Pharmacological specificity of the discriminative stimulus effects of Δ^9-tetrahydrocannabinol in rhesus monkeys

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Received 20 July 1995; accepted 7 September 1995

Abstract

Δ^9-Tetrahydrocannabinol (Δ^9-THC) discrimination has been used as an animal model of cannabis intoxication in humans. While numerous studies have examined the discriminative stimulus effects of cannabinoids in rats and pigeons, studies with monkeys have been rare. In the present study, rhesus monkeys, trained to discriminate Δ^9-THC from vehicle in a two-lever drug discrimination procedure, were tested with a variety of psychoactive drugs, including cannabinoids as well as drugs from other classes. Results showed that Δ^9-THC discrimination showed pharmacological specificity, in that none of the non-cannabinoid drugs fully substituted for Δ^9-THC. In contrast, the classical cannabinoids, Δ^9-THC and Δ^8-THC, and the novel cannabinoids, WIN 55212-2 and 1-butyl-2-methyl-3-(1-naphthoyl)indole, produced full dose-dependent substitution for Δ^9-THC in all monkeys. A heptyl indole derivative failed to substitute for Δ^9-THC, but it also did not displace [^{3}H] CP 55940 from its binding site. These findings are consistent with those of previous cannabinoid discrimination studies with rats and suggest that results of Δ^9-THC discrimination studies in rhesus monkeys may be predictive of the subjective effects of cannabinoid drugs in humans.

Keywords: Δ^9-tetrahydrocannabinol; WIN 55212-2; CNS depressants; Indoles; Drug discrimination

1. Introduction

Δ^9-Tetrahydrocannabinol (Δ^9-THC), the primary psychoactive ingredient of marijuana, produces a number of characteristic behavioral effects in mice, including antinociception, hypothermia, catalepsy, and decreases in spontaneous activity (Compton et al., 1991). In addition, studies with rats and pigeons have shown that Δ^9-THC produces characteristic discriminative stimulus effects (Järbe et al., 1976; Järbe et al., 1977; Balster and Prescott, 1992). Cannabinoids with a variety of chemical structures, including CP 55940 ((-)-cis-3-[2-hydroxy-4(1,1-dimethyl-heptyl)phenyl]-trans-4-(3-hy droxy propyl)cyclohexanol) (Gold et al., 1992), WIN 55212-2 (an aminoalkylindole (AAI) analog) (Compton et al., 1992), and $\Delta^{9,11}$-tetrahydrocannabinol ($\Delta^{9,11}$-THC) (Wiley et al., 1993), substitute for Δ^9-THC in Δ^9-THC-trained rats. Generally, it has been found that Δ^9-THC shares discriminative stimulus effects with cannabinoids that bind to brain cannabinoid receptors with high affinity (Compton et al., 1993) and that are psychoactive in humans (for a review, see Balster and Prescott, 1992). Anandamide, a proposed endogenous ligand for cannabinoid receptors, also produces Δ^9-THC-like discriminative stimulus effects (Wiley et al., 1995). Further, the discriminative stimulus effects of cannabinoids appear to be pharmacologically specific, as non-cannabinoid drugs typically do not elicit cannabimimetic effects in drug discrimination studies (Balster and Ford, 1978; Browne and Weissman, 1981; Balster and Prescott, 1992; Barrett et al., 1995). For these reasons, Balster and Prescott (1992) have proposed that Δ^9-THC discrimination in rats can serve as an animal model of marijuana intoxication in humans.

Although a number of studies have investigated the discriminative stimulus effects of cannabinoids in rodents or pigeons, only a few studies have reported results of tests in monkeys trained to discriminate Δ^9-THC (Ferraro et al., 1974; Gold et al., 1992; Wiley et al., 1993). In these studies, tests conducted with Δ^9-THC

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(Ferraro et al., 1974), CP 55940, a synthetic bicyclic cannabinoid (Gold et al., 1992), and $\Delta^{9,11}$-THC, an exocyclic analog of Δ^9-THC (Wiley et al., 1993), showed that these three cannabinoids produced dose-dependent substitution for Δ^9-THC in rhesus monkeys. None of the studies included tests with non-cannabinoid compounds. In addition, none included tests with cannabinoid compounds that did not possess a bicyclic or tricyclic structure similar to that of Δ^9-THC. The present study represents a more extensive characterization of Δ^9-THC discrimination in rhesus monkeys. Its purpose is three-fold: (a) to test cannabinoids with classical and novel structures for Δ^9-THC-like effects and to compare these results to those obtained with other species; (b) to examine the pharmacological specificity of the discriminative stimulus effects of Δ^9-THC in monkeys; and (c) to determine the duration of the discriminative stimulus effects of Δ^9-THC in monkeys. Because drugs with CNS depressant properties have shown the greatest degree of partial substitution in rodent Δ^9-THC discrimination procedures (Browne and Weissman, 1981; Mokler et al., 1986), many of the drugs tested during the pharmacological specificity phase of the study were chosen from this class.

2. Method

2.1. Subjects

Four adult male rhesus monkeys (8–12 kg), used in previous Δ^9-THC discrimination studies (Gold et al., 1992; Wiley et al., 1993) served as subjects. They were individually housed in a temperature-controlled environment with a 12-h light-dark cycle (lights on at 7 a.m.) and were food-restricted for 18 h before each daily session (Monday–Friday). Monkeys were given a multivitamin and their food supplement (135–205 g of monkey chow) in two daily feedings that occurred after daily sessions. Free access to water was always available.

2.2. Apparatus

Immediately before the start of an experimental session, removable two-lever panels, constructed with standard operant components (Coulbourn Instruments, Lehigh Valley, PA) and 1-g pellet dispensers (BRS/LVE, Laurel, MD), were attached to the front of the home cage of each monkey. Food pellets were delivered to a food cup located between the two response levers. Lights were located above the food cup and above each lever. A microcomputer with Logic '1' interface (MED Associates, East Fairfield, VT) and MED-PC software (MED Associates) was used to control the scheduling of reinforcement and to record data.

2.3. Drugs

Δ^9-THC (National Institute on Drug Abuse, Rockville, MD) was suspended in a 1:1:18 vehicle of absolute ethanol, Emulphor-620 (Rhone-Poulenc, Inc., Princeton, NJ) and saline to form a stock suspension of 10 mg/ml Δ^9-THC (Carney et al., 1977). Lower concentrations were obtained by further dilution with the vehicle solution. Individual training doses of Δ^9-THC were obtained for the monkeys by adjusting the volume of a 1.2-mg/ml suspension of Δ^9-THC. Δ^8-THC (NIDA, Rockville, MD), WIN 55212-2 (Sterling Drug Co. Inc., Rensselaer, NY), and 1-butyl-2-methyl-3-(1-naphthoyl)indole and 1-heptyl-2-methyl-3-(1-naphthoyl)indole (synthesized in our laboratories) were also suspended in a vehicle of 1:1:18 (ethanol:emulphor:saline). Synthesis and structures of these indole-derived cannabinoids have been published previously (Huffman et al., 1994). Injections of each cannabinoid were given 30 min before the start of the session, except during the time course phase of the study. Buspirone hydrochloride, desipramine hydrochloride, morphine sulfate, sodium pentobarbital and phencyclidine hydrochloride (NIDA, Rockville, MD) were dissolved in saline. Chlorpromazine hydrochloride and sodium phenobarbital (Elkins-Sinn, Cherry Hill, NJ) were purchased commer-

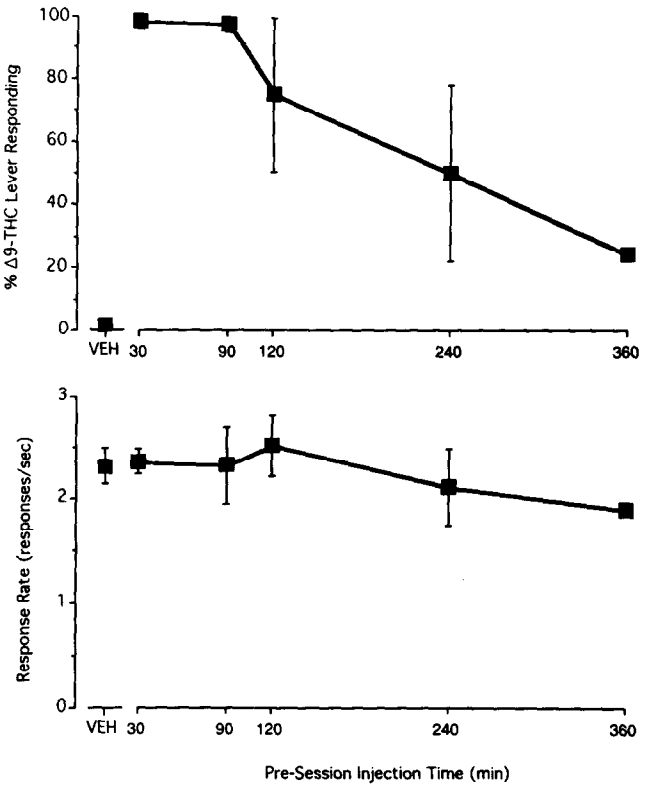

Fig. 1. Time course for the effects of Δ^9-THC on mean (± S.E.M.) percentage of Δ^9-THC-lever responding (upper panel) and mean (± S.E.M.) response rate (lower panel) during separate tests conducted up to 6 h post-injection. Each monkey was injected with an individually determined training dose of Δ^9-THC (dose range 0.04–0.17 mg/kg, i.m.). Points above VEH represent results of a control test with vehicle (0.1 ml/kg, i.m., 30 min pre-session). $N = 4$ for all time points except 360 min where $n = 1$.

cially and diluted to appropriate doses with saline. Diazepam (Elkins-Sinn) was suspended in a vehicle of 1:4 emulphor:sterile distilled water. Dosages of all non-cannabinoid drugs except diazepam refer to the salt; diazepam doses refer to the free base. Pre-session injection intervals for each drug were chosen based on data from previous behavioral research with these compounds. The pre-session injection time for chlorpromazine, pentobarbital, phenobarbital and desipramine was 60 min; for diazepam and buspirone, 15 min; and for morphine and phencyclidine, 10 min. With the exception of the training dose of Δ^9-THC, injections were generally administered at a volume of 0.1 ml per kg of body weight. All injections were delivered intramuscularly (i.m.).

2.4. Procedure

Training procedures were identical to those used in previous studies (Gold et al., 1992; Wiley et al., 1993). Each monkey was trained to discriminate Δ^9-THC from vehicle in a two-lever drug discrimination procedure with individually determined training doses ranging from 0.04 to 0.17 mg/kg, i.m. During training sessions, Δ^9-THC and vehicle injections were administered in a double alternation sequence. For half of the monkeys, the right lever was active (correct) following Δ^9-THC injection and the left lever was active following administration of vehicle. The position of the drug-associated lever was reversed for the other half of the monkeys. Food reinforcement was delivered contingent upon 50 (n = 1) or 100 (n = 3) consecutive responses on the correct lever. A light over the food cup was illuminated during pellet delivery. Responses on the incorrect lever reset the ratio requirement on the correct lever. Training sessions consisted of four 5-min trials with three intervening 15-min time-out periods for a total session duration of 65 min. During trials, the lights over both levers were illuminated. During time-out periods, lights over the levers were turned off and responses were recorded but had no programmed consequences. Test sessions con-

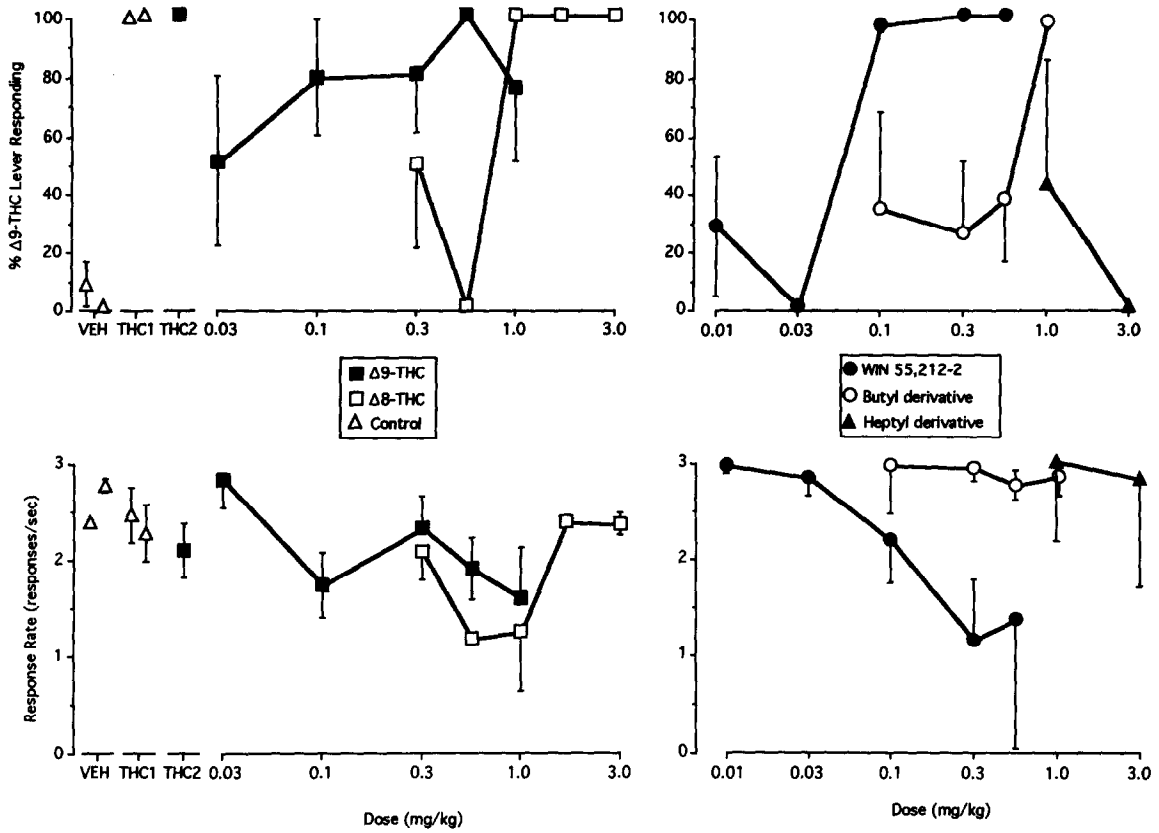

Fig. 2. Effects of the classical cannabinoids, Δ^9-THC and Δ^8-THC (left panels), and the novel cannabinoids, WIN 55212-2 and butyl and heptyl indole derivatives (right panels), on mean (± S.E.M.) percentage of Δ^9-THC-lever responding (upper panels) and mean (± S.E.M.) response rate (lower panels) in rhesus monkeys trained to discriminate Δ^9-THC from vehicle; training doses were individually determined for each monkey and ranged from 0.04–0.17 mg/kg, i.m. Points above VEH and THC1 represent the results of control tests with vehicle and the training dose of Δ^9-THC conducted near the beginning and at the end of the study. Points above THC2 represent results of tests with the training dose of Δ^9-THC conducted as part of the Δ^9-THC dose-effect curve. Four monkeys were tested with Δ^9-THC and WIN 55212-2, three monkeys were tested with the butyl indole derivative and Δ^8-THC, and two monkeys were tested with the heptyl indole derivative (due to limited supply).

Table 1
Comparison of the potencies of classical and novel cannabinoids for generalization from Δ^9-THC in Δ^9-THC-trained rats and rhesus monkeys

Compound	Molecular weight	Monkey ED_{50} (μmol/kg)	Rat ED_{50} (μmol/kg)
Δ^9-THC	314.5	0.03 (0.003–0.3)	2.2[a] (1.0–5.4)
Δ^8-THC	314.5	1.3 (0.2–8.6)	5.8[b] (n/d)
WIN 55212-2	522.6	0.1 (0.04–0.2)	0.3[c] (n/d)
Butyl indole derivative	341	1.8 (1.3–2.5)	7.2[d] (3.0–17.1)
Heptyl indole derivative	383	Did not fully substitute in either species	

[a]From Gold et al., 1992.
[b]From Balster and Prescott, 1992.
[c]From Compton et al., 1992. Drug was administered 90 min pre-session.
[d]J.L. Wiley, unpublished data.

sisted of a single 5-min trial during which consecutive responses on either lever were reinforced according to the fixed-ratio schedule.

All drugs were tested for substitution for Δ^9-THC. Occasionally, replications were performed with individual doses. In these cases, data for both determinations were included in calculations of group averages. Control tests with vehicle and Δ^9-THC were conducted near the beginning and at the end of the study. During the time course phase of the study, the training dose of Δ^9-THC was injected 90–360 min before the start of a regular test session.

2.5. Data analysis

For each test session, mean percentage of responses on the drug lever and response rate (responses/s) were calculated. Where appropriate, ED_{50}'s (with 95% confidence intervals) were calculated separately for each drug using least-squares linear regression on the linear part of the dose-effect curves (Goldstein, 1964) for percentage of drug-lever responding, plotted against $\log_{10}$ transformation of the dose. Data on lever selection for monkeys that had ≤ 0.05 responses/s during a test session were excluded from data analysis.

3. Results

The time course for discriminative control by the training dose of Δ^9-THC (0.04–0.17 mg/kg) is shown in Fig. 1 (upper panel). At 30 and 90 min after injection, nearly all responding was on the Δ^9-THC lever, with discriminative control declining thereafter. One-half of the subjects could still detect Δ^9-THC at 4 h after injection. Detection was essentially absent at 6 h. Response rates following Δ^9-THC administration were similar across all time points (Fig. 1, lower panel).

In substitution tests with cannabinoid compounds, the classical cannabinoids, Δ^9-THC and Δ^8-THC (Fig. 2, upper left panel), produced dose-dependent substitution for Δ^9-THC, as did WIN 55212-2 and the butyl indole derivative (Fig. 2, upper right panel). In contrast, the heptyl indole derivative failed to substitute fully for Δ^9-THC (Fig. 2, upper right panel). Responding during control tests with vehicle and Δ^9-THC (training dose)

Table 2
Results of substitution tests with non-cannabinoid drugs in rhesus monkeys trained to discriminate Δ^9-THC from vehicle

Compound	Dose range[a] (mg/kg)	Max %DLR[b]	Rate 1[c]	Rate 2[d]	N[e]
Buspirone	0.1–0.3 (0.1)	0.5 (0.5)	2.02 (0.51)	0 (0)	4
Chlorpromazine	0.01–1.0 (0.01)	25 (25)	2.83 (0.07)	0.18 (0.18)	4
Desipramine	1.0–3.0 (3.0)	33 (33)	2.31 (0.21)	2.31 (0.21)	3
Diazepam	0.025–1.2 (0.1)	31 (20)	1.44 (0.47)	1.44 (0.47)	4
Morphine	0.1–1.0 (1.0)	0 (0)	1.54 (0.69)	1.54 (0.69)	3
Pentobarbital	0.1–3.0 (1.0)	0 (0)	2.64 (0.64)	2.60 (0.92)	2
Phencyclidine	0.03–0.3 (0.1)	0 (0)	0.91 (0.90)	0 (0)	3
Phenobarbital	1.0–30.0 (30.0)	33 (29)	1.26 (0.51)	1.26 (0.51)	4
Vehicle[f]	n/a	0.03 (0.03)	2.73 (0.07)	2.73 (0.07)	3

[a]Dose range tested; dose at which maximal %DLR occurred is given in parentheses.
[b]Maximum mean (± S.E.M.) percentage of Δ^9-THC-lever responding produced by indicated drug.
[c]Mean (± S.E.M.) rates of responding (responses/s) produced by the dose which produced maximal %DLR.
[d]Mean (± S.E.M.) rates of responding (responses/s) for dose that produced the largest decrease in response rates (typically the highest dose tested).
[e]Number of animals tested with indicated drug.
[f]Vehicle data given for comparison purposes.

was predominantly on the injection-appropriate lever. ED_{50}'s, calculated for Δ^9-THC-like cannabinoids, are presented in Table 1. Response rates were not severely decreased by any of the drugs at the doses tested (Fig. 2, lower panels).

Table 2 shows the results of substitution tests with a variety of non-cannabinoid drugs. None of these drugs fully substituted for Δ^9-THC. Response rate decreasing effects were evident at higher doses of buspirone, chlorpromazine, phencyclidine and phenobarbital.

4. Discussion

The discriminative stimulus effects of Δ^9-THC were time-dependent with the maximal effect of the training dose occurring at 30 and 90 min post-injection. At later time intervals, full substitution occurred in progressively fewer monkeys, although two monkeys continued to respond almost exclusively on the Δ^9-THC-associated lever up to 4 h after injection with Δ^9-THC. Since maximal effect was apparent at the earliest time point tested, time to onset of action cannot be determined from the present data. Data on bioavailability in rhesus monkeys following a single intramuscular injection of Δ^9-THC suspended in an emulphor:ethanol:saline vehicle have confirmed that measurable serum levels of Δ^9-THC are obtained almost immediately and persist for several hours (Perlin et al., 1985). In addition, a similar time course was obtained in rats following intraperitoneal injection with Δ^9-THC or CP 55940 (Gold et al., 1992) and in pigeons following intramuscular injection with Δ^9-THC (Järbe and Mathis, 1992).

The classical cannabinoids, Δ^9-THC and Δ^8-THC, as well as the novel cannabinoids, WIN 55212-2 and the butyl indole derivative, produced dose-dependent substitution for Δ^9-THC in all monkeys. In contrast, the heptyl indole derivative did not fully substitute for Δ^9-THC, although limited drug supply prevented completion of a full dose-effect curve with this drug in all of the monkeys. Unlike with the other cannabinoids, the greatest degree of partial substitution of the heptyl indole derivative occurred at the lowest dose tested.

The present results are consistent with those obtained in cannabinoid discrimination studies with rats and pigeons in which Δ^9-THC (Prescott et al., 1992), Δ^8-THC (Järbe et al., 1976), WIN 55212-2 (Compton et al., 1992) and the butyl indole derivative (unpublished observations) produced dose-dependent substitution. The heptyl indole derivative also failed to substitute for CP 55940 in rats (unpublished observations). Potency estimates (Table 1) for each species reveal that Δ^8-THC, WIN 55212-2 and the butyl indole derivative are 3–5 times more potent in monkeys than in rats. Although a larger potency difference was seen with Δ^9-THC (73-fold), the ED_{50} for the effects of this drug in monkeys may be an underestimate due to the poor fit of these data to the regression line. The confidence limits around the Δ^9-THC ED_{50} are more than twice as wide as those around any other ED_{50}. The rank order potency of the five cannabinoid drugs was similar in rats and monkeys, with the exception that WIN 55212-2 was more potent than Δ^9-THC in rats and vice versa in monkeys. In rats, WIN 55212-2 produced behavioral disruption at doses which substituted for Δ^9-THC (Compton et al., 1992); this disruption was not apparent in the monkeys. Affinity (K_i) for inhibition of [^{3}H] CP 55940 binding in rat brain for both classical cannabinoids (Compton et al., 1993), WIN 55212-2 (Jansen et al., 1992) and the butyl indole derivative (Huffman et al., 1994) fell within the range of values typical of behaviorally active cannabinoids. High concentrations of the heptyl indole derivative failed to displace [^{3}H] CP 55940 from its binding site (Huffman et al., 1994). Taken together with results with other psychoactive cannabinoids tested in rhesus monkeys (Gold et al., 1992; Wiley et al., 1993), these results with Δ^8-THC, WIN 55212-2 and the indole-derived cannabinoids show that Δ^9-THC discrimination in this species is a useful model for characterizing the behavioral effects of cannabinoid derivatives and related drugs.

A principal goal of the study was to determine the pharmacological specificity of Δ^9-THC discrimination in rhesus monkeys. None of the non-cannabinoid drugs tested in the present study reliably produced full dose-dependent substitution, although partial ($\approx$30%) substitution occurred occasionally when a single monkey selected the Δ^9-THC lever at a particular drug dose. The greatest degree of partial substitution (25–33%) was produced by desipramine, diazepam, phenobarbital and chlorpromazine. These results are only partially consistent with those of Δ^9-THC discrimination studies in rats. While studies in rats have found that antidepressants and antipsychotics, such as desipramine and chlorpromazine, usually produce minimal substitution for Δ^9-THC (<10% drug-lever responding) (Browne and Weissman, 1981; Balster and Prescott, 1992), these drugs produced partial substitution in monkeys. One of the monkeys tested with each of these drugs responded predominantly on the Δ^9-THC lever at one of the test doses; the other monkeys tested produced completely negative results. In rats, diazepam and phenobarbital usually produce partial substitution for Δ^9-THC (Browne and Weissman, 1981; Mokler et al., 1986), although there are exceptions (Järbe and Hiltunen, 1988). Diazepam and phenobarbital produced some substitution in monkeys, as well, although the pattern of substitution produced by these drugs did not resemble the pattern produced by cannabinoids (i.e., lack of dose dependency).

The other non-cannabinoid drugs tested in the present study included buspirone (a serotonergic anxiolytic), morphine (an opiate) and phencyclidine (a dissociative anesthetic). Injection with each of these drugs resulted in predominantly vehicle-lever responding. Response rate

decreases, which would indicate behavioral activity, were achieved with several of the non-cannabinoid drugs, including buspirone, chlorpromazine, phencyclidine and phenobarbital. Since definite behavioral activity was not demonstrated with the other non-cannabinoid drugs at the doses tested in this model, it is possible that higher doses of these drugs would have produced greater substitution. Although this possibility cannot be completely ruled out, the fact that the pattern of drug lever selection produced by cannabimimetic drugs differed from that produced by drugs from other classes argues against this hypothesis. The partial substitution observed following administration of several of the non-cannabinoid drugs in the present study typically occurred at lower doses and was not dose-dependent. In contrast, cannabinoid drugs produced minimal Δ^9-THC-lever responding at lower doses, but fully substituted ($\geq$80%) at all doses higher than the minimally effective dose. Further, data from rat Δ^9-THC discrimination studies (Barrett et al., 1995) tend to produce a similar pattern of full substitution by cannabinoids and only partial, if any, substitution by drugs from other classes, even at response rate decreasing doses.

In summary, studies in several species, including rhesus monkeys, rats and pigeons, have found that Δ^9-THC discrimination shows pharmacological specificity for drugs which bind to brain cannabinoid receptors with high affinity. Structures of the cannabinoids that were behaviorally active in monkeys are diverse and include the classical tricyclic structure as well as derivations of an indole structure. This evidence that only cannabinoids and related drugs produce full substitution in rhesus monkeys is consistent with results of similar studies in rats (Balster and Prescott, 1992) and supports the use of Δ^9-THC discrimination in monkeys as a non-human primate model of cannabimimetic intoxication.

Acknowledgements

The authors wish to express appreciation to Darrell Britt for his excellent technical assistance. This research was supported by National Institute on Drug Abuse grant DA-03672 (Billy R. Martin), training grant DA-07027 (Jenny L. Wiley) and grant DA-03590 (John W. Huffman).

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