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Effects of voluntary alcohol intake on nicotine-induced behavioural sensitisation in rats

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Abstract

Behavioural sensitisation has been suggested to play a role in the acquisition and maintenance of addictive behaviour. The aim of the present study was to assess nicotine-induced behavioural sensitisation in chronic voluntary alcohol drinking rats. Subjects had free access to alcohol/water or glucose/water solutions since weaning. Rats were pretreated after 2 months of voluntary alcohol drinking. Pretreatment consisted of once-daily intraperitoneal injection of nicotine (0.5 mg/kg) or saline administered for five consecutive days. The nicotine-induced behavioural sensitisation of locomotor activity was tested 3 weeks latter. Horizontal motor activity was monitored for 30 min and expressed as distance travelled (in centimetres). During all the experimental procedure, the animals were maintained under 1-h limited access to alcohol. In glucose-drinking animals, results indicated that nicotine induced locomotor activity sensitization: The locomotor effects of nicotine challenge in the nicotine-pretreated group of rats were significantly enhanced as compared with the saline-pretreated group (Duncan, $P < .01$). Instead, in the alcohol-drinking animals, no significant differences were observed between the nicotine- and saline-pretreated groups. Thus, chronic alcohol consumption at mild doses prevented the development and/or the long-term expression of the nicotine-induced sensitisation at the doses tested.

Keywords: Behavioural sensitisation; Nicotine; Ethanol; Locomotor activity; Oral intake; Rat

1. Introduction

Behavioural sensitisation is the augmentation of a response to a stimulus following repeated exposures to that stimulus. Like initial stimulant responses, locomotor sensitisation is a common response to most drugs that are abused by humans. This process of behavioural sensitisation has been suggested to play a role in the acquisition and maintenance of addictive behaviour (Hunt and Lands, 1992; Robinson and Berriges, 1993; De Vries et al., 1998, Deroche et al., 1999).

Alcohol-induced long-term behavioural sensitisation to morphine, but not to amphetamine, has been reported in rats (Nestby et al., 1997). In mice, alcohol-induced long-term behavioural sensitisation to cocaine (Manley and Little, 1997; Itzhak and Martin, 1999), as well as to amphetamine (Manley and Little, 1997), has been also shown, while alcohol pretreatment did not affect animals' response to nicotine challenge (Itzhak and Martin, 1999). Nicotine-induced behavioural locomotor sensitisation in mice after chronic alcohol intake has been also observed (Watson and Little, 1999). However, all these results were obtained in forced alcohol administration procedures (i.e., liquid diet or ip). In a voluntary alcohol drinking paradigm, Fahlke et al. (1995) reported that amphetamine had a greater locomotor stimulant effect in rats with high alcohol intake than in those with low intake when tested 4 weeks after the cessation of alcohol drinking. Nevertheless, in all these studies, drug challenge was performed in an alcohol-free period. There is considerable evidence that withdrawal hyperexcitability causes neuronal changes, many of which are long lasting and may influence such phenomena as sensitisation to other drugs.

The mechanisms of action of alcohol involves multiple subcellular sites in the central nervous system (CNS), thereby influencing the function of most, if not all, neuronal systems at molecular, cellular and system levels (Fadda and Rossetti, 1998). The NMDA-receptor-mediated enhancement of excitatory neurotransmission, as a consequence of

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the chronic alcohol treatment, can be considered as a major neuroadaptative process causing the excitatory syndrome that results upon the withdrawal of chronic alcohol consumption (Fadda and Rossetti, 1998). The neuronal nicotinic acetylcholine receptor is also a potential target site of alcohol and may mediate some of its effects on the CNS (Aistrup et al., 1999), thus, the cholinergic function of nicotinic-type acetylcholine receptors could be altered in chronic alcohol-drinking rats. The stimulating effects of nicotine on locomotor activity result from the activation of nicotinic receptors, as pretreatment with mecamylamine, which is a classical noncompetitive antagonist at central nicotinic receptors, inhibits this effect of nicotine (Miller et al., 2001). Furthermore, the central nicotinic receptors have been recently involved in the development of psychostimulant-induced sensitisation (Schoffelmeer et al., 2002). Therefore, the nicotine-induced behavioural sensitisation could be affected by a chronic alcohol exposure. The aim of the present study was to assess the nicotine-induced behavioural sensitisation in chronic voluntary alcohol drinking in rats, within a continuous limited access alcohol paradigm.

For this purpose, we have used a free-choice drinking procedure that provides an early availability of the alcoholic solution (alcoholism primary praecox, APP procedure; Darbra et al., 2002). We have modified our intake induction procedure, described in previous studies (Nadal et al., 1992; Pallarès et al.,1992; Pallarès et al., 1997), based on the limited access paradigm and the addition of glucose to increase palatability and reward. Sweetened solutions were used to avoid taste aversion and to ensure a rapid, high and stable alcohol consumption. The use of sweet alcohol solutions in animal models of alcoholism is appropriate because it has been shown that taste factors, such as sweetness, are not the primary factors in controlling alcohol consumption in Wistar rats (Samson et al., 1996; Goodwin and Amit, 1998). Likewise, restricted food access procedures were applied because it is well established that animals with limited time access to food will readily self-administer alcohol in quantities sufficient to produce intoxication (Koob and Bloom, 1988). Moreover, restricted access to drug increases self-administration, even for alcohol (Heyser et al., 1997). We have used the nicotine-induced behavioural locomotor activity procedure to assess the nicotine-induced behavioural sensitisation in voluntary alcohol drinking rats. Moreover, blood alcohol levels (BALs) were evaluated before the nicotine pretreatment to verify the alcohol consumption.

2. Materials and methods

2.1. Subjects

Twenty-eight male Wistar rats (Laboratori de Psicobiologia, Universitat Autònoma de Barcelona) were used. They were 21 days old at the beginning of the experiment and were housed in a temperature-controlled environment on a 12-h light–dark (8:00–20:00 h) cycle. The Autonomous University of Barcelona Institutional Animal Care and Use Committee approved the care and use of the subjects, and the experimental protocol was in compliance with the European Community Council Directive of 24 November 1986 (86/609/EEC) for care and use of laboratory animals.

2.2. Drugs, solutions and reagents

An alcoholic-sweetened solution (ethanol 10% v/v and glucose 3% w/v) was prepared from 99.9% ethanol (Normasolv, Barcelona, Spain) and D(+)-Glucose anhydrous (Panreac, Barcelona, Spain) diluted in distilled water. A sweetened solution was prepared from D(+)-Glucose anhydrous (3% w/v) diluted in distilled water. Nicotine (0.5 mg/kg salt weight, Sigma-Aldrich, Madrid, Spain) was dissolved in sterile saline and injected 1 ml/kg ip. For the analysis of BAL, thricholoroacetic acid solution (6.25% w/v) and an enzymatic pack (Sigma-Aldrich) were used.

2.3. Procedure

2.3.1. APP procedure

2.3.1.1. Free-access phase. At weaning, the subjects were housed (four or five per cage) and randomly distributed into two groups: alcohol ($n=14$) and glucose ($n=14$). The alcohol group had free access to two bottles, one containing the alcoholic-sweetened solution and the other tap water. The glucose group had free access to two bottles, one containing sweetened solution and the other tap water. The positions of the bottles were randomly changed daily, until the end of the study, to avoid the development of positional preferences. All subjects had ad libitum access to food. This phase lasted for 3 weeks.

2.3.1.2. First limited access phase. During the two following weeks, on Friday, the bottle containing the alcohol-sweetened solution or sweetened solution was removed and substituted by tap water. Bottles containing the alcohol-sweetened solution or sweetened solution were replaced again on Monday.

2.3.1.3. 1-h Limited access phase. All subjects were individually housed when they were 2 months old. The alcohol group had access to two solutions, alcoholic-sweetened and tap water for 1 h, and, for the rest of the day, it had free access to two tap water bottles. The glucose group had access to two bottles, containing sweetened solution and tap water for 1 h, and, for the rest of the day, it had free access to two water bottles. On Saturday and Sunday, the subjects had access to two water bottles. Food access was limited to 3 h/day for all groups. The 1-h access to alcoholic-sweetened or sweetened solution coincided with the first hour of

food access. This food timetable was from Monday to Friday for all subjects, and, at weekend, the subjects had free access to food. All subjects were weighted every Monday and Friday, and solution intakes (g) were recorded daily. This phase lasted until the end of the procedure.

2.3.2. BAL

One month after the beginning of the 1-h limited access phase (90 old days), BALs were assessed. Blood samples were drawn from the tail tip of the experimental subjects (all subjects) immediately after the 1-h limited access to solutions; 0.2 ml of the blood was allocated into tubes containing 1.8 ml of thricholoroacetic acid solution (6.25% w/v), and they were shaken. Blood samples were then centrifuged at 2000 rpm for 5 min, and the supernatant was drawn and frozen to −40 °C. Subsequently, BALs were determined by the spectrophotometric method using the enzymatic pack.

2.3.3. Induction of behavioural sensitisation

Nicotine pretreatment was started 1 month after the beginning of the 1-h limited access phase (90 old days) and 1 day after the blood samples were obtained. The two groups (alcohol and glucose) were pretreated with nicotine or saline. Pretreatment consisted of once-daily intraperitoneal injection of nicotine (0.5 mg/kg) or saline, administered in the home cages, for five consecutive days. The dose referred to the salt form of the drug, and the injection volume was always 1 ml/kg. All injections were given 3 h after the 1-h limited access to solutions. During pretreatment and until the end of the experiment, the animals were maintained under 1-h limited access phase (see above). The dose of nicotine was chosen based on previous behavioural and neurochemical studies, in which this dose was used to induce an increase of the locomotor activity in rodents (Ericson et al., 2000; Kiianmaa et al., 2000; Schoffelmeer et al., 2002; Shim et al., 2001, 2002).

2.3.4. Determination of locomotor activity

Three weeks after the drug pretreatment period, horizontal motor activity was measured in wooden cages (50 × 50 × 35 cm) using an activity monitoring system (SMART, Letica, Barcelona, Spain). This system is based on the automated analysis of real-time video images, acquired by a video camera, which is suspended from the ceiling over the arena. White noise was used to minimize the influence of surrounding sounds. Locomotor challenge tests were conducted as follows. The day before the nicotine-induced locomotor activity determination (3 h after the 1-h limited access to solutions), the animals were allowed to habituate to the test cages for 30 min, during which activity was monitored. On the test day, 3 h after the 1-h limited access to the solutions, the animals were challenged with nicotine (0.5 mg/kg ip), and locomotor activity was monitored for 30 min. Horizontal locomotor activity, expressed as distance travelled (in centimetres), was calculated as the total distance moved during the 30-min period after the drug challenge.

2.4. Statistical analysis

We used the STATISTICA package (StatSoft, Tulsa, USA) for the data analyses. The normality of the data was assessed by means of the Kolmogorov–Smirnov test. To analyse the pretreatment effect on the solution intake, a mixed analysis of variance was performed, with drug (nicotine, saline) as the between-subjects factor and time (weekly mean of consumption, three levels) as the within-subjects factor. The nicotine challenge effect on the solution

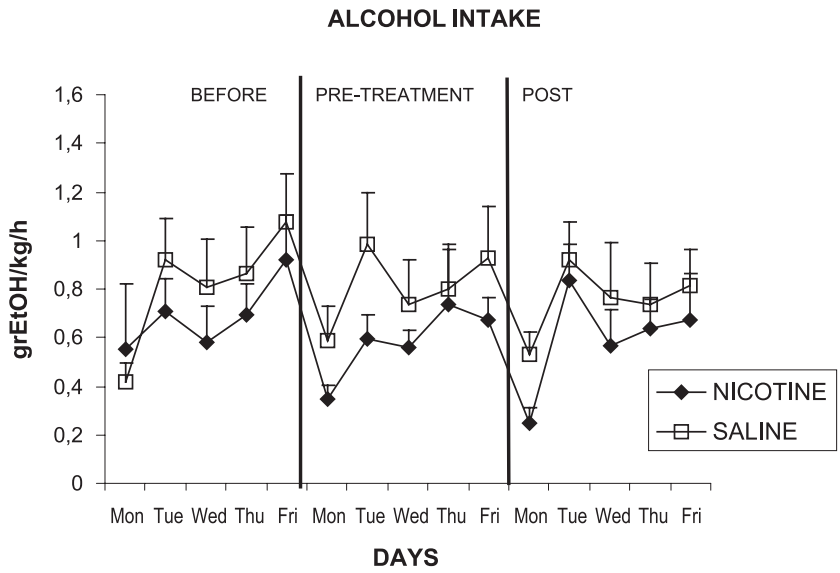

Fig. 1. Alcohol intake for the week before treatment (before), the 5 days of exposure to nicotine (pretreatment) and the week immediately following nicotine treatment (post). The animals were maintained under 1-h limited access phase, and alcohol was not presented on weekends (nicotine: group pretreated with nicotine; saline: group pretreated with saline).

intake was analysed using a mixed analysis of variance, with group (alcohol/saline, alcohol/nicotine, glucose/saline and glucose/nicotine) as the between-subjects factor and day (pre- and postingested daily dose) as the within-subjects factor. To analyse the nicotine-induced behavioural sensitisation, a mixed analysis of variance was used, with group (alcohol/saline, alcohol/nicotine, glucose/saline and glucose/nicotine) as the between-subjects factor and session (habituation, test) as the within-subject factor. Moreover, an analysis of covariance, with activity (total distance travelled during habituation session) as the covariate, was also used to control the subjects' basal activity levels. Post hoc Duncan's test analyses were used when necessary. A two-tailed Pearson test was used for correlation analyses. Data are shown in mean ± S.E.M.

3. Results

3.1. Solution intake

During the first 4 weeks of the 1-h limited access phase, the averages of alcohol intake were 0.52 ± 0.05, 0.54 ± 0.06, 0.74 ± 0.10 and 0.75 ± 0.10 g alcohol/kg body weight/h, respectively. On the other hand, the BALs obtained were 10.52 ± 4.54 mg EtOH/dl blood (BALs were obtained the last day of the fourth week of the 1-h limited access phase). Moreover, BALs showed a significant positive correlation with the alcohol dose (g alcohol/kg body weight/h) ingested [Pearson's correlation, $r(11)=.60$; $P=.029$; the blood sample from one subject was wrongly processed]. No significant differences in the alcohol intake

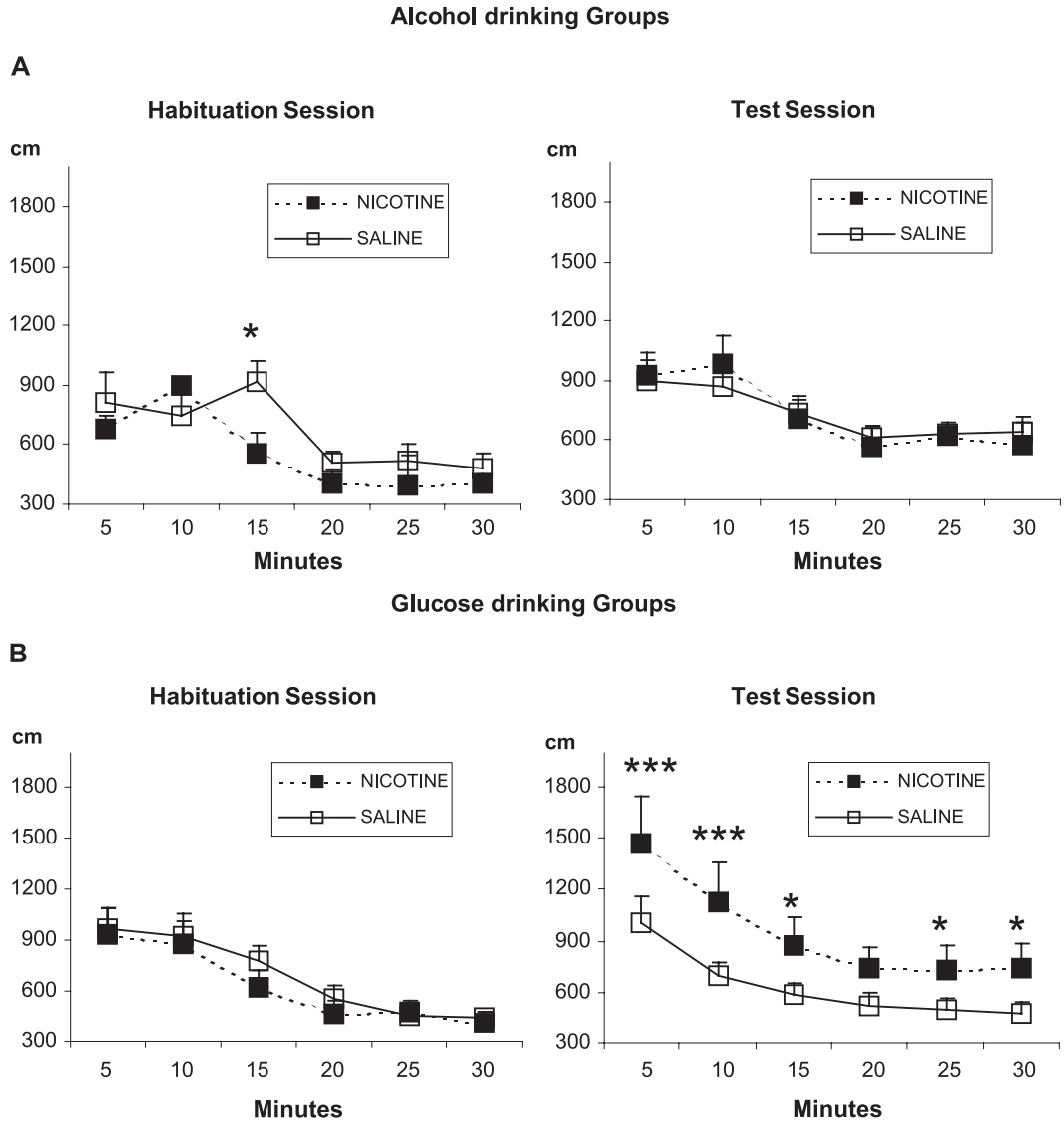

Fig. 2. Time course of the effect of nicotine challenge on locomotor activity in alcohol-drinking (A) and control (B) groups. Locomotor activity is expressed as total distance travelled during the 5-min blocks across the two 30-min sessions, i.e., habituation (left) and test (right) sessions. *** $P<.001$, nicotine vs. saline; ** $P<.01$, nicotine vs. saline; and * $P<.05$ nicotine vs. saline.

due to the nicotine administration during the pretreatment period were observed [drug: $F(1,12)=1.008$, $P>.05$; time: $F(2,24)=0.491$, $P>.05$; Drug × Time: $F(2,24)=0.173$; $P>.05$]. The alcohol intake was not different between the subjects that received the nicotine and the subjects that received saline, neither in the pretreatment week nor in the week after injections (see Fig. 1). In the same way, no significant differences were found in the sweetened solution intake. However, the ANOVA of sweetened solution intake data revealed significant main effects of time [$F(2,24)=9.718$; $P<.001$], independent of the pretreatment received. The sweetened solution consumption during the week before the pretreatment was higher than the intake during the pretreatment week (Duncan, $P<.001$) and during the week after the pretreatment (Duncan, $P<.001$). No significant differences were observed between these two latter weeks. Sweetened solution intake during the pretreatment week and the week after was not different between the subjects that received the nicotine and subjects that received saline.

The ANOVA of the solutions intake data revealed no significant differences due to the nicotine challenge, neither in the alcohol intake nor in the sweetened solution intake groups. Moreover, no significant differences in the solution intake were found as a consequence of the drug received in the pretreatment.

3.2. Nicotine-induced behavioural sensitisation

The locomotor effects of nicotine challenge (0.5 mg/kg) in the saline- and nicotine-pretreated, both in alcohol-drinking and control, rats are presented in Fig. 2. The ANOVA of locomotor activity data revealed significant main effects of session [$F(1,24)=7.926$, $P<.01$], along with a significant interaction of Group × Session [$F(3,24)=3.105$, $P<.05$]. That is, locomotor activity increased across sessions, but this effect was dependent on the group. In glucose-drinking animals, the locomotor effects of nicotine challenge in the nicotine-pretreated group of rats was significantly enhanced compared with that observed in the saline-pretreated group (Duncan, $P<.01$; see Fig. 3). Instead, in the alcohol-drinking animals, no significant differences were observed in the locomotor effects of nicotine challenge between the nicotine- and saline-pretreated groups. Furthermore, in the test session, the locomotor activity observed in the nicotine-pretreated glucose-drinking group was significantly greater than the locomotor activity observed in the nicotine-pretreated alcohol-drinking group (Duncan, $P<.05$; see Fig. 3). No significant differences were observed between the alcohol-drinking and control saline-pretreated groups. The analysis of covariance also showed that locomotor activity was dependent on the group [$F(3,23)=2.982$, $P=.05$]: The increased locomotor activity shown in the nicotine-pretreated glucose-drinking animals remained significant (Duncan, $P<.05$), while no significant differences between the nicotine- and saline-pretreated groups were observed in the alcohol-drinking animals.

Moreover, no significant differences due to the pretreatment were observed in the locomotor activity during the habituation to the test cage, neither in the alcohol-drinking group nor in the glucose group. On the other hand, no significant differences in the novelty-induced locomotor activity (habituation session) were observed due to the voluntary alcohol intake.

4. Discussion

Behavioural sensitisation was seen in the control rats, as expected, and it was not seen in the alcohol-drinking rats.

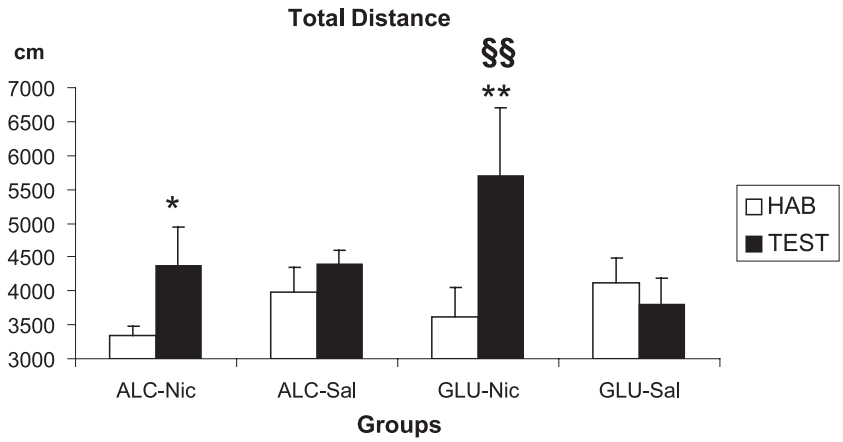

Fig. 3. Lack of the development and/or expression of nicotine-induced behavioural sensitisation by chronic voluntary alcohol consumption. Locomotor activity is expressed as total distance travelled during the two session, i.e., habituation (white columns) and test (black columns). ALC-Nic: alcohol-drinking group pretreated with nicotine; ALC-Sal: alcohol-drinking group pretreated with saline; GLU-Nic: control group pretreated with nicotine; and GLU-Sal: control group pretreated with saline; ** significantly different from GLU-saline pretreated rats on the test day, $P<.01$; §§significantly different from GLU-nicotine pretreated rats on the habituation session, $P<.01$; and * significantly different from GLU-nicotine pretreated rats on the test day, $P<.05$.

Thus, our investigation indicates a lack of nicotine-induced behavioural sensitisation in voluntary alcohol drinking rats. Drug-induced sensitisation strongly depends on the experimental conditions. Furthermore, it has been suggested that nicotine-induced sensitisation may be primarily context-dependent (Reid et al., 1996). In this sense, no behavioural sensitisation to nicotine has been found in mice, following a procedure that diminishes context-dependent sensitisation (Itzhak and Martin, 1999), and an interaction between the effects of the environment on the actions of nicotine after the forced alcohol consumption (liquid diet) has also been reported in mice (Watson and Little, 1999). Although the procedure in the present study uses context-independent sensitisation by delivering the drug and saline injection in the animals' home cage, nicotine pretreatment induces long-term behavioural sensitisation in control rats under the present experimental conditions (see Fig. 3). Earlier studies using the same context-independent sensitisation (injections in animals' home cage) and the same doses of nicotine as our experiment consistently induced long-lasting sensitisation (Schoffelmeer et al., 2002). Thus, our results suggest that the behavioural sensitisation observed was primarily drug dependent. In any case, the lack of nicotine-induced behavioural sensitisation in the alcohol group cannot be attributable to the experimental conditions because nicotine pretreatment induces long-term behavioural sensitisation in control rats. Behavioural sensitisation consists of two separable phenomena: induction (acquisition) and expression. Due to the experimental design, it is not possible to conclude whether the effect of chronic alcohol consumption is related to the development and/or the expression of nicotine-induced sensitisation. Because of the locomotor activity in a novel environment is positively correlated with the sensitivity to psychomotor and to the reinforcing effects of psychomotor stimulants (Piazza et al., 1989; Hooks et al., 1991a,b), we have performed a data analysis (i.e., both the mixed analysis of variance and the analysis of covariance) to control the individual variability.

On the other hand, the initial sensitivity to the locomotor effects of nicotine was not affected by the chronic voluntary alcohol intake because there were no differences between saline-pretreated alcohol-drinking rats and their controls. Thus, the main result of the present study is that under these conditions, it appeared that chronic alcohol consumption at mild doses prevented the development and/or the long-term expression of the nicotine-induced sensitisation at the doses tested.

Repeated nicotine administration results in dynamic changes in neuronal function, expressed as behavioural sensitisation in animals and addiction in smokers (Miller et al., 2001). Furthermore, it has been reported that the nicotine-induced, long-lasting locomotor sensitisation results from the activation of central nicotinic receptors (Miller et al., 2001). In this regard, alcohol can change the rate of desensitisation (Wu and Miller, 1994) and stabilize the neuronal nicotinic receptor into a desensitizated state (Wu et al., 1994). It has been suggested that chronic alcohol treatment does not elicit enough receptor desensitisation to produce central nicotinic receptor up-regulation (Collins et al., 1996). Because receptor desensitisation is functionally equivalent to receptor blockade, it may be that the development of nicotine-induced behavioural sensitisation was inhibited by chronic alcohol treatment. Nevertheless, other authors have reported that forced long-term treatment (5 months) with alcohol results in increases in rat brain [^{3}H]-nicotine binding (Yoshida et al., 1982). It is also possible that alcohol could shift the nicotine dose effect curve without really blocking the process or mechanisms of sensitisation. In this sense, nearly 70% of alcoholics smoke more than one and a half packs of cigarettes per day, while only 10% of the nondrinking population smokes at this level (Huges, 1994). Moreover, in the present study, we have used a free-choice drinking procedure that provides an early availability of the alcoholic solution, i.e., alcohol was available from weaning. Because the administration of intoxicating doses of alcohol is associated with neuroadaptative changes that are not the same in juveniles and adolescents than they are in adults, part of the present results are very likely attributable to the neuroadaptative process as a consequence to the early availability of the alcoholic solution.

In relation to the novelty-induced locomotor activity (habituation session) no significant differences were observed related to the voluntary alcohol intake. It has been reported that locomotor activity was higher after voluntary alcohol drinking than after saccharine or water drinking in alcohol-preferring AA rats (Païvärinta and Korpi, 1993). However, this increase was statistically significant from min 3 to 9 after the end of the 10-min period of voluntary alcohol consumption, and it was observed after two sessions of habituation. Thus, these discrepancies may also be explained by the different experimental conditions.

Nicotine effects on the voluntary alcohol intake were not observed, neither in the pretreatment period nor in the challenge test. It has been reported that repeated nicotine pretreatment increases alcohol consumption in a free-choice paradigm in rats (Blomqvist et al., 1996; Ericson et al., 2000). It should be noted that these effects were obtained in an experimental condition, in which nicotine drug treatment (0.4 mg/kg sc, 15 days) was carried out in the absence of alcohol. Recent studies have reported a nicotine challenge effect on voluntary alcohol consumption (Olausson et al., 2001). Nevertheless, in this latter study, the nicotine treatment was also carried out in the absence of alcohol and in an intermittent access to alcohol procedure. In alcohol-preferring Wistar rats maintained on the 4-h limited access to 10% alcohol, acute treatment of nicotine (0.1 or 0.6 mg/kg sc and administered immediately prior to the start of the limited access to alcohol) decreases the amount of alcohol consumed (Dyr et al., 1999). A decrease in the alcohol intake was also observed after repeated treatment with nicotine (0.35 and 0.7 mg/kg

sc for 3 and 1 weeks, and administered 30 min before the alcohol self-administration sessions) in rats that had approximately 8 weeks of experience drinking 10% alcohol before nicotine treatment began (Sharpe and Samson, 2002). When nicotine was administered once daily, after the daily alcohol self-administration, with the use of an operant model, it had no effect on the amount of alcohol consumed (Nadal and Samson, 1999). Taking into account the possible interaction of alcohol with nicotine receptors, the methodological aspects may explain these discrepancies. In the present study, nicotine administration (i.e., pretreatment and challenge) was 3 h after the 1-h limited access to alcohol. The nicotine administration was delayed to avoid a possible nicotine-induced alteration (i.e., increase or decrease) on voluntary alcohol consumption. It should be noted that with the APP procedure, we obtain a chronic pattern of voluntary oral consumption of steady moderate levels of alcohol in nonselected male Wistar rats. Besides, at the age in which rats were pretreated (90 days), APP rats were tolerant to alcohol depressant effects, as we have shown recently (Darbra et al., 2002). The dose regimen for nicotine delivery may also have contributed to the difference in results, as it has been suggested by others authors (Sharpe and Samson, 2002). Regarding BALs, we obtained a positive significant correlation with the alcohol consumption on the day in which blood was drawn, as we expected. On the other hand, the moderate BALs obtained are also expected because it is well documented that in the presence of food in the gastric cavity, the absorption of alcohol to blood decreases compared with an empty gastric cavity (Agarwal and Goedde, 1990). In addition, it has been shown that sugars can reduce the BALs following the oral (Koch-Weser et al., 1976; Matthews et al., 2001) or intravenous administration of alcohol (Mascord et al., 1988).

In summary, nicotine-induced behavioural sensitization in control glucose-drinking rats. Voluntary alcohol intake did not affect the acute effects of nicotine on locomotion because there were no differences in locomotion between the saline-pretreated alcohol-drinking rats and the saline-pretreated glucose-drinking rats. And, finally, chronic voluntary alcohol consumption at mild doses prevented the development and/or the long-term expression of the nicotine-induced behavioural sensitisation in rats at the doses tested. This result suggests a possible effect of chronic alcoholism on the nicotinic cholinergic mechanism involved in the locomotor behavioural sensitisation. Chronic alcohol consumption could neutralize some effects of nicotine on locomotor behaviour.

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