The CB1 cannabinoid receptor antagonist rimonabant chronically prevents the nicotine-induced relapse to alcohol

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Preclinical and clinical research shows that the cannabinoid brain receptor type 1 (CB1) modulates alcohol- and nicotine-related behaviors. Throughout the nicotine-induced relapse to alcohol, the rats were pre-treated for 10 days with the CB1 cannabinoid receptor antagonist rimonabant (0, 0.03, 0.3 and 3.0 mg/kg i.p.). In this condition, a long-lasting nicotine-induced relapse to alcohol was observed, and this effect was reversed in a dose-dependent manner with rimonabant. Surprisingly, rats that were not exposed to nicotine developed tolerance to the effects of rimonabant from the sixth day. Also, 3.0 mg/kg of rimonabant reduced the responses for sucrose. Evaluation in the Elevated Plus-Maze after nicotine treatment did not reveal anxiogenic effects. Finally, at the conclusion of rimonabant treatment, a rapid reinstatement of alcohol consumption was detected. These results suggest that rimonabant can prevent the relapse to alcohol, even when an interaction with nicotine exists—the most frequent situation in human alcohol abuse.© 2006 Elsevier Inc. All rights reserved.

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Introduction

In the last 9 years, numerous studies have been published that demonstrate the interaction between the cannabinoid system and alcohol. Neurochemical research has revealed that chronic alcohol treatment elicits the release of endogenous cannabinoid brain receptor type 1 (CB1) agonists, causing a down-regulation of this receptor and its signal transduction (Basavarajappa and Hungund, 2002; Hungund and Basavarajappa, 2004). In addition, lower cannabinoid function is related to greater vulnerability to alcohol consumption (Ortiz et al., 2004), and to the existence of cannabinoid-altered gene expression after intermittent exposure to alcohol (Rimondini et al., 2002).

Some research has focused on the CB1 receptors and the consumption, motivation and preference for alcohol. Generally, these studies can be classified either by the use of:

1. Cannabinoid receptor agonists: treatment with the CB1 cannabinoid receptor agonists WIN 55,212 and CP-55,940 has been shown to increase alcohol consumption in Wistar and Sardinian alcohol-preferring (sP) rats (Gallate et al., 1999; Colombo et al., 2002, 2005; Lopez-Moreno et al., 2004a).

2. Cannabinoid receptor antagonists: treatment with the CB1 cannabinoid receptor antagonist rimonabant (SR 141716 or ACOMPLIA™) has been demonstrated to reduce operant alcohol self-administration and alcohol intake (Rodriguez de Fonseca et al., 1999; Freedland et al., 2001; Cippitelli et al., 2005; Economidou et al., 2006); to reduce motivation to consume alcohol (Gallate et al., 2004); to block the alcohol deprivation effect (ADE) (Serra et al., 2002); to prevent the acquisition of drinking behavior (Serra et al., 2001); and to suppress extinction of the response for alcohol in sP rats (Colombo et al., 2004). Furthermore, the new selective antagonist of the CB1 cannabinoid receptor, SR147778, is able to reduce alcohol consumption and the motivational properties of alcohol (Rinaldi-Carmona et al., 2004; Gessa et al., 2005).

3. Mice lacking the CB1 receptor: these mice show less preference for alcohol and higher concentrations of ethanol in blood (Lallemand and de Witte, 2004); reduced ethanol-induced Conditioned Place Preference (Houchi et al., 2005; Thanos et al., 2005); decreased alcohol self-administration and increased alcohol sensitivity (Naassila et al., 2004; Thanos et al., 2005); and a lack of alcohol-induced dopamine release in the nucleus accumbens (Hungund et al., 2003).

Moreover, it seems that the CB1 receptor is also implicated in nicotine addiction. For a review, see Fagerstrom and Balfour (2006). For instance, rimonabant causes decreased operant self-administration of nicotine in rats and reverses nicotine seeking after withdrawal (Cohen et al., 2002, 2005). In addition, mice...
lacking the CB$_1$ receptor do not show nicotine-induced Conditioned Place Preference (Castane et al., 2002). As of 2004, rimonabant was in phase III clinical trials (Annual report from Sanofi-Aventis).

Despite all this evidence, the role of rimonabant in the interaction between alcohol self-administration and nicotine has not yet been studied. This is probably due, in part, to the complex interaction between alcohol and nicotine (Larsson and Engel, 2004). Several authors have shown that nicotine can either increase or decrease alcohol intake (Nadal and Samson, 1999; Ericson et al., 2000; Sharpe and Samson, 2002; Lê et al., 2003). However, we have demonstrated previously that when nicotine is administered during the stage of alcohol deprivation, there is a long-term dose-dependent increase in the relapse to alcohol, with the highest effect at the dose of 0.8 mg/kg of nicotine (Lopez-Moreno et al., 2004b). Furthermore, other studies noted that this dose induced an increase in alcohol self-administration in rats (Lê et al., 2003). In the present study, a protocol of Elevated Plus-Maze (EPM) was carried out in order to evaluate a possible role of anxiety produced by nicotine. Finally, three additional groups responding for a natural reinforcer (sucrose) were added in order to evaluate whether the reduction of the response for alcohol with rimonabant treatment was exclusively for alcohol and could be extended to a non-drug reinforcer (sucrose).

Materials and methods

Animals

Adult male Wistar rats (Harlan, Barcelona, Spain) weighing 200–225 g at the start of the experiments were housed two per cage in a room with a controlled reversed light/dark photoperiod (lights on at 20:00) and controlled temperature/humidity environment (23±1°C). Food and water were available ad libitum in the home cage. All experiments were conducted under dim red light, between 9:00 and 21:00. All procedures described in the present study were in accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health.

Drugs

(−)-Nicotine ([−]-1-methyl-2[3-pyridyl]pyrrolidine), minimum 99% (GC), liquid (Sigma Chemical Co., Madrid, Spain); 0.8 mg/kg was dissolved in sterile physiological saline and administered subcutaneously (s.c.) between the shoulder blades in a volume of 1 ml/kg. Nicotine was prepared daily before injection and adjusted to a pH of 7–7.2 with dilute NaOH. Alcohol solution was prepared daily as a 10% alcohol w/v. Rimonabant, [N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide], was a kind gift from Sanofi-Aventis (Paris, France). Doses of 0, 0.03, 0.3 and 3.0 mg/kg were first mixed with 0.1% Tween 80, and then physiological saline was slowly added. Rimonabant was administered intraperitoneally (i.p.) in a volume of 1 ml/kg.

General protocol used—drug during alcohol deprivation

Previous research in our laboratory has shown that exposure to drugs (i.e. nicotine and WIN 55,212-2) in the stage of alcohol deprivation is a useful method for evaluating long-lasting drug-induced changes (Lopez-Moreno et al., 2004a,b). Here, we have used this model as depicted in Fig. 1. Briefly, the animals received intermittent (Monday to Friday) and limited (30-min sessions) access to alcohol/sucrose per week. The experiments started once baseline had been reached following at least a 6-week period of access to alcohol (10% w/v) or sucrose (0.25%). The exposure to rimonabant was made 30 min before alcohol access.

Once this experiment was completed, two extra groups were added; these groups were used to assess the anxiogenic/anxiolytic effects of nicotine by means of the EPM test, 24 h after the last injection of nicotine.

Training procedure for operant alcohol/sucrose self-administration

Training was achieved using a modification of the method described by Samson et al. (1999) that is described extensively in Lopez-Moreno et al. (2004a). In brief, rats were placed on a water...
restriction schedule for 2–4 days to facilitate training of lever pressing. During the first 3 days of training, the animals received 10% sucrose solution in the dipper. Thereafter, the following sequence on a fixed ratio 1 schedule was used: 10% sucrose for four sessions, 10% sucrose and 2% ethanol (EtOH) for two sessions, 8% sucrose and 4% EtOH for two sessions, 6% sucrose and 6% EtOH for four sessions, 4% sucrose and 8% EtOH for four sessions, 2% sucrose and 10% EtOH for four sessions, and 10% EtOH for 10–20 sessions. The chambers were equipped with two retractable levers located on either side of a drinking reservoir (0.1 ml) positioned in the center of the front panel of the chamber. The levers were counterbalanced to respond as either the active or inactive lever. Once animals had acquired stable responses to EtOH, the inactive lever was presented. A similar procedure was used in the response for sucrose. Initially the animals had access to a 10% sucrose solution and the sucrose level was reduced progressively similar to the EtOH schedule (but without EtOH) until a 0.25% sucrose solution was reached. This concentration was chosen because the animal response was similar to the alcohol solution.

Elevated Plus-Maze

The EPM apparatus consisted of four arms (50 cm long × 10 cm wide). The two enclosed arms had 40 cm-high dark walls, whereas the two open arms had 0.5 cm high ledges. Lighting on the center of the open arms was 50 lx. The maze was elevated to a height of 50 cm. Rats were placed individually onto the center of the apparatus and faced toward an open arm. The 5-min experimental sessions were recorded by video camera and viewed by a trained experimenter who was blind to the group assignment.

Data analysis

Data from weekly operant responses were analyzed by one way ANOVA (rimonabant treatment), whereas daily operant responses were performed by two-way repeated-measures ANOVA: number of days (within-subjects factor) and different rimonabant treatment (between-groups factor). Data from the EPM were compared by the t-test for unpaired variables (nicotine/saline treatment). Only significant effects (p values < 0.05) in ANOVA analysis were subjected to Tukey’s honestly significant difference test (between-groups factor), and the post hoc analysis for repeated measures subprogram of the SPSS statistical (Chicago, IL) software package (version 13.0) for Windows.

Results

Rimonabant avoids the long-lasting nicotine-induced relapse to alcohol

Figs. 2A and B show that the nicotine-induced relapse to alcohol was suppressed in a dose-dependent manner by rimonabant (SR) (ANOVA Week-3: F4,49 = 3.22, p < 0.05; ANOVA Week-4: F4,49 = 4.39, p < 0.01; ANOVA Week-5, rimonabant withdrawal, F4,49 = 0.48, NS). The highest dose of rimonabant (3.0 mg/kg) fully reversed the increase in the nicotine-induced response for alcohol, as well as the alcohol intake in animals that were not treated with nicotine; (Tukey post hoc analysis p < 0.05 and p < 0.01). This last finding is consistent with previous studies (i.e. Rodriguez de Fonseca et al., 1999; Colombo et al., 2005). In contrast, the
exposure to nicotine induced long-lasting relapse to alcohol when compared with the group that was not exposed to nicotine (p<0.05). However, after rimonabant withdrawal, a significant rebound increase in alcohol consumption was observed (panel C). Interestingly, this rebound also occurred with a mild dose of rimonabant (0.3 mg/kg).

The reversion of nicotine-induced relapse to alcohol after rimonabant treatment did not show tolerance throughout the 10 days (see Fig. 3). Also, Fig. 3 highlights the time course of alcohol response during the two consecutive cycles of alcohol deprivation. As can be seen, the first day after alcohol abstinence alone there was the characteristic ADE in all groups when compared with the baseline (t-paired test; p<0.01). This pattern is strongly supported in the scientific literature (Vengeliene et al., 2005). However, the exposure to nicotine during the abstinence from alcohol noticeably changed this pattern of relapse for the next 2 weeks. The group with the highest response for alcohol was the Nic-Veh group, and the response was even higher than the group Saline-Veh, that was exposed neither to nicotine nor to rimonabant (Week-3: ANOVA between treatments $F_{4,45} = 3.22$, p<0.05; interaction between days and treatment $F_{16,180} = 1.47$, p=0.12 NS; within days $F_{4,180} = 1.11$, p=0.35 NS/Week-4: ANOVA between treatments $F_{4,45} = 4.39$, p<0.01; interaction between days and treatment $F_{16,180} = 1.16$, p=0.20 NS; within days $F_{4,180} = 1.15$, p=0.29 NS). There were no significant differences among any of the groups for the inactive lever (data not shown).

Alternatively, Fig. 4 shows the cumulative alcohol reinforcers obtained by the animals in three representative points: the last day of baseline, and the first and second Monday after nicotine exposure. It can be observed that two cycles of alcohol deprivation lead to a similar increase in the number of alcohol reinforcers obtained (Fig. 4A). However, the nicotine-induced relapse to alcohol showed a slight increase in alcohol intake over time (Fig. 4B). In contrast, the groups treated with rimonabant showed a dose-dependent decrease in the number of alcohol reinforcers, and the slope of the cumulative alcohol intake changed nearly to a plane line (Figs. 4C–E). Generally, the number of cumulative reinforcers reached 50–60% in the first 5 min, 75–85% at 10 min and 92–94% at 20 min.

**Development of tolerance to the relapse-preventing effects of rimonabant in animals not exposed to nicotine**

The two groups shown in Fig. 5 were added to evaluate whether or not the relapse-preventing effects of rimonabant on animals that had not been exposed to nicotine were specific. These animals were deprived of alcohol for 7 days and both groups were treated only with saline. The highest dose of rimonabant (3.0 mg/kg) was chosen because it was the only one that totally reversed the nicotine-induced relapse to alcohol. Intriguingly, the results showed that the chronic ability of rimonabant to prevent the relapse to alcohol seems to be specific for animals exposed to nicotine. Chronic rimonabant pre-treatment prevented relapse to alcohol only the first 5 days when compared with the vehicle-group (panel A) (t-independent test p<0.001). Despite the presence of rimonabant pre-treatment, the next 5 days were followed by the reinstatement of the response for alcohol and there were significant differences when compared with the previous alcohol response (panel B) (t-independent test p<0.001) that reached similar levels of alcohol consumption to that of the control-group. Non-significant differences were found after rimonabant withdrawal (panel C). The two-way ANOVA analysis for the data shown in the Fig. 5D revealed statistically significant differences during the first five days (ANOVA between treatments $F_{1,14} = 59.51$, p<0.0001;
interaction between days and treatment $F_{4,56}=1.65$, $p=0.17$ NS; within days $F_{4,56}=6.08$, $p<0.001$), whereas the next days did not show any significant differences, excepting the 8 day pre-treatment with rimonabant, where a transient increase in response for alcohol was observed ($p<0.05$). As can be seen in Fig. 5, there was no rebound in alcohol consumption after rimonabant withdrawal, contrary to animals that were exposed to nicotine.

Fig. 4. Cumulative alcohol reinforcers obtained by the animals during the 30 min session in three representative days: the last baseline day, the first and second Monday after nicotine treatment. Only saline and vehicle groups showed significant differences when compared with the last baseline day (A, B) (note the different response patterns), in contrast with the groups treated with rimonabant (C–E) (Tukey post hoc analysis; *$p<0.05$). Each point represents the cumulative reinforcers obtained in 5-min intervals (note that SEMs are not present in order to clarify the figure).

Ninocine had no effect on the relapse to sucrose, but rimonabant decreased the response for sucrose

On the one hand, we found that after a period of abstinence from nicotine, the relapse to sucrose was not modified for a solution of 0.25%. On the other hand, we observed that rimonabant decreased the response for sucrose at 0.25% w/v concentration. Panels a and b of Fig. 6 show that the dose of 3.0 mg/kg of rimonabant significantly reduced the sucrose intake ($p<0.01$). This dose of rimonabant was used because it had proven previously that this dose produced the greatest reduction in the nicotine-induced response for alcohol. Similarly, the same as the response for alcohol, there were no significant differences for the inactive lever (data not shown), and there was a rebound increase in sucrose consumption after rimonabant withdrawal (panel C) ($t$-paired test; $p<0.01$).

Nicotine had no effect on the anxiety-like behavior in the Elevated Plus-Maze 24 h later

Twenty-four hours after the last nicotine injection, no significant differences in anxiety-like behavior were found (Fig. 7) (percent open arm, $t$-test; $p<0.43$, NS/percent open in the center, $t$-test; $p<0.75$, NS/number of entries to the closed arms, $t$-test; $p<0.73$ NS).

Body weight changes during operant alcohol/sucrose self-administration

Fig. 8 shows the day-by-day time course of body weight during two relapses after two forced deprivations: with or without nicotine. During the nicotine-induced relapse to alcohol, the animals were pre-treated with rimonabant. Here, the data are presented as mean±SEM (ANOVA within days: $F_{24,1176}=60.16$, $p<0.0001$; interaction between days and treatments: $F_{96,1176}=2.99$, $p<0.0001$; between treatments: $F_{4,49}=4.29$, $p=0.005$). The animal’s weight (mean 384±3.95) from the week of baseline was used as 100% weight. Only significant differences between the sucrose group and all alcohol groups are represented (*$p<0.05$; **$p<0.01$). Those receiving the highest dose of rimonabant (3 mg/kg) showed a more significant reduction in body weight as compared with the sucrose group from the second day with rimonabant treatment ($##p<0.01$), but there were no differences between alcohol groups. However, this slight difference in body weight with the highest dose of rimonabant disappeared after rimonabant withdrawal.

Discussion

The main findings of this study are as follows: (1) Rimonabant pre-treatment at 3.0 mg/kg totally abolished the relapse to alcohol during the first 5 days in the animals that were not exposed to nicotine during the phase of alcohol deprivation. (2) Exposure to nicotine during the stage of alcohol deprivation produced a long-term increase in the relapse to alcohol; however, this effect was reversed in a dose-dependent manner when the rats were chronically pre-treated with the cannabinoid receptor antagonist rimonabant before the alcohol trial. The nicotine-induced relapse to alcohol seems to be specific to alcohol because nicotine treatment did not increase the intake of a natural reward (sucrose). (3) The animals showed a rebound increase in alcohol consumption when chronic treatment with 0.3 and 3.0 mg/kg rimonabant was
removed. (4) The group of rats that was not exposed to nicotine developed tolerance to the reducing effect of rimonabant in alcohol responses from the sixth day. (5) The anti-motivational effects of 3.0 mg/kg of rimonabant seemed to be not specific for alcohol, since there was also a significantly reduced response for 0.25% sucrose. (6) Nicotine treatment had no anxiogenic effects 24 h after the last nicotine injection in the EPM.

The finding that rimonabant is a molecule that is able to modulate the relapse to alcohol and alcohol-related behaviors is not new (Gallate and McGregor, 1999; Rodriguez de Fonseca et al., 2005; Colombo et al., 2005; Cippitelli et al., 2005; Economidou et al., 2006). However, here we report the first evidence that rimonabant is able to suppress the relapse to alcohol when an interaction with nicotine exists, which is by far the most common situation with a prevalence of 91.5% (Johnson, 2004). Nicotine acts on the nicotinic acetylcholine receptors (nAChRs), and usually activation of these receptors leads to an increase in the presynaptic release of neurotransmitters (e.g. GABA, glutamate, acetylcholine and dopamine) (Role and Berg, 1996). On the other hand, alcohol interacts with several neurotransmitter systems, including the GABA, glutamate and dopamine systems, as well as others (Larsson and Engel, 2004). Successive relapses to alcohol cause an imbalance between the two main excitatory and inhibitory neurotransmitters: GABA and glutamate (De Witte, 2004). The interactions between alcohol and nicotine occur in the mesolimbic/mesocortical reward system, as well as other regions (Dani and Harris, 2005). Therefore, in this study, the proposed final common molecular pathway for the reinforcing effects of the abused drugs (Nestler, 2005; Pierce and Kumaresan, 2005) could be compromised in some way.

Thus, the greater increase in the response for alcohol after nicotine treatment compared with the increase in alcohol intake after two consecutive relapses could suggest a specific phenomenon of cross-tolerance or/cross-sensitization to the effects of alcohol, because sucrose responding was not altered. Importantly, this increase would be usually masked when two drugs are administered at approximately the same time (either left-shifting the dose–response curve for alcohol or decreasing the total alcohol intake). In addition, we have avoided any conditioned nicotine responses (i.e. nicotine-sensitization related to an environment),

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**Fig. 5.** Effects of chronic administration of rimonabant (SR) (3.0 mg/kg) during the relapse to alcohol after saline treatment in the phase of alcohol deprivation. Panel A shows the prevention of alcohol relapse during the relapse to alcohol and the near abolition of alcohol response, as compared with the control group (***p<0.001). However, during the following week (B), these animals showed the development of tolerance to the relapse-preventing effects of rimonabant as compared with the previous week (###p<0.001). After withdrawal of rimonabant treatment (C), no significant changes were observed. Panel D depicts the day-by-day time course of the response for alcohol corresponding to the weeks depicted above (A–C) (***p<0.001; *p<0.05).
because it was administered in a context that was different from the alcohol operating boxes, and was not contingent on alcohol access.

We are aware that nicotine-induced relapse to alcohol could be mediated by other factors, such as stress or a nicotine abstinence syndrome. For this reason, trials were carried out in the EPM, a paradigm widely used to evaluate anxioselective effects of drugs, as well as withdrawal (Carobrez and Bertoglio, 2005). A recent study has demonstrated that repeated alcohol abstinences prevent withdrawal-induced elevations of corticosterone and withdrawal-induced anxiety evaluated in the EPM (Borlikova et al., 2006). Despite previous studies showing the anxiogenic effects of 0.8 mg/kg of nicotine in mice (Balerio et al., 2005, 2006) evaluated with...
the EPM, anxiogenic effects were not found here. This could be due to the fact that the test trial was 24 h after the last injection of nicotine (in order to investigate “post-effects” of nicotine in a similar way to what would occur in the operant alcohol boxes, instead of acute nicotine effects). Therefore, if the rats had access to alcohol 72 h after the last injection of nicotine (Monday), and in a very familiar context (the operating boxes), it would be less likely that stress or the nicotine withdrawal syndrome was the key element to explain the greater relapse to alcohol following nicotine exposure. Interestingly, through internal data (and published results, Lopez-Moreno et al., 2004b), we have observed that the nicotine-induced aversion in the Conditioned Place Preference paradigm after acute treatment (0.8 mg/kg) may be dissociated from posterior anxiogenic effects in the EPM. However, it has been demonstrated that the effect of rimonabant could be modulated by the time following nicotine exposure. Le Foll and Goldberg (2004) have shown that rimonabant blocked the nicotine-induced Conditioned Place Preference while administered immediately after the conditioning phase, but not after prolonged nicotine withdrawal (Forget et al., 2005). These evidences, together with our results, strongly suggest complex interactions between nicotinic-acetylcholine and CB1 receptors.

CB1 receptors are widely distributed throughout the brain (including the mesocorticolimbic system) and they are the most abundant G protein-coupled receptors (Pagotto et al., 2006). The cannabinoid system modulates neurotransmitter release via pre-synaptic cannabinoid receptors (Schlicker and Kathmann, 2001). Contrary to the main role of the nACHRs (the increase in neurotransmitter release), the activation of the CB1 receptor inhibits the neurotransmitter release (GABA, glutamate, dopamine, noradrenaline, serotonin, among others.) Logically, this wide range of effects decreases the potential for elucidating the particular mechanism of rimonabant in the prevention of the nicotine-induced relapse to alcohol. There are several studies that describe the reduction of alcohol consumption after rimonabant treatment (Gallate and McGregor, 1999; Rodriguez de Fonseca et al., 1999; Colombo et al., 2005; Cippitelli et al., 2005). However, it seems that this effect is not specific for alcohol, as supported here. Moreover, it reduced the response for natural reinforcers, such as 0.25% and 5% sucrose, chocolate, food and NaCl in sodium-depleted rats (Duarte et al., 2004; De Vries et al., 2005; Economidou et al., 2006; Gessa et al., 2006), as well as other drugs of abuse: nicotine, cocaine and heroin (Le Foll and Goldberg, 2005; De Vries and Schoffelmeier, 2005). Therefore, in a more general way, the blockade of the cannabinoid system may be affecting motivated behaviors. This raises the question: could the blockade of the cannabinoid system be a general approach to the treatment of addiction? If so, this would be useful in the case of drug abuse: (1) when several drugs are co-abused, as is the most frequent situation in addiction (the aim of this work), or (2) using a sub-threshold dose of rimonabant in combination with other sub-threshold doses of Acamprosate, Disulfiram or Naltrexone, the current treatments for alcoholism approved by the U.S. Food and Drug Administration (Williams, 2005). In fact, it has been demonstrated that low doses of either naltrexone or naloxone (which did not have effects on alcohol intake per se), in combination with a sub-threshold dose of rimonabant significantly decreased alcohol consumption (Gallate et al., 2004; Colombo et al., 2005).

These two points would have important clinical implications in the psychopharmacology of alcoholism. On the one hand, rimonabant could be used in the comorbid treatment of alcohol and nicotine dependence (as well as other drugs of abuse), and on the other hand, its use in combination with other medications could lead to a reduction in the doses for the treatment of alcohol dependence, and in consequence, a reduction in side effects. According to previous studies, we have data (not shown) that the highest dose of rimonabant used (3.0 mg/kg) neither caused motor impairment nor reward/aversive effects evaluated in the Conditioned Place Preference paradigm (Singh et al., 2004; Forget et al., 2005). Furthermore, the rimonabant-mediated prevention of the relapse to alcohol was persistent throughout the 10 days and did not show any effect of tolerance or sensitization. This lack of tolerance/sensitization was only observed in the animals that were exposed to nicotine during the alcohol deprivation period. Intriguingly, this is in contrast with results when the animals were not exposed to nicotine; following 5 days of administration of rimonabant, tolerance to the protective effect in alcohol relapse was developed. Furthermore, a similar pattern has been demonstrated, but with food reward: the tolerance to the anorectic effects of rimonabant was developed after 5 days (Colombo et al., 1998).

A rebound increase in alcohol consumption was found with 0.3 and 3.0 mg/kg of rimonabant. It would be possible to misunderstand the ability of low doses to inhibit the greater nicotine-induced responding for alcohol; i.e. the dose of 0.3 mg/kg did not suppress alcohol intake, but was effective in reducing the extra alcohol consumption induced by nicotine. Interestingly, this reducing effect is evidenced after rimonabant withdrawal, when alcohol response rebounds significantly.

In conclusion, the regulation of the endocannabinoid system could be an important therapeutic target for alcoholism, even when an interaction with nicotine exists, the most frequent situation (Hughes, 1995; Johnson, 2004). However, it seems that supplementary strategies would be needed to avoid the reinstatement of alcohol consumption after the withdrawal of rimonabant treatment.

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