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Nicotine–alcohol interactions and cognitive function in rats

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Abstract

Nicotine and ethanol are the most widely abused drugs in the world. They are very often used and abused together. However, little is known about the functional interaction of nicotine and ethanol. The current project studied the interactive effects of nicotine and ethanol on working memory in the eight-arm radial maze. Adult female rats were trained on a radial arm maze for 18 sessions to reach asymptotic levels of choice accuracy. During the maintenance phase of radial arm maze testing, which indexed working memory function, the rats were injected with nicotine (0, 0.15, 0.3, 0.6, and 1.2 mg/kg sc, 20 min before testing) with and without ethanol pretreatment (0 or 1.5 g/kg, 16% v/v ip, 30 min before testing). All animals received the treatments in a counterbalanced order with at least 1 week between treatments. Higher doses of nicotine had a significant interaction with ethanol in terms of radial arm maze choice accuracy. Nicotine plus ethanol coadministration precipitated a significant choice accuracy impairment at doses that when given alone had no effect on performance. At the lower dose range of nicotine, ethanol coadministration eliminated the nicotine-induced memory improvement. No significant effects were seen with either nicotine or ethanol treatment or their interaction on response latency in the radial arm maze. The nicotine–ethanol interactive effects on memory were compared with the interaction of their well-characterized hypothermic effects. Nicotine and alcohol, when injected separately or in combination, induced hypothermia with no significant interactive effect. This study found that ethanol blocked low-dose nicotine-induced memory improvement and precipitated memory impairment with high-dose nicotine treatment. This interaction may be an important consideration for nicotine and ethanol coabuse and the possible therapeutic use of nicotinic drugs for memory dysfunction.

Keywords: Working memory; Cognition; Radial arm maze; Body temperature

1. Introduction

The use of alcohol is often accompanied by the use of other psychoactive substances, particularly tobacco. Epidemiological data show that alcoholics have a high incidence of smoking (over 85%, among the highest rate of any population subgroup) and alcoholics who smoke use more cigarettes per day than nonalcoholic smokers do. Functional interactions between ethanol and nicotine in the central nervous system have been known for some time (Collins, 1990; Collins et al., 1988, 1995, 1996; El-Fakahany et al., 1983; Yoshida et al., 1982). Given that alcohol drinking and tobacco smoking are very often conducted together (Hughes, 1995), it is important to understand the ethanol and nicotine relationships. Therefore, it is critically important to understand the pharmacological mechanism of interactions of nicotine and ethanol.

Although the mechanism(s) of this relationship is not fully understood, it is clear that the interaction between these two drugs is complex. On the biochemical level, ethanol has been found to enhance the initial rate of binding of various ligands to the ion channel associated with nicotinic receptors (El-Fakahany et al., 1983). Both chronic nicotine and chronic alcohol treatments have been shown to increase the number of brain nicotinic receptors (Yoshida et al., 1982). Thus, it appears that both alcohol and nicotine up-regulate the brain nicotinic receptors that parallel the development of tolerance to nicotine (Collins et al., 1988). Further, it has been demonstrated that rats withdrawn from chronic alcohol treatment exhibit greater sensitivity toward tremorigenic effects of nicotine compared to control. Elevation of nicotinic receptors by chronic alcohol treatment has been implicated as the mechanism that underlies the increase in seizure susceptibility (Gothoni, 1983; Gothoni and Ikola, 1985). However, other mechanisms such as down-regulation of GABA-ergic receptors cannot be ruled out. It also has been shown that (−)-nicotine attenuates the

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acute ethanol-induced increase in the glucose utilization in the mouse cerebellum (Anwer and Dar, 1995). Since pretreatment with hexamethonium, a nicotinic receptor antagonist, completely blocked the attenuation by nicotine, it has been suggested that cerebellar cholinergic–nicotinic receptor mechanism(s) is involved in ethanol-induced increase in glucose utilization (Anwer and Dar, 1995).

In addition, it has been demonstrated that the acute alcohol-induced motor incoordination involves some participation of brain nicotinic receptors (Dar et al., 1994). Intracerebellar infusions of nicotine significantly attenuated ethanol-induced motor incoordination in a dose-dependent manner. The attenuation of ethanol-induced motor incoordination by nicotine can be blocked by intracerebellar administration of nicotine antagonist, hexamethonium (Dar et al., 1994), suggesting the involvement of neuronal nicotinic receptors. It also has been demonstrated that pretreatment with nicotine prevents, in a dose-dependent manner, ethanol-induced impairment of both arial righting reflex and performance as well as reference and working memory in an eight-arm radial maze in rats (Tracy et al., 1999).

Differential effects of nicotine on selectively bred high-alcohol sensitivity (HAS) and low-alcohol sensitivity (LAS) rats and long-sleep (LS) and short-sleep (SS) mice provide more evidence suggesting a common neuronal substrate factor for alcohol and nicotine effects (de Fiebre et al., 1990). These investigators have suggested that ethanol may exert some of its depressant actions on locomotion and temperature regulation via a nicotinic system (de Fiebre et al., 1991).

Also, it has been shown that LS mice are more sensitive to an acute challenge of nicotine than are the SS mice. Interestingly, segregation analysis (F1, F2, back-cross) suggests that ethanol and nicotine sensitivity segregate together (de Fiebre and Collins, 1989; de Fiebre et al., 1990). Similarly, the observation that the LS mice develop greater tolerance to both alcohol and nicotine than do the SS mice suggests that the same neuronal substrate may be involved in the development of tolerance to these drugs.

The current project attempts to determine these relationships as they relate to cognition and change in body temperature in adult female rats. The rat model has been shown to provide clear and consistent effects of both nicotine and ethanol. Improved understanding of nicotine–ethanol relationships in experimental models may provide important new possibilities for combating both nicotine and alcohol addiction.

2. Materials and methods

2.1. Animals

A total of 36 adult female Sprague–Dawley rats were used for these experiments. Rats weighed 220 ± 5.5 g at the beginning of the experiment. Rats were housed in groups of three under constant room temperature of 21 ± 1 °C and reversed 12-h light–dark cycle (7 a.m. to 7 p.m. dark). The rats had ad libitum access to drinking water but were kept on a restricted feeding schedule to maintain their body weights at 80–85% of free-feeding levels, adjusted for growth. They were fed daily after testing on a radial arm maze for food reinforcement. The Duke University Institutional Animal Care and Use Committee has approved our experimental protocols.

2.2. Drug administration

The drugs to be administered by systemic route (nicotine tartrate at 0.15-, 0.3-, 0.6-, and 1.2-mg/kg doses) were dissolved in 0.9% saline and injected subcutaneously in a volume of 1 ml/kg. The nicotine doses are expressed as nicotine tartrate salt. A moderate dose of 1.5 g/kg ethanol (16% v/v) was chosen for these experiments. The ethanol solution was prepared with saline and 200 proof ethanol for intraperitoneal administration.

2.3. Experimental protocol

Rats were trained on an eight-arm radial maze for 18 sessions. After the acquisition of the task, the following three experiments were carried out.

2.3.1. Experiment 1

Twelve rats received the following combinations in a random order design: saline + saline, saline + 0.6 mg/kg nicotine, saline + 1.2 mg/kg nicotine, ethanol + saline, ethanol + 0.6 mg/kg nicotine, or ethanol + 1.2 mg/kg nicotine. Their performances in the radial arm maze and their body temperatures were assessed as described below.

2.3.2. Experiment 2

To confirm the results of high dose of nicotine in Experiment 1, another group of rats ($N = 12$) were given the following combinations: saline + saline, saline + 1.2 mg/kg nicotine, ethanol + saline, or ethanol + 1.2 mg/kg nicotine and their performances in the radial arm maze and their body temperature were assessed.

2.3.3. Experiment 3

To expand our dose range for nicotine, the third group of rats ($N = 12$) received the following treatments: saline + saline, saline + 0.15 mg/kg nicotine, saline + 0.3 mg/kg nicotine, ethanol + saline, ethanol + 0.15 mg/kg nicotine, or ethanol + 0.3 mg/kg nicotine (see Table 1) and similar to Experiments 1 and 2 their performances in the radial arm maze and their body temperature were assessed.

The doses selected for alcohol was 1.5 g/kg (16% v/v). Each animal in each group received all treatments for that group following a random order design. The interval between two consecutive injections was 10 min. Change in

Table 1
Experimental design for all three experiments is summarized below

n	First injection (intraperitoneal)	Second injection (subcutaneous)
Experiment 1		
12	S	S
	S	Nic, 0.6
	S	Nic, 1.2
	E	S
	E	Nic, 0.6
	E	Nic, 1.2
Experiment 2		
12	S	S
	S	Nic, 1.2
	E	S
	E	Nic, 1.2
Experiment 3		
12	S	S
	S	Nic, 0.15
	S	Nic, 0.3
	E	S
	E	Nic, 0.15
	E	Nic, 0.3

The first injection (saline or ethanol) was given intraperitoneally and the second injection (saline or nicotine) was given 10 min later subcutaneously. Body temperature and working memory were assessed 20 and 21 min after the second injection, respectively. S = 1 ml/kg saline, E = 1.5 g/kg ethanol, Nic = mg/kg nicotine.

body temperature was assessed 30 min after the first injection. Immediately after measuring body temperature, animals were tested on the automated eight-arm radial maze for assessing working memory.

2.4. Radial arm maze

Cognitive testing in the radial arm maze was conducted using a working memory task that we have found in many previous studies to be sensitive to the effects of acute and chronic nicotine in rats (Levin and Simon, 1998). The automated eight-arm radial maze (Med Associates, Georgia, VT, USA) consists of a central platform 50 cm in diameter with eight arms (10 × 70 cm) extending radially. Food cups for the reinforcers are located at the end of each arm. The maze is located in a room illuminated by a regular light during testing that contains many extra maze visual cues such as a table, a printer, a computer, a chair, and a cabinet. The rats had ad libitum access to drinking water but were kept on a restricted feeding schedule to maintain their body weights at 80–85% of free-feeding levels, adjusted for growth. They were fed daily after testing on a radial arm maze for food reinforcement. During the acquisition phase, the rats were tested on the maze once daily three to four times a week. The rat underwent 18 sessions of training.

To assess working memory, all eight arms were baited with a reinforcer (40-mg food pellets). The rat was then placed in a central arena, which was connected to all eight arms through eight gates. To begin the session, the gates were automatically lifted 10 s after the rat was placed in the central arena. Then the rat was allowed to move freely about the maze and explore each arm. Arm choices were recorded both by computer and an observant. When the rat placed all of its paws into an arm and approached the end of the arm to eat the pellet it was considered an arm entry. Since the arms were not rebaited during the session, only the first entry into an arm was rewarded. Subsequent entries into an arm previously entered were counted as errors. The session continued until either the rat entered all baited arms or 5 min elapsed. Drug challenges were administered after the 18 sessions of training period. The experimenter was blind to the treatment.

Errors in this task are repeated arm entries: a greater number of arm entries before a repeat indicates better performance. This task directly measures spatial working memory, because animals need to remember locations recently visited in order to refrain from repeating entries. Score of 8 is considered a perfect working memory score in this task.

Response latency was calculated by dividing the total time the animal spent in the maze divided by the numbers of entries (Levin and Simon, 1998).

2.5. Core body temperature

Both ethanol (Rezvani et al., 1986) and nicotine (de Fiebre et al., 1991) have been shown to lower body temperature. To determine the effects of different treatments on body temperature, a thermistor probe lubricated with Vaseline was gently inserted about 3 cm into the animal's rectum and the core body temperature was measured 30 min after the first injection (Rezvani et al., 1986). Each animal was probed only once in each session. The experimenter was blind to the treatment.

2.6. Statistical analysis

The data were assessed for significance by an analysis of variance for repeated measures. Significant interactions were followed-up by tests of the simple main effects. An alpha level of $P < .05$ was used as a cutoff for statistical significance. A one-tailed test of significance was used for the low dose range of nicotine, which has previously been found to cause memory improvements on the radial arm maze (Levin and Simon, 1998).

3. Results

3.1. Radial arm maze

3.1.1. Experiment 1

The radial arm maze choice accuracy measure, entries to repeat (ETR), showed a significant interaction of the high doses of nicotine and ethanol. The main effect of nicotine

was significant [$F(2,22) = 3.62$, $P < .05$]. The main effect of ethanol was nearly significant [$F(1,11) = 4.32$, $P < .07$]. But, because the Nicotine × Ethanol interaction was also significant [$F(2,22) = 4.25$, $P < .05$], the effect of nicotine with and without ethanol coadministration was assessed in tests of the simple main effects. No effect of 1.5 g/kg of ethanol was seen in the absence of nicotine (Fig. 1). Nicotine plus ethanol coadministration precipitated significant choice accuracy impairment. A combination of a high dose of 1.2 mg/kg of nicotine (which did not by itself affect choice accuracy) and 1.5 g/kg of ethanol caused a significant [$F(1,22) = 14.04$, $P < .005$] impairment in choice accuracy. With the lower dose of 0.6 mg/kg of nicotine, ethanol caused an intermediate response, which was not significant.

No significant effects were seen with either nicotine or ethanol treatment or their interactions on response latency (data not shown).

3.1.2. Experiment 2

This experiment replicated the working memory impairment when the high 1.2-mg/kg dose of nicotine was combined with the 1.5-g/kg dose of ethanol in another group of rats. Two rats did not respond on the maze at the high dose of nicotine. Their data were removed from the analysis. As before, there was a significant main effect of high-dose nicotine [$F(1,9) = 27.59$, $P < .005$] as well as a significant interaction of Nicotine × Ethanol [$F(1,9) = 5.68$, $P < .05$]. As shown in Fig. 1 (replication), the tests of simple main effects showed a significant [$F(1,9) = 5.95$, $P < .05$] choice accuracy impairment of the high-dose nicotine plus ethanol compared to the 1.2-mg/kg nicotine or ethanol alone. Similar to Experiment 1, a dose of 1.5 g/kg ethanol alone did not exert a significant effect on choice accuracy.

3.1.3. Experiment 3

To expand the nicotine dose range, lower nicotine doses of 0.15 and 0.3 mg/kg were also studied. In this dose range, differential effects of ethanol were also significant (Fig. 2). A significant ethanol main effect was seen [$F(1,11) = 6.03$, $P < .05$]. However, the ethanol dose used (1.5 g/kg) as in Experiments 1 and 2 did not by itself cause significant memory impairment. An ethanol-induced choice accuracy impairment was only seen when it was given in combination with 0.3 mg/kg of nicotine [$F(1,11) = 4.55$, $P < .05$]. This was due to ethanol eliminating the increase in choice accuracy seen with this more moderate dose range of nicotine (Fig. 2). We have previously seen this dose range of nicotine to significantly improve choice accuracy on the radial arm maze (for review, see Levin and Simon, 1998). In the current study, the rats were performing so near the ceiling of perfect performance, that there was little room left for improvement by nicotine. Despite this, compared with control saline, the 0.3-mg/kg nicotine dose without ethanol showed a significant improvement in performance in the ra-

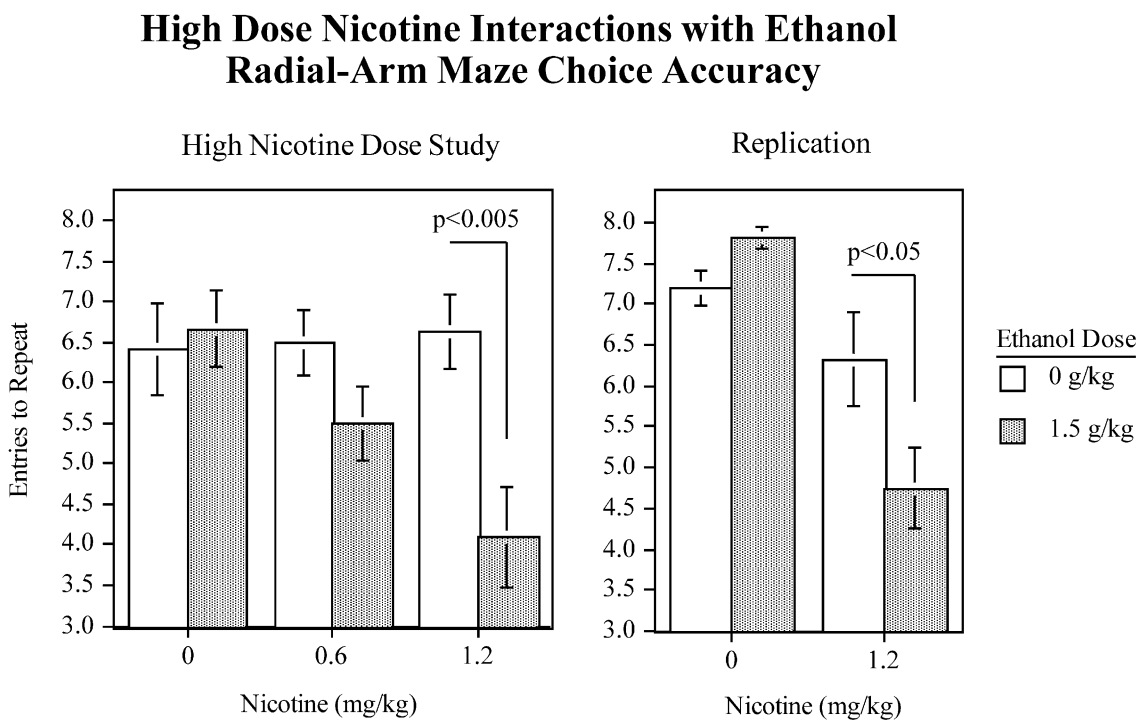

Fig. 1. Effects of different doses of subcutaneous administration of nicotine alone or in combination with 1.5 g/kg ethanol ip on working memory in rats. Data represent mean ± S.E.M. of 12 adult female rats. The main effect of nicotine was significant [$F(2,22) = 3.62$, $P < .05$]. The Nicotine × Ethanol interaction was also significant [$F(2,22) = 4.25$, $P < .05$].

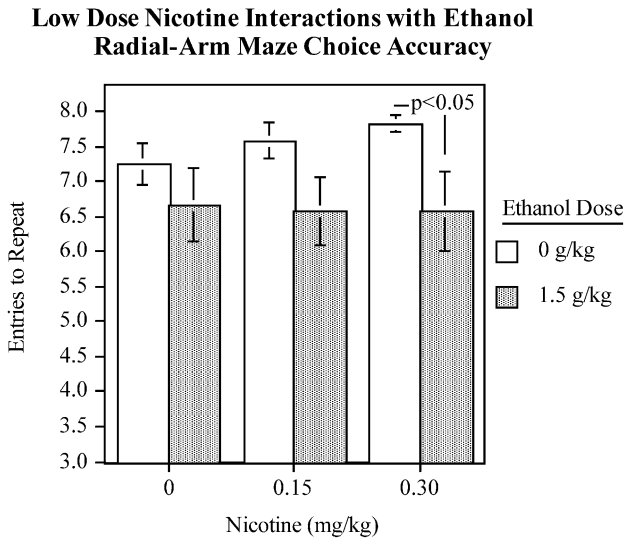

Fig. 2. Effects of different doses of subcutaneous administration of nicotine alone or in combination with 1.5 g/kg ethanol ip on working memory in rats. Data represent mean ± S.E.M. of 12 adult female rats.

dial arm maze in a one-tailed test ($P < .05$). In contrast, there was no hint of nicotine-induced improved memory performance when this dose of nicotine was given with 1.5 g/kg of ethanol. As cited above, the addition of ethanol to 0.3 mg/kg of nicotine significantly suppressed choice accuracy when compared to 0.3 g/kg of nicotine alone.

No significant effects were seen with either nicotine or ethanol alone or in combination on response latency (data not shown).

3.2. Body temperature

3.2.1. Experiment 1

Both nicotine and ethanol reduced body temperature. The main effect of nicotine was highly significant [$F(2,22) = 18.22$, $P < .0005$]. The main effect of ethanol was also clearly significant [$F(1,11) = 11.23$, $P < .01$]. The Nicotine - × Ethanol interaction was not significant. The hypothermic effects of either drug are potentiated by the other drug in this experiment (Fig. 3).

3.2.2. Experiment 2

With the high-nicotine dose replication in another group of rats, there was again a very significant [$F(1,11) = 96.94$, $P < .0005$] main effect of nicotine-induced hypothermia. In this study, the main effect of ethanol was not significant but the Ethanol × Nicotine interaction was quite significant [$F(1,11) = 27.02$, $P < .0005$]. Tests of the simple main effects showed that nicotine alone [$F(1,11) = 25.8$, $P < .005$] and in combination with ethanol [$F(1,11) = 154.60$, $P < 0.0001$) caused significant hypothermia (Fig. 3).

3.2.3. Experiment 3

With the lower doses of nicotine (0.15 and 0.3 mg/kg), there were still significant main effects of nicotine [$F(2,22) =$

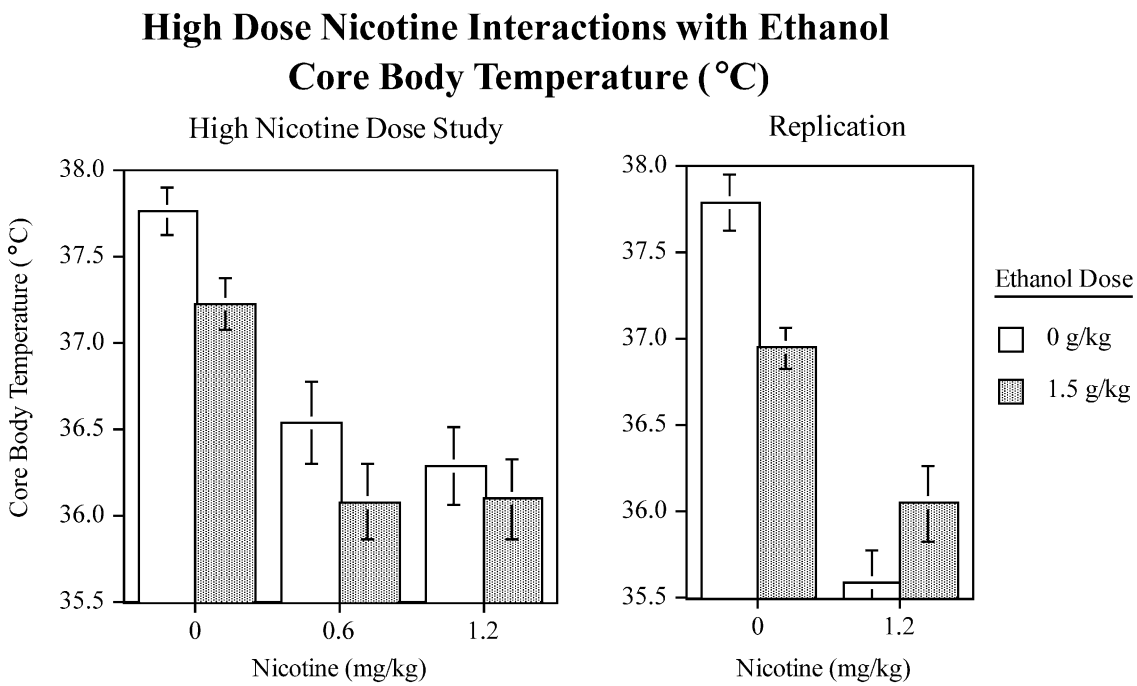

Fig. 3. Effects of different doses of subcutaneous administration of nicotine alone or in combination with 1.5 g/kg ethanol ip on core body temperature in rats. Data represent mean ± S.E.M. of 12 adult female rats.

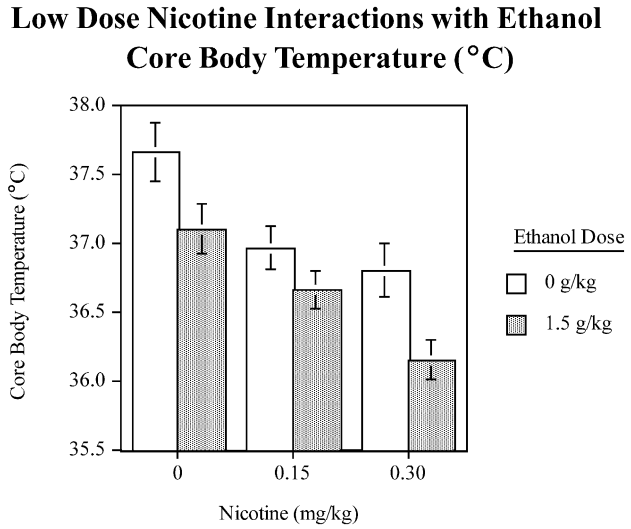

Fig. 4. Effects of different doses of subcutaneous administration of nicotine alone or in combination with 1.5 g/kg ethanol ip on core body temperature in rats. Data represent mean ± S.E.M. of 12 adult female rats.

24.97, $P < .0001$] and ethanol [$F(1,11) = 28.47$, $P < .0005$] with both causing hypothermia (Fig. 4). No interaction of Ethanol × Nicotine was seen with these doses of nicotine and ethanol.

4. Discussion

Both the neurobehavioral effects of nicotine and ethanol have been widely characterized in rodents. However, their interactions have not been widely studied, despite the fact that these two drugs are very often used and abused together. The present experiments examined the effects of nicotine and ethanol alone and in combination on the radial arm maze choice accuracy for assessing memory function and on body temperature. Our findings showed that nicotine and ethanol given alone did not exert a significant effect on choice accuracy in these experiments. However, coadministration of nicotine and ethanol resulted in a significant choice accuracy impairment. It seems that ethanol, at a dose that did not by itself impair memory, blocked the memory improvement reported in the literature with low to moderate doses of nicotine (Levin and Simon, 1998) and precipitated an impairment with high doses of nicotine.

A significant improvement in memory function with nicotine was not seen in the current study. There was a trend toward such an improvement with the 0.3-mg/kg dose on nicotine. Compared with the vehicle condition, the rats showed a nearly significant ($P < .07$) improvement with this dose. Because the rats were performing close to perfect in the control condition, a ceiling effect was imposed, which limited the possibility of improvement. The improvement that was seen at this dose was significant on a one-tailed basis. Confirming previous data showing the efficacy of this dose range of nicotine in improving radial arm maze performance (Levin and Simon, 1998) provides support for the reality of nicotine-induced improvement in this study. The significant ($P < .05$, two-tailed) difference between performance with 0.3 mg/kg of nicotine alone and 0.3 mg/kg of nicotine plus ethanol (Fig. 2) suggests an improving action for nicotine.

Experimental evidence has demonstrated that acute and chronic alcohol intake causes cognitive impairment in rats (Givens, 1995; Matthews et al., 1995; Tracy et al., 1997). It also has been shown that treatment with nicotinic receptor agonists or cholinesterase inhibitors reverses alcohol-induced learning deficits (Beracochea et al., 1986; Hodges et al., 1991). Recently, it has been demonstrated that nicotine enhances latent inhibition and ameliorates ethanol-induced deficits in latent inhibition in mice (Gould et al., 2001). Also, it has been shown that pretreatment with nicotine reduces the effects of ethanol on both reference and working memory in rats (Tracy et al., 1999). These findings suggest a functional interaction between ethanol and nicotinic receptors. Our results differ from these findings possibly because ethanol was given before nicotine. The order of the drug administration might have a critical effect. The current findings, contrary to our original hypothesis, showed a surprising interaction of higher doses of nicotine with ethanol coadministration causing a significant impairment in memory performance.

In the first experiment, the combination of the higher dose of nicotine (1.2 mg/kg) and ethanol caused a significant impairment in memory performance in the radial arm maze. This effect was replicated in the second experiment. When given alone neither nicotine nor ethanol at these doses significantly affected choice accuracy performance. The lower dose range of nicotine showed an indication of improved memory performance such as has been reported previously (Levin and Simon, 1998). This effect was blocked by ethanol pretreatment. It appears that ethanol blocked critical mechanisms by which nicotine improves memory performance but did not block the additional critical mechanisms by which higher doses of nicotine lose the ability to improve memory performance. Thus, with no countervening memory improving effect, the higher doses of nicotine caused an outright impairment when given with ethanol. This might be related to a slight sedation or disturbance in coordination. However, slight sedation or incoordination would not in themselves alter choice accuracy in the radial maze, as the same motor response is required for correct and incorrect choices. These findings need to be confirmed in male rats as well since the estrous cycle may affect the animal's behavior in this task.

The functional relationship between ethanol and nicotine is complex and not very well understood. The interactions between alcohol and nicotine are not likely to be of pharmacokinetics origin since previous studies have shown that neither drug influences the elimination rate of the other

(Collins et al., 1988). Thus, it seems that the interaction between ethanol and nicotine is pharmacodynamic rather than pharmacokinetic. Both drugs have been shown to increase the number of the nicotinic receptors in the brain (Yoshida et al., 1982) and modulate the release of several neurotransmitters by activating $\alpha 4\beta 2$-type nicotinic receptors (Aistrup et al., 1999; Cardoso et al., 1999). Several of these neurotransmitters including dopamine, serotonin, glutamate, and GABA are involved in cognitive functions. Dopamine, which is involved in the regulation of body temperature (Salmi et al., 1993), motor activity (Museo and Wise, 1990) as well as reward pathway (DiChiara and Imperato, 1985, 1988) has been shown to be released by both nicotine and ethanol (DiChiara and Imperato, 1985, 1988; Museo and Wise, 1990). Thus, it is likely that these two drugs interact by modulating dopaminergic pathways in the brain.

Nicotine has been shown to reliably induce hypothermia (Luo et al., 1994). Ethanol also has been demonstrated to cause hypothermia (Rezvani et al., 1986) in rats. The combination of nicotine and alcohol at doses used in these experiments potentiated the hypothermia. It can be speculated that the exaggerated hypothermia may be attributed to more dopamine release after administration of the nicotine and ethanol together. However, this cannot be confirmed with the present data.

These studies provide important practical information regarding the complex nature of nicotine–ethanol interactions, i.e., that ethanol blocks lower dose nicotine-induced memory improvement and at the presence of ethanol, a high dose of nicotine produces a memory impairment. With more specific nicotinic ligands further studies could uncover the true mechanism of nicotine–ethanol interactions and provide novel avenues for development of better nicotinic based treatments for memory impairment.

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