7 |
| | | 0.16 | 30 (8) | 0.10 (0.04) | 5/7 |
| | | 0.30 | no response | no response | 0/7 |
| MDL 72222 | 30 | 3.0 | 1 (0.6) | 0.53 (0.08) | 7/7 |
| | | 6.0 | 17 (13) | 0.32 (0.07) | 7/7 |
| | | 9.0 | 3 (2) | 0.42 (0.06) | 8/8 |
| | | 12.0 | – – | 0.01 (0) | 0/8 |
| (+)-MDMA | 30 | 1.25 | 3 (2) | 0.63 (0.14) | 6/7 |
| | | 2.50 | 50 (17) | 0.13 (0.05) | 4/7 |
| | | 5.0 | – – | 0.01 (0) | 0/7 |
| Midazolam | 30 | 0.1 | 1 (0.2) | 0.63 (0.1) | 7/7 |
| | | 0.3 | 15 (14) | 0.64 (0.14) | 7/7 |
| | | 1.0 | 2 (1) | 0.53 (0.09) | 7/7 |
| | | 10.0 | 36 (35) | 0.18 (0.16) | 2/4 |
| Muscimol | 30 | 0.1 | 1 (0.4) | 0.6 (0.12) | 7/7 |
| | | 0.3 | 1 (1) | 0.8 (0.13) | 7/7 |
| | | 1.0 | 7 (4) | 0.5 (0.1) | 7/7 |
| | | 3.0 | 5 (3) | 0.5 (0.1) | 7/7 |
| | | 10.0 | no response | no response | 0/7 |
| *l*-PIA | 10 | 0.003 | 5 (3) | 0.67 (0.09) | 7/7 |
| | | 0.010 | 2 (2) | 0.69 (0.12) | 7/7 |
| | | 0.020 | 17 (14) | 0.62 (0.06) | 6/6 |
| | | 0.025 | 1 (1) | 0.67 (0.11) | 6/6 |
| | | 0.030 | 4 (4) | 0.01 (0) | 7/7 |
| | | 5.0 | 48 (13) | 0.28 (0.06) | 7/8 |

[a] Duration of time (min) between the IP injection and the beginning of the 2-min test session
[b] mg/kg
[c] Mean (± SEM) percentage of THC-lever responding
[d] Mean (± SEM) rates of responding (responses/s)
[e] Number of animals responding at > 0.05 respones/s (data included in mean %THC-lever responding)/number of animals tested whose data are included in mean response rate

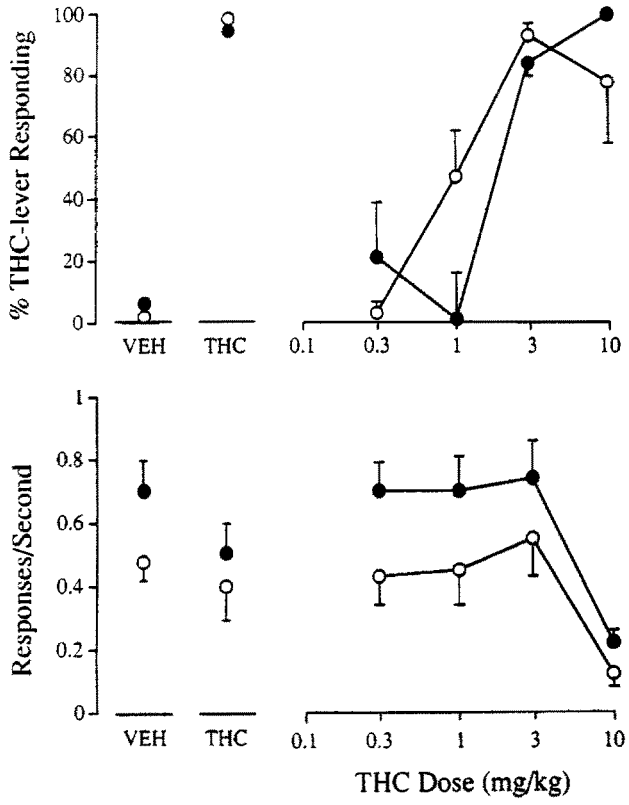


**Fig. 1** Percentage of THC-lever responding (*top panel*) and responses rate (*bottom panel*) during dose-effect curves for THC at the beginning (●) and end of the study (○). The results of control testing with vehicle (*VEH*) and 3.0 mg/kg THC conducted before each dose-effect determination are also shown. The results are presented as means (± SEM) ($n$ = 7 or 8)

occurring at the 10 mg/kg or 3 mg/kg dose in the first and second curves, respectively. Only the highest test dose (10 mg/kg) of THC decreased rates of responding [$F(3, 21) = 16.4$, $P = 0.0001$]; hence, THC produced discriminative stimulus effects at a dose (3 mg/kg) that did not effect overall response rates. Time of testing had negligible effects on both dependent measures and there were no significant interactions between dose and time of testing for either variable.

None of the test drugs fully substituted for THC (> 80% THC-lever responding), and with the exception of diazepam and (+)-MDMA, none produced greater than chance (50%) levels of THC-lever responding (see Table 1). A behaviorally active dose range was evaluated in each dose-effect curve, as indicated by decreased rates of responding produced by the highest dose of each drug.

Diazepam and (+)-MDMA produced partial substitution. The 2.5 mg/kg dose of (+)-MDMA produced a maximum of 50% THC-lever responding. This maximum was accompanied by a large decrease [$F(2, 12) = 17.53$, $P = 0.0003$] in rates of responding, with only five of seven animals responding at all. The next higher dose tested (5 mg/kg) eliminated responding in all subjects. In the case of diazepam, maximum levels of THC-lever responding of 67% THC-lever responding were obtained at 3 mg/kg. A higher dose (10 mg/kg) produced slightly less (48%) responding on the THC lever. Compared to the 0.5 mg/kg dose, the 3 and 10 mg/kg doses were associated with significant decreases in rates of responding [$F(3, 20) = 10.24$, $P = 0.0003$]. In contrast to diazepam, neither of the other two benzodiazepines, chlordiazepoxide or midazolam, produced greater than chance levels of THC-lever responding.

## Discussion

The results of the present study support previous reports that THC can serve as a viable discriminative stimulus over an extended period of time. Similar to results with other discriminable drugs, THC produced dose-dependent increases in drug-lever responding. Further, it retained this ability over the 20-month time span covered by the study with no statistically significant differences between the pre- and post-study THC dose-effect curves.

Previous research has suggested that THC's discriminative stimulus effects are specific to cannabinoids that produce cannabis-like effects in humans (Browne and Weissman 1981; Balster and Prescott 1992); however, only a limited number of non-cannabinoid drugs have been tested in this model. In the present study, we examined a number of compounds representative of drug classes which had not, as yet, been tested systematically for THC-like discriminative stimulus effects in rats. None of these drugs produced full substitution for THC.

The classes of drugs examined included an adenosine agonist (*l*-PIA), an atypical neuroleptic (clozapine), a 5-$HT_3$ antagonist (MDL-72222), an 5-$HT_{1A}$ agonist/antagonist (buspirone), a substituted phenethylamine stimulant/hallucinogen [(+)-MDMA], a noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist (dizocilpine), and an antitussive/sigma agonist/NMDA antagonist (dextromethorphan). Previous THC substitution tests of compounds in these drug classes were limited in nature and yielded similar negative results: Browne and Weissman (1981) tested single doses of the noncompetitive NMDA antagonist, phencyclidine, and of the typical antipsychotic, haloperidol. Although (+)-MDMA produced 50% THC-lever responding, this partial substitution occurred only at a high dose that substantially affected rates of responding. In contrast, THC and other cannabinoids produce full substitution at doses that do not alter response rates (present study; Gold et al. 1992; Wiley et al. 1993). Thus, it is likely that (+)-MDMA's effect in this study reflects disruption of the discrimination rather than any overlap of its discriminative stimulus effects with THC.

A number of benzodiazepines (chlordiazepoxide, diazepam, and midazolam) and a direct $GABA_A$ agonist, muscimol, were also tested in this study. Earlier THC discrimination studies with this class of compounds had produced somewhat conflicting results (Mokler et al. 1986; Järbe and Hiltunen 1988). Whereas Mokler et al. (1986) showed that diazepam produced partial substitution in a sub-group of THC-trained rats, Järbe and Hiltunen (1988) found little evidence of cross-substitution of THC and diazepam in THC-trained pigeons or in THC- or diazepam-trained gerbils. Interestingly, pentobarbital has also been reported to produce substantial (74%) substitution in THC-trained rats (Mokler et al. 1986). In the present study, diazepam was the only GABAergic drug that produced greater than chance levels of THC-lever responding. Consistent with previous THC substitution tests that yielded positive results with diazepam and pentobarbital, diazepam's partial substitution in the present study was associated with modest (but statistically significant) response-rate decreases. Lower levels of substitution ($\leq 36\%$ THC-lever responding) were obtained with midazolam and chlordiazepoxide. In addition, the direct $GABA_A$ agonist, muscimol, produced essentially no substitution. Thus, the degree of substitution for THC of various GABA agonists acting at the same (diazepam, chlordiazepoxide, and midazolam) and different (muscimol) receptor sites is variable, with the most consistent substitution seen with diazepam.

The mechanism for the partial substitution obtained with diazepam is not clear, although there is some evidence pointing to interactions of cannabinoids with drugs that affect GABAergic neurotransmission (Pertwee et al. 1988; Onaivi et al. 1990). First, cannabinoids and GABAergics share a number of pharmacological effects, including decreased motor activity, hypothermia, muscle relaxation, catalepsy and sedation (Pertwee 1992). In addition, the pharmacological and behavioral effects of cannabinoids can be enhanced by benzodiazepines and other GABAergics (Sethi et al. 1986; Pertwee and Greentree 1988; Pertwee and Wickens 1991); e.g., $\Delta^9$-THC acts synergistically with $GABA_A$ (muscimol) and $GABA_B$ [(–)-baclofen] agonists to produce catalepsy and hypothermia, and these interactions are blocked by the corresponding GABA antagonists (Pertwee et al. 1988). While studies have shown that the effects of benzodiazepines can be enhanced by cannabinoids, this enhancement does not involve an alteration in the GABA receptor (Sung and Jakobovic 1987; Yamamoto et al. 1992). Thus, although the benzodiazepines and other GABAergic drugs interact with THC and share some of its behavioral effects, it is clear that the effects of these drugs, including diazepam, can easily be distinguished from those of THC and other THC-like cannabinoids in THC discrimination procedures. In these procedures, THC produces full substitution without accompanying response rate suppression. GABAergic drugs produce partial substitution, at best, which are often associated with decreases in response rates.

In conclusion, this study provides further support for the premise that THC produces a pharmacologically unique discriminative stimulus in rats. Although psychoactive cannabinoids consistently produce other pharmacological effects which may be shared with other drug classes, particularly the benzodiazepines, drugs from diverse pharmacological classes fail to produce clear THC-like effects in drug discrimination procedures. These drugs also fail to produce a marijuana-like behavioral profile in humans (Kelly et al. 1993) and benzodiazepine antagonists do not block THC's subjective effects (Hollister and Gillespie 1990). These results support the use of THC discrimination in animals as a model for cannabis intoxication (Balster and Prescott 1992).

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