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Antagonism of the Discriminative Stimulus Effects of Δ^9-Tetrahydrocannabinol in Rats and Rhesus Monkeys[1]

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ABSTRACT

A newly developed cannabinoid antagonist, SR141716A [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride], binds to brain cannabinoid receptors and has been shown to block characteristic pharmacological effects of the aminoalkylindole cannabinoid agonist, WIN 55,212-2 {*R*-(+)-(2,3-dihydro-5-methyl-3-[(4-morpho-linyl)methyl]pyrol-(1,2,3-de]-1,4-benzoxazin-6-yl)(1-naphthalenyl)methanone monomethanesulfonate}. In the present study, the effects of this compound in an animal model of cannabis intoxication were investigated. Rats were trained to press one lever after being injected with 3 mg/kg of Δ^9-tetrahydrocannabinol (Δ^9-THC) and to press a second lever after injection with vehicle. Rhesus monkeys also were trained to discriminate between Δ^9-THC and vehicle. Results of tests with various doses of SR141716A in combination with 3 mg/kg of Δ^9-THC showed that SR141716A produced reversible, dose-dependent antagonism of the discriminative stimulus properties of Δ^9-THC in rats, with recovery within 24 hr. SR141716A also blocked the discriminative stimulus effects of Δ^9-THC in monkeys. Furthermore, in rats, 1 mg/kg of SR141716A produced a 12-fold rightward shift in the Δ^9-THC dose-effect curve and a 43-fold rightward shift in the WIN 55,212-2 dose-effect curve. When SR141716A was administered alone, it did not substitute for Δ^9-THC in rats. The present results suggest that SR141716A blocks the discriminative stimulus effects of Δ^9-THC *via* a receptor-mediated mechanism. This drug is the first reliable antagonist of cannabinoid discrimination and would be predicted to block or reverse cannabis intoxication in humans.

The cannabis plant and its constituents have a long history of medicinal and religious use which dates back to ancient China. The primary psychoactive ingredient of *Cannabis sativa* is Δ^9-THC and it is predominantly this substance which produces the subjective "high" associated with smoking the plant and is the chemical basis for cannabis abuse (Gaoni and Mechoulam, 1964). Although a desired effect by cannabis users, these subjective effects of Δ^9-THC limit its attractiveness as an alternative medication for asthma, glaucoma and nausea, conditions for which it has shown some effectiveness (Hollister, 1986).

Studies in animals of effects of Δ^9-THC related to the subjective feelings produced by the psychoactive ingredients of marijuana in humans have been achieved through Δ^9-THC discrimination, an animal model of cannabis intoxication (Balster and Prescott, 1992). Validation of this model through tests with cannabinoid and noncannabinoid drugs has demonstrated that the discriminative stimulus effects of Δ^9-THC show pharmacological specificity for cannabinoids that bind to brain cannabinoid receptors and that are psychoactive in humans (Browne and Weissman, 1981; Balster and Prescott, 1992; Compton *et al.*, 1993). In addition, anandamide, a putative endogenous ligand for brain cannabinoid receptors (Devane *et al.*, 1992), produces discriminative stimulus effects similar to Δ^9-THC in this model (Wiley *et al.*, 1995a). Conversely, noncannabinoid drugs do not substitute for Δ^9-THC (Barrett *et al.*, 1995; Balster and Ford, 1978; Browne and Weissman, 1981).

Previous attempts to antagonize the discriminative stimulus effects of Δ^9-THC with cannabinoid and noncannabinoid compounds have been unsuccessful (Järbe and Henriksson, 1974; Järbe and Ohlin, 1977; Browne and Weissman, 1981; Wiley *et al.*, 1993), although SR141716A [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride] (fig. 1), a newly developed cannabinoid antagonist (Rinaldi-Carmona *et al.*, 1994), has been shown to block the discriminative stimulus effects of a synthetic bicyclic cannabinoid agonist, CP 55,940 [(−)-*cis*-3-[2-hydroxy-4(1,1-dimethyl-heptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol], in CP 55,940-trained rats (Wiley *et al.*, 1995b). Rinaldi-Carmona *et al.* (1994) reported that SR141716A also antagonized cannabimimetic effects of an

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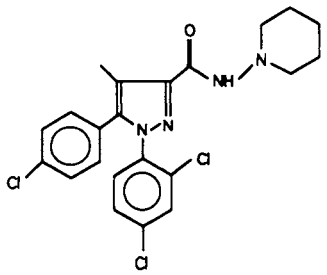
ABBREVIATIONS: Δ^9-THC, Δ^9-tetrahydrocannabinol; Anandamide, arachidonylethanolamide; FR, fixed-ratio.



SR141716A

Fig. 1. Structure of SR141716A.

aminoalkylindole cannabinoid, WIN 55,212–2 {*R*-(+)-(2,3-dihydro-5-methyl-3-[(4-morpholinyl)methyl]pyrol-(1,2,3-de]-1,4-benzoxazin-6-yl)(1-naphthalenyl)methanone monomethanesulfonate}, in simple pharmacological tests in rodents.

The purpose of the present study was to investigate the effects of SR141716A in animals trained to discriminate Δ^9-THC from vehicle in two-lever drug discrimination procedures. In rats, SR141716A was tested alone and in combination with Δ^9-THC or the aminoalkylindole cannabinoid agonist, WIN 55,212–2. The cross-species generality of antagonistic effects of SR141716A also was examined by testing it in rhesus monkeys trained in a Δ^9-THC discrimination procedure.

Methods

Subjects. Adult male Sprague-Dawley rats (290–350 g), obtained from Charles River (Wilmington, MA), were housed individually in a temperature-controlled (20–22°C) environment with a 12-hr light-dark cycle (lights on at 7:00 A.M.). Rats were maintained within the indicated weight range by restricted postsession feeding. Rats were drug naive at the beginning of the study.

Three adult male rhesus monkeys (8–12 kg), housed individually in a temperature-controlled environment with a 12-hr light-dark cycle (lights on at 7:00 A.M.), were food-restricted for 20 hr before each daily session (Monday-Friday). Each monkey received a multivitamin and his daily food supplement (135–205 g of monkey chow) after daily sessions. Monkeys had free access to water in their home cages. They had been used in previous Δ^9-THC discrimination studies (Gold *et al.*, 1992; Wiley *et al.*, 1993).

Apparatus. Rats were tested in standard operant conditioning chambers (Lafayette Instruments Co., Lafayette, IN) housed in sound-attenuated cubicles. A pellet dispenser delivered 45-mg BIO SERV (Frenchtown, NJ) food pellets to a food cup located between two response levers mounted on the front wall of the chamber. Fan motors provided ventilation and masking noise for each chamber. Four-watt houselights were located above each lever; both were illuminated during training and testing sessions.

Monkeys were tested in their home cages. During experimental sessions, 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 each cage. A food cup was located between the two response levers. Lights were located above the food cup and above each lever. For both monkeys and rats, an IBM-clone computer 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.

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 of Δ^9-THC (Carney *et al.*, 1977). Lower concentrations were obtained by further dilution with the vehicle solution. Doses of SR141716A [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride] (Pfizer Inc., Groton, CT) and WIN 55,212–2 {*R*-(+)-(2,3-dihydro-5-methyl-3-[(4-morpho-linyl)methyl]pyrol-(1,2,3-de]-1,4-benzoxazin-6-yl)(1-naphthalenyl)methanone monomethanesulfonate} (Research Biochemicals International, Natick, MA) were mixed as needed in a vehicle of 1:1:18 emulphor-ethanol-saline. For both species, SR141716A was injected 40 min before the start of the session and Δ^9-THC was injected 30 min presession. WIN 55,212–2 was injected 30 min presession. In rats, all drugs were administered i.p. at a volume of 1 ml/kg. Monkeys received i.m. injections of each drug at a volume of 0.1 ml/kg. 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. Limited supplies of SR141716A precluded testing a greater number of doses and dosage combinations in monkeys.

Rat drug discrimination procedure. Rats (n = 9) were trained to press one lever after injection with Δ^9-THC (3 mg/kg) and to press another lever after administration of vehicle. During each training session, responses on only one of the two levers delivered reinforcement under a FR-10 schedule of food reinforcement. The position of the reinforced (correct) lever was determined by the type of injection the rat received on a given day. A response on the incorrect lever reset the ratio requirement on the correct lever. The daily injections for each rat were administered in a double alternation sequence of drug and vehicle. Rats were injected and returned to their home cages for 30 min until the start of the experimental session. Acquisition training occurred during 15-min sessions 5 days a week (Monday-Friday) until the rats had met three criteria during 10 consecutive sessions: 1) first completed FR-10 on the correct lever; 2) percentage of correct-lever responding ≥ 80%; and 3) response rate ≥ 0.5 responses/sec.

Substitution and antagonism tests were conducted on Tuesdays and Fridays with continued training during sessions on Mondays, Wednesdays and Thursdays. During test sessions, consecutive responses on either lever delivered reinforcement according to a FR-10 schedule. In order to be tested, rats must have met the three acquisition criteria (see above) during at least one of the vehicle training sessions and at least one of the Δ^9-THC training sessions occurring within the week before testing. Test sessions lasted 15 min. All rats were tested with Δ^9-THC; then, they were divided into two groups. The first group (n = 6) received further tests with various doses of SR141716A in combination with 3 mg/kg of Δ^9-THC, various doses of Δ^9-THC in combination with 1 mg/kg of SR141716A and various doses of SR141716A alone. In addition, a probe test with Δ^9-THC alone was conducted 24 hr after the combination test with 1 mg/kg of SR141716A and 3 mg/kg of Δ^9-THC. The purpose of this probe test was to determine the duration of the antagonistic effects of the SR141716A to be certain that they would not interfere with the discriminative stimulus effect of Δ^9-THC during subsequent training sessions. The second group of rats (n = 3) received tests with various doses of WIN 55,212–2 alone and with a combination of 1 mg/kg of SR141716A and various doses of WIN 55,212–2. These rats also were tested with 1 mg/kg of SR141716A and 3 mg/kg of Δ^9-THC (data included in the first antagonist dose-effect curve determination described above). Control tests with vehicle and Δ^9-THC (3 mg/kg) were conducted before the Δ^9-THC and WIN 55,212–2 dose-effect curve determinations and before the series of tests with SR141716A.

Rhesus monkey drug discrimination procedure. Monkeys had been trained previously to discriminate Δ^9-THC from vehicle in a two-lever drug discrimination procedure under a FR-100 schedule of food reinforcement (Gold *et al.*, 1992). Training doses were determined individually for each monkey and ranged from 0.08 to 0.16 mg/kg i.m. In the present study, discrimination training continued with a double alternation sequence of Δ^9-THC and vehicle injections. A response on the incorrect lever reset the ratio requirement on the correct lever. Training sessions were comprised of four trials of 5 min

each, alternating with three 15-min timeout periods for a total session duration of 65 min. During trials, the lights over both levers were illuminated; during pellet delivery, the light over the food cup was illuminated. Lights over the levers were turned off during timeout periods and responses were recorded but had no programmed consequences. A test session consisted of a single 5-min trial during which consecutive responses on either lever were reinforced according to the FR-100 schedule. In order to be tested, a monkey must have pressed the first FR on the correct lever, responded greater than 80% on the correct lever and responded more than 0.05 responses per sec during at least one of the vehicle training sessions and at least one of the Δ^9-THC training sessions occurring within the week before testing.

Data analysis. For each test session, percentage of responses on the Δ^9-THC lever and response rate (responses per sec) were calculated. ED_{50} or AD_{50} values (with 95% confidence intervals) were calculated separately for each drug (where appropriate) by using least-squares linear regression on the linear part of the dose-effect curves for percentage of drug-lever responding of each rat, plotted against $\log_{10}$ transformation of the dose (Tallarida and Murray, 1987). Data on lever selection for rats and monkeys that had response rates $\leq$ 0.05 responses per sec during a test session were excluded from data analysis. Means (±S.E.M.) were calculated for percentage of responses on the drug lever and for response rates (responses per sec) in the rhesus monkeys.

Results

In rats trained to discriminate 3 mg/kg of Δ^9-THC from vehicle, SR141716A [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride] dose-dependently antagonized the discriminative stimulus effects of the training dose of Δ^9-THC without producing Δ^9-THC-like effects of its own (fig. 2, top panel). Furthermore, the antagonistic effects of SR141716A were reversible, as rats responded almost exclusively on the Δ^9-THC-associated lever when tested with 3 mg/kg of Δ^9-THC alone 24 hr after the test with a combination of 1 mg/kg of SR141716A and 3 mg/kg of Δ^9-THC. The AD_{50} for the combination of SR141716A and 3 mg/kg of Δ^9-THC was 0.8 mg/kg (95% CL, 0.2–2.7). Throughout the study, rats responded predominantly on the injection-appropriate lever during control tests with vehicle and the training dose of Δ^9-THC. Response rates were affected minimally by SR141716A over the dose range tested (fig. 2, bottom panel).

As expected, Δ^9-THC, when tested alone, fully and dose-dependently substituted for the training dose in both groups of rats (data shown only for first group) (fig. 3, top panel). SR141716A (1 mg/kg) produced a 12-fold shift to the right in the Δ^9-THC dose-effect curve for percentage of Δ^9-THC-lever responding (fig. 3, top panel). [For Δ^9-THC alone, the ED_{50} = 0.8 mg/kg (95% CL, 0.3–2.7); for the combination of Δ^9-THC and 1 mg/kg of SR141716A, the ED_{50} = 9.8 mg/kg (95% CL, 4.5–21.5).] SR141716A (1 mg/kg) also antagonized the response rate suppression that typically occurs at 30 and 56 mg/kg of Δ^9-THC, although responding was still not at levels obtained after vehicle injections (fig. 3, bottom panel).

The aminoalkylindole cannabinoid agonist, WIN 55,212–2 [*R*-(+)-(2,3-dihydro-5-methyl-3-[(4-morpho-linyl)methyl]pyrol-(1,2,3-de]-1,4-benzoxazin-6-yl)(1-naphthalenyl)methanone monomethanesulfonate], completely substituted for Δ^9-THC in the second group of rats (fig. 4, top panel). SR141716A (1 mg/kg) produced a rightward shift in the WIN 55,212–2 dose-effect curve (fig. 4, top panel). [For WIN 55,212–2 alone, the ED_{50} = 0.2 mg/kg (95% CL, 0.09–0.4); for the combination of WIN 55,212–2 and 1 mg/kg of SR141716A, the ED_{50} = 8.6 mg/kg (95% CL, 1.5–48.2).] Similar to the results of combination tests with SR141716A and higher doses of Δ^9-THC, SR141716A antagonized the response rate decreases associated with administration of higher doses (≥4.2 mg/kg) of WIN 55,212–2.

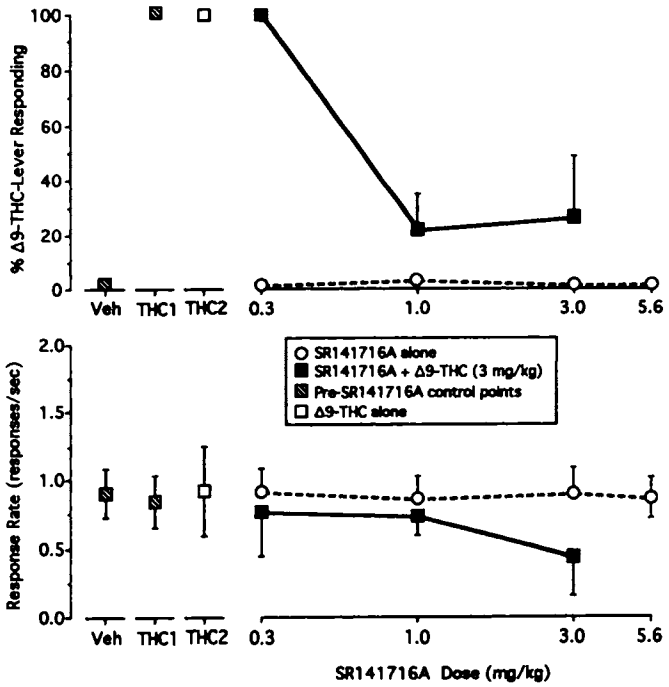


Fig. 2. Percentage of Δ^9-THC-lever responding (top) and response rate (bottom) as a function of dose of SR141716A alone or in combination with 3 mg/kg of Δ^9-THC in rats trained to discriminate 3 mg/kg of Δ^9-THC from vehicle (Veh). Points above Veh and THC1 represent results of control tests with Veh and 3 mg/kg of Δ^9-THC conducted before the combination dose-effect curve determination. Points above THC2 represent results of a test with 3 mg/kg of Δ^9-THC alone, conducted 24 hr after the test with this dose of Δ^9-THC in combination with 1 mg/kg of SR141716A. Values for each dose represent means (±S.E.M.) of data for four to nine rats.

In rhesus monkeys, responding occurred primarily on the injection-appropriate lever during control tests with vehicle and with the training dose of Δ^9-THC. Coadministration of SR141716A and the training dose of Δ^9-THC decreased the percentage of responses occurring on the Δ^9-THC-associated lever at lower doses (0.03 and 0.1 mg/kg) and eliminated responding on this lever in all monkeys at the highest dose (0.3 mg/kg) (fig. 5, top panel). Overall response rates were only slightly decreased by the combination (fig. 5, bottom panel).

Discussion

The results of the present study show that SR141716A [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride] produces reversible, dose-dependent antagonism of the discriminative stimulus effects of Δ^9-THC in rats trained to discriminate 3 mg/kg of Δ^9-THC from vehicle. Although some cannabinoids (*e.g.*, $\Delta^{9,11}$-THC, cannabidiol) and noncannabinoids (*e.g.*, atropine) attenuate one or more of the pharmacological effects of Δ^9-THC (Brady and Balster, 1980; Beardsley

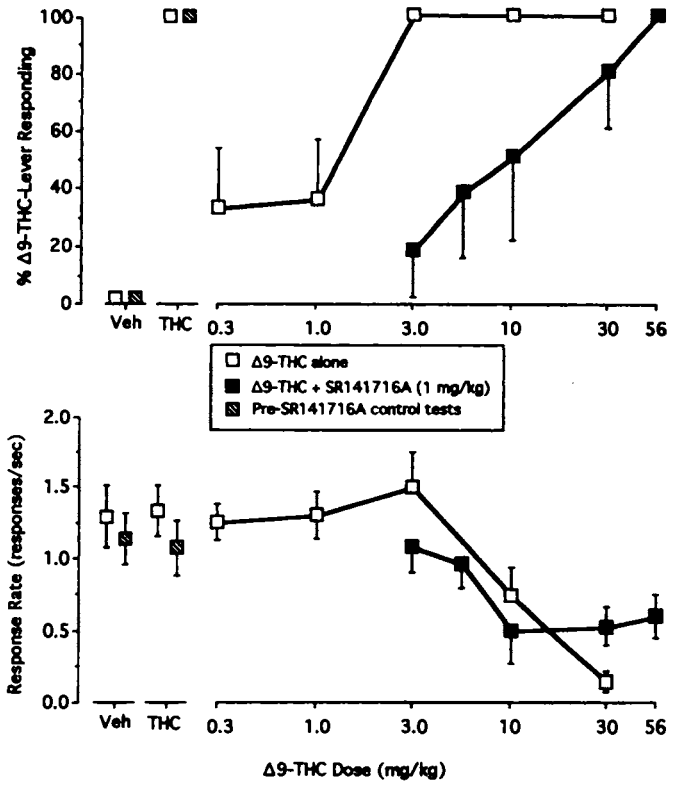


Fig. 3. Percentage of Δ^9-THC-lever responding (top) and response rate (bottom) as a function of dose of Δ^9-THC alone or in combination with 1 mg/kg SR141716A in rats trained to discriminate 3 mg/kg of Δ^9-THC from vehicle (Veh). Points above Veh and THC represent results of control tests with Veh and 3 mg/kg of Δ^9-THC conducted before the Δ^9-THC dose-effect curve determination and before the dose-effect curve determination with the combination of Δ^9-THC and SR141716A. Values for each dose represent means (±S.E.M.) of data for four to six rats.

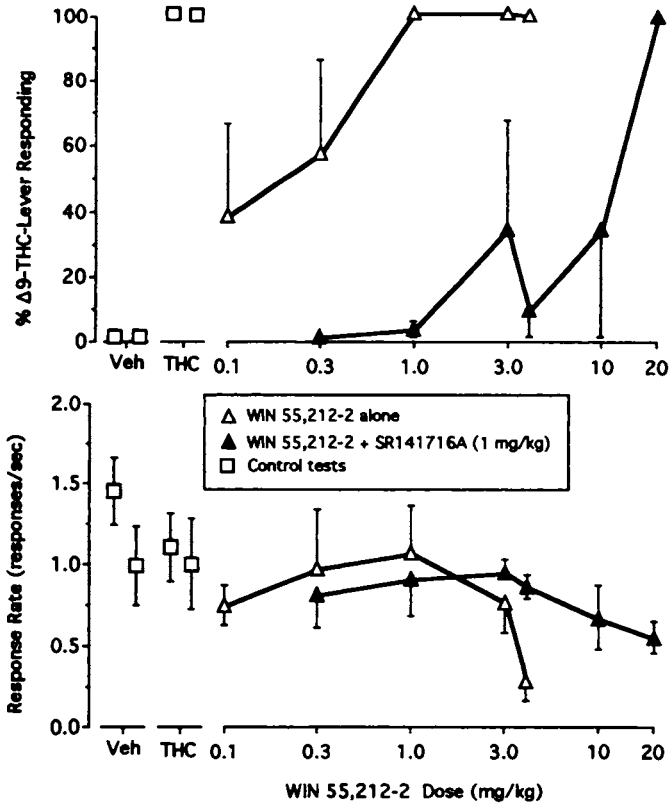


Fig. 4. Percentage of Δ^9-THC-lever responding (top) and response rate (bottom) as a function of dose of WIN 55,212-2 alone or in combination with 1 mg/kg of SR141716A in rats trained to discriminate 3 mg/kg of Δ^9-THC from vehicle (Veh). Points above Veh and THC represent results of control tests with Veh and 3 mg/kg of Δ^9-THC conducted before the WIN 55,212-2 dose-effect curve determination and before the dose-effect curve determination with the combination of WIN 55,212-2 and SR141716A. Values for each test represent means (±S.E.M.) of data for three rats.

et al., 1987; Prescott *et al.*, 1992), these drugs and others have had no effect on the discriminative stimulus effects of Δ^9-THC (Järbe and Henriksson, 1974; Järbe and Ohlin, 1977; Browne and Weissman, 1981; Wiley *et al.*, 1993). Hence, the results of this study represent the first report of successful antagonism of Δ^9-THCs discriminative stimulus effects. Furthermore, SR141716A dose-dependently antagonized the discriminative stimulus effects of WIN 55,212-2 [*R*-(+)-(2,3-dihydro-5-methyl-3-[(4-morpho-linyl)methyl]pyrol-(1,2,3-de]-1,4-benzoxazin-6-yl)(1-naphthalenyl)methanone monomethanesulfonate], a cannabinoid agonist which is structurally distinct from Δ^9-THC. Unlike Δ^9-THC, the behavioral activity of WIN 55,212 rests in the (+)-isomer (Compton *et al.*, 1992). A related study found that SR141716A also blocks the discriminative stimulus effects of a synthetic cannabinoid, CP 55,940 (−)-*cis*-3-[2-hydroxy-4(1,1-dimethyl-heptyl)phenyl]-trans-4-(3-hydroxy-propyl)cyclohexanol, in rats trained to discriminate CP 55,940 from vehicle (Wiley *et al.*, 1995b). Antagonism occurred over approximately the same dose range as in the present study.

Consistent with results of the present study, SR141716A blocks other pharmacological effects induced by WIN 55,212–2 and CP 55,940, including inhibition of the vas deferens twitch response in mice, inhibition of forskolin-stimulated adenylyl cyclase activity in substantia nigra synaptosomal preparations in rats, hypothermia in mice or rats and antinociception and ring immobility in mice (Rinaldi-Carmona *et al.*, 1994). In the present study, when SR141716A was coadministered with either Δ^9-THC or WIN 55,212–2, it attenuated the decreases in response rates typically observed with administration of higher doses of Δ^9-THC and WIN 55,212–2 (Compton *et al.*, 1992; Wiley *et al.*, 1993). SR141716As antagonism of the *in vitro* effects of cannabinoids is not specific to effects produced by classical or synthetic cannabinoids, as SR141716A produces a rightward shift in the concentration-effect curves for the effects of the putative endogenous cannabinoid, anandamide, on the mouse vas deferens twitch response and on rat forskolin-stimulated adenylyl cyclase activity (Rinaldi-Carmona *et al.*, 1994).

A number of lines of evidence suggest that SR141716A produces its blockade of the discriminative stimulus and other pharmacological effects of Δ^9-THC *via* competitive antagonism at brain cannabinoid receptors. First, Rinaldi-Carmona *et al.* (1994) have demonstrated that SR141716A selectively displaces [^{3}H]CP 55,940 from rat brain cannabinoid receptors (CB1), but shows no affinity for rat peripheral cannabinoid receptors (CB2) in the spleen, except at very high doses. Furthermore, SR141716A does not bind to non-cannabinoid receptors, including dopamine, histamine, benzodiazepine or serotonin receptors (Rinaldi-Carmona *et al.*,

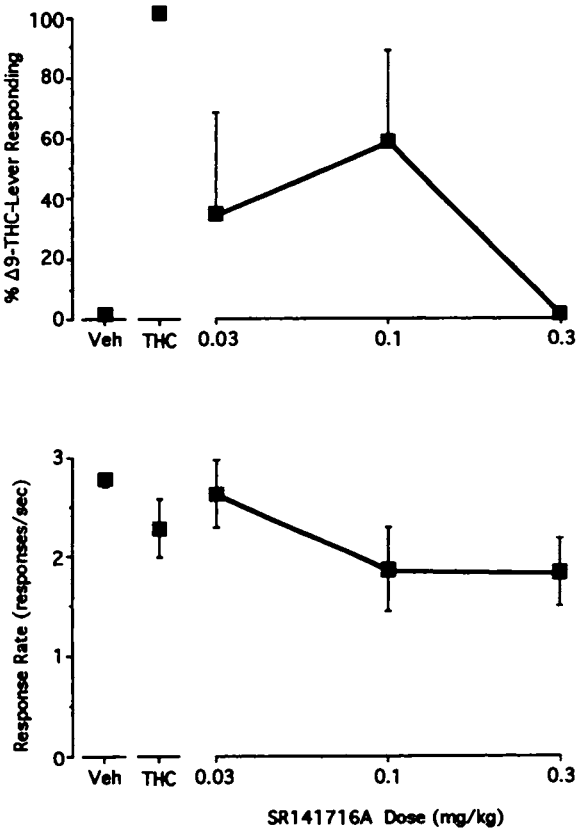


Fig. 5. Percentage of Δ^9-THC-lever responding (top) and response rate (bottom) as a function of the combination of SR141716A and the training dose of Δ^9-THC in rhesus monkeys trained to discriminate Δ^9-THC from vehicle (Veh). Training dose was determined individually for each monkey and ranged from 0.08 to 0.16 mg/kg. Points above Veh and THC represent results of control tests with Veh and the training dose of Δ^9-THC conducted before the combination dose-effect curve determination. Values for each dose represent means (±S.E.M.) of data for three rhesus monkeys.

1994). Second, as discussed above, SR141716A blocks the discriminative stimulus effects of three cannabinoid agonists, Δ^9-THC, WIN 55,212–2 and CP 55,940, which differ drastically in structure. Potency of various cannabinoids in Δ^9-THC discrimination tasks, as well as their potency in characteristic *in vivo* pharmacological tests of cannabimimetic activity, is strongly and positively correlated with binding affinity at brain cannabinoid receptors (Compton *et al.*, 1993). The results of the present study and previous studies show that SR141716A reversibly and dose-dependently antagonizes these receptor-mediated effects of cannabinoids (D. R. Compton, unpublished observations; Rinaldi-Carmona *et al.*, 1994; Wiley *et al.*, 1995b).

As would be expected of any competitive cannabinoid antagonist, SR141716As antagonistic effects are not observed in only one species. When coadministered with cannabinoid agonists, SR141716A produces cross-species antagonism of cannabimimetic effects in a number of pharmacological assays performed with rats and with mice (D. R. Compton, unpublished observations; Rinaldi-Carmona *et al.*, 1994). In the present study, cross-species antagonism of the discriminative stimulus effects of Δ^9-THC was observed. SR141716A blocked the discriminative stimulus effects of Δ^9-THC in rats and in rhesus monkeys. The minimally effective dose for full antagonism of the discriminative stimulus effects of the training dose of Δ^9-THC in rhesus monkeys was approximately 3 times less than the dose needed to antagonize Δ^9-THCs stimulus effects in rats. The increased sensitivity of rhesus monkeys to the behavioral effects of drugs occurs with other cannabinoids such as Δ^9-THC (indeed, the training dose is lower in monkeys than in rats) (see also, Gold *et al.*, 1992; Wiley *et al.*, 1993).

Whereas SR141716A binds to the cannabinoid receptor, it is possible that it may produce its antagonistic effects by acting as a partial agonist; however, results of substitution tests with SR141716A alone do not support this hypothesis. SR141716A given alone produced minimal responding on the Δ^9-THC-associated lever over a dose range which includes doses at which it blocks Δ^9-THCs discriminative stimulus effects in rats. Furthermore, when administered alone, SR141716A does not produce other characteristic *in vitro* and *in vivo* cannabinoid effects, such as inhibition of the vas deferens twitch response in mice, inhibition of forskolin-stimulated adenylyl cyclase activity in rat substantia nigra synaptosomal preparations, hypothermia in mice or rats and antinociception and ring immobility in mice (Rinaldi-Carmona *et al.*, 1994).

With the cloning of the cannabinoid receptor (Matsuda *et al.*, 1990) and isolation of endogenous ligands such as anandamide (Devane *et al.*, 1992) that bind to these receptors, important tools are now available to study the roles of the endogenous cannabinoid system in controlling behavior. The new antagonist, SR141716A, represents another such tool that will allow separation of those behavioral effects of cannabinoids that are produced *via* interaction with cannabinoid receptors from those that are mediated through other receptor systems. The fact that this drug blocks an animal model of the subjective high produced by marijuana and that this effect occurs in two different species is encouraging for further investigation of this new compound; however, the fact that it also blocks other Δ^9-THC-like pharmacological effects suggests that either: 1) the pharmacological effects of Δ^9-THC (and perhaps, its therapeutic effects as well) and its discriminative stimulus effects are mediated by the same subpopulation of receptors, and hence, are not separable; or 2) drugs with greater selectivity for specific subpopulations of cannabinoid receptors are needed. The finding of an antagonist of Δ^9-THC discrimination raises the possibility of developing SR141716A, or a similar compound, as an antidote for cannabis intoxication and/or as a treatment medication for cannabis abuse. A cannabinoid antagonist may have other therapeutic effects as well because of the apparent role that cannabinoid receptors play in a number of pharmacological effects (Hollister, 1986).

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