ORIGINAL ARTICLE

Blockade of Effects of Smoked Marijuana by the CB1-Selective Cannabinoid Receptor Antagonist SR141716

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Background: SR141716, a recently developed CB1 cannabinoid receptor antagonist, blocks acute effects of Δ-9-tetrahydrocannabinol (THC) and other CB1 cannabinoid agonists in vitro and in animals. These findings suggest that CB1 receptors mediate many of the effects of marijuana, but this has not been evaluated in humans.

Methods: Sixty-three healthy men with a history of marijuana use were randomly assigned to receive oral SR141716 or a placebo in an escalating dose (1, 3, 10, 30, and 90 mg) design. Each subject smoked an active (2.64% THC) or placebo marijuana cigarette 2 hours later. Psychological effects associated with marijuana intoxication and heart rate were measured before and after antagonist and marijuana administration.

Results: Single oral doses of SR141716 produced a significant dose-dependent blockade of marijuana-induced subjective intoxication and tachycardia. The 90-mg dose produced 38% to 43% reductions in visual analog scale ratings of "How high do you feel now?" "How stoned on marijuana are you now?" and "How strong is the drug effect you feel now?" and produced a 59% reduction in heart rate. SR141716 alone produced no significant physiological or psychological effects and did not affect peak THC plasma concentration or the area under the time × concentration curve. SR141716 was well tolerated by all subjects.

Conclusions: SR141716 blocked acute psychological and physiological effects of smoked marijuana without altering THC pharmacokinetics. These findings confirm, for the first time in humans, the central role of CB1 receptors in mediating the effects of marijuana.

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WIDESPREAD medical, recreational, and religious uses of *Cannabis sativa* preparations (eg, marijuana, hashish) have occurred throughout history.[1,2] Δ-9-Tetrahydrocannabinol (THC), the primary psychoactive component of marijuana, produces behavioral, cardiovascular, analgesic, psychomotor, and cognitive effects that are mediated through the cannabinoid CB1 receptor, a G protein–linked receptor located primarily in the central and peripheral nervous systems.[3-5] A second cannabinoid receptor subtype (CB2) seems to be concentrated in the peripheral immune system.[6,7] The identification of specific cannabinoid receptors has led to the discovery of endogenous cannabinoid agonists, including the arachidonic acid derivatives anandamide and 2-arachidonoylglycerol.[8,9]

Development of SR141716, the first selective CB1 receptor antagonist, has provided an important new tool for identifying functions of the endogenous cannabinoid system. Acute administration of SR141716 blocks in vitro and in vivo effects of cannabinoid agonists[10,11] and precipitates withdrawal signs in animals given

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THC for long periods.[12] These findings suggest that CB1 receptors play an important role in mediating the effects of THC in animals. This article reports (for the first time in humans) the ability of SR141716 to antagonize the psychological effects and tachycardia produced by smoked marijuana in research volunteers with histories of marijuana use.

RESULTS

SUBJECT CHARACTERISTICS

Subjects in the 8 treatment groups differed significantly in number of days of

SUBJECTS AND METHODS

SUBJECTS

Subjects were recruited from the community according to the following eligibility criteria: physically and psychologically healthy men aged between 21 and 45 years; marijuana use of at least 1 year; no current physical dependence on any substance other than nicotine or caffeine; use of other drugs no more than twice in the 2 weeks prior to study entry; regular alcohol intake of no more than 4 standard drinks per day (≥5 days per week); no use of hallucinogens during the past year; smoking fewer than 30 cigarettes per day; Shipley Institute of Living estimated IQ greater than 85; and no history of seizures, head trauma with loss of consciousness greater than 3 minutes, current major psychiatric disorder, or lifetime non–drug-related psychosis. Current marijuana use was verified by a positive urine cannabinoid test result at 50 ng/mL. Health status was evaluated by medical history, physical examination, blood chemistry, complete blood cell count, urinalysis, viral antibody screening (hepatitis B, hepatitis C, human immunodeficiency virus), tuberculosis skin test (with chest x-ray film as clinically indicated), electrocardiogram, electroencephalogram, pulmonary function tests, clinical psychiatric interview, and standard psychological tests. The study was approved by the National Institute on Drug Abuse (NIDA) institutional review board. All subjects gave written informed consent and were paid for their participation.

STUDY DESIGN

A randomized, placebo-controlled, double-blind, ascending dose design was used. Sixty-three subjects were randomly assigned (within the constraints of dose escalation) to 1 of 12 groups: placebo SR141716/placebo marijuana (n=10); placebo SR141716/active marijuana (n=10); active SR141716/placebo marijuana (n=2 at 1, 3, 10, 30, and 90 mg SR141716); and active SR141716/active marijuana (n=8 at 1 mg; n=7 at 3 mg; n=6 at 10, 30, and 90 mg SR141716). Randomization within each dosage group was based on computer-generated random numbers. The original study design included 1-, 3-, and 10-mg doses. Groups receiving 30 mg and 90 mg were added when a blinded review of data from lower doses suggested no evidence of efficacy and the doses were well tolerated by subjects. Subjects received a single oral dose of active or placebo SR141716 at 9 AM, then smoked an active or placebo marijuana cigarette 2 hours later. A 2-hour interval was used to match the expected time of peak SR141716 plasma concentration (unpublished data, Sanofi-Synthelabo Inc).

Subjects resided on the closed clinical research unit of the NIDA [National Institute on Drug Abuse] Intramural Research Program for at least 1 day prior to dosing and 2 days afterward. To avoid the possibility of precipitating marijuana withdrawal, SR141716 was not administered until urine cannabinoid concentration was below 20 ng/mL. Medical evaluations were repeated prior to unit discharge and at a follow-up visit 1 week after dosing. Review of adverse events and clinical laboratory data suggested no dose-dependent trends. No subject left the study because of an adverse event attributed to SR141716.

MEDICATIONS

SR141716 and matching placebo capsules were obtained from Sanofi-Synthelabo Inc, Malvern, Pa. Each subject took 3 capsules containing 0, 1, 10, or 30 mg of SR141716 as needed to achieve his assigned dose. Marijuana was supplied by the NIDA Research Technology Branch in machine-rolled cigarettes, weighing an average of 764 mg. Active cigarettes contained 2.64% THC by weight, confirmed by gas chromatography/mass spectrometry (GC/MS) assay, and were estimated to contain 20 mg of THC. Placebo cigarettes were identical in appearance and smell, except that cannabinoids were removed by solvent extraction. Subjects smoked 8 puffs at 60-second intervals beginning 110 minutes after oral dosing with SR141716.

ASSESSMENTS

Primary outcome measures were subjective report of intoxication and heart rate, reliable measures of acute marijuana

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marijuana use in the 30 days prior to study entry ($F_{7,55}$ = 2.72, P=.02), but did not differ significantly in years of lifetime marijuana use ($F_{7,55}$ = 0.87, P=.54), age ($F_{7,55}$ = 0.75, P=.63), race (Fisher exact test = 2.24, P=.98), or body mass index ($F_{7,55}$ = 0.84, P=.56) (**Table**). The 90-mg SR141716 group had the highest recent marijuana use (25 days) and the 1-mg SR141716 group had the lowest (4.6 days).

EFFECTS OF MARIJUANA AND SR141716 ALONE

Marijuana smoking alone produced expected physiological and psychological effects. Marijuana significantly (t_{49}= 4.67, P<.001) increased heart rate, producing a mean increase of 30 beats per minute 15 minutes after smoking (**Figure 1**). Marijuana also increased scores on the composite VAS (t_{47} = 6.58, P<.001), individual VAS questions (t_{47} = 6.63, P<.001; t_{47} = 6.24, P<.001; and t_{47} = 6.61, P<.001, for "drug high," "stoned," and "drug strength," respectively), and the M scale (t_{47} = 3.85, P<.001) (Figure 1). Peak effects occurred within 60 minutes after smoking.

SR141716 alone produced no significant effects on any of the outcome measures (Figure 1) (t_{49} = 0.01, P=.99; t_{47} = 0.03, P=.98; t_{47} = 0.13, P=.90; t_{47} = 0.10, P=.92; t_{47}= 0.03, P=.98; and t_{47} = 0.22, P=.83 for heart rate, composite VAS, individual VAS questions, and M scale, respectively). In addition, visual inspection of data collected from all subjects during the 2 hours between SR141716 dosing and smoking (data not shown), and during the placebo marijuana smoking session showed no evidence of any significant changes from baseline.

BLOCKADE OF MARIJUANA EFFECTS BY SR141716

The 90-mg dose of SR141716 (compared with placebo SR141716) significantly reduced the effects of mari-

intoxication.[13,14] Marijuana intoxication was assessed by 3 visual analog scale (VAS) questions and the Marijuana (M) scale. Each VAS question was given separately on a video monitor. Subjects responded by moving the cursor along a 100-mm line labeled "Not at all" on the left and "Extremely" on the right. The 3 questions were "How high do you feel now?" "How stoned on marijuana are you now?" and "How strong is the drug effect you feel now?" Visual analog scale scores were analyzed as a composite score (mean of the 3 individual scores) and as individual scores. The M scale is a 12-item subset of the Addiction Research Center Inventory.[15] Each item describes a sign or symptom commonly associated with marijuana intoxication, to which subjects respond true or false. The VAS questions and M scale were completed 1 hour before SR141716 dosing, 1 hour before marijuana smoking, and at 5, 10, 15, 20, 25, 55, and 65 minutes after marijuana smoking.

Heart rate was monitored continuously during the session using a 2-lead Passport NR Physiological Monitor (Datascope Corp, Paramus, NJ) and analyzed in terms of average heart rate during consecutive 5-minute intervals. Heart rate baseline was the 5-minute interval immediately preceding the start of the smoking period.

Blood for SR141716 and THC assays was drawn from an indwelling venous catheter in the arm 10 minutes before SR141716 dosing, 5 minutes before marijuana smoking, and at 2, 5, 10, 15, 20, 40, 60, 80, and 100 minutes after smoking. Heparinized plasma was stored at –20°C until analysis (SR141716 was assayed by liquid chromatography–tandem mass spectrometry with a 1-ng/mL limit of detection). Δ-9-Tetrahydrocannabinol was assayed by chemical ionization gas chromatography/mass spectrometry using a modification of the method of Foltz et al,[16] with a 0.5-ng/mL limit of detection.

STATISTICAL ANALYSES

Data from the 62 randomized subjects who received SR141716 and smoked a marijuana cigarette were used in the analysis (1 subject did not smoke marijuana because of administrative issues and was not included in the analysis). Psychological data from 3 subjects and heart rate data from 1 subject were not used because they provided fewer than 4 data points during the 60 minutes following smoking. Comparison of baseline subject characteristics across treatment groups was conducted using 1-way analysis of variance (ANOVA) for continuous variables and the Fisher exact test for categorical variables.

Data were expressed as peak change from baseline for heart rate and peak effect for psychological variables for 1 hour after smoking because previous results indicated that peak effects occurred within 1 hour after smoking marijuana.[13,14] Peak effect data from all variables were analyzed using a 2-way ANOVA with marijuana cigarette (placebo, active) and SR141716 dose (0, 1, 3, 10, 30, 90 mg) as factors. Planned pairwise contrasts were used to compare the antagonism of marijuana effects by each dose of SR141716 with antagonism by placebo and to examine the effects of marijuana and SR141716 alone. Residual variances for each group were used in the analysis because of observed group differences in variance. A secondary analysis on composite VAS score, heart rate, and M scale was conducted using orthogonal polynomial trend tests to examine the dose-response effect of SR141716 after active marijuana administration. The trend tests were performed on log (SR141716 dose), replacing the 0-mg dose with 0.01 mg. All statistical tests were 2-tailed with $\alpha = .05$.

Percent blockade at each SR141716 dose was calculated as 100 × [(placebo SR141716/active marijuana) – (active SR141716/active marijuana)]/[(placebo SR141716/active marijuana) – (placebo SR141716/placebo marijuana)]. The Feiller theorem was used to calculate 95% confidence intervals (CIs) for percent blockade. The effects of marijuana alone were evaluated by comparing data from the placebo SR141716/placebo marijuana group (n=10) and the placebo SR141716/active marijuana group (n=10). The effects of SR141716 alone were evaluated by comparing the effects of placebo SR141716/placebo marijuana (n=10) with those of the combined group receiving active SR141716/placebo marijuana (n=10).

juana on the composite VAS (t_{47} = 2.23, P=.03) and individual VAS questions (t_{47} = 2.49, P=.02; t_{47} = 1.97, P=.05; and t_{47} = 2.37, P=.02, for "drug high," "stoned," and "drug strength," respectively) and produced a trend toward reduced tachycardia (t_{49} = 1.79, P=.08) and M scale scores (t_{47} = 1.97, P=.06) (Figure 1). The percent reductions (95% CI) in peak marijuana effect produced by 90-mg SR141716 (**Figure 2**) were heart rate, 59% (range, –7% to 153%); composite VAS, 41% (range, 4%-85%); drug high, 43% (range, 8%-87%); stoned on marijuana, 38% (range, –1% to 86%); drug strength, 43% (range, 6%-88%); and M scale, 75% (range, –2% to 209%). Percent reductions of peak marijuana effects at lower doses of SR141716 were not statistically significant. Polynomial trend tests indicated a significant linear trend for SR141716 dose on heart rate ($F_{1,49}$=4.03, P=.05), composite VAS ($F_{1,47}$=5.59, P=.02), and M scale ($F_{1,47}$=6.22, P=.02). The only nonlinear term to achieve statistical significance was a quadratic term for the M scale ($F_{1,47}$=6.60, P=.01).

PHARMACOKINETIC MEASURES

There was no significant difference in mean peak plasma THC concentration between subjects receiving placebo SR141716 (139 ng/mL, 95% CI, 121-157) and those receiving 90-mg SR141716 (130 ng/mL, 95% CI, 113-147). There was also no significant difference in the THC area under the curve (0-1.8 hours after smoking) between the placebo SR141716 (43.6 ng·h/mL, 95% CI, 38.2-49.0) and 90-mg SR141716 (36.2 ng·h/mL, 95% CI, 30.5-41.9) treatment groups.

COMMENT

These findings of significant blockade of smoked marijuana effects after pretreatment with the selective CB1 receptor antagonist SR141716 suggest that in humans, many of the acute psychological and physiological effects of marijuana are mediated, at least in part, by

Characteristics of Participants According to Treatment Group*

Characteristic	Group 1 (n = 10)	Group 2† (n = 10)	Group 3 (n = 10)	Group 4 (n = 8)	Group 5 (n = 7)	Group 6 (n = 6)	Group 7 (n = 6)	Group 8 (n = 6)
Age, y	26.4 (2.6)	28.8 (7.7)	28.8 (5.2)	29.3 (5.1)	27.9 (4.6)	27.3 (7.6)	28.7 (6.3)	23.8 (2.5)
Race, %								
White	30	20	30	38	43	33	0	33
Black	70	80	70	62	57	67	83	67
Hispanic	0	0	0	0	0	0	17	0
BMI, kg/m^2	22.9 (2.9)	24.8 (4.4)	25.4 (4.3)	26.4 (3.9)	24.7 (3.3)	24.2 (3.0)	25.9 (3.2)	26.1 (3.0)
Marijuana use								
Lifetime, y	9.3 (4.6)	12.2 (6.4)	13.4 (6.8)	10.5 (6.9)	9.3 (3.3)	9.5 (7.5)	7.7 (6.9)	8.3 (4.0)
Past month, d	16.6 (10.7)	18.0 (8.3)	16.1 (10.4)	4.6 (5.9)	16.3 (11.0)	13.3 (10.3)	12.5 (9.3)	25.0 (6.6)

*Data are given as mean (SD) unless otherwise indicated. Group 1 indicates placebo SR141716 (SR)/placebo marijuana; group 2, active SR/placebo marijuana; group 3, placebo SR/active marijuana (2.64% THC); group 4, 1 mg SR/active marijuana; group 5, 3 mg SR/active marijuana; group 6, 10 mg SR/active marijuana; group 7, 30 mg SR/active marijuana and group 8, 90 mg SR/active marijuana. Groups differed only with respect to past month marijuana use (P = .02).

†Group consisted of n = 2 at each active dose of SR141716 (1, 3, 10, 30, and 90 mg).

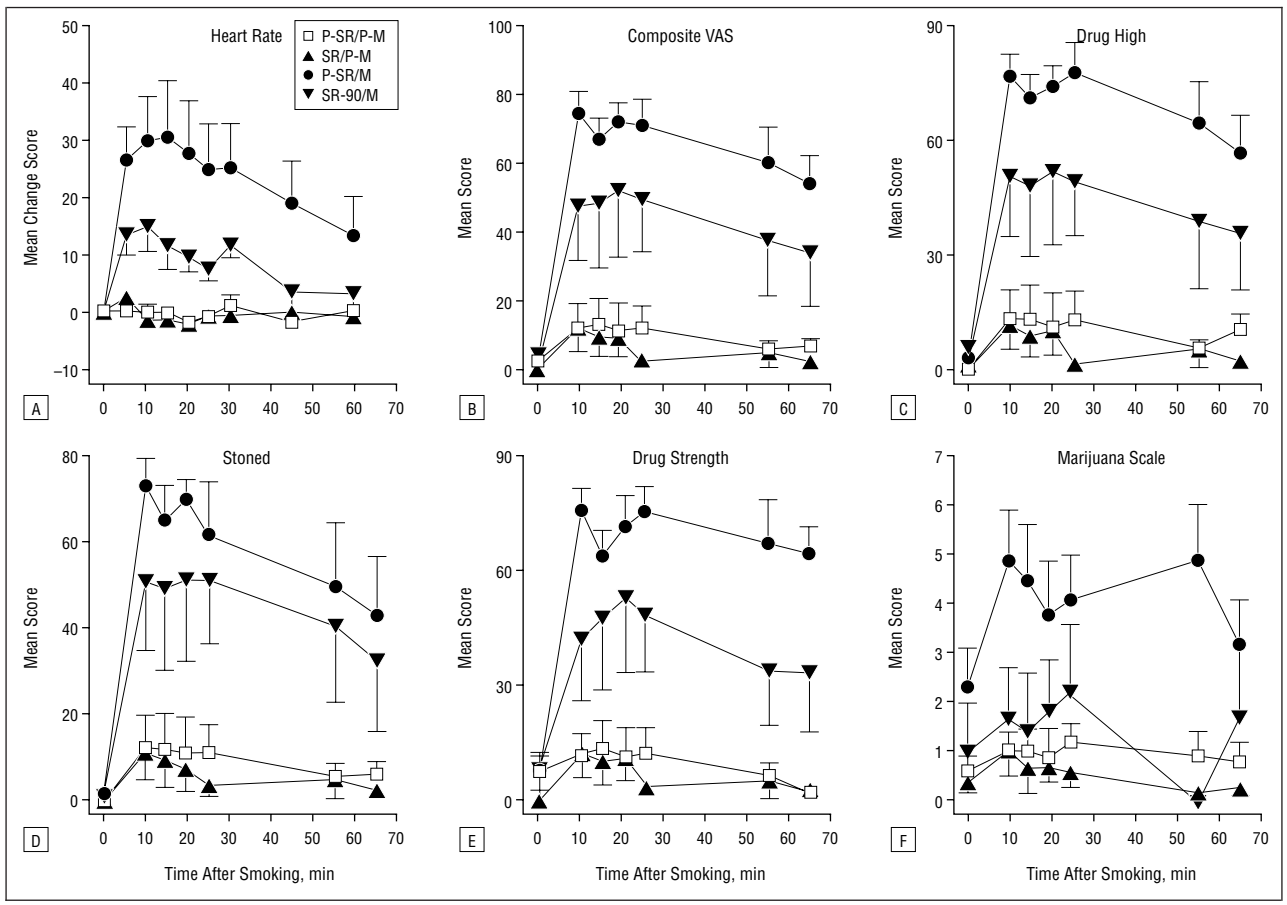

Figure 1. *Time course of SR141716 blockade of marijuana's effects for the following treatment groups: placebo SR141716/placebo marijuana (P-SR/P-M, n=10), active SR141716/placebo marijuana (SR/P-M, n=10), placebo SR141716/active marijuana (P-SR/M, n=10), and 90-mg SR141716/active marijuana (SR-90/M, n=6). Data are responses (mean±SE) during the 60 minutes (heart rate) or 65 minutes (psychological measures) after smoking. VAS indicates visual analog scale.*

interaction with CB1 receptors. In particular, the antagonism of psychological effects of acute marijuana intoxication is consistent with animal studies showing that SR141716 blocks the discriminative stimulus effects of THC in rats, monkeys, and pigeons,[17-20] suggesting that agonist activity at CB1 receptors plays an important role in human marijuana abuse. A pharmacokinetic explanation for these findings (ie, an SR-induced decrease in achieved concentration of THC) seems unlikely because there were no significant differences in peak THC concentration or THC area under the curve between subjects receiving active or placebo SR141716.

Group differences in recent marijuana use (Table) were also unlikely to have influenced these results. Regardless of marijuana use in the past month, no sub-

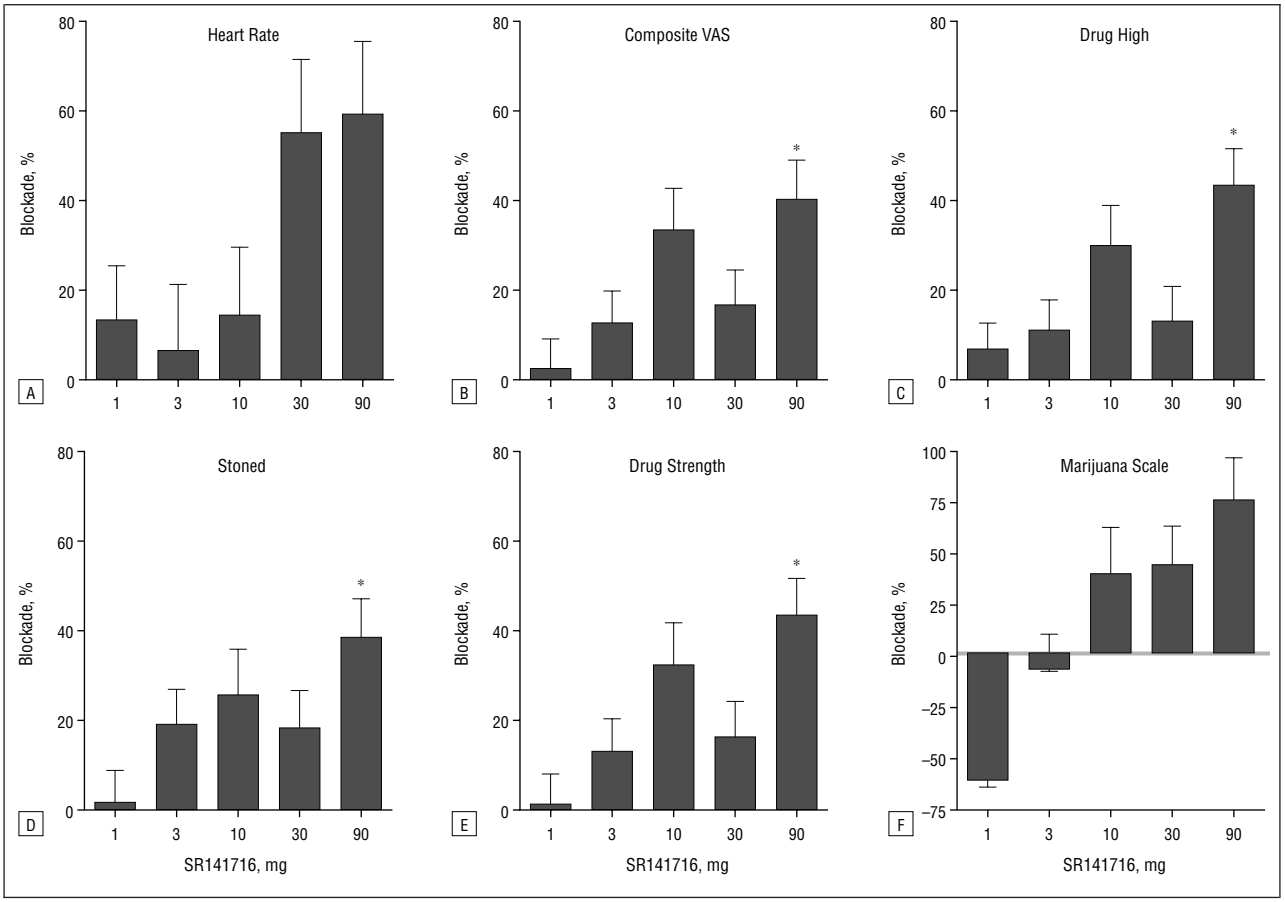

Figure 2. *Percent blockade (mean±SE) of peak marijuana effects produced by single oral doses of 1 mg (n=8), 3 mg (n=7), 10 mg (n=6), 30 mg (n=6), and 90 mg (n=6) SR141716. VAS indicates visual analog scale; asterisk, percent blockade of marijuana effects by 90-mg SR141716 compared with placebo SR141716 (P≤.05).*

ject was administered SR141716 until substantially all marijuana had been eliminated from the body. Subjects spent a mean±SD of 6.4±5.1 days on the closed NIDA research unit prior to dosing. This monitored drug-free interval did not vary significantly among the treatment groups ($F_{7,55}$=0.57, P=.77). Significant tolerance to cardiovascular (eg, tachycardia) and psychological effects of smoked marijuana or oral THC has been reported in human experimental studies involving repeated administration lasting from days to weeks.[21-25] This tolerance dissipates within 2 to 7 days of abstinence for tachycardia[21-23] and 4 to 7 days for psychological effects.[21-25] Thus, differences among treatment groups in persisting tolerance to marijuana effects were unlikely to account for the observed blockade in marijuana effects after administration of SR141716.

In THC-naive rodents, SR141716 sometimes produced behavioral effects including stimulation of locomotor activity, increased wakefulness, improved memory, hyperalgesia, suppression of sucrose and alcohol ingestion, and defensive behavior.[26-31] Most of these actions are opposite to those expected from a CB1 receptor agonist or from marijuana. It is not clear to what extent these SR141716 effects are due to blockade of endogenous cannabinoid "tone" or to potential inverse agonist action of SR141716. Recent studies with human CB1 receptors expressed in isolated cell cultures suggest that SR141716 can act as an inverse agonist at the G-protein level.[32-34] There was no evidence for an inverse agonist effect of SR141716 in humans in this study because SR141716 alone produced no significant effect on any measure. Thus, the observed blockade of acute marijuana effects probably was not due to opposing SR141716 effects partially masking the pure agonist effects of marijuana.

The mechanism of marijuana-induced tachycardia in humans remains unclear, in part because there is no good animal model (the acute effect of marijuana in animals is bradycardia).[35] Limited human data suggest that the tachycardia may be related to increased sympathetic and decreased parasympathetic autonomic activity.[35,36] Regardless of whether these actions are centrally or peripherally mediated, the finding of this study that a CB1 receptor antagonist partially blocked marijuana-induced tachycardia suggests that CB1 receptors play an important role in the cardiovascular effects of marijuana.

This study has several limitations. Subjects received a single dose of SR141716, achieving only 40% to 75% reductions in acute marijuana effects at the highest dose (90 mg). Thus, the maximum possible blockade of marijuana effects by CB1 receptor antagonism remains unknown, leaving uncertain the degree to which mechanisms other than CB1 action (such as CB2 receptor agonism) might mediate the acute effects of mari-

juana in humans. Future studies with higher single doses or multiple doses of SR141716 (whose long half-life would lead to accumulation of the drug) could better define maximal blockade of CB1 receptors by the antagonist. To avoid possible precipitation of acute marijuana withdrawal, SR141716 was not administered until subjects' urine cannabinoid concentrations were below 20 ng/mL. Administration of SR141716 closer to the time of last marijuana use, with higher blood (and brain) cannabinoid concentrations, might produce different results. Finally, all subjects were healthy men aged 21 to 45 years. The generalizability of these findings to a more representative, heterogeneous population of both sexes, varying ages, and with medical and psychiatric comorbidities remains unknown.

The findings of this study have significant implications for understanding the neurobiology of the endogenous cannabinoid system in humans and its potential role in the pathophysiology and treatment of a variety of clinical disorders. High densities of CB1 receptors in the human cortex, hippocampus, anterior cingulate, basal ganglia, and cerebellum suggest a role for the endogenous cannabinoid system in attention, cognition, and motor control.[37-39] Animal studies have shown that CB1 receptor agonists impaired learning and memory[31,40] and increased appetite and food intake,[41] whereas CB1 receptor antagonists enhanced learning and memory[31,40] and reduced food intake.[26] Cannabinoid systems may play a role in psychotic disorders,[42] as suggested by the recent finding of increased anandamide concentrations in the cerebrospinal fluid of schizophrenic patients.[43] The results of the present study support the importance of these roles by demonstrating, for the first time in humans, blockade of well-characterized physiological and psychological effects of smoked marijuana by the selective CB1 receptor antagonist SR141716. Further research into the role of CB1 receptors and the pharmacology of marijuana may lead to improved treatment for disorders related to dysfunction of the endogenous cannabinoid system and to the development of novel therapeutic agents.

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