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# Evaluation of the reinforcing effects of the cannabinoid $CB_1$ receptor antagonist, SR141716, in rhesus monkeys

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**Abstract**

The abuse liability of a selective cannabinoid $CB_1$ receptor antagonist, SR141716 (*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxyamide hydrochloride), was evaluated in rhesus monkeys. Four rhesus monkeys with chronically indwelling venous catheters were initially trained to self-administer cocaine (30 μg/kg/injection) during daily 1-h sessions under a fixed ratio 50 (FR50) schedule of reinforcement. SR141716 was subsequently substituted for cocaine, and SR141716 dose was varied from 1 to 100 μg/kg/injection. Each dose of SR141716 was tested for four consecutive sessions and each unit dose was separated by at least three sessions of cocaine self-administration. Substitution of SR141716 for cocaine resulted in rapid extinction of lever pressing and none of the doses of SR141716 tested was self-administered above the vehicle levels. When the highest dose of SR141716 (100 μg/kg/injection) was evaluated, self-administration behavior was suppressed below vehicle levels suggesting that behaviorally active doses were evaluated. Since positive results in self-administration tests are generally predictive of abuse potential, the negative results with SR141716 suggest that this drug would likely have low abuse liability. 

*Keywords:* SR141716; Cocaine; Self-administration; (Rhesus monkey)

## 1. Introduction

SR141716 (*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxyamide hydrochloride) is the first identified centrally acting, potent and selective antagonist of cannabinoid $CB_1$ receptors (Rinaldi-Carmona et al., 1994). SR141716 blocks several behavioral and neurochemical effects of tetrahydrocannabinol, the active ingredient of marijuana, as well as the effects of synthetic cannabinomimetics in laboratory animals (e.g., Tanda et al., 1997; Wiley et al., 1995a,b). Recently, it has been shown that SR141716 pretreatment blocks intravenous tetrahydrocannabinol self-administration in nonhuman primates (Tanda et al., 2000) and effects of smoked marijuana in humans (Huestis et al., 2001). These latter findings suggest that SR141716 might have a role as a pharmacotherapeutic in the treatment of marijuana addiction. SR141716 also attenuates ethanol-seeking and ethanol consumption in rats (Arnone et al., 1997; Freedland et al., 2001), which suggests additional, anti-addictive roles for SR141716 as a pharmacotherapeutic. Other potential clinical applications for SR141716 have been proposed. For example, SR141716 has been shown to enhance memory (e.g., Terranova et al., 1996; Lichtman, 2000) and immune function (Gross et al., 2000), and to act as an appetite suppressant (Colombo et al., 1998).

The abuse liability of potential medications with behavioral activity has to be considered before they are more widely distributed. This consideration is particularly important if the medication is to be used in treating patients with drug abuse histories. Similarly, as tetrahydrocannabinol appears to be unique in its behavioral effects when compared with other drugs of abuse, SR141716 has also a relatively complex behavioral profile. Several recent findings suggest that it may share some behavioral effects with psychomotor stimulants. SR141716 administration produces conditioned place preference (Sanudo-Pena et al., 1997; Cheer et al., 2000) even though not all the studies confirmed this finding (e.g., Chaperon et al., 1998). It increases *fos*-like immunoreactivity in mesocorticolimbic areas

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(Alonso et al., 1999) and norepinephrine outflow in the anterior hypothalamus (Tzavara et al., 2001) in similar ways, as does cocaine. SR141716 also potentiates the locomotor stimulant effects of amphetamine (Masserano et al., 1999) and mimics other effects of amphetamine-like psychomotor stimulants, such as reducing food intake (Colombo et al., 1998) and increasing wakefulness (Santucci et al., 1996). These cocaine-like effects of SR141716 further underscore the importance of evaluating the abuse potential of SR141716. In the present study, SR141716 was evaluated for its ability to support self-administration when tested in a substitution procedure in rhesus monkeys trained to self-administer cocaine. There is a strong, positive correlation between those drugs that are self-administered by rhesus monkeys in this procedure and those that are recreationally abused by humans (Johanson and Balster, 1978; Griffiths and Balster, 1979; Ator and Griffiths, 1987; Balster, 1991), and results using this procedure have been used by regulatory bodies in making drug-scheduling recommendations.

## 2. Material and methods

### 2.1. Subjects

Four adult male rhesus monkeys (*Macaca mulatta*) were used. Their weights were as follows: M1252 (12.7 kg), M1304 (8-9.5 kg), M1258 (7.3 kg) and M1306 (9.3 kg). Monkeys were chronically housed in experimental cubicles described below, were fed with Purina Monkey Chow twice daily (morning and evening), and received ad libitum water. Dietary supplements consisting of a chewable multiple vitamin tablet, Prima Treats (BioServ, Frenchtown, NJ), and fresh fruits or vegetables were provided daily. All monkeys had previously participated in other self-administration studies.

Each monkey was surgically implanted with an indwelling silicone catheter (0.08 i.d.; Ronsil Rubber Products, Belle Mead, NJ) under phencyclidine (1 mg/kg, i.m.)/pentobarbital (10–30 mg/kg, i.v.) anesthesia. The right or left internal and external jugular, femoral, or brachial veins could be catheterized. If patency was lost in a catheter, the catheter was removed and an alternate vein was then recatheterized. The catheters ran subcutaneously to the midscapular region where they exited through the skin. Catheters were protected by a stainless steel harness and restraining arm through which they passed to the rear of the cubicle and were then connected to peristaltic pumps. The catheter-protection harness and tether were equipped with swivels allowing animals nearly complete freedom of movement within the cubicles.

The research was conducted under NIH Guidelines for the Care and Use of Laboratory Animals. The protocol was approved by the Institutional Animal Care and Use Committee of the Virginia Commonwealth University.

### 2.2. Apparatus

The animals were housed in airtight fiberglass chambers ($1 \times 1 \times 1$ m) with a transparent front door. The air supply for the cubicles was passed through an air filtration system. Two response levers and associated stimulus lights were located on the front door of each cubicle. A peristaltic pump (Masterflex, Cole-Palmer, Chicago, IL) was attached to each catheter and delivered 1-ml infusions in 10 s. Scheduling of infusions and collection of data were controlled by a PDP-11-based computer system (Digital Equipment, Maynard, MA) operating SKED-11 laboratory control software (State Systems, Kalamazoo, MI).

### 2.3. Procedure

Each monkey had been trained to press the left lever for 30 μg/kg/infusion cocaine hydrochloride under a fixed ratio 50 (FR50) schedule of reinforcement during daily (7 days/week) 1-h experimental sessions. Daily experimental sessions began at approximately 1400 h during the light portion of the light–dark cycle. Availability of the drug was signaled by illumination of two white stimulus lights above the lever. During infusions, the white stimulus lights were extinguished and a red light located between them was illuminated.

Substitution tests were conducted when infusion rates on three successive cocaine self-administration sessions did not show increasing or decreasing trends and did not differ by more than 20% from the mean of those three sessions (typically, this difference was much less). Substitution tests were conducted for four consecutive sessions. At least three doses of SR141716 were tested in each monkey within the range of 1 to 100 μg/kg/injection. A dose great enough of SR141716 to apparently suppress behavior, as evidenced by its engendering fewer infusions than those of its vehicle, was tested to maximize the likelihood that behaviorally active doses were included in the evaluations. Between testing each dose, the subjects were returned to cocaine baseline for at least three sessions until response rates were again stable. Four-day substitution tests with saline and with the vehicle used for SR141716 were conducted before the testing of the doses of SR141716, and these substitutions served as negative controls.

### 2.4. Drugs

SR141716 (*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxyamide HCL) was obtained from Sanofi Recherche (Paris Cedex, France). It was prepared for intravenous administration in a 1:1:18 mixture of Alkamus EL-620 (Rhone-Poulenc, Cranbury, NJ)/ethyl alcohol (USP absolute-200 proof)/0.9% sterile saline vehicle. This stock solution was then filtered (22 μm Sterile Arcodisc; Gelman Sciences, Ann Arbor, MI) to insure sterility. All doses were delivered in

1.0 ml/kg volume in 10-s infusions. ( − )-Cocaine HCl was obtained from the National Institute on Drug Abuse (Rockville, MD) and dissolved in sterile 0.9% saline for intravenous administration. Doses of all drugs refer to the salt.

### 2.5. Data analysis

Individual monkey and group mean numbers of infusions were analyzed for cocaine, saline, SR141716, and vehicle and portrayed graphically. Results with SR141716 for each subject were then compared to its vehicle and saline control data. A test dose of SR141716 was considered to serve as a reinforcer and be self-administered when the average number of infusions occurring during the last 3 days of a substitution condition exceeded the average numbers of vehicle and saline control infusions, and their ranges did not overlap in individual subjects. Data from the first days of substitution were excluded from these comparisons because they represent the monkeys' initial experience with each test substance and are often not indicative of typical performances. Infusion rates during these initial sessions reflect a transition between rates of cocaine-maintained responding and responding under the test condition.

The time course of infusions over the 1-h sessions was also examined. For these time course analyses, the numbers of SR141716 infusions self-administered during successive 15-min segments of the 1-h test session were expressed. Descriptions of the time courses of infusion after SR141716, cocaine and vehicle infusion were then made.

## 3. Results

### 3.1. Substitution tests

Mean infusions obtained per session during cocaine, SR141716, vehicle and saline self-administration are shown in Fig. 1. A 30 μg/kg/infusion dose of cocaine maintained

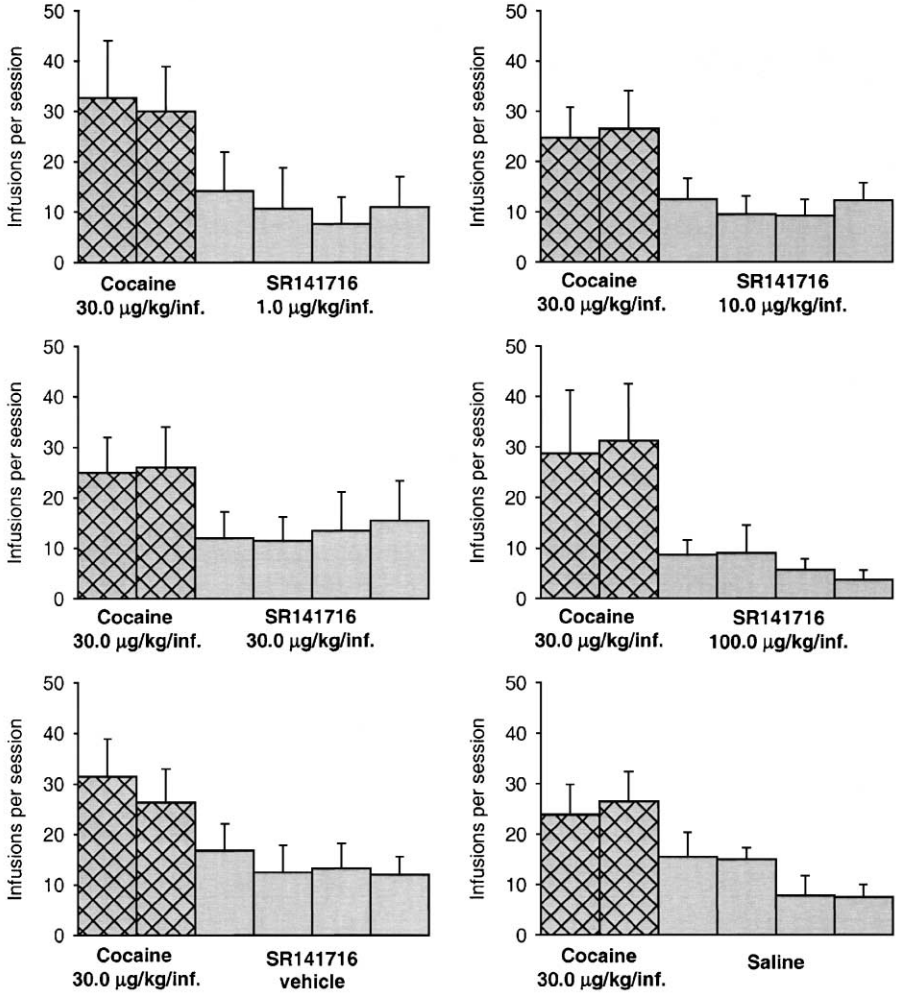


Fig. 1. Effects of different i.v. doses of SR141716 and vehicle in rhesus monkeys trained to i.v. self-administer 30 μg/kg/infusion cocaine. Cross-hatched bars represent responding during two consecutive cocaine sessions immediately preceding substitution tests. Open bars represent responding during four consecutive substitution sessions when saline and different doses of SR141716 and its vehicle were tested. Results are expressed in infusions per 1-h session. Data are means ± S.E.M. from three to four subjects.

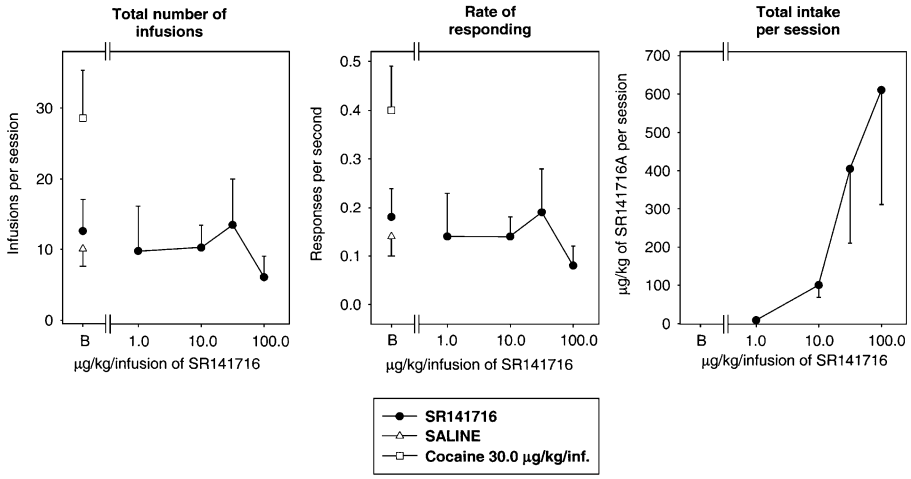


Fig. 2. SR141716 dose–response curves (filled circles) in rhesus monkeys trained to self-administer cocaine. Numbers of infusions per session (left panel), response rates (middle panel) and total SR141716 intake (right panel) are presented as a function of unit dose of SR141716. Each value represents the mean ± S.E.M. of the last three sessions from $n = 3–4$ monkeys under each SR141716 unit dose condition and under a vehicle condition. Open triangles represent the mean ± S.E.M. of the last three sessions under saline self-administration, open squares represent the mean ± S.E.M. of the last three sessions under cocaine (30 μg/kg/injection) self-administration, and filled circles above B (baseline) represent the mean ± S.E.M. of the last three sessions under vehicle self-administration conditions in the same subjects. The cocaine data point was obtained from three sessions immediately preceding substitution tests with SR141716's vehicle. B = baseline condition (i.e. saline, vehicle, or cocaine).

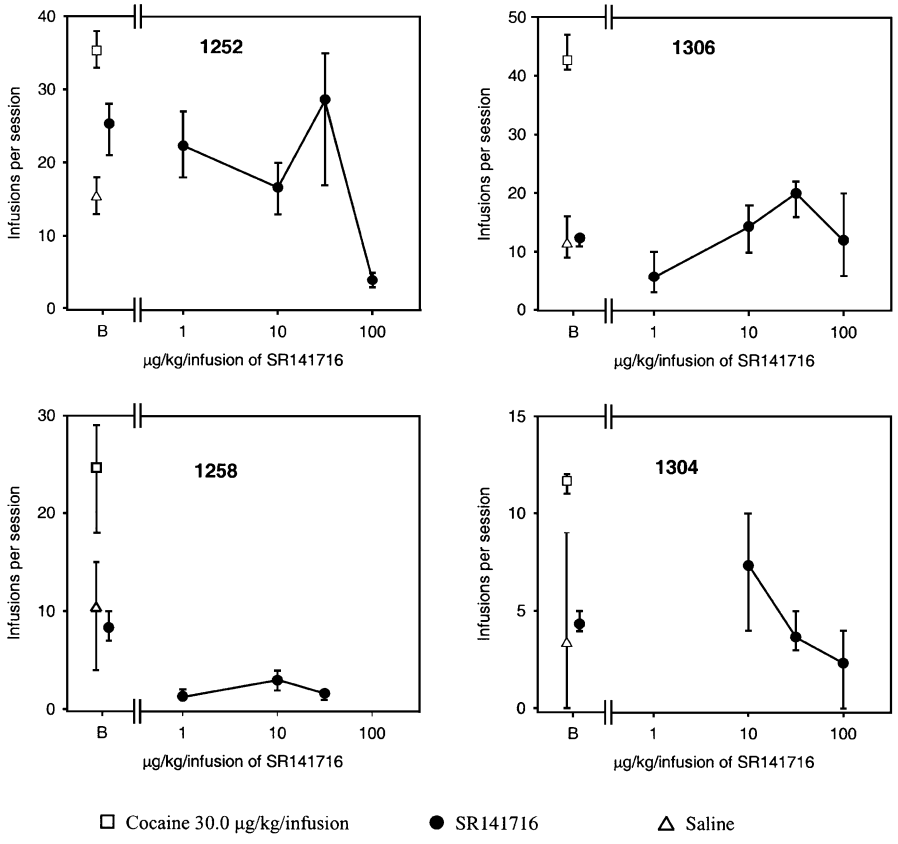


Fig. 3. SR141716 dose–response curves (filled circles) in individual monkeys. Numbers of infusions per session are presented as a function of unit dose of SR141716. Each value represents the mean ± range of the last three sessions under each SR141716 unit dose condition or under a vehicle condition. Open triangles represent the mean ± range of the last three sessions under saline self-administration, open squares represent the mean ± range of three sessions under cocaine (30 μg/kg/injection) self-administration, and filled circles above B (baseline) represent the mean ± S.E.M. of the last three sessions under vehicle self-administration conditions in the same subjects. The cocaine data points were obtained from three sessions immediately preceding substitution tests with SR141716's vehicle. B = baseline condition (i.e. saline, vehicle, or cocaine).

high numbers of infusions throughout the entire experiment. As a group, the monkeys self-administered, on average, about 29 infusions of cocaine during the two training sessions immediately prior to each substitution. When saline or SR141716's vehicle was substituted for cocaine, infusion rates decreased rapidly reflecting the extinction of responding. Similarly, when doses from 1 to 30 μg/kg of SR141716 were substituted for cocaine, infusion rates declined during the first substitution session and stabilized near saline and vehicle levels. At 100 μg/kg/infusion of SR141716, self-administration behavior was nearly eliminated on days 3 and 4 of substitution.

### 3.2. SR141716 dose–response curve

The group SR141716 dose–response curve is presented in Fig. 2 (left frame) and the individual dose–effect curves are shown in Fig. 3. None of the doses of SR141716 were

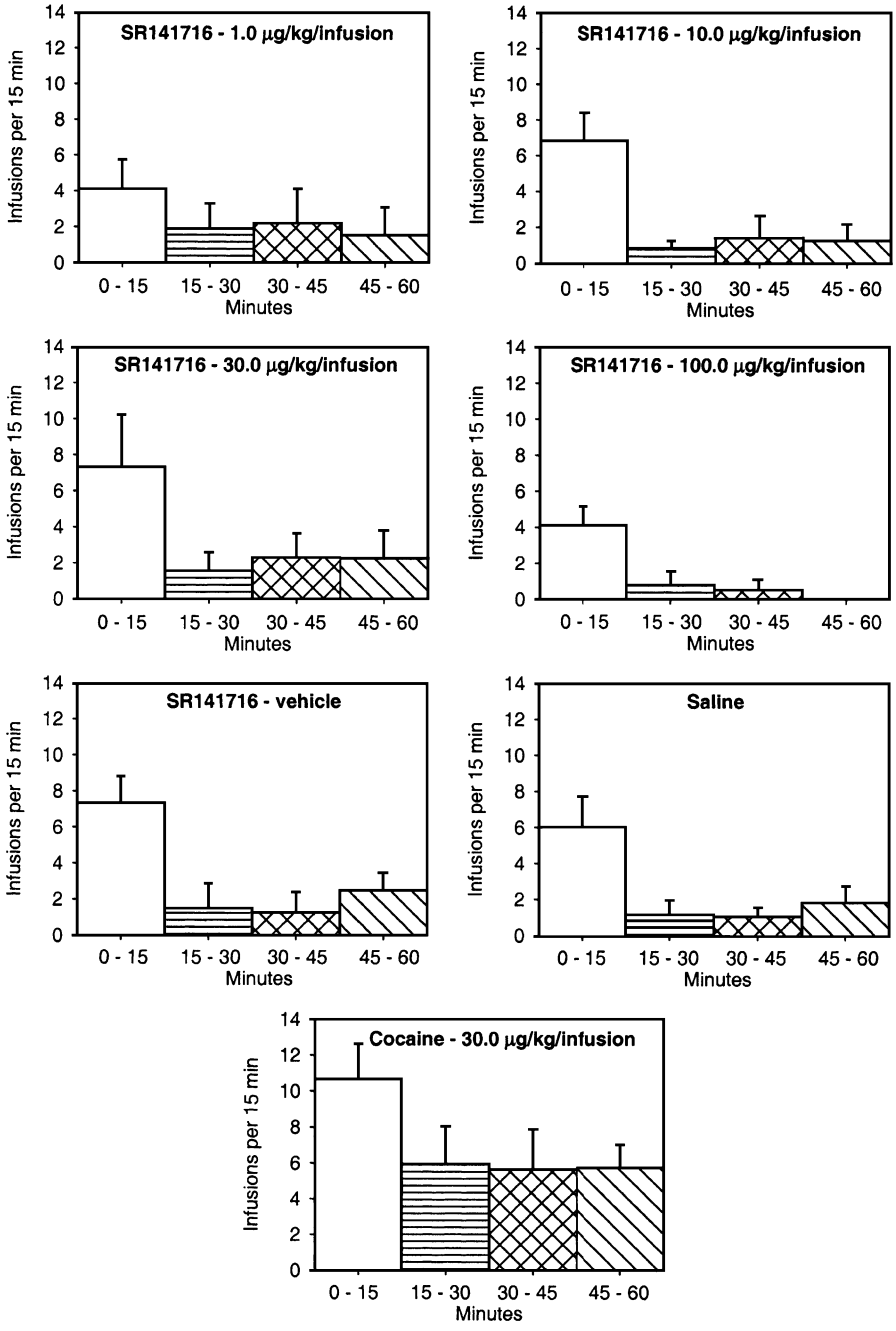


Fig. 4. Within session distribution of cocaine, saline, SR141716 and vehicle for infusions. Bars represent number of infusions within the first, second, third and the fourth 15-min segment of the session. Each value represents the mean ± S.E.M. of the last three sessions from $n = 3–4$ monkeys.

self-administered above saline and vehicle levels by any monkey. Furthermore, the ranges of infusion rates during SR141716 substitution tests and during vehicle or saline controls overlapped in all the subjects (Fig. 3). Increasing the dose of SR141716 from 30 μg/kg/infusion to 100 μg/kg/infusion resulted in decreased numbers of infusions with a consequent increase in SR141716 intake (μg/kg/1-h session) by only about 50% (Fig. 2, right panel). The mean numbers of infusions obtained of SR141716 at the highest dose tested in each monkey were reduced relative to the mean number of vehicle infusions obtained (Fig. 3).

### 3.3. Distribution of infusions within the session

The distribution of infusions within sessions is presented in Fig. 4. Although the monkeys obtained more cocaine infusions during the initial loading phase in the first quarter of the sessions, a homogenous and substantial rate of infusion was maintained across all remaining quarters of the test sessions (Fig. 4, bottom panel). In contrast, the time courses of vehicle and saline infusions were characteristic of within-session extinction of responding with most infusions obtained during the first 15 min of the session and with near-zero levels obtained later. Similar to vehicle and saline results, the time course of SR141716 infusions was typically characterized by the greatest proportion of infusions occurring during the first 15 min of the test session with near-zero levels occurring at other times.

## 4. Discussion

The aim of the present study was to evaluate the ability of a selective cannabinoid $CB_1$ receptor antagonist, SR141716, to serve as a reinforcer in rhesus monkeys. Substitution of SR141716 for cocaine in rhesus monkeys trained to self-administer cocaine resulted in rapid extinction of drug taking behavior. None of the doses of SR141716 tested was self-administered above saline or vehicle levels. Furthermore, the number of obtained SR141716 infusions decreased within test sessions, which is usually an indication that extinction of responding was occurring (e.g., Comer et al., 1995). All these findings suggest that SR141716 did not serve as a reinforcer under the test conditions and would likely have a low abuse liability. Before making this conclusion, however, several issues have to be discussed.

One explanation for failure to obtain self-administration with SR141716 might be that too low and neuropharmacologically nonrelevant doses of SR141716 were tested. The present findings, however, support that a behaviorally active dose range of SR141716 was evaluated. First, at the highest tested doses, rates of infusion of SR141716 were decreased to below those for vehicle. Second, the total mean intravenous intake of SR141716 per session was about 0.6 mg/kg. This dose corresponds with behavioral active doses of SR141716 in other primate studies. For example, a 0.3 mg/kg dose of SR141716 administered i.m. totally suppressed tetrahydrocannabinol self-administration in squirrel monkeys (Tanda et al., 2000). Similarly, 1.0 mg/kg of SR141716 given i.m. totally antagonized effects of tetrahydrocannabinol on learning in another study in squirrel monkeys (Nakamura-Palacios et al., 2000), and 1.0 mg/kg of SR141716 given orally reduced sweet food intake in marmosets (Simiand et al., 1998). Finally, an absolute dose of 90 mg administered orally to humans reversed most effects of smoked marijuana (Huestis et al., 2001). All these observations suggest that the dose range used in the present study was neuropharmacologically relevant.

Another explanation for negative results in the present experiment might be the training drug used to maintain responding under baseline conditions. It is more likely that the drug functions as a reinforcer of operant responding if the drug with a similar mechanism of action is used as the baseline (e.g., Beardsley et al., 1990). Because SR141716 differs from all compounds reported to maintain self-administration behavior, a training drug from another drug class had to be used. Also, because SR141716 shares some behavioral effects with psychomotor stimulants (Masserano et al., 1999; Colombo et al., 1998; Santucci et al., 1996), selecting cocaine as the baseline drug appears appropriate. SR141716 has been demonstrated to block tetrahydrocannabinol (Tanda et al., 2000), heroin and morphine (Navarro et al., 2001) self-administration, and it is thus unlikely that it would support self-administration behavior if cannabinoids or opioids were used as training drugs. Furthermore, SR141716 can precipitate withdrawal in subjects exposed chronically to both cannabinoids (e.g., Beardsley and Martin, 2000; Cheer et al., 2000) and opioids (Navarro et al., 2001). It is also unlikely that SR141716 would be self-administered more robustly if drugs from different classes, such as phencyclidine (e.g., Beardsley et al., 1990) or sedatives (reviewed by Ator and Griffiths, 1987), were used as a baseline drug since SR141716's behavioral effects are opposite to these drugs. SR141716, for example, enhances memory (Terranova et al., 1996; Lichtman, 2000) and increases wakefulness (Santucci et al., 1996), unlike what is typically found with phencyclidine (reviewed by Willetts et al., 1990).

Negative results in the present experiment are contradictory to previous reports that SR141716 supports development of conditioned place preference in a similar way as cocaine in some (Sanudo-Pena et al., 1997; Cheer et al., 2000) but not all the studies (e.g., Chaperon et al., 1998). One explanation for this discrepancy might be the use of animals with extensive drug histories in the present study and the use of naïve animals in place preference studies. The differences in procedure or in the route of administration rather than differences in the history might, however, more likely account for these opposing findings. Similarly, as in the present study, drug-naïve mice did not self-administer SR 141716 more than their yoked controls in two recent studies (Martellotta et al., 1998; Navarro et al., 2001), suggesting that the influence of drug history on SR141716's reinforcing

properties may not have played an important role. Predictive validity of self-administration studies is, furthermore, likely stronger than the predictive validity of conditioned place preference studies because self-administration entails drug-taking behavior whereas the latter does not. In conditioned place preference studies, animals receive drugs passively (experimenter-controlled), whereas in self-administration studies, subjects actively determine when the drugs are administered (subject-controlled) similar to human users. Also, in self-administration studies, drugs are usually injected i.v. and immediate behavioral effects are thus achieved, whereas in conditioning place preference studies, substances are given either s.c. or i.p., which may result in a delayed onset of action.

The experimental design of the self-administration procedure used in the present study has been validated in numerous previous studies using almost identical conditions. Studies with buspirone, minaprine and nefazodone using the procedures nearly identical to that which was used to study SR141716 failed to find evidence for the reinforcing effects of these compounds (Balster and Woolverton, 1982; Beardsley and Balster, 1987; Gold and Balster, 1991), consistent with other evidence that these new anxiolytics and antidepressants have no abuse liability. On the other hand, new stimulant drugs with now known abuse potential (methylenedioxy-methamphetamine and 4-methylaminorex) are self-administered under these conditions (Beardsley et al., 1986; Mansbach et al., 1990). This correlation is not perfect, however. For example, $\gamma$-hydroxybutyric acid (GHB) was not self-administered under similar test conditions, yet it is considered to have abuse liability (Beardsley et al., 1996).

In conclusion, since positive results in self-administration tests are generally predictive of abuse potential, the negative results with SR141716 suggest that this drug would likely have low abuse liability.

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