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Involvement of the sigma$_1$ receptor in the motivational effects of ethanol in mice

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Abstract

In the present study, we examined the involvement of the sigma$_1$ (σ_1) receptor in several behavioral manifestations of ethanol addiction. Administration of ethanol (0.5, 1, and 2 g/kg) in Swiss mice dose-dependently induced locomotor stimulation, conditioned place preference, and conditioned taste aversion, which are considered as behavioral index of drug-induced reward. Pretreatment with the selective σ_1 receptor antagonist *N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(dimethylamino)ethylamine (BD1047, 3–30 mg/kg) dose-dependently blocked ethanol (1 g/kg)-induced hyperlocomotion and taste aversion and ethanol (2 g/kg)-induced place preference. Pretreatment with the selective σ_1 receptor agonist 2-(4-morpholino)ethyl 1-phenylcyclohexane-1-carboxylate (PRE-084, 1–10 mg/kg) before ethanol (0.5 g/kg) failed to affect the resulting locomotor stimulation, but dose-dependently enhanced the conditioned place preference. Each σ_1 receptor ligand was devoid of behavioral effect by itself. These observations show that activation of the σ_1 receptor is a necessary component of ethanol-induced motivational effects and suggest a new pharmacological target for alleviating ethanol addiction.

Keywords: Ethanol; Sigma$_1$ (σ_1) receptor; Hyperlocomotion; Conditioned place preference; Reward; Conditioned taste aversion; Mouse

1. Introduction

Activation and plasticity of the mesolimbic dopaminergic system contribute, as a common neurobiological process, to the acquisition and expression of the rewarding effects of drugs of abuse (Di Chiara, 1998). This has been extensively detailed for dopaminergic abused drugs, including amphetamine or cocaine (Kuhar, 1992; Koob, 1996). It is also true for opiate drugs like morphine, cannabinoids, and ethanol. Although several neurotransmitter systems contribute to ethanol reward and dependence, dopaminergic pathways are prominent substrates for the neuroadaptations involved (Tabakoff and Hoffman, 1996; Koob et al., 1998). Indeed, systemic administration or oral self-administration of ethanol stimulated dopamine release preferentially in the nucleus accumbens and bed nucleus of stria terminalis of rats (Di Chiara and Imperato, 1988; Weiss et al., 1993; Carboni et al., 2000). Moreover, ethanol reward or self-administration could be modulated using dopamine receptor agonists or antagonists (Samson et al., 1993a,b; Boyce and Risinger, 2000). In addition, dopamine D2 receptor knock-out mice failed to develop ethanol-induced conditioned place preference, confirming that dopamine D2 receptors are involved in ethanol reward (Cunningham et al., 2000). Therefore, pharmacological strategies may consist in treatments with drugs acting directly on dopaminergic receptors, which include D1-like receptors, namely D1 and D5, and D2-like receptors, namely D2, D3, and D4 (Civelli et al., 1993). Both D1- and D2-like receptors are present in reward-related brain structures, including the olfactory bulb, ventral tegmental area, nucleus accumbens, amygdala, frontal cortex, septum, and bed nucleus of stria terminalis (Koob, 1992; Civelli et al., 1993; Carboni et al., 2000). In turn, effective direct strategies may use dopaminergic antagonists showing a very high selectivity in vivo, and this has been still difficult to achieve. Alternate strategies could also be proposed through effective neuromodulatory systems. In particular, the sigma$_1$ (σ_1) receptor may represent such putative target.

The σ_1 receptor, localized intracellularly within neurons, is a 223-amino acid protein, cloned in several animal species and humans (Hanner et al., 1996; Kekuda et al., 1996; Seth et al., 1997, 1998; Pan et al., 1998). The σ_1 receptor appeared

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devoid of analogy with any other known mammalian protein. Its regional distribution, determined in rodents using in situ hybridization or immunohistochemistry (Zamanillo et al., 2000; Kitaichi et al., 2000; Alonso et al., 2000), showed moderate to intense staining in most of the dopaminergic structures, including the caudate–putamen, nucleus accumbens, amygdala, septum, and frontal cortex (Alonso et al., 2000; Maurice et al., 2002). The σ_1 receptor mediates a potent modulation of several neurotransmitter systems by affecting intracellular second messengers systems, particularly Ca^{2+} mobilization (Hayashi et al., 2000; Hayashi and Su, 2001). Noteworthy, σ_1 ligands efficiently modulate the dopaminergic neurotransmission and several studies reported the effect of σ_1 ligands on dopamine synthesis, metabolism, and release or electric activity of dopaminergic neurons (for review, see Maurice et al., 2002).

The σ_1 receptor has recently been demonstrated to be involved in cocaine's rewarding effects (Romieu et al., 2000, 2002). The σ_1 receptor is involved in the acquisition or expression of cocaine-induced conditioned place preference in mice, as demonstrated using selective σ_1 receptor antagonists or antisense oligodeoxynucleotide probes. We also observed that a repeated 4-day cocaine treatment increased the expression of the σ_1 receptor mRNA in the nucleus accumbens, suggesting that the drug is able to induce overexpression of σ_1 gene and that neuroadaptations involving the σ_1 receptor occurred in mesolimbic structures involved in addiction (Romieu et al., 2002).

In the present study, we characterized the involvement of the σ_1 receptor in the motivational effects of ethanol in Swiss mice. We used different behavioral procedures including locomotor activity measures, conditioned place preference, and taste aversion. Place conditioning is frequently used to index the rewarding properties of abused drugs (Carr et al., 1989; Tzschentke, 1998; Romieu et al., 2000, 2002). Conditioned taste aversion is produced by most of abused drugs. It has been proposed to be related with the sensitivity to drug reward (Hunt and Amit, 1987). Animals were thus treated with ethanol and/or the selective σ_1 receptor antagonist *N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(dimethylamino)ethylamine (BD1047) (Matsumoto et al., 1995) or the selective σ_1 receptor agonist 2-(4-morpholino)ethyl 1-phenylcyclohexane-1-carboxylate (PRE-084) (Su et al., 1991). We investigated here whether treatment with selective σ_1 antagonist or agonist affect the ethanol-induced effects on all behavioral measures in order to examine whether the σ_1 receptor activation is involved in acquisition of the motivational effects and reward induced by ethanol.

2. Methods

2.1. Subjects

Male Swiss OF1 mice (Breeding Center of the Faculty of Pharmacy, Montpellier, France), aged 5–6 weeks and weighing 30 ± 2 g, were used. Animals were housed in plastic cages in groups. They had free access to laboratory food and water, except during behavioral experiments, and they were kept in a regulated environment (23 ± 1 °C, 40–60% humidity) under a 12-h light–dark cycle (light on at 7:00 a.m.). Animals submitted to taste conditioning had their access to fluids restricted as described herein. Experiments were carried out between 9:00 a.m. and 5:00 p.m. in a sound-attenuated and air-regulated experimental room to which mice were habituated at least 30 min before each experiment. All animal procedures were conducted in strict adherence with the European Community Council Directive of 24 November 1986 (86-609/EEC).

2.2. Drugs

Ethanol (Carlo Erba, Rodano, Italy) was diluted in saline solution to the final concentrations (200 and 400 g/l corresponding to the 1- and 2-g/kg doses, respectively) by taking into account the density (0.79). BD1047 was given by Dr. Wayne D. Bowen (NIDDK, NIH, Bethesda, MD, USA) and PRE-084 by Dr. Tsung-Ping Su (IRP, NIDA, NIH, Baltimore, MD, USA). BD1047 and PRE-084 were diluted in saline solution. Injections were performed through the intraperitoneal route in a volume of 100 μl/20 g body weight.

2.3. Locomotor activity

Mice were placed in a Plexiglas cage (25 × 40 × 15 cm high) for 40 min, between $t = 0$ and $t = 40$ min. The σ_1 receptor ligand, BD1047 or PRE-084, was injected at $t = 30$ and ethanol or saline was injected at $t = 40$ min. Animals were again placed in the cage for 40 min, between $t = 40$ and $t = 80$ min. The locomotion was recorded using infrared light sources and detectors positioned opposite to each other at 1-in. intervals on the walls of the monitoring system (Opto-Varimex, Columbus Instruments, Columbus, OH, USA). Locomotion was measured in terms of infrared light beams interrupted over 10-min periods, between $t = 40$ and $t = 80$ min (time-course profiles), and summed over 30 min, between $t = 50$ and $t = 80$ min (global activity scores).

2.4. Conditioned place preference

The apparatus consisted of a PVC box divided into two compartments of equal size (15 × 15 × 35 cm high) separated by sliding doors. The first compartment had black walls and floor, the second one had white walls and floor. Each compartment presented different floor textures, smooth for the black one and covered by a wire mesh grid for the white. A 60-W lamp lit the white compartment during all experiments.

The procedure consisted of three different phases (Romieu et al., 2000, 2002): preconditioning (Day 1), conditioning (Days 2–5), and postconditioning (Day 6). For the preconditioning phase, each mouse was placed in the white

compartment and after 5 s, the sliding doors were raised. The animal was allowed to freely explore the apparatus for 10 min. The preconditioning phase was repeated after 6 h. The exploration was videotaped and the amount of time spent in each compartment was determined in order to assess the unconditioned preference. Animals showing a strong unconditioned preference (>570 s), i.e., less than 5%, were discarded. Place preference conditioning was conducted using an unbiased procedure. In each experimental group, half of the animals received ethanol in the spontaneously preferred compartment and the other half in the nonpreferred compartment. Immediately after the drug injection, each mouse was confined to the drug-paired compartment for 15 min. In coadministration experiments, mice received the σ_1 receptor ligand 10 min before ethanol. After a 6-h washout period, they were administered the vehicle solutions and confined to the other compartment for 15 min. The postconditioning test was performed the last day. Each mouse was again placed in the white compartment and after 5 s, the doors were raised. The animal was allowed to freely explore the apparatus for 10 min. The exploration was videotaped and the amount of time spent in each compartment was determined. The conditioned score represented the difference of time spent in the drug-paired compartment between the post- and preconditioning sessions.

2.5. Conditioned taste aversion

The taste conditioning test was conducted in home cages, animals being housed by groups of five per cage ($n = 10$ cages per treatment group). Fluids were presented at room temperature in 50-ml graduated glass cylinders fitted with stainless-steel drinking spouts inserted through the grid of the cage. Consumption was measured over 1-h periods by weighing the drinking tubes and was corrected for evaporation and spillage by subtracting the mean fluid loss measured in three drinking tubes placed onto an empty cage for an equal amount of time. Subjects were adapted to a water restriction regimen over a 7-day period, with 2-h of water per day from 9:00 to 11:00 a.m. At 48-h intervals over the next 10 days, mice had access to a 0.2-M NaCl solution between 9:00 and 10:00 a.m. (Risinger and Cunningham, 1992; Risinger et al., 1999, 2001). For the first four trials, immediately after access to the NaCl solution, each mouse was administered intraperitoneally with BD1047 (0, 3, 10, or 30 mg/kg) and ethanol (0 or 1 g/kg). Animals also received 30-min access to tap water 5 h after each NaCl access period, to prevent dehydration. On the final trial, animals were given access to the NaCl solution without further injection. On intervening days, mice had a 2-h access to water (9:00–11:00 a.m.). Experimental data represented the mean NaCl solution intake per cage.

2.6. Statistical analyses

All measures (locomotor activity counts, conditioned scores, or NaCl solution intakes) were expressed as mean ± S.E.M. and analyzed using the Newman–Keuls or Dunnett tests for multiple comparisons after parametric one- or two-way analyses of variance (ANOVA, F values). The criterion for statistical significance was $P < .05$.

3. Results

3.1. Locomotor activity

Intraperitoneal injections of ethanol induced in Swiss mice a dose-dependent stimulation of locomotor activity, as measured using infrared beam interruptions. Locomotion was measured every 10 min after injections for 40 min and global activity was determined as the total activity during the last 30 min. Vehicle-treated animals showed a global activity in the 741- to 755-count range ($n = 12–13$, Figs. 1A and 2A) and activity decreased regularly with time [ANOVA: $F(3,47) = 6.63$, $P < .01$, and test for linear trend: $F = 19.28$, $P < .0001$, open circles, Fig. 1B; ANOVA: $F(3,51) = 5.66$, $P < .01$, and test for linear trend: $F = 16.47$, $P < .001$, open circles, Fig. 2B]. The ethanol treatment increased this score to 1289 ± 89 ($n = 14$, $P < .05$ vs. vehicle-treated group, Fig. 1A) at the dose of 0.5 g/kg and 1794 ± 89 ($n = 12$, $P < .01$ vs. vehicle-treated group, Fig. 2A) at the dose of 1 g/kg. This increase corresponded to a similar augmentation of the activity over the 40 min of measure and activity decreased regularly with time [ANOVA: $F(3,55) = 32.96$, $P < .0001$, and test for linear trend: $F = 7.05$, $P < .0001$, closed circles, Fig. 2B].

The effect of the selective σ_1 receptor agonist PRE-084 was first examined, in the 1- to 10-mg/kg dose range, on the locomotor increase induced by 0.5 g/kg ethanol. The drug failed to affect the locomotor response when administered alone (Fig. 1A). The hyperlocomotion was observed in all groups treated with ethanol [$F(7,103) = 2.54$, $P < .01$], and the PRE-084 pretreatment failed to induce any significant change (Fig. 1A,B). The effect of the selective σ_1 receptor antagonist BD1047 was then examined in the 3- to 30-mg/kg dose range on the locomotor increase induced by 1 g/kg ethanol. The drug failed to affect the locomotor response when administered alone (Fig. 2A). However, the hyperlocomotion observed in the ethanol-treated group was diminished in a dose-dependent manner by the BD1047 pretreatment [$F(7,95) = 5.44$, $P < .0001$]. In particular, at the highest dose tested, BD1047 allowed a complete blockade of the ethanol (1 g/kg)-induced locomotor increase, in terms of global activity (Fig. 2A) or time-course profile (Fig. 2B).

3.2. Conditioned place preference

Repeated administration of ethanol (0.5–2 g/kg) over 4 days in Swiss mice and confinement in the drug-paired compartment led to the development of a dose-dependent place preference. Indeed, a significantly positive conditioned score was measured [$F(3,76) = 3.63$, $P < .05$, Fig. 3A].

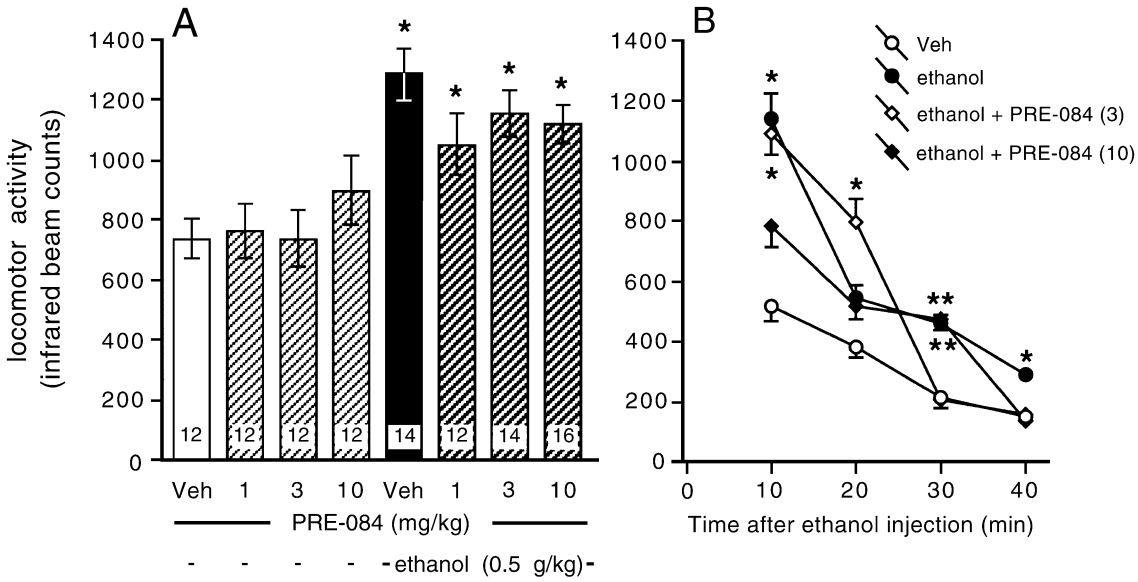

Fig. 1. Effect of the selective σ_1 receptor agonist PRE-084 on ethanol-induced locomotor hyperactivity: (A) total activity during the last 30 min of the session and (B) time-course. Each mouse was placed in the experimental cage for 40 min. PRE-084 (1, 3, and 10 mg/kg ip) or the vehicle solution (Veh) was injected 10 min before ethanol (0.5 g/kg ip). Locomotor activity was measured immediately after ethanol injection in terms of number of occlusions of infrared light beams every 10 min during 40 min. The number of animals per group is indicated within the columns in (A). $*P<.05$, $**P<.01$ vs. vehicle-treated group, Newman–Keuls' test.

Previous studies, using the same experimental procedure, showed that the selective σ_1 receptor ligands, PRE-084 and BD1047, failed to induce conditioned place preference when injected alone (Romieu et al., 2000, 2002). However, pre-administration of PRE-084 in the 1- to 3-mg/kg dose range dose-dependently facilitated the development of place preference after treatment with a low, subactive dose of 0.5 g/kg ethanol [$F(2,52)=3.74$, $P<.05$, Fig. 3B]. In particular, animals treated with 3 mg/kg PRE-084 and ethanol acquired place preference, the conditioned score being significantly higher than mice treated with ethanol acquired place preference, the conditioned score being significantly higher than mice treated with ethanol alone (Fig. 3B). Moreover, pre-administration of BD1047 in the 3- to 10-mg/kg dose range

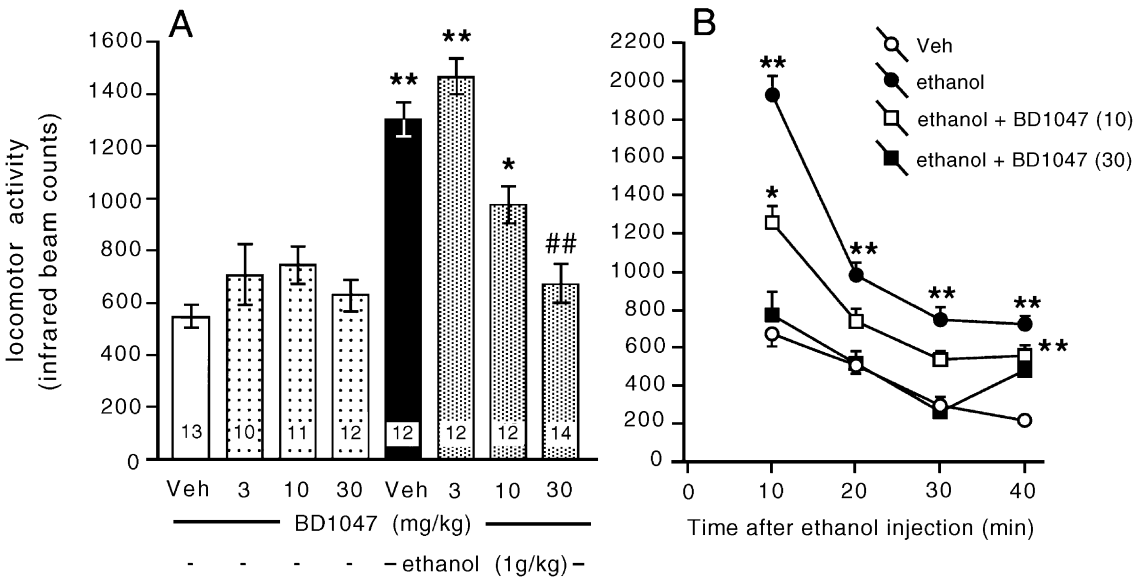

Fig. 2. Effect of the selective σ_1 receptor antagonist BD1047 on ethanol-induced locomotor hyperactivity: (A) total activity during the last 30 min of the session and (B) time-course. Each mouse was placed in the experimental cage for 40 min. BD1047 (3, 10, and 30 mg/kg ip) or the vehicle solution (Veh) was injected 10 min before ethanol (1 g/kg ip). Locomotor activity was measured immediately after ethanol injection in terms of number of occlusions of infrared light beams every 10 min during 40 min. The number of animals per group is indicated within the columns in (A). $*P<.05$, $**P<.01$ vs. the vehicle-treated group; $^{\#\#}P<.01$ vs. the ethanol-treated group, Newman–Keuls' test.

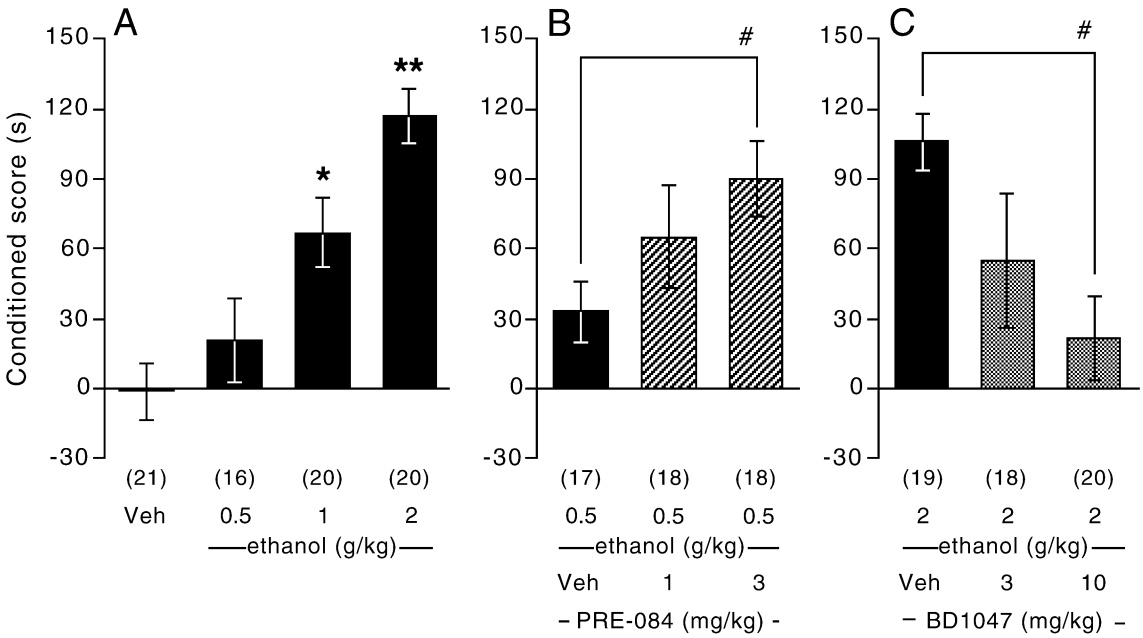

Fig. 3. Effect of selective σ_1 receptor ligands on acquisition of ethanol-induced conditioned place preference: (A) dose–response effect of ethanol, (B) pretreatment of the selective σ_1 receptor agonist PRE-084, and (C) pretreatment of the selective σ_1 receptor antagonist BD1047. The σ_1 receptor ligands were administered intraperitoneally 10 min before ethanol (0–2 g/kg ip), which was given immediately before placement in the compartment during the conditioning test. The conditioned score represents the difference in time spent in the drug-paired compartment between the post- and preconditioning sessions. The number of animals per group is indicated between parentheses. $^{*}P<.05$, $^{**}P<.01$ vs. the vehicle (Veh)-treated group, $^{\#}P<.05$ vs. the ethanol-treated group, Dunnett's test.

dose-dependently inhibited the acquisition of place preference induced by 2 g/kg ethanol [$F(2,55)=6.13$, $P<.01$, Fig. 3C]. Animals treated with 10 mg/kg BD1047 and ethanol failed to show any place preference (Fig. 3C). In other words, pretreatment with the σ_1 receptor agonist facilitated acquisition of ethanol-induced reward, while pretreatment with the σ_1 antagonist blocked ethanol-induced reward.

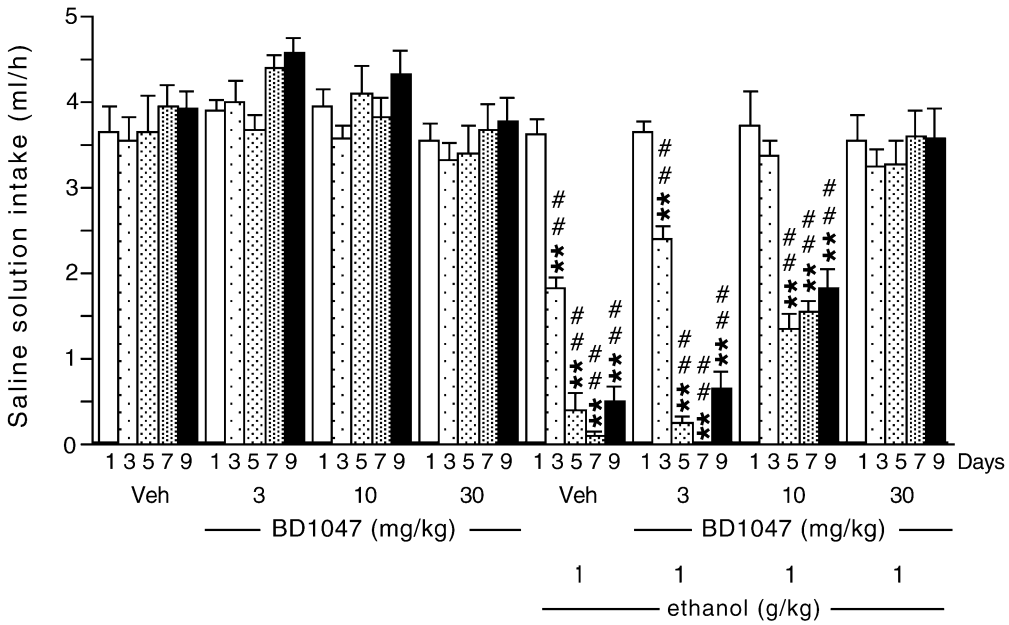

Fig. 4. Effect of the selective σ_1 receptor antagonist BD1047 on ethanol-induced conditioned taste aversion. Mean 0.2 M NaCl solution intake were measured during 1 h. On Days 1, 3, 5, 7, and 9, after the 1-h access to NaCl solution, groups received either saline solution (Veh) or BD1047(3 and 10 mg/kg ip) and/or ethanol (1 g/kg ip). Animals received 2-h access to tap water on intervening days. The number of animals per group was $n=10$. $^{*}P<.05$, $^{**}P<.01$ vs. the vehicle-treated group on the same day, $^{\#}P<.05$, $^{\#\#}P<.01$ vs. the same group on Day 1, Newman–Keuls' test.

3.3. Conditioned taste aversion

Ethanol (1 g/kg) injection gradually reduced NaCl solution intake on Days 3, 5, 7, and 9, indicating the development of conditioned taste aversion (Fig. 4). This reduction was not due to a decrease in liquid intake because a preliminary experiment showed that replacing NaCl solution by tap water resulted in a similar liquid intake by vehicle- or ethanol-treated animals (data not shown). The σ_1 receptor antagonist BD1047 failed to affect NaCl solution intake by itself. However, pretreatment with BD1047 dose-dependently blocked the ethanol-induced decrease in NaCl solution intake. Treatment × Day analysis showed significant effects for treatment [$F(7,360) = 119.79$, $P < .001$], day [$F(4,360) = 32.80$, $P < .001$], and Treatment × Day [$F(28,360) = 11.42$, $P < .001$]. As shown in Fig. 4, NaCl intake measured for the group treated with BD1047 (30 mg/kg) and ethanol were similar as those measured for the vehicle-treated group on all days.

4. Discussion

The present pharmacological study showed that selective σ_1 receptor ligands potently modulated the motivational effects of ethanol in the Swiss mouse. First, the σ_1 antagonist BD1047 dose-dependently attenuated ethanol-induced locomotor activity. Second, the σ_1 agonist PRE-084 facilitated, while BD1047 blocked, the acquisition of ethanol-induced conditioned place preference. Third, BD1047 blocked the acquisition of ethanol-induced conditioned taste aversion. The σ_1 receptor is a unique intraneuronal protein, mediating an effective and wide-range neuromodulatory action in the brain. In particular, a recent hypothesis suggests that it acts a sensor/modulator of intracellular Ca^{2+} mobilization and homeostasis on the endoplasmic reticulum membrane because activation of the receptor by agonists, including synthetic compounds, such as PRE-084 or cocaine, or endogenous steroids, such as dehydroepiandrosterone or pregnenolone sulfates, enhanced binding of inositol 1,4,5-triphosphate ($InsP_3$) to its receptor and Ca^{2+} mobilization from $InsP_3$ receptor-sensitive pools (Hayashi et al., 2000; Hayashi and Su, 2001; Su and Hayashi, 2001). Consequently, the σ_1 receptor activation has been implicated in several neuroadaptative changes, as observed in learning and memory, depression, schizophrenia, and reward and behavioral sensitization induced by cocaine or methamphetamine (Maurice et al., 1999, 2001, 2000). Indeed, cocaine- and methamphetamine-induced hyperlocomotor activity, stereotyped behaviors, and sensitization of these behavioral responses after repeated administration could be blocked by the selective σ_1 receptor antagonists α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazine butanol (BMY-14,802), rimcazole, 6-[6-(4-hydroxypiperidinyl)hexyloxy]-3-methylflavone (NPC 16377), BD1008, BD1047, or 1-[2-(3,4-dichloro-phenyl)ethyl]-4-methylpiperazine (BD1063) (Menkel et al., 1991; Witkin et al., 1993; Ujike et al., 1992, 1996; McCracken et al., 1999). More recently, activation of the σ_1 receptor was also demonstrated in the acquisition and expression of cocaine-induced conditioned place preference in C57BL/6 mice (Romieu et al., 2000, 2002). Activation of the σ_1 receptor may thus result from the activation of dopaminergic systems, particularly in mesolimbic structures, and may, conversely, mediate the modulation of dopaminergic tonus (for a review, see Maurice et al., 2002).

In mice, ethanol produces locomotor stimulation at doses in the 0.5 to 2 g/kg ip range (Risinger and Oakes, 1996). A positive correlation between ethanol-induced locomotor stimulation and ethanol-induced reward has been evoked through the euphorigenic effects of ethanol as part of the rewarding properties (Wise and Bozart, 1987; Phillips and Shen, 1996). The dopaminergic involvement in ethanol-induced locomotor stimulation was suggested by studies showing that the D2 dopamine receptor antagonist haloperidol blocked the response (Risinger et al., 1992). It must be outlined that haloperidol is also the most potent σ_1 receptor antagonist known to date, and the putative involvement of the σ_1 receptor blocked in such effect is unresolved. We observed here that BD1047 blocked the ethanol-induced hyperlocomotor activity, indicating that the σ_1 receptor is involved in this acute response to ethanol. Activation of the mesolimbic dopaminergic pathways, particularly within the nucleus accumbens has been evoked as responsible of this behavioral response, and σ_1 receptors are highly present within this structure (Maurice et al., 2002). In addition, we previously observed that a 4-day treatment of C57BL/6 mice with cocaine (20 mg/kg) resulted in an increased expression of the σ_1 receptor selectively in the nucleus accumbens (Romieu et al., 2002), suggesting that σ_1 receptors located within this key structure are particularly sensitive to psychostimulants.

Ethanol produces conditioned place preference (Cunningham et al., 1992, 2000; Risinger and Oakes, 1996), and this behavioral procedure is routinely considered as a reliable index of neurophysiological mechanisms involved in drug reward (Schechter and Calcagnetti, 1993). A crucial role for the σ_1 receptor activation was clearly observed here because the σ_1 agonist was able to potentiate acquisition of place preference while the σ_1 antagonist blocked it. The pharmacological systems sustaining ethanol-induced place preference are still under question. Serotogenic and GABAergic systems, rather than dopaminergic or opioid systems, have been involved in the acquisition of ethanol-induced place preference (Risinger et al., 2001). Pharmacological studies must be performed in order to determine whether an effect of σ_1 receptors present within mesolimbic dopaminergic neurons can be ruled out for acquisition of place preference by ethanol, contrarily to what has been evoked for cocaine (Romieu et al., 2000, 2002).

Conditioned taste aversion is a particularly interesting behavioral response because it reflects a highly integrated response observed in alcoholics. Pairing a distinctive flavor with exposure to ethanol leads to the development of a conditioned aversion for the flavor (Hunt and Amit, 1987;

Sherman et al., 1998). Pharmacological studies implicated dopaminergic systems in ethanol-induced conditioned taste aversion through mainly D2, but also D1 and D4 receptors (Risinger et al., 1999, 2001). In the present study, ethanol provoked conditioned taste aversion, which is observable after the ethanol administration as soon as the second day of measure. BD1047 blocked acquisition of ethanol-induced conditioned taste aversion, in line with previous observations. The present study thus showed a similar involvement of the σ_1 receptor in three different behavioral responses to ethanol. In particular, we did not observe a pharmacological dissociation between ethanol-stimulated activity and acquisition of conditioned place preference as evoked by Risinger et al. (2001). The wide-range neuromodulatory effect induced by σ_1 receptor ligands suggested that this receptor affects several kind of neurotransmission systems, including glutamate-, acetylcholine-, dopamine-, serotonin-, and noradrenaline-induced responses (Maurice et al., 1999, 2001). At the physiological level, the σ_1 receptor may be involved in the modulation of particular neuroadaptative changes, such as behavioral sensitization or reward, rather than particular neurochemical pathways. Consequently, it may be involved in the common neuroadaptive processes induced by cocaine or ethanol.

The precise brain structures involved in the σ_1 receptor-mediated effect, and particularly the participation of mesolimbic dopaminergic systems, must however be examined. The mechanism of the σ_1 receptor activation within these structures must be determined because at present there are no data suggesting a direct effect of ethanol on the σ_1 receptor. The role of the σ_1 receptor in ethanol tolerance, dependence, and withdrawal must also be examined. The σ_1 receptor has been proposed to play a particular role in neuronal plasticity and long-term changes (Maurice et al., 1999; Su and Hayashi, 2001). Prolonged or repeated ethanol intake leads to reduced behavioral response to ethanol, i.e., to cellular tolerance. Ethanol withdrawal is characterized by the development of anxiety, depressive responses, and increased seizures susceptibility. The σ_1 receptor may be putatively involved in the resulting changes in expression and function appearing in these neuroadaptive responses as soon as acute or repeated injections.

In summary, this study brought evidence that activation of the σ_1 receptor is a necessary component for the acquisition of ethanol-induced reward and related behavioral manifestations. A selective antagonist, BD1047, allowed to block ethanol-induced locomotor stimulation, conditioned place preference, and conditioned taste aversion. Acting through the σ_1 receptor may offer a new pharmacological strategy to counteract ethanol addiction.

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