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# Cannabinoid receptor antagonist SR141716A decreases operant ethanol self administration in rats exposed to ethanol-vapor chambers[1]

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**KEY WORDS** ethanol; self administration; cannabinoid receptors; SR141716A

## ABSTRACT

**AIM**: To study the potential role of dependence status on $CB_1$-mediated blockade of ethanol self-administration. **METHODS**: We examined the effects of the cannabinoid antagonist SR141716A (0, 0.03, 0.3, and 3 mg/kg) on operant ethanol (10 % v/v) self-administration in male Wistar rats that were made ethanol-dependent by chronic (14 d) exposure to ethanol vapor-chambers or exposed to air in identical vapor chambers. **RESULTS**: Dependent animals responded more for ethanol than did air control nondependent rats. The acute administration of a 3 mg/kg dose of SR141716A almost suppressed ethanol self-administration only in ethanol dependent animals. However, operant responses for food were not affected by the administration of SR141716A. **CONCLUSION**: These results further support that cannabinoid $CB_1$ receptor blockade may have a potential utility for the treatment of alcoholism.

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## INTRODUCTION

Converging lines of evidence suggest that cannabinoid $CB_1$ receptors not only mediate the reinforcing properties of the psychoactive constituents of marijuana[1], but also modulate several neural circuits involved in reinforcement, including those using the neurotransmitters dopamine, GABA, opioid peptides, and corticotropin-releasing factor. Thus, cannabinoid $CB_1$ receptor activation 1) increases the activity of dopaminergic cells of the ventral tegmental area, resulting in enhanced dopamine release in the nucleus accumbens[1-3]; 2) blocks neuronal GABA uptake in the basal ganglia[4,5]; 3) modulates the synthesis of endogenous opioid transmitters in the caudate-putamen and the paraventricular nucleus of the hypothalamus[6-8]; and 4) affects the release of corticotropin releasing factor in the hypothalamus and the central amygdala[9,10]. The role of the endogenous cannabinoid system in reward induced by abused drugs is further supported by human genetics studies in which a particular homozygosity for the 5 ≥ alleles of a microsatellite polymorphism of $CB_1$ receptor gene was found to be associated with specific types of drug dependence[11] and with significant alterations in the P300 event-related potential[12], similar to those found in alcoholics and sons of alcoholics[13]. These neurobiological features support a role of the endogenous cannabinoid system in reward processing and open a new field for the development of potential therapeutic strategies for the treatment of addiction.

Among the different drugs of abuse, ethanol has been considered for a cannabinoid receptor-based therapy. In fact, ethanol and cannabis constitute one

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of the most frequently found associations of drugs in human addicts[1] and the neurobiological substrates of alcohol and cannabinoid dependence exhibits marked similarities. As an example, chronic exposure to both classes of drugs resulted in the same neuroadaptions in both mesencephalic dopaminergic cells projecting to the nucleus accumbens[14-16] and amygdalar corticotropin-releasing factor neurons[10,17]. The recent development of a selective cannabinoid $CB_1$ receptor antagonist[18] has allowed the examination of the effects of $CB_1$ receptor blockade in animal models of alcohol intake. These studies have shown that $CB_1$ cannabinoid receptor blockade reduces ethanol intake in mice and in both normal and ethanol preferring sP rats[19-21]. Supporting these findings, $CB_1$ cannabinoid receptor stimulation was found to increase motivation for the intake of ethanol in rats[22,23]. However, there are no studies addressing the contribution of the ethanol-dependence status to the $CB_1$ cannabinoid receptor blockade-induced suppression of ethanol intake. This is a very important issue, since it is well established that ethanol self-administration is maintained in both humans and animals not only for its euphorigenic effects, but also to avoid or reverse negative withdrawal symptomatology[24-26].

In the present study we examined the effects of the induction of alcohol dependence on the effectiveness of the cannabinoid receptor antagonist SR141716A [*N*-piperidino-5-(4-chorophenyl)-1-(2, 4-dichlorophenyl)-4-methylpyrazole-3-carboxamide] on suppression of ethanol self-administration.

## MATERIALS AND METHODS

**Animals** Male Wistar rats from Charles River laboratories (Hollister, California, USA), weighing 250 g upon arrival, and (600 ± 72) g at the end of testing, were used for ethanol self-administration and food reinforcement studies. The rats were housed 2 per cage with food and water available *ad lib* (except for limited access to either food or water as required). Lights were on a 12/12 h light/dark cycle with lights on at 6:00 am. All procedures met the guidelines of the National Institutes of Health (USA) detailed in the Guide for the Care and Use of Laboratory Animals.

**Drugs** SR141716A [*N*-piperidino-5-(4-chorophenyl)-1-(2, 4-dichlorophenyl)-4-methyl-pyrazole-3-carboxamide] was obtained through SANOFI Research, Montpellier, France. It was freshly prepared on each experimental day in a vehicle solution (5 % Tween 80, 5 % propylenglycol, 90 % saline 0.9 %, v/v), and injected ip 60 min before testing ethanol self-administration or food reinforcement.

**Ethanol self-administration** Rats were trained to lever press for ethanol using a variation of the sweetened solution fading procedure developed by Samson *et al*[27]. For the first three days of training, rats were restricted to 2 h of wates per day and were placed in the operant chambers for 30 min wherein responses on the one extended level resulted in delivery of a 2 % saccharin solution. Water was again made freely available, and animals were tested another 4 d with responses on a single lever resulting in 5 % ethanol/0.2 % saccharin solution. The active lever was alternated between left and right throughout! this initial training phase to minimize positional biases. For the rest of the training, as well as during testing, both levers were extended during the sessions, with one of the levers producing ethanol/saccharin solution and the other producing water. The position of the ethanol/saccharin water drinking cups remained constant; however, the levers that produce these solutions were alternated between left and right on consecutive days. Over the next 15 days, ethanol concentrations were gradually raised from 5 % to 10 %, and the saccharin was gradually eliminated from the solution. Rats were allowed to respond for the final solution of 10 % ethanol (with no saccharin) for 2 wk until stable responding was achieved.

The animals were then divided into 2 groups and exposed to either ethanol vapor or air for 2 wk prior to the retesting in the operant boxes, using previously described methods[26]. Concentrations of the ethanol vapor were adjusted in order to achieve target blood alcohol levels of 150 – 200 mg per 100 mL plasma. These rats were then used in a study examining the effects of intra-amygdala muscimol (GABA-A receptor agonist) administration on operant responding during ethanol withdrawal (See details in reference [26]). All rats received 3 central injections of muscimol and 2 saline, each separated by four days of additional vapor (ethanol or air) exposure. Following this experiment, the rats continued to receive daily 30-min sessions in the operant boxes where 10 % ethanol and water were

made available. The animals were kept on this schedule during three weeks prior to investigation of cannabinoid receptor antagonist effects. To this end, each rat received SR141716A 0, 0.03, 0.3, or 3 mg/kg in a Latin-square design with tests separated by four days. The days before and after, drugs probes were used for baseline and recovery tests, respectively. Data were analyzed separately for air- and ethanol vapor-exposed animals, using two-way within-subjects analysis of variance with the factors testing session (baseline, SR141716A injection, recovery) and SR141716A dose. Subsequent individual mean comparisons were conducted with the Newman-Keuls *a posteriori* test.

**Food reinforcement** A separate group of rats were trained to lever press for food (45 mg food pellet; Bio-Serve, Frenchtown, New Jersey, USA) on a fixed-ratio 1 (FR1) schedule of reinforcement and food restricted to 20 g chow/rat per day. Once stable responding was achieved, animals were trained to acquire a FR5, time-out 2 min, schedule of food reinforcement. They were kept on food restriction for the rest of the experiment (20 g chow/day, plus the food earned during the operant session). When a stable baseline was achieved, they were used for studying the effects of acute administration of SR141716A. To this end, the animals received ip injections of either vehicle or the $CB_1$ receptor antagonist (0, 0.03, 0.3, 3 mg/kg) in a Latin-square design fashion, either 60 min or 5 min before the test session. Baseline sessions were interposed between testing sessions for assessing carryover effects.

## RESULTS

Animals exposed to either air (Fig 1) or ethanol (Fig 2) chambers exhibited a preference for ethanol over water, suggesting that ethanol was established as a reinforcer before vapor exposure. However, animals with a history of ethanol dependence (those exposed to ethanol vapor chambers) responded more than air-exposed ones. The acute administration of SR141716A 3 mg/kg decreased operant responses for ethanol (Fig 2A) in animals with a history of ethanol dependence [$F_{(3,15)} = 7.3$, $P < 0.01$] but not in air-exposed (Fig 1A) nondependent animals [$F_{(3,12)} = 0.05$, $P = 0.98$]. There were no carryover effects, since the animals resumed ethanol self-administration normally on the day after testing with SR141716A. Recovery values for the ethanol-dependent animals were ($\bar{x} \pm s$): 1) vehicle: 29.5 ± 17.9; 2) SR141716A (0.03 mg/kg): 28.7 ± 16.6; 3) SR141716A (0.3 mg/kg): 36.6 ± 11.8; 4) SR141716A (3 mg/kg): 38.8 ± 22.7. Operant responses for water were not affected by SR141716A in both nondependent [$F_{(3,12)} = 0.28$, $P = 0.83$] and ethanol dependent rats [$F_{(3,15)} = 0.84$, $P = 0.49$] (Fig 1B, 2B). Lastly, the acute administration of the cannabinoid antagonist did not affect operant responses for food, neither when injected 60 min prior to the testing session (Tab 1), nor when it was delivered 5 min before the session (Data not shown).

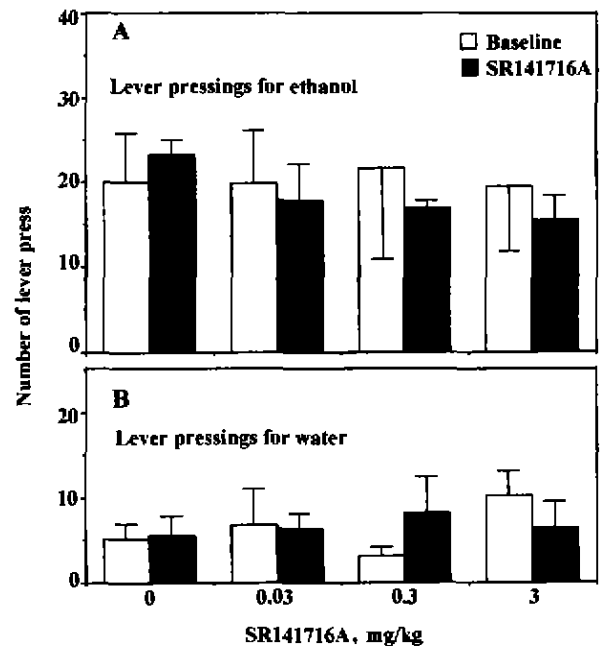


**Fig 1. Effects of the $CB_1$ receptor antagonist SR141716A (0, 0.03, 0.3 and 3 mg/kg) on operant responding for 10 % ethanol solution (A) or water (B), in a free-choice, continuous reinforcement (FR1) schedule by air-exposed nondependent rats. SR141716A was administered 60 min prior to the onset of the testing session. $\bar{x} \pm s$.**

## DISCUSSION

The present study confirms previous observations of the effectiveness of cannabinoid $CB_1$ receptor blockade in decreasing ethanol preference and/or self-

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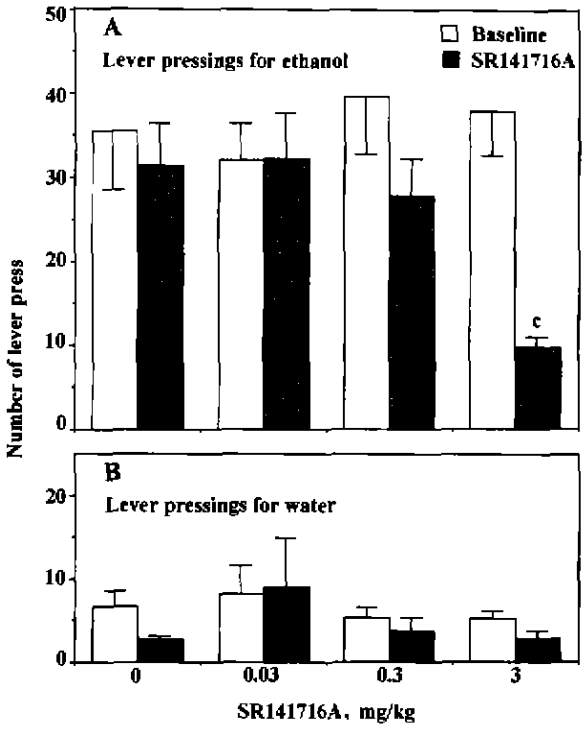


**Fig 2. Effects of the $CB_1$ receptor antagonist SR141716A (0, 0.03, 0.3, and 3 mg/kg) on operant responding for 10 % ethanol solution (A) or water (B), in a free-choice, continuous reinforcement (FR1) schedule by ethanol vapor-exposed rats. SR141716A was administered 60 min prior to the onset of the testing session. $\bar{x} \pm s$. $^cP < 0.01$ *vs* Baseline.**

**Tab 1. Lack of effects of acute ip injection of the cannabinoid $CB_1$ receptor antagonist SR141716A on operant responding for food (60-min sessions, fixed ratio = 5, time-out = 2 min). SR141716A was administered 60 min prior to the onset of the test. Data are expressed as the number of reinforcers delivered to at least 9 animals per group. $\bar{x} \pm s$.**

| | Vehicle | SR141716A (mg/kg) | | |
|---|---|---|---|---|
| | | 0.03 | 0.3 | 3 |
| Baseline | 29.1±1.6 | 29.9±0.3 | 29.7±0.6 | 29.4±0.8 |
| SR141716A | 29.6±0.6 | 29.9±0.3 | 29.7±0.6 | 29.4±0.6 |

administration[19-22]. The animals made ethanol-dependent by chronic exposure to alcohol vapor exhibited a great number of operant responses for ethanol and a marked sensitivity to the administration of the cannabinoid antagonist. The lack of effect of SR141716A on operant responses for ethanol in air-exposed non-dependent animals may be related both to the lower daily ethanol intake displayed by these animals, low enough to keep the endogenous cannabinoid system unaltered, and to the administration of uneffective doses of the antagonist. A previous study[20] has also shown that SR141716A is more effective in supressing the intake of a 4.5 % ethanol solution than in altering operant responses for a 0.5 % ethanol beverage. Since the studies already published found the effective doses of SR141716A to be on the range of 1 - 3 mg/kg[10, 19-22], we believe that the low ethanol intake is responsible for the absence of clear effects of the antagonists in motivated responses for ethanol in air-exposed animals. Indeed, SR141716A administration did not disrupt the reinforcing value of food (Tab 1), a finding described also in former studies[19]. Additionally, recent reports have established that chronic ethanol exposure induced profound changes in the synthesis of the endogenous cannabinoid ligand precursor, *N*-arachidonoyl-phosphatidylethanolamine, which is enhanced by ethanol[28]. A potential hyperactive state of the endogenous cannabinoid system may induce a desensitization of cannabinoid $CB_1$ receptors, a recent finding in animals exposed chronically to ethanol[29,30]. Since many $CB_1$ receptors seem to be located in GABA neurons in the brain[31], where they at least modulate GABA uptake[4,5], one hypothesis would be a dysregulation in GABA transmission, which is considered as an important component of alcohol dependence[26,32]. The dynamic adaptive changes in cannabinoid transmission associated with ethanol dependence could be abruptly reversed by the administration of the cannabinoid receptor antagonist which also displays inverse agonist properties[1,10]. As a result, operant responses for ethanol would be decreased in our experimental model. Further research is necessary to confirm this hypothesis. Additional mechanisms may include dopamine and opioid neurotransmission, upon which cannabinoid $CB_1$ receptors seems to play a modulatory role. A recent report[33] has confirmed that the endogenous cannabinoid transmission can be activated by dopamine $D_2$ receptors, in an attempt to "brake" ongoing dopamine signaling. Whether or not $CB_1$ activation

may decrease or potentiate ongoing reward signals remains a matter of controversy. However, we recently observed that SR141716A was able to decrease heroin self-administration with a similar potency to that observed in the present experiment supporting, as stated in the introduction, the existence of a role for cannabinoid receptors in the regulation of the reward circuits commonly activated by abused drugs[34].

Lastly, the profile of the cannabinoid antagonist in suppressing ethanol self-administration resembles that of opioid antagonists such as naltrexone. Not only do both drugs decrease ethanol intake in animal models[15,19-25] but they also reduce sucrose consumption in experimental animals[19,35], suggesting a common role for opioids and anandamide in the regulation of caloric intake. Moreover, both drugs are capable of inducing a withdrawal syndrome in either opiate-dependent or cannabinoid-dependent animals[8,10], suggesting the existence of convergent neuroadaptive mechanisms in both transmission systems as a result of continuous drug exposure. Indeed, recent studies have located opioid and cannabinoid receptors in the same neurons of reward-relevant limbic structures[8].

Alcoholism is a prevalent psychiatric disorder, appearing in 7 % - 8 % of the population in United States. It has a very poor prognosis, with total abstinence being an often elusive therapeutic goal. Although recently introduced pharmacotherapies (acamprosate and naltrexone) have shown promise in the treatment of alcoholism relapse, we still need new and more effective therapeutic alternatives[24,25]. In this regard, the blockade of the endogenous cannabinoid system in ethanol dependent subjects, as described in the present study, may contribute to reduce not only ethanol intake but also alcohol craving, expanding the possibilities of reaching the goal of effectively treating alcoholics.

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**大麻酚类受体拮抗剂 SR141716A 减少乙醇蒸气室中大鼠的自发反应性乙醇自身给药行为**

R971.2

**关键词** 乙醇; 自身给药; 大麻酚类受体; SR141716A

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