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Nicotine-induced behavioral disinhibition and ethanol preference correlate after repeated nicotine treatment

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Abstract

This study investigated the effects of repeated daily nicotine (0.35 mg/kg; 15 days) treatment on behavioral inhibition and locomotor activity in the elevated plus-maze and on voluntary ethanol consumption. When challenged with nicotine before the test, rats pretreated with repeated nicotine spent more time on and made more entries onto the open arms of an elevated plus-maze than did vehicle-pretreated animals. The ethanol preference and intake, measured during 3 h after a nicotine injection, was also higher in the nicotine-pretreated animals. In ethanol consumption experiments, there was a positive correlation between the % time and % entries made onto open arms vs. the ethanol preference and intake. However, no correlation between the total number of entries made in the elevated plus-maze and the measures of ethanol consumption was observed. These findings suggest that the ability of repeated nicotine administration to increase ethanol consumption is related to development of a nicotine-induced reduction of inhibitory control rather than development of locomotor sensitization. © 2001 Published by Elsevier Science B.V.

Keywords: Nicotine; Behavioral inhibition; Ethanol intake; Ethanol preference; Elevated plus-maze; Sensitization, (Rat)

1. Introduction

Drugs of abuse produce a variety of neurochemical effects which are drug-specific, but a common feature appears to be their ability to activate the mesolimbic dopamine system (Di Chiara and Imperato, 1988; Koob, 1992) and to stimulate locomotor activity (Wise and Bozarth, 1987). In experimental animals, repeated treatment with most addictive drugs, including nicotine, progressively enhances the drug-induced effects mediated via this dopamine pathway, leading to a long-lasting behavioral and neurochemical sensitization (Post and Rose, 1976; Segal and Mandell, 1974; Clarke and Kumar, 1983; Kalivas et al., 1993; Nestler and Aghajanian, 1997; Pierce and Kalivas, 1997; Balfour et al., 1998). The neurobiological processes underlying drug-induced sensitization have been proposed to be involved in transforming the wanting of a drug into craving, and may thus involve an enhancement of the incentive motivational qualities of the drugs and other drug-associated (conditioned) stimuli (Robinson and Berridge, 1993). Supporting this theory, previous drug experience increases subsequent self-administration (Horger et al., 1990, 1992; Piazza et al., 1990; Pierre and Vezina, 1997), and enhances the rewarding and reinforcing effects of the drug itself and that of conditioned stimuli (Lett, 1989; Shippenberg and Heidbreder, 1995; Taylor and Horger, 1999). However, few studies have demonstrated a direct relationship between locomotor sensitization to dependence producing drugs and drug intake. Therefore, it is possible that the role of sensitization in drug-taking behavior is permissive rather than causally related to the increased drug-intake observed after repeated drug exposure, and that other neural mechanisms are more directly related to the quantity of drug consumed.

The role of inhibitory control and impulsivity has lately received increased attention in the research on drug abuse (Jentsch and Taylor, 1999; Olausson et al., 1999, 2000; Robbins and Everitt, 1999; Rogers et al., 1999; Söderpalm and Svensson, 1999). It is well established that drug addicts abusing different kinds of dependence-producing drugs display decreased inhibitory control when assessed

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in different neuropsychological tests (Allen et al., 1998; Lejoyeux et al., 1998; Bickel et al., 1999; Kirby et al., 1999). It is possible that this inhibitory control deficit may contribute to the inability of the drug addict to control the drug use. Repeated drug exposure has been proposed to impair inhibitory control that, in addition to the effects on incentive motivation, may be involved in the compulsive drug-seeking and drug-intake encountered in drug addicts (Jentsch and Taylor, 1999; Olausson et al., 1999; Olausson, 2000).

We have previously demonstrated that repeated intermittent treatment with compounds acting at peripheral or both peripheral and central nicotinic acetylcholine receptors, including nicotine, increases voluntary ethanol consumption in rats (Blomqvist et al., 1996; Ericson et al., 2000a). Interestingly, these same treatments were recently found to promote the development of nicotine-induced behavioral disinhibition in the elevated plus-maze (Olausson et al., 1999; Ericson et al., 2000b), but, with the exception of nicotine, not locomotor sensitization to nicotine. Therefore, interestingly, there appears to be a dissociation between the effects of nicotinergic compounds on locomotor sensitization and behavioral disinhibition. Moreover, these data provide circumstantial evidence that this dissociation is reflected also in the relation between these effects and voluntary ethanol intake, and behavioral disinhibition appears more closely related to the intake of ethanol in rats than locomotor sensitization. Consequently, it is possible that the neuronal mechanisms underlying nicotine-induced behavioral disinhibition after repeated nicotine treatment are more closely related to those involved in the increased voluntary ethanol consumption observed after such treatments rather than to those mediating sensitization to the locomotor stimulatory effects of nicotine. Therefore, this study was designed to directly investigate the relationship between the nicotine-induced behavioral disinhibition and voluntary ethanol consumption. In order to do so, we used a dose of nicotine (0.35 mg/kg s.c.) that we previously have found to produce both locomotor sensitization and behavioral disinhibition as well as to increase ethanol intake. The effects of repeated treatment with this nicotine dose on nicotine-induced behavioral inhibition and locomotor activity in the elevated plus-maze and on voluntary ethanol consumption were examined and the data subjected to correlation analysis.

2. Materials and methods

2.1. Animals

Male Wistar rats ($n = 28$) weighing 225–250 g at the start of the experiments were supplied by B&K Universal (Sollentuna, Sweden) and used in all experiments. The rats were housed in separate cages under constant cage temperature (20°C), humidity (40–50%) and a controlled reversed 12-h light–dark cycle (light on at 6 p.m. and off at 6 a.m.). The rats had free access to food and tap water at all times, and a 6% v/v ethanol solution during certain periods of the experiments (see Experimental design). Animals were allowed to adapt to the animal department facilities for at least 1 week before the start of any experiment. The present experiments were conducted in a manner consistent with Swedish Legislation for Animal Welfare and were approved by the Ethics Committee for Animal Experiments, Göteborg, Sweden.

2.2. Drugs

Ethanol (95%; Svensk Sprit, Sweden) was used in the ethanol consumption experiments. (−)-Nicotine ditartrate 0.35 mg/kg s.c. (weight of the free base; Sigma, USA) was dissolved in a 0.9% NaCl solution and injected 2 ml/kg. The pH of the nicotine solution was neutralized with sodium bicarbonate.

2.3. Experimental techniques

2.3.1. Studies of behavioral inhibition

To evaluate the behavioral inhibition, the performance in the elevated plus-maze was investigated. This conflict model is based on the observation that the contrast between the elevated open and closed arms in the elevated plus-maze inhibits the exploratory behavior normally displayed by rats placed in a novel environment. The exploration of open arms is thus suppressed and in the present setting a normal, untreated, rat usually spends and makes about 20–30% of the total arm time and entries on the open arms. Manipulations that increase the percentage of time and entries made onto the open arms therefore produce behavioral disinhibition, whereas treatments that increase the total number of entries are considered to stimulate locomotor activity.

The experimental apparatus consisted of a plus-formed maze with a mesh-wire floor, elevated approximately 0.75 m above the ground in a semi-illuminated room. The arms of the plus-maze were 40 cm long and 10 cm wide. Two opposing arms were surrounded by black 10 cm high walls (closed arms), while the other arms were devoid of walls (open arms). Animals were allowed 1 h of habituation to the testing room before the start of the experiment. To stimulate exploratory behavior, the animals were put into an unfamiliar environment (a dark box with a grid floor) for 5 min, after which it was placed in the center of the plus-maze facing a closed arm. Entry into one arm was defined as the animal placing all four paws into the arm. The investigator was situated 2 m from the center of the maze. After every tested animal, the maze was carefully wiped with a wet cloth. The time spent in, and the number of entries made into, open and closed arms were recorded during a 5-min-long test session. The time and number of

entries made onto open arms were expressed as percent of the total time and total entries made into both open and closed arms.

2.3.2. Voluntary ethanol consumption

The rats had free access to one bottle of water and one bottle containing a weak ethanol solution. The ethanol concentration was gradually increased (2–4–6% v/v) over a 2-week period. Thereafter, the rats had access to two bottles (plastic 300 ml bottles with ball-valve sprouts) containing either tap water or 6% (v/v) ethanol solution. This ethanol concentration was used since previous observations (Fahlke, 1994) have indicated that the ethanol consumption is maximal at approximately this concentration in the Wistar rats used in the present study. The amount (g) of ethanol solution 6% (v/v) consumed in percent of total fluid intake (g) was used as an index of ethanol preference.

2.3.2.1. Screening. The intake of water and ethanol was measured twice a week. The bottles were cleaned and filled with fresh liquids and body weight was recorded once a week throughout the screening period. The position of the bottles was rotated at every measurement occasion (i.e. twice per week).

2.3.2.2. Nicotine-induced ethanol consumption. The animals had limited access (3 h/day, starting at 9 a.m.) to the ethanol solution, a procedure that was repeated daily for 2 weeks. On the testing days, the rats received nicotine (0.35 mg/kg s.c.) or vehicle immediately before the ethanol solution was accessible.

2.4. Experimental design

All animals ($n = 28$) were subjected to the ethanol consumption screening procedure outlined above, and the rats were subsequently divided into two balanced groups ($n = 14$) based on their ethanol preference in the latter part of the screening period. The mean ethanol intake during the screening period was 1.37 ± 0.57 g/kg/day. The ethanol solution was then removed. Two weeks later the drug treatment was initiated and the animals were treated with nicotine (0.35 mg/kg s.c.) or vehicle once daily for 15 consecutive days. On treatment day 16, all animals were tested in the elevated plus-maze after nicotine (0.35 mg/kg s.c.) challenge. The nicotine treatment was then terminated and the animals were then put on a limited access design for 2 weeks, during which the ethanol solution was only present during 3 h each day. The mean ethanol intake during the limited access paradigm was 0.81 ± 0.11 g/kg/3 h. After 2 weeks, the nicotine-induced ethanol intake (during the 3-h period) was studied in a balanced cross-over design, i.e. all animals received vehicle or nicotine before the 2 consecutive days with drinking tests in a cross-over fashion. The difference between the measures of ethanol consumption after the nicotine and that after the vehicle injection was used as a measure of nicotine-induced alteration in voluntary ethanol consumption.

2.5. Statistics

The data from the ethanol consumption experiments and the elevated plus-maze were statistically analyzed using a one-way analysis of variance (ANOVA) with pretreatment as the independent factor. The total number of entries was included as a covariant in the analysis of behavioral inhibition (% time and % entries) in order to control for the influence of drug-induced locomotor stimulation on these measures. Correlations were evaluated with the Fisher's r to z test. A probability value (P) less than 0.05 was considered statistically significant. Two rats were excluded from the final statistical analysis. One rat fell down from the elevated plus-maze during testing and the other rat had a leaking water bottle on 1 day of the final ethanol consumption experiments.

3. Results

3.1. Behavioral inhibition

In the elevated plus-maze experiments, there was main effects of pretreatment on all dependent measures, e.g. the % time ($F(1,24) = 5.136$; $P \leq 0.05$; Fig. 1), the % entries ($F(1,24) = 5.015$; $P \leq 0.05$; Fig. 1) and total entries ($F(1,24) = 6.348$; $P \leq 0.05$; Fig. 1). The nicotine-treated animals spent more time on and made more entries onto open arms of the elevated plus-maze after a nicotine challenge compared to vehicle-treated animals receiving a single dose of nicotine. The total number of entries made

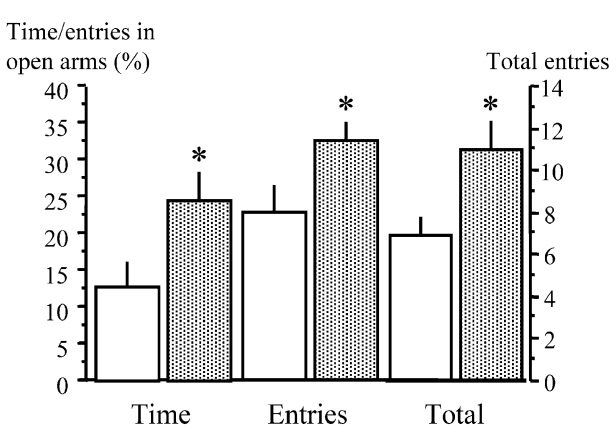

Fig. 1. Effects of repeated daily treatment with nicotine (0.35 mg/kg s.c.) for 15 days on nicotine-induced behavior in the elevated plus-maze. Open bars are vehicle-pretreated rats, and closed bars are the nicotine-pretreated animals. Shown are the means + S.E.; $n = 13$, both groups. Statistics: ANOVA followed by Fisher's PLSD test. $^{*}P \leq 0.05$.

in any arm in the elevated plus-maze was also higher in nicotine-pretreated than in vehicle-pretreated animals.

3.2. Ethanol intake

There were statistically significant main effects of pretreatment both for the percent change in ethanol preference ($F(1,24) = 4.426$; $P \leq 0.05$; Fig. 2) and ethanol intake ($F(1,24) = 11.725$; $P \leq 0.01$; Fig. 2), and the ethanol consumption after an acute challenge dose with nicotine (0.35 mg/kg s.c.) were significantly higher in nicotine-pretreated than in vehicle-pretreated rats. The effect of nicotine on H_2O intake ($F(1,24) = 0.339$; $P = 0.534$; Fig. 2) or total fluid intake ($F(1,24) = 3.555$; $P = 0.074$; Fig. 2) did not significantly differ between the vehicle-pretreated and nicotine-pretreated animals.

3.3. Correlation

A total of 26 animals were used in the correlation analysis. All results are outlined in Table 1A–C. There were significant positive correlations between the % time made into open arms in the elevated plus-maze after nicotine challenge and the nicotine-induced ethanol preference ($P \leq 0.01$; $r = 0.527$) and ethanol intake ($P \leq 0.01$; $r = 0.497$). There were significant positive correlations between the % entries made into open arms in the elevated plus-maze after nicotine challenge and the nicotine-induced ethanol intake ($P \leq 0.01$; $r = 0.462$) and ethanol intake ($P \leq 0.05$; $r = 0.459$). There were no significant correlations between the total number of entries made in the elevated plus-maze and the ethanol preference ($P = 0.096$, $r = 0.321$) or ethanol intake ($P = 0.280$, $r = 0.213$).

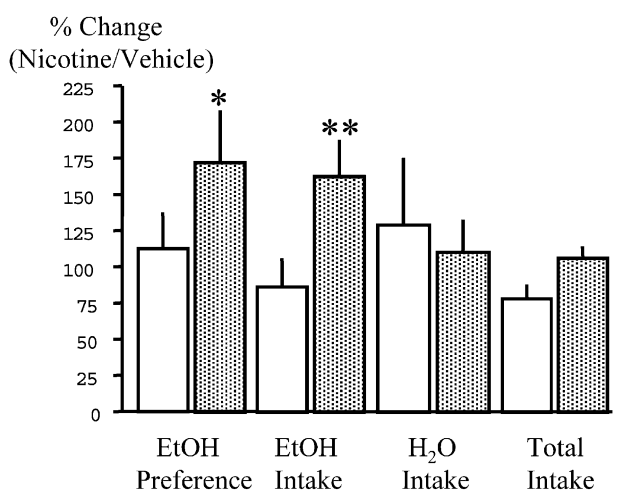

Fig. 2. Effects of repeated daily nicotine (0.35 mg/kg s.c.) treatment for 15 days on nicotine-induced ethanol consumption during 3 h in a limited access two-bottle free-choice paradigm. Shown are the nicotine-induced changes (%) compared to the ethanol consumption after vehicle-treatment. Shown are the means + S.E.; $n = 13$, both groups. Open bars are vehicle-pretreated rats, and closed bars are the nicotine-pretreated animals. Statistics: ANOVA followed by Fisher's PLSD test. $^{*}P \leq 0.05$ and $^{**}P \leq 0.01$.

Table 1
Correlation between voluntary ethanol intake and measures of behavioral inhibition and locomotor activity
Correlations between the nicotine-induced ethanol consumption and (A) the % time spent in open arms, (B) the % entries made onto open arms, (C) the total number of entries made into any arm of the elevated plus-maze in rats repeatedly treated with nicotine (0.35 mg/kg s.c.) or vehicle for 15 days; $n = 13$, each group.

Observation	Correlation	*P*-value
A		
Time % open vs. ethanol preference after vehicle	0.221	0.261
Time % open vs. ethanol preference after nicotine	0.527	0.003**
Time % open vs. ethanol intake after vehicle	0.256	0.191
Time % open vs. ethanol intake after nicotine	0.427	0.006**
Time % open vs. H_2O intake after vehicle	−0.350	0.068
Time % open vs. H_2O intake after nicotine	−0.287	0.140
Time % open vs. total intake after vehicle	0.045	0.823
Time % open vs. total intake after nicotine	0.143	0.470
B		
Entries % open vs. ethanol preference after vehicle	0.183	0.355
Entries % open vs. ethanol preference after nicotine	0.462	0.002**
Entries % open vs. ethanol intake after vehicle	0.210	0.286
Entries % open vs. ethanol intake after nicotine	0.459	0.013*
Entries % open vs. H_2O intake after vehicle	−0.327	0.009
Entries % open vs. H_2O intake after nicotine	−0.209	0.290
Entries % open vs. total intake after vehicle	0.040	0.842
Entries % open vs. total intake after nicotine	0.195	0.325
C		
Total entries vs. ethanol preference after vehicle	0.095	0.633
Total entries vs. ethanol preference after nicotine	0.321	0.096
Total entries vs. ethanol intake after vehicle	−0.035	0.860
Total entries vs. ethanol intake after nicotine	0.213	0.280
Total entries vs. H_2O intake after vehicle	−0.297	0.125
Total entries vs. H_2O intake after nicotine	−0.186	0.345
Total entries vs. total intake after vehicle	−0.323	0.094
Total entries vs. total intake after nicotine	0.002	0.990

$^{*}P \leq 0.05$.
$^{**}P \leq 0.01$.

4. Discussion

The present study was designed to elucidate the tentative relationship between the effects of repeated nicotine treatment on nicotine-induced effects on behavioral inhibition and ethanol consumption. In line with our previous findings (Olausson et al., 1999; Ericson et al., 2000b), repeated daily treatment with nicotine (0.35 mg/kg s.c.) for 15 consecutive days increased the percentage of time spent on and entries made onto the open arms of the elevated plus-maze after a nicotine injection compared to that of vehicle-pretreated animals. Since the normal exploratory behavior in the elevated plus-maze is inhibited (see Materials and methods), the increased exploration of open arms reflects a nicotine-induced behavioral disinhibition in the nicotine-pretreated animals. Disinhibited behav-

ior in the elevated plus-maze is often considered to reflect an alleviation of anxiety (Pellow et al., 1985; Pellow, 1986). However, disinhibited behavior in animal models which invoke conflict situations, like the elevated plus-maze, may also reflect a loss of inhibitory control or impulsivity, since an animal that confronts an aversive stimuli may be equally anxious as an animal that does not, but may rather not be able to inhibit the response (Soubrié, 1986), in this case an exploratory urge. Thus, even though the elevated plus-maze is not a validated experimental model of impulsivity, the present data together with our previous observations (see Olausson et al., 1999; Ericson et al., 2000b for discussions) may imply that repeated nicotine treatment lowers inhibitory control.

In line with our previous observations (Olausson et al., 1999), repeated nicotine treatment also increased the nicotine-induced locomotor activity in the elevated plus-maze (i.e. the total number of entries). This increase indicates that repeated treatment sensitized the effects of nicotine on locomotor activity, an observation in line with the results observed using traditional locomotor activity recording equipment (Clarke and Kumar, 1983; Ksir et al., 1987; Johnson et al., 1995; Olausson et al., 1999). Consequently, the nicotine-induced disinhibition was associated with an increase in locomotor activity. Such drug-induced stimulation of locomotor activity has been suggested to produce non-specific disinhibition towards the elevated open arms, and it could therefore be argued that the behavioral disinhibition observed in nicotine-sensitized rats is but a consequence of the nicotine-induced locomotor stimulation. The connection between locomotor activity and the measures of behavioral inhibition in the elevated plus-maze has previously been investigated using factor analysis and correlation procedures (Pellow et al., 1985; File et al., 1993; Ouagazzal et al., 1999). These studies suggest that under normal circumstances, the measures of behavioral inhibition (i.e. % time and % entries in open arms) and the total number of entries made during the test are largely independent variables. This view is further supported by other studies that also have failed to observe a positive correlation between the exploration of open arms and locomotor activity (Söderpalm and Engel, 1988; Söderpalm et al., 1989). Nevertheless, to control the potential influence of the nicotine-induced effects on locomotor activity, the total number of entries was included as a covariant in the statistical analysis of the measures of behavioral inhibition.

The present findings that a single dose of nicotine increased the ethanol preference and the ethanol intake during a 3-h period in nicotine-pretreated animals, but not in controls, is in line with our previous reports that repeated nicotine pretreatment in the rat increases ethanol consumption in the free-choice paradigm here used (Blomqvist et al., 1996; Ericson et al., 2000a). Interestingly, the effects of subchronic repeated nicotine pretreatment on the behavioral inhibition and ethanol consumption observed after a single dose of nicotine appear to be closely related, since there were significant positive correlations between the percentage of time and entries spent on the open arms and both the ethanol preference and ethanol intake after a nicotine challenge. On the contrary, there were no significant correlations between the nicotine-induced effect on the total number of entries made on the plus-maze and the measures of ethanol consumption after nicotine injection. Indeed, also in a previous study, we failed to find significant correlations between spontaneous locomotor activity, nicotine-induced locomotor activity, or nicotine-induced locomotor sensitization and voluntary ethanol intake or preference in rats (Blomqvist et al., 1996). Thus, it appears possible that mechanisms underlying the behavioral disinhibition produced by repeated nicotine exposure also could be involved in mediating the increased ethanol consumption observed after this treatment, whereas mechanisms related to locomotor sensitization to nicotine probably are less important. Further support for this conclusion comes from evidence indicating that induction of sensitization to the locomotor stimulatory effects of nicotine involve intermittent stimulation of central nicotinic acetylcholine receptors, whereas, surprisingly, development both of nicotine-induced disinhibition and enhanced ethanol consummatory behavior may instead invoke intermittent blockade of peripheral nicotinic acetylcholine receptors (Ericson et al., 2000a,b).

The present results are further supported by observations indicating that a high liability of rats to consume ethanol is associated with impaired impulse control (Poulos et al., 1995; Johansson and Hansen, 1999). Indeed, also various pharmacological manipulations that increase or decrease ethanol consumption may well produce these effects by influencing neuronal mechanisms involved in inhibitory control (see Söderpalm and Svensson, 1999). Thus, repeated pretreatment with nicotinic acetylcholine receptor antagonists, both central and peripheral, and with amphetamine have been demonstrated to increase both ethanol intake (Fahlke et al., 1994; Ericson et al., 2000a) and drug-induced behavioral disinhibition (Ericson et al., 2000b; Olausson et al., 2000). Moreover, the expression of drug-induced behavioral disinhibition is counteracted by the selective 5-HT reuptake inhibitor citalopram (Olausson et al., 1999) as well as by the 5-HT_{1A} receptor agonist (±)-8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; Olausson et al., unpublished), and both selective 5-HT reuptake inhibitors (Engel et al., 1992; Balldin et al., 1994; LeMarquand et al., 1994) and 5-HT_{1A} receptor agonists (Svensson et al., 1989; Engel et al., 1992; LeMarquand et al., 1994) have been reported to decrease ethanol consumption in rats and humans. Furthermore, depletion of brain 5-HT by means of selective neurotoxins increases both behavioral disinhibition in animal conflict models (Soubrié, 1986) and ethanol consumption in rodents (Engel et al., 1992; LeMarquand et al., 1994), and signs of low 5-HT neurotransmission have been observed in human alcoholics

(Wiberg et al., 1977; Oreland et al., 1983; von Knorring et al., 1991; Higley and Linnoila, 1997). In addition, benzodiazepines in low doses enhance ethanol consumption and produce behavioral disinhibition in experimental animals, whereas inverse agonists at benzodiazepine receptors reduce both these measures. Finally, evidence was recently presented indicating that naloxone reduces behavioral disinhibition in the 5-HT depleted rat by means of a weak $GABA_A$ receptor antagonistic action and it was suggested that this effect could underlie also the ethanol intake reducing effect of the drug in human alcoholics (Söderpalm and Svensson, 1999).

In conclusion, the present findings suggest that nicotine-induced behavioral disinhibition and ethanol consumption are closely related behaviors. Based on the present and previous findings (see above), it appears possible that the increased ethanol consumption observed after repeated nicotine treatment may involve a decrease in inhibitory control. Since loss of behavioral inhibition and/or impulsivity is often observed in drug addicts, it is possible that pharmacological treatment that counteract the expression of such drug-induced behavioral disinhibition may prove useful as one component in a wider treatment program for drug abuse.

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