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Dependence on Δ^9-Tetrahydrocannabinol: Studies on Precipitated and Abrupt Withdrawal[1]

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ABSTRACT

A cannabinoid antagonist, SR 141716A, dose dependently precipitated a behavioral withdrawal syndrome in rats continuously infused i.p. for only 4 days with relatively low-dose regimens of Δ^9-tetrahydrocannabinol. The following dose regimens, expressed as mg/kg/24 hr, were used for days 1 through 4: high—12.5, 25, 50 and 100; medium—2.5, 5, 10 and 20; and low—0.5, 1, 2 and 4. The major withdrawal signs of the syndrome were scratching, rubbing face with paws, licking, wet-dog shakes, arched back and ptosis (at least 50% closure of eyelids). At the highest dose regimen, other signs noted in fewer subjects were biting, tongue rolling, retropulsion, head shakes, extended limbs or high stepping, ataxia, myoclonic spasms and front paw treading. During abrupt withdrawal (Δ^9-tetrahydrocannabinol was discontinued and vehicle substituted) abstinence signs were also noted; however, except during a 48-hr observation period, withdrawal was not sufficiently robust to achieve statistical significance. The results of this study provide evidence that a modest course of Δ^9-tetrahydrocannabinol can produce physical dependence. Hence, the risk and incidence of marijuana dependence in humans may be greater than previously projected.

Recent comprehensive surveys indicate that marijuana is still the most commonly used illicit substance in the United States. Acute and chronic use of cannabis, the generic name of preparations obtained from the plant *Cannabis sativa*, can have profound adverse effects on the health of the user. Evidence for the prevalence of cannabis abuse comes from the Epidemiological Catchment Area study that involved interviews with 20,000 people (Robins and Regier, 1991). According to the criteria established by the American Psychiatric Association (DSM-111-R), cannabis use and/or dependence was diagnosed in 4.4% of the sample. Data suggest that 17 to 33% of the daily users satisfy DSM-111-R criteria. The major complaints of dependent cannabis users who seek treatment are loss of control, cognitive and motivational impairments and depression. Significantly, groups at high risk of experiencing adverse effects from chronic exposure include adolescents, women of child-bearing age and people with preexisting diseases. Much of the skepticism regarding dependence on cannabinoids is probably related to the fact that only a mild abrupt withdrawal syndrome has been observed in humans in contemporary Western societies (Jones and Benowitz, 1976; Jones *et al.*, 1981; Compton *et al.*, 1990). Although physical dependence is no longer obligatory for the diagnosis of dependence, it nevertheless provides additional strong evidence for the existence of such a state and assists in unraveling underlying neural and biochemical mechanisms. Indeed, insights regarding these mechanisms could help resolve the question of cannabis as a gateway drug to abuse of even more dangerous illegal drugs. Additionally, development of an animal model of dependence would be beneficial in designing a rational treatment for cannabis dependence.

Although some investigators were unable to demonstrate physical dependence on cannabis (Leite and Carlini, 1974; Harris *et al.*, 1974), others reported success (Dewey, 1986; Pertwee, 1991; Jones *et al.* (1976); Kaymakcalan *et al.* (1977). The relevance of many of these findings has been questioned because of the robust dose regimens used. Recently, Rinaldi-Carmona *et al.* (1994) reported that SR 141716A bound selectively and with high affinity to the central cannabinoid receptor and was a potent antagonist of cannabinoids. Subsequently, SR 141716A was found to block the effects of a potent psychoactive constituent of marijuana, THC on hypoactivity, hypothermia and antinociception in mice (Compton *et al.*, in press). SR 141716A also antagonized the discriminative stimulus properties of THC in rats and monkeys (Wiley *et al.*, 1995), and the cardiovascular effects in rats (Varga *et al.*, 1995). An antagonist should precipitate with-

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ABBREVIATIONS: SR141716A, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide · HCl; THC, Δ^9-tetrahydrocannabinol; veh, vehicle; 5-HT, serotonin.

drawal in a physically dependent subject. It should compress, intensify and evoke a clear-cut withdrawal syndrome. Using a continuous infusion model, we showed that relatively low-dose regimens of THC, produced physical dependence. Withdrawal characterized by intense behavioral activation followed SR 141716A challenge in these preliminary studies (Aceto *et al.*, 1995a; Aceto *et al.*, 1995b). Another preliminary investigation also demonstrated that SR 141716A precipitated withdrawal in rats on an intermittent dose regimen of THC (Tsou *et al.*, 1995).

The availability of a cannabinoid antagonist has allowed us to systematically study some important aspects of dependency on cannabinoids. Our purpose was to compare the physical dependence syndromes observed after abrupt withdrawal (discontinuation of the agonist, THC and subsequent infusion of vehicle) and withdrawal precipitated by the antagonist, SR 141716A after chronic exposure to different dose regimens of THC. Another important objective was the dose-effect responsivity of SR 141716A.

Methods

All animals received care according to "Guide for the Care and Use of Laboratory Animals," DHHS Publication, Revised, 1985. The facilities are certified by the American Association for the Accreditation of Laboratory Care. These studies were approved by the Institutional Animal Care and Use Committee at Virginia Commonwealth University.

Continuous-infusion studies in rats

Adult male Sprague-Dawley rats were purchased from Harlan Sprague Dawley, Inc., Indianapolis, IN). On arrival, the rats were examined by a licensed veterinarian and placed in quarantine. They weighed 250 to 280 g when assigned to a study. Once selected they were housed individually in stainless steel cages. The vivarium was temperature and humidity controlled with alternating light-dark cycles (lights on at 06:00 hr and off at 24:00 hr).

The method described by Teiger (1974) was used with modifications indicated below. The rats were allowed to acclimate to their new surroundings for at least 3 days before i.p. cannulae were implanted. They were anesthetized with pentobarbital (45 mg/kg/i.p.). The lateral side of the lower left abdomen and back of the neck was shaved and the exposed skin cleansed with Pavidone-Iodine solution (Redi-Product, Prichard, WV). Each rat was fitted with a cannula (PE90 tubing, Clay Adams, Parsippany, NJ). The cannula passed s.c. from the nape of the neck to the lateral side of the lower abdomen. The peritoneal end of the cannula was enclosed in silastic tubing to prevent foreign body reaction. It was introduced into the peritoneal cavity through a stab-wound entry site. The cannula was secured with sutures at both sites. Each rat was fitted with a harness 3 or 4 days after surgery. The harness consisted of a flat stainless steel plate fitted with a shoulder collar and a flexible spring coil. A small piece of Velcro was fastened to the harness. Another narrow strip of Velcro girdled the chest and secured the harness. A spring coil enclosed the cannula that was then attached to a flow-through swivel (Instech Lab., Horsham, PA). The swivel allowed the rat to move about in the cage and eat and drink normally. An infusion pump (Harvard Apparatus, S. Natick, MA, model-975) delivered the selected dose regimen in a volume of 8 ml every 24 hr. After weighing each subject daily, fresh solutions were prepared.

Experimental procedures in rats

THC dose-response. Two experiments were conducted, the second to confirm the results of the first and to extend the dose range. A condensed version is presented in table 1. In both experiments, the rats were randomly allocated to one of six treatment regimens or groups and were also assigned to a numbered cage on a rack to prevent bias. The challenge dose of SR 141716A was 10 mg/kg i.p. This dose was based on studies reported by Rinaldi-Carmona *et al.* (1994) and on other studies conducted in this laboratory.

The rats were scored 1 hr before challenge with either SR 141716A or its vehicle. Then, all infusions of THC were stopped and appropriate challenges given by i.p. injection. Scoring of the signs designated scratching; head shakes; facial tremors; rubbing face with paws; biting; chewing; tongue rolling; licking; ear twitch; forepaw treading; backward locomotion or retropulsion; wet-dog shakes; body jerks or myoclonic spasms; immobility or lying still; arched back; and ptosis (at least 50% closure of eyelids) followed. The signs wet-dog shakes and rubbing were quantified. All other signs were scored as either present or absent. The same trained observer was used throughout these studies. The data were then grouped by treatment regimen and analyzed statistically as indicated below.

THC infusion-SR 141716A dose-response. The same procedure outlined above was followed except that a THC dose regimen of 2.5, 5, 10 and 20 mg/kg/day from days 1 through 4, respectively, was selected. This dose regimen was chosen because it produced a robust withdrawal and did not alter body weight during the prechallenge

TABLE 1
Synopsis of THC dose-response, rat-infusion experiments

Treatment	Dose (mg/kg/24 hr, i.p.) Day 1	Day 2	Day 3	Day 4	Challenge[a] (mg/kg i.p.)	No. of Subjects
High THC	12.5	25	50	100	SR 141716A[b]	4[c,d]
High THC	12.5	25	50	100	Vehicle[e]	5[c]
Med THC	2.5	5	10	20	SR 141716A[b]	9[f]
Med THC	2.5	5	10	20	Vehicle[e]	9[f]
Low THC	0.5	1	2	4	SR 141716A[b]	5[g]
Low THC	0.5	1	2	4	Vehicle[e]	4[c]
Vehicle[e]		8 ml/24 hr			SR 141716A[b]	9[f]
Vehicle[e]		8 ml/24 hr			Vehicle[e]	9[f]

[a] All infusions were stopped just before challenge with SR 141716A or vehicle.
[b] SR 141716A challenge dose was 10 mg/kg.
[c] Number of subjects in the first experiment.
[d] Although five rats were infused with THC, one rat was removed from the study because some SR 141716A solution was observed at the site of the injection after its administration.
[e] Vehicle for THC and SR 141716A was emulphor-ethanol-sterile saline (1:1:18).
[f] Combined number of subjects from experiments 1 and 2.
[g] Number of subjects in the second experiment.

infusion period. Doses of SR 141716A were 1, 3, 10 and 30 mg/kg. The number of subjects per treatment regimen was five.

Statistical analysis

In the THC dose-response study, the quantified data from the behavioral withdrawal signs of wet-dog shakes and facial rubbing and daily body weight measurements were collated by treatment regimens (see Table 1). In the THC-SR 141716A dose-response experiment, data were assembled similarly by treatment regimen.

Statistical analysis of the quantified data in rats was performed by repeated measures analysis of variance using the Bonferonni/Dunn (comparison to vehicle) or the Scheffe (comparison among all groups) for post hoc analysis. The scored data were analyzed using the nonparametric Kruskal-Wallis one-way analysis of variance. *Post hoc* comparisons were made using the Mann-Whitney U test. In all cases, significance was set at $P = .05$. The StatView statistical package (Brainpower, Inc., Agoura Hills, CA) was used for these analyses.

Chemical supplies

The cannabinoid antagonist, SR 141716A, was synthesized at Pfizer Central Research as the free base. THC and naloxone-HCl were obtained from the National Institute on Drug Abuse. Morphine sulfate was purchased from Mallinckrodt, Inc., St. Louis, MO. THC and SR 141716A were dissolved in 1:1:18 (emulphor-ethanol-sterile saline). Emulphor (EL-620), a polyoxyethylated vegetable oil, GAF Corp., Linden, NJ, sterile saline (USP), Baxter Healthcare Corp., Deerfield, IL, and other supplies were obtained commercially.

Results

Many overt behavioral signs were observed during these studies. Some occurred spontaneously in all rats as part of their normal behavioral repertoire. Other behavioral signs were noted exclusively in THC-infused rats. Some behavioral signs were seen occasionally in SR 141716A-treated controls and vehicle controls and in rats receiving the high dose regimen of THC (see table 2).

A list of signs that were observed in rats treated with vehicle or with the high dose regimen of THC and challenged with either vehicle or SR 141716A was prepared (table 2). Signs that occurred in at least 75% of the subjects were designated major. These signs constituted the core of the withdrawal syndrome. They were scratching, rubbing face with paws, licking, wet-dog shakes, arched back and eyelid ptosis. As shown in table 2, other signs were observed in only one-quarter to one-half of the subjects and for that reason are designated minor signs. It should be noted that many rats receiving the other treatment regimens also displayed wet-dog shakes, facial rubbing and scratching. Nevertheless, table 2 does not reflect the frequency of withdrawal signs; it simply indicates whether or not any one sign was observed in a rat during the observation period. A comparison of the data in table 2 for the signs wet-dog shakes and facial rubbing with quantified data for these signs in figure 2 clearly illustrates this point.

TABLE 2

Behavioral withdrawal signs observed in rats chronically treated with either vehicle or the high dose regimen of THC and challenged with either vehicle or SR 141716A

Signs	Veh-Veh	Veh-SR	High THC-	High THC-SR
Scratching		+++	+++	+++
Licking	+			+++
Biting			+	+
Ptosis		+	+++	++++
Tongue rolling				+
Arched back	+	+	+	+++
Wet-dog shakes	+++	+++++	+++	++++
Rubbing	++++	++++	++	++++
Ear-twitch			+	
Chewing			+	
Walking backward				+
Head shakes				++
High stepping				++
Ataxia				+
Myoclonic spasms				+
Front paw treading				+

The rats chronically treated with vehicle and challenged with either vehicle or SR 141716A (Veh-Veh and Veh-SR, respectively) each contained five animals, whereas the groups chronically administered the high dose regimen of THC and challenged with either vehicle or SR 141716A (high-vehicle and high-SR, respectively) contained four animals. A + simply indicates that an animal exhibited a particular sign during the observation period. It does not reflect the intensity or frequency of occurrence during the observation period.

The THC dose-response data expressed as the averages of the total number of behavioral signs observed for each group before and after challenge with SR 141716A are illustrated in figure 1. Application of the Kruskal-Wallis one-way analysis of variance test revealed no significant differences among the groups before challenge with SR 141716A ($H = 8.569$, χ^2 .05(7) = 14.07). The low and medium THC-treated groups and the vehicle group given SR 141716A-vehicle show essentially equivalent responses. The mean for the high-dose THC group receiving SR-vehicle is elevated most likely because some THC-associated behavioral signs were already present at challenge. This probably reflects some behavior generated by the increased background activity associated with the filling of the syringes and injection of the rats rather than behavior associated with abrupt withdrawal. Importantly, these are not statistically significant differences. After SR 141716A challenge, a significant difference among treatment groups was obtained ($H = 28.103$, χ^2 0.05(7) = 14.07). For the THC groups receiving SR 141716A, a dose-response relationship is evident. *Post hoc* determinations revealed that the medium- and high-dose THC treatment groups given SR 141716A were significantly different ($P < .05$) from their corresponding veh-treated groups. Some activation was observed in the veh-SR 141716A controls.

Due to their protean characteristics, it was not possible to evaluate each behavioral sign. However, the signs wet-dog shakes and facial rubbing were selected for quantitative evaluation because of their distinguishing traits. The incidence of the signs wet-dog shakes and facial rubbing increased markedly only in the THC-infused animals receiving the medium- and high-dose regimens approximately 10 min after SR 141716A precipitated withdrawal. This activation subsided somewhat within the hour. A gauge of the intensity of the precipitated behavioral activation for the sign wet-dog shakes is depicted in figure 2. Repeated measures analysis of variance of the sign wet-dog shakes indicated that treatment produced a highly significant sign effect ($F = 3.622$, $P < .003$), a sign effect over time ($F = 15.202$, $P < .0001$) and a significant interaction between treatment and time ($F = 6.341$, $P < .0001$). *Post hoc* comparisons of the treatment regimens showed significant differences ($P < .05$) only for the medium and high Δ^9-THC regimens challenged with SR 141716A when compared to their respective controls at the 1 hr after challenge. The medium and high treatment regimens were not significantly ($P < .05$) different from one another. This probably reflects an upper limit of responsiveness due to

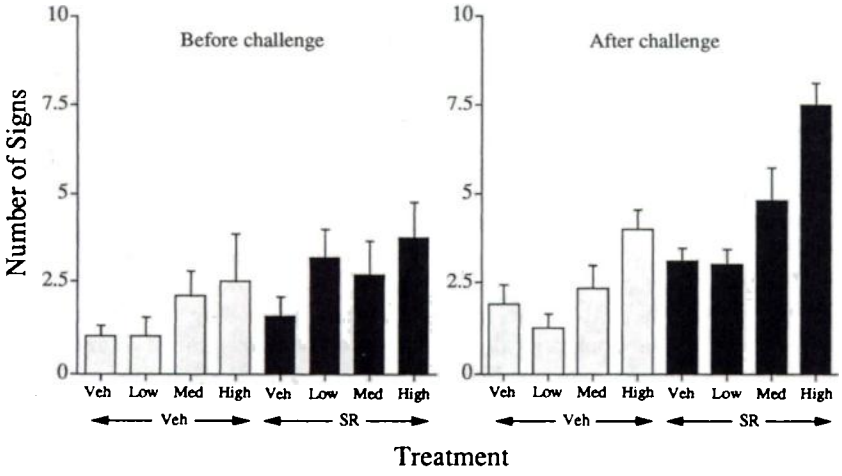

Fig. 1. The incidence of withdrawal signs in rats before and after challenge with SR 141716A (10 mg/kg). Rats were infused with either vehicle, low, medium or high dose THC regimens for 4 days. During a 1-hr period before SR 141716A challenge, the presence or absence of each withdrawal sign was noted for each animal so that the total number of signs could be recorded for each animal. The animals were then challenged with either a vehicle or SR 141716A injection (as indicated on the x-axis) and then monitored for 1 additional hr. The designation of veh and SR in the x-axis of the "before challenge" panel indicates which groups subsequently received these challenges. The results are presented as means + S.E.M.

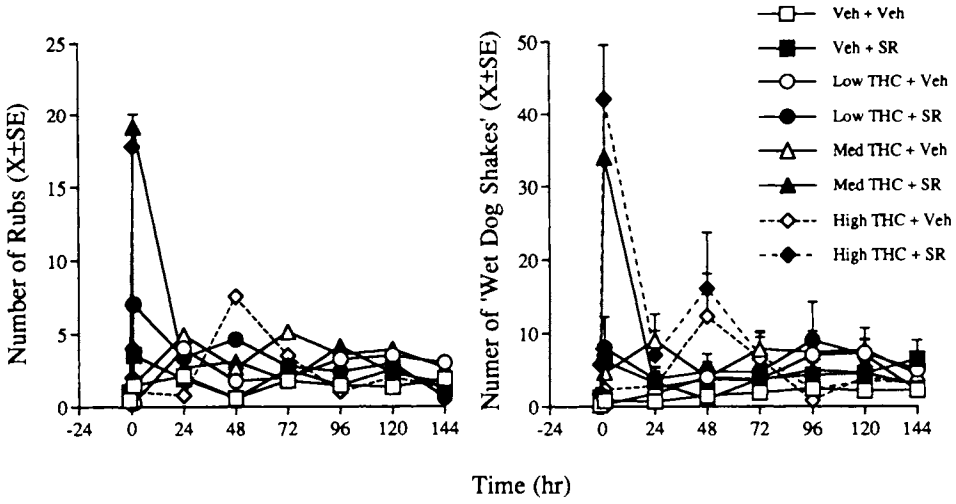

Fig. 2. The number of SR 141716A-precipitated rubbing and wet-dog skakes in rats infused with either vehicle, low, medium or high THC treatment regimens. The animals were observed for 1-hr periods before and after challenge with either vehicle or SR 141716A (10 mg/kg), and on the 6 days after challenge. The data are presented as means ± S.E.M.

the numerous other expressed and competing behaviors. None of the THC-infused rats challenged with vehicle demonstrated significant withdrawal-like behavior. The incidence of rubbing was analyzed by analysis of variance (repeated measures). The wet-dog shakes observed during the 24 to 144 hr post-SR 141716A intervals suggest some abrupt withdrawal activity. However, significance ($P < .05$) was established only for the high THC groups challenged with either SR 141716A or vehicle when compared with the veh + veh controls at the 48-hr observation period.

Similar observations were also made for the sign facial rubbing (fig. 2). Repeated measures analysis of variance showed that treatment produced a significant effect ($F = 4.194$, $P < .0012$). The effect over time was significant ($F = 17.951$, $P < .0001$), and there was a significant interaction between treatment and time ($F = 6.394$, $P < .001$). *Post hoc* comparisons also indicated that the medium THC and high THC groups challenged with SR 141716A significantly ($P < .05$) increased the number of facial rubbings during precipitated withdrawal. The only other significant elevations occurred at the 48- and 72-hr observation periods for the high THC + veh and high THC + SR 141716A groups, respectively, compared with the veh + veh controls.

Body weight was closely monitored (fig. 3). Statistical evaluation using repeated measures analysis of variance revealed highly significant treatment effects ($F = 4.364$, $P < .0009$) and day effects ($F = 177.5$, $P < .0001$). A significant

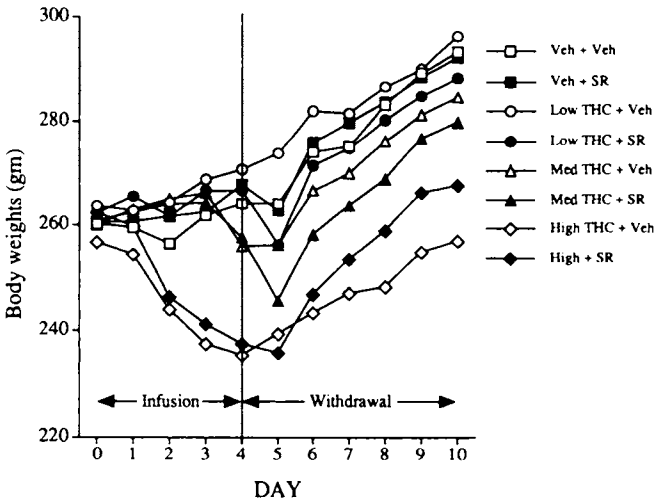

Fig. 3. Body weights of rats during the 4-day infusion with either vehicle, low, medium or high THC dose regimens and after challenge with either vehicle or SR 141716A (10 mg/kg). The results are presented as the means of body weights in grams.

treatment day interaction was also obtained ($F = 6.104$, $P < .0001$). Inspection of the data show significant body weight loss with the groups receiving the high dose regimen during the infusion of THC. Recovery after challenge was gradual. Although the body weights in the medium dose regimens

appear to be dropping, especially after day 4, significance was not established when compared with vehicle control. There was no significant loss of body weight observed after SR 141716A or vehicle challenges.

Regarding the SR 141716A dose-response study, repeated measures analysis of variance of the sign wet-dog shakes indicated no significant difference among the treatment groups ($F = 1.390$, $P < .2534$). However, there was a significant effect over time ($F = 17.21$, $P < .0001$). In addition, a significant interaction between treatment and time was found ($F = 4.070$, $P < .0001$). The results are illustrated in figure 4. The only indication of a dose response was in the time interval designated precipitated withdrawal or immediately after challenge with different doses of SR 141716A. The 10 and 30 mg/kg doses of SR 141716A were significantly different ($P < .002$) from the veh + veh and THC + veh groups, whereas the 1 and 3 mg/kg dose groups did not achieve statistical significance. Although there were sporadic increases in wet-dog shakes during abrupt withdrawal in the period 24 to 144 hr after SR 141716A or vehicle challenge of THC-infused rats, *post hoc* testing revealed no significant differences when compared to controls.

Similar results were found for the sign facial rubbing. Repeated measures analysis of variance revealed only a statistical trend for a sign difference among different treatments ($F = 2.023$, $P = .0958$). There was a significant effect over time ($F = 21.458$, $P < .0001$) as well as a significant interaction between treatment and time ($F = 4.287$, $P < .0001$). Regarding *post hoc* comparisons, the same observations indicated above for wet-dog shakes apply. The numbers of facial rubs in the groups challenged with 3, 10 and 30 mg/kg SR 141716A were significantly different from the veh + veh and THC + veh groups during the 1 hr after challenge. The incidence of rubbing during the 24- to 144-hr period were not significantly different for any group.

Discussion

Cannabinoid abstinence syndromes have been described by a number of investigators in animals and humans. Using rhesus monkeys that received gradually increasing doses of THC (up to 1.6 mg/kg/day for 36 days), Kaymakcalan (1972) recorded the behavioral signs designated aggressiveness, hyperirritability, tremors, yawning, photophobia, hallucinatory behavior and anorexia. This syndrome appeared 12 hr after THC was discontinued and lasted for 5 days. Many of the overt behaviors noted above have been observed by others studying THC in monkeys (Kaymakcalan and Deneau, 1972; Stadnicki *et al.*, 1974; Fredericks and Benowitz, 1980). Beardsley and coworkers (1986) were able to demonstrate marked response-time disruption of food-maintained operant behavior in rhesus monkeys. THC was given continuously at the rate of 0.05 mg/kg/hr i.v. for 10 days. The dose regimen was within the range of human intake by heavy abusers. Overt behavioral signs observed but not quantified included aggressiveness, bruxism and hyperactivity.

An abrupt withdrawal syndrome in rats has been described by Kaymakcalan *et al.* (1977). It included many behaviors that we noted in this study; however, the sign rubbing was not mentioned and wet-dog shakes were seen rarely. Other investigators found that challenge with the biogenic amine reuptake inhibitors fluoxetine, clomipramine and imipramine also elicited a similar syndrome (Verberne *et al.*, 1980; Taylor and Fennessy, 1982). These investigators rarely observed wet-dog shakes. It should be noted that the amine or reuptake inhibitions were given 24 hr after abrupt withdrawal of THC. Thus, strictly speaking, the syndrome was not precipitated. In any case, these studies provided evidence that serotonergic mechanisms might be involved because each of the amine reuptake inhibitors induced changes that correlated with their ability to block the reuptake of 5-HT. It was suggested that THC decreased 5-HT release leading to neuroadaptations in the form of increased sensitivity of postsynaptic 5-HT receptors.

Despite the evidence cited above, numerous investigators have been unable to obtain similar findings on termination of chronic cannabinoid exposure. It is well known that cannabinoids produce a behavioral syndrome in dogs that is highly specific for this class of compounds (Walton *et al.*, 1937). Using this model, McMillan *et al.* (1971) examined the consequences of chronic exposure of Δ^9-THC to dogs. They found that administration of active doses of Δ^9-THC on a daily basis produced tolerance to this effect and that increasing the dose to very high levels did not overcome this tolerance. However, the administration of increasingly large doses of Δ^9-THC to

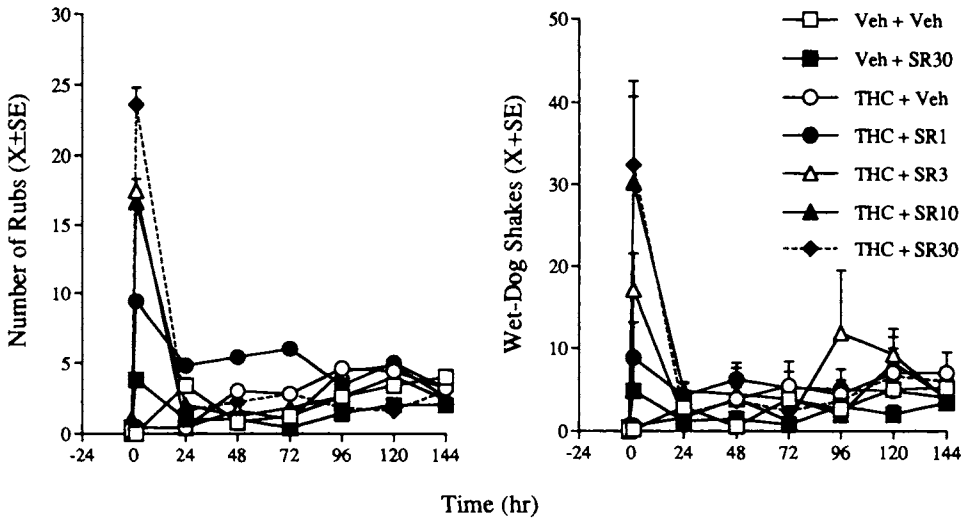

Fig. 4. The dose-responsiveness of SR 141716A-precipitated rubbing and wet-dog skakes in rats infused with either vehicle or the medium THC treatment regimens. The animals were observed for 1-hr periods before and after challenge, and on the 6 days after challenge. The animals were challenged with either vehicle or 1, 3 or 10 mg/kg of SR 141716A. The data are presented as means plus S.E.M.

dogs over an 11-day period did not produce withdrawal symptoms during abstinence. These same researchers also treated pigeons with daily intramuscular injections of very high doses of Δ^9-THC (up to 180 mg/kg) and failed to detect withdrawal signs when the drug exposure was terminated (McMillan *et al.*, 1971). Failure to characterize cannabinoid dependence in rodents was also reported (Leite and Carlini, 1974).

As for marijuana dependence in humans, the first indications arose from uncontrolled clinical observations after cessation of chronic drug intake (Fraser, 1949; Soueif, 1967). However, Jones and Benowitz (1976) studied the effects of THC in human volunteers. Using increasing doses up to 210 mg/day, in divided oral doses, these investigators demonstrated behavioral and physiological signs associated with abrupt withdrawal. They included changes in mood, appetite and increased body weight. Restlessness, hyperactivity, tremulousness, nausea, abdominal distress, perspiration, chills, fever, salivation, hemoconcentration, rebound waking EEG changes and intraocular pressure increases were also noted. The relevance of both uncontrolled and controlled clinical studies to human usage of marijuana has been questioned because of the relatively low incidence of withdrawal symptoms in the marijuana using population studies (Jones *et al.*, 1981).

That a selective cannabinoid antagonist is capable of precipitating withdrawal provides key evidence for cannabinoid dependence. It should be stressed that the dose regimens used by the investigators cited above varied widely. Furthermore, the doses and/or length of exposure to THC were much greater than those used in our study. However, in our laboratory precipitated withdrawal was demonstrated after only 4 days of infusion of THC. Our results suggest that the prevalence of physical dependence on cannabis may be more widespread than estimated. The behavioral sequelae also provide evidence for activation of multiple neural substrates and cannabinoid receptors.

The development of an animal model not only offers strong support for marijuana dependence, but provides the first opportunity to fully explore cannabinoid dependence on a systematic basis. It will be important to determine whether a withdrawal syndrome can be precipitated in other species, and optimal treatment regimens for producing dependence. Equally important, the identification of agents that can ameliorate SR 141716A-precipitated withdrawal may provide leads for the development of treatment strategies for those experiencing difficulty in terminating the use of marijuana.

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