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Potentiation of Ethanol-Induced Loss of the Righting Reflex by Ascorbic Acid in Mice: Interaction With Dopamine Antagonists

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WU, C. F., H. L. ZHANG AND W. LIU. *Potentiation of ethanol-induced loss of the righting reflex by ascorbic acid in mice: Interaction with dopamine antagonists.* PHARMACOL BIOCHEM BEHAV **66**(2) 413–418, 2000.—The present investigation was carried out to determine the effect of ascorbic acid on ethanol-induced loss of the righting reflex (LORR) and the interactions between ascorbic acid and dopamine receptor antagonists in affecting this action of ethanol in mice. To test the effect of each drug on ethanol-induced LORR, ascorbic acid (31.25, 62.5, 125, 250, 500, 1000 mg/kg intraperitoneally [IP]) and dopamine receptor antagonists (haloperidol 0.5, 1.0 mg/kg; L-sulpiride 20, 40, 80 mg/kg; clozapine 0.625, 1.25, 2.5 mg/kg; SCH 23390 0.5, 1.0, 2.0 mg/kg subcutaneously [SC]) were administered, respectively, 30 min before ethanol (4.0 g/kg IP) administration. Ascorbic acid, at the dose of 1000 mg/kg, significantly potentiated ethanol-induced LORR in mice. Dopamine D_2 antagonists haloperidol (0.5, 1.0 mg/kg SC), and L-sulpiride (80 mg/kg SC) also significantly prolonged the duration of LORR induced by ethanol. Clozapine and SCH 23390, at the doses used, did not affect ethanol-induced LORR. In the interaction study, the synergistic effect of ascorbic acid (1000 mg/kg IP) on ethanol-induced LORR was significantly enhanced by dopamine D_2 antagonists haloperidol, L-sulpiride, and clozapine, and the highest dose of dopamine D_1 antagonist SCH 23390. These results suggest that ascorbic acid may potentiate ethanol-induced LORR partially via a mechanism mainly linked to blockade of dopamine D_2 receptors. © 2000 Elsevier Science Inc.

Ethanol Ascorbic acid SCH 23390 Haloperidol L-Sulpiride Clozapine
Loss of the righting reflex Mouse

LARGER doses of ethanol cause a central depressant effect, which induces sleep behavior in animals, or more scientifically, loss of the righting reflex (LORR) in mice and rats. The exact mechanisms of ethanol-induced LORR in animals are not clear. Accumulated data show that some drugs, such as naloxone (9), and glucocorticoids (35), can antagonize, whereas others such as apomorphine (11), haloperidol, clozapine (6), taurine (15), NMDA (16), and benzodiazepine receptor ligand Ro-15-4513 (29) can potentiate ethanol-induced LORR in mice. These observations suggest that a variety of neurochemical effects may be involved in this ethanol-induced phenomenon.

It is well recognized that the dopaminergic system is involved in the central actions of ethanol. Acute administration of ethanol increases dopamine synthesis (4) and release (18). Dopamine antagonists, such as D_2 receptor antagonist raclopride, haloperidol (6,31), D_1 receptor antagonist SCH 23390 (6,31), or D_1 and D_2 receptor antagonists used in combination (31), reduce ethanol-induced hyperactivity. However, the reports on the effects of dopaminergic system on ethanol-induced central depression are complicated. For example, apomorphine potentiates ethanol-induced LORR in Long-Sleep (LS) mice, but does not alter this soporific effect of ethanol in Short-Sleep (SS) mice (11). D_2/D_3 dopamine antagonist haloperidol, but not tiapride and D_1 antagonist SCH 23390, potentiates LORR induced by ethanol in mice (6).

In recent years, much attention has been paid to the role of ascorbic acid in the brain (19). It is considered that ascorbic acid acts not only as an antioxidant but also a neuromodulator in the brain. There are also reports dealing with the interactions between ascorbic acid and ethanol in the central nervous system. Exogenous administration of sodium ascorbate antagonizes ethanol-induced impairment of swimming in mice (2), attenuates some of the depressant effects of ethanol,

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but not the stimulatory effect from a low dose of ethanol in mice (14), and rises the survival rate in ethanol-intoxicated mice (43). More recently, it has been shown that acute administration of ethanol can stimulate ascorbic acid release in the striatum and the nucleus accumbens in rats (34,39,40), demonstrating the existence of the interaction between ethanol and ascorbic acid in the central nervous system.

The extracellular levels of ascorbic acid in the striatum can be increased by dopamine receptor agonists. It is proposed that the enhancement of striatal ascorbic acid release is a common property of all indirect dopamine agonists (28), such as amphetamine (28) and ethanol (39,40). Our preliminary experiments have demonstrated that D_2 dopamine antagonist L-sulpride suppressed ethanol-induced ascorbic acid release in rat striatum (24), suggesting a functional linkage may exist between the dopaminergic system, ascorbic acid, and ethanol. Because experiments have shown that ascorbic acid can affect dopaminergic functions by inhibiting dopamine and its ligands binding to dopamine receptors (17,20), potentiating the cataleptic behavior induced by haloperidol (10,30), and it is suggested that ethanol-ascorbic acid interaction may involve a dopaminergic mechanism (14), the present study further evaluates the roles of ascorbic acid and some dopamine antagonists in ethanol-induced sleep and their interactions with each other.

METHOD

Female Swiss mice, weighing between 20 and 22 g, were used in the present investigation. The animals were provided by the Experimental Animal Center of Shenyang Pharmaceutical University. All mice were housed in plastic cages at room temperature (22° ± 2°C) with 12/12 h light/dark cycle for 3 days for adapting to the laboratory environment before use in the experiments. The animals were fed commercial pellet food and tapwater ad lib and used in the experiments only once.

Ethanol-Induced LORR

Ethanol (4 g/kg intraperitoneally [IP]) was administered to each mouse. The LORR was measured as the time interval between loss of the righting reflex and recovery of the righting reflex after ethanol administration. Recovery of the righting reflex was defined as the ability of the animal to re-right himself 3 times within 60 sec after being placed on his back (14).

Mice received saline or ascorbic acid (31.25, 62.5, 125, 250, 500, 1000 mg/kg, IP) 30 min before IP injection of ethanol 4 g/kg. Dopamine receptor antagonists were administered subcutaneously (SC) 30 min before ethanol injection. In the interaction study, ascorbic acid (1000 mg/kg) was administered IP and dopamine receptor antagonists were administered SC, to prevent the possible interference with each other, at the same time, 30 min before ethanol injection.

Blood Ethanol Assay

The concentration of ethanol in peripheral blood collected from the tip of the mouse tail was determined by gas chromatography (Shimadzu GC-17A, Japan). Dopamine receptor antagonists (administered SC) and ascorbic acid (1000 mg/kg IP) were administered 30 min before ethanol (4 g/kg IP). The blood samples were collected in nonheparinized tubes 15 min, 30 min, and 60 min after ethanol administration. The tubes were capped and after the blood was allowed to clot; the blood samples were centrifuged; 0.1 μl of the serum was injected into the gas chromatograph as quickly as possible (7). The instrument was equipped with a Poropak-Q column (2.6 mm inside diameter × 2 m length). Column and injection port temperatures were 150°C. The flow of the nitrogen carrier was 100 ml/min. The ethanol value was calculated using external standard method.

Drugs

Ascorbic acid (Shenyang Reagent Co., Shenyang, China) was dissolved in saline before use and kept in a light-resistant container. Ethanol (Shenyang Reagent Co., Shenyang, China) was diluted by saline to 20%. L-Sulpiride (Ravizza, Milan, Italy) was dissolved in 0.12 M acetic acid saline solution. Clozapine (Changzhou Pharmaceutical Co., Changzhou, China) was dissolved in 0.3 M hydrochloride acid saline solution. Haloperidol hydrochloride (Shanghai Haipu Pharmaceutical Co., Shanghai, China) and SCH 23390 maleate (Schering Corporation, Bloomfield, NJ) were dissolved in saline. All drugs were dissolved before use and the doses refer to their salts.

Statistical Analysis

All data were analyzed by two-way analyses of variance (ANOVA). Post hoc testing was done using Fisher's Least Significant Difference (LSD) test.

RESULTS

The effect of ascorbic acid on ethanol-induced LORR is shown in Fig. 1. Ascorbic acid at the doses above 250 mg/kg show a tendency toward potentiation of LORR induced by ethanol, but it was only the highest dose (1000 mg/kg) used in this experiment that showed a statistical significance ($p < 0.05$). Therefore, this dose of ascorbic acid was used in the following experiments to study the interaction of dopamine antagonists and ascorbic acid on ethanol-induced LORR.

L-Sulpiride, at the doses of 20 and 40 mg/kg, did not affect LORR induced by ethanol. However, it significantly potentiated ethanol-induced LORR at the dose of 80 mg/kg ($p < 0.01$). When ascorbic acid was used in combination with L-sulpiride, the duration of LORR induced by ethanol significantly increased. Two-way ANOVA showed a significant synergism

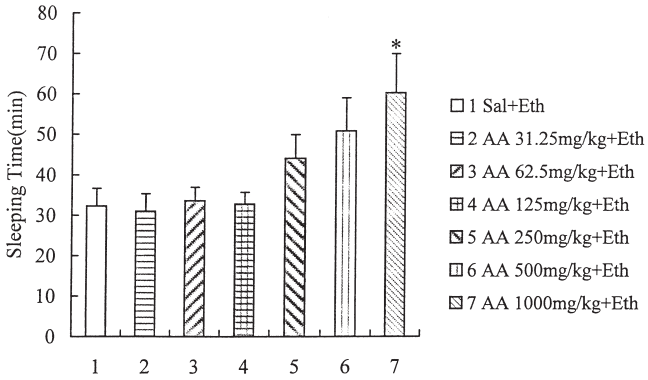

FIG. 1. Effect of ascorbic acid on ethanol-induced sleep-time in mice. Ascorbic acid is given 30 min prior to ethanol (4 g/kg, IP). Each value represents the mean ± SEM of 10 to 14 mice. Sal = saline; Eth = ethanol; AA = ascorbic acid. *$p < 0.05$ compared with saline + ethanol group.

between ascorbic acid and L-sulpiride 40 mg/kg, $F(1, 41) = 8.54$, $p < 0.01$, and L-sulpiride 80 mg/kg, $F(1, 40) = 6.82$, $p < 0.05$, respectively (Fig. 2).

Haloperidol significantly increased ethanol-induced LORR at the doses of 0.5 and 1.0 mg/kg ($p < 0.01$). When ascorbic acid was used in combination with haloperidol at these doses, the duration of LORR induced by ethanol was further lengthened. Two-way ANOVA showed a significant synergism between ascorbic acid and haloperidol 0.5 mg/kg, $F(1, 52) = 4.28$, $p < 0.05$. But only a tendency of synergism was seen between ascorbic acid and haloperidol 1.0 mg/kg, $F(1, 52) = 3.75$, $p > 0.05$ (Fig. 3).

Clozapine, at the doses of 0.625, 1.25, and 2.5 mg/kg, did not affect ethanol-induced LORR. However, when ascorbic acid was used in combination with clozapine at above doses, a tendency of dose-dependent increase in ethanol-induced LORR was observed. Two-way ANOVA showed significant synergism between ascorbic acid and clozapine 2.5 mg/kg, $F(1, 45) = 13.03$, $p < 0.01$ (Fig. 4).

SCH 23390, at the doses of 0.5, 1.0, and 2.0 mg/kg, used alone did not affect ethanol-induced LORR. However, at the highest dose of 2.0 mg/kg used in combination with ascorbic acid it potentiated the effect of ascorbic acid on the ethanol-induced LORR (Fig. 5).

The concentration of ethanol in the blood was measured at 15, 30, and 60 min after IP administration of ethanol. The protocol of drug administration was the same as in the interaction study, but only the highest doses of the dopamine antagonists were used in order to examine the potential influence of these drugs on ethanol clearance from blood. The results are shown in Table 1. Ascorbic acid significantly decreased the blood ethanol concentration 15 and 30 min after ethanol administration. Clozapine and SCH 23390 increased blood ethanol concentration at 30 and 60 min, and as did L-sulpiride at 15 and 60 min, after ethanol administration. However, haloperidol showed no effect on blood ethanol concentration. When the dopamine antagonists were used in combination with ascorbic acid, the blood ethanol concentrations were significantly higher in haloperidol, L-sulpiride, and SCH 23390 groups at 30 min, and in clozapine and SCH 23390 groups at 60 min respectively, after ethanol administration, than that in ethanol control group. However, the interactions between ascorbic acid and dopamine antagonists evaluated by two-way ANOVA showed that only L-sulpiride (at 30 min, $F(1, 21) = 5.35$, $p < 0.05$) and SCH 23390 (at 30 and 60 min, $F(1, 20) = 20.37$, $p < 0.01$; $F(1, 21) = 4.93$, $p < 0.05$) has interaction with ascorbic acid, respectively, in affecting blood ethanol concentration (Table 1).

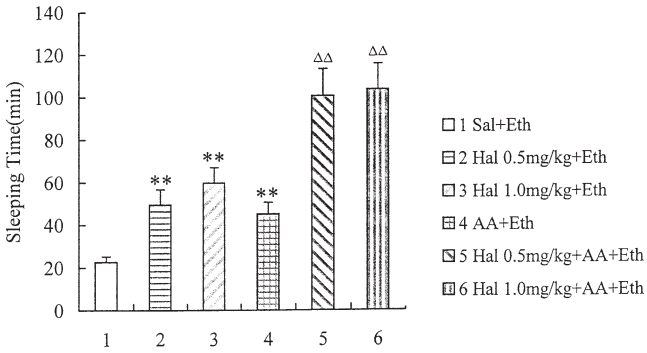

FIG. 3. Effect of haloperidol on ethanol-induced sleep-time in mice and its interaction with ascorbic acid. Haloperidol (SC) and ascorbic acid (1000 mg/kg, IP) are given 30 min prior to ethanol (4 g/kg, IP). Each value represents the mean ± SEM of 13 to 15 mice. Sal = saline; Eth = ethanol; AA = ascorbic acid; Hal = haloperidol. $^{**}p < 0.01$ compared with saline + ethanol group. $^{\Delta\Delta}p < 0.01$ compared with ascorbic acid + ethanol group.

DISCUSSION

The present studies show that ascorbic acid, at the dose of 1000 mg/kg, potentiates the duration of LORR induced by ethanol in mice, whereas lower doses of ascorbic acid were without any effect. This result is similar to that observed by Ferko (14) who found that L-ascorbic acid, at the dose of 500 mg/kg, significantly enhanced ethanol-induced hypnosis, but at higher doses of 1000 mg/kg and 1500 mg/kg, increased the onset of sleep in mice. The minor differences for the most effective doses that potentiated the effect of ethanol between the

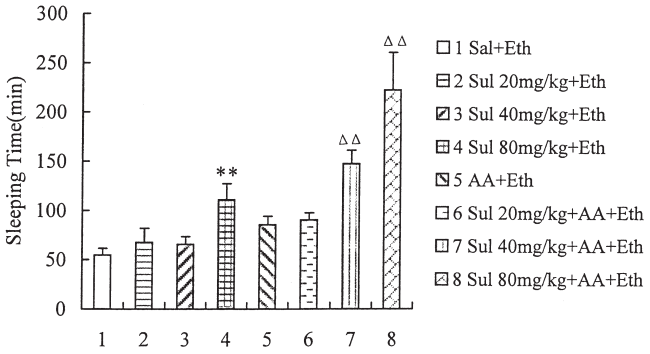

FIG. 2. Effect of L-sulpiride on ethanol-induced sleep-time in mice and its interaction with ascorbic acid. L-Sulpiride (SC) and ascorbic acid (1000 mg/kg IP) are given 30 min prior to ethanol (4 g/kg IP). Each value represents the mean ± SEM of 12 mice. Sal = saline Eth = ethanol; AA = ascorbic acid; Sul = L-sulpiride. $^{**}p < 0.01$ compared with saline + ethanol group. $^{\Delta\Delta}p < 0.01$ compared with ascorbic acid + ethanol group.

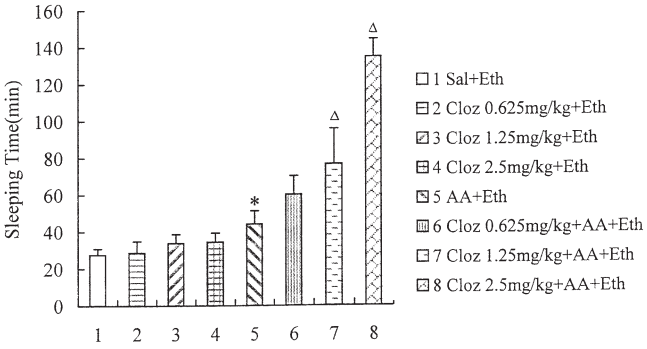

FIG. 4. Effect of clozapine on ethanol-induced sleep-time in mice and its interaction with ascorbic acid. Clozapine (SC) and ascorbic acid (1000 mg/kg IP) are given 30 min prior to ethanol (4 g/kg IP). Each value represents the mean ± SEM of 12 to 13 mice. Sal = saline; Eth = ethanol; AA = ascorbic acid; Cloz = clozapine. $^{*}p < 0.05$ compared with saline + ethanol group. $^{\Delta}p < 0.05$ compared with ascorbic acid + ethanol group.

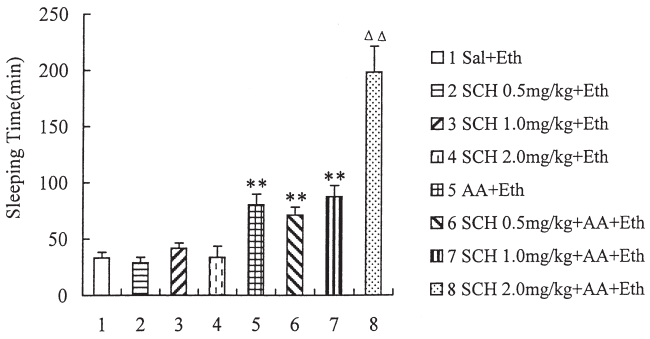

FIG. 5. Effect of SCH 23390 on ethanol-induced sleep-time in mice and its interaction with ascorbic acid. SCH 23390 (SC) and ascorbic acid (1000 mg/kg IP) are given 30 min prior to ethanol (4 g/kg IP). Each value represents the mean ± SEM of 10 to 12 mice. Sal = saline; Eth = ethanol; AA = ascorbic acid; SCH = SCH 23390. $^{**}p < 0.01$ compared with saline + ethanol group. $^{\Delta\Delta}p < 0.01$ compared with ascorbic acid + ethanol group.

present study and Ferko's studies might be due to the gender different of the animals used, because male Swiss-Webster mice were used in Ferko's experiment (4). However, Yanai et al. (41) reported that ascorbic acid enhanced the sleeping time in a large range of doses from 430 to 1720 mg/kg.

The potentiating effect of ascorbic acid on ethanol-induced LORR could be partially explained by its interaction with the dopaminergic system in the brain. Several experiments have shown that central administration of ascorbic acid attenuated the behavioral response to amphetamine (37,38), and systemic administration of ascorbic acid potentiated the behavioral effects of haloperidol in rats (30). These observations suggest a neuroleptic-like action of neostriatal ascorbic acid (10,30). In the present study, a significant synergism between ascorbic acid and dopamine D_2 antagonists L-sulpiride, haloperidol, and clozapine on ethanol-induced LORR was observed, strongly providing further evidence for the existence of the interaction of ascorbic acid and the central dopaminenergic system.

The mechanism of the synergistic actions between dopamine D_2 receptor antagonists and ascorbic acid on ethanol-induced LORR is not exactly understood. However, the interference of ascorbic acid with the dopamine binding sites should be considered. Auto-oxidation of 3,4-dihydroxyphenylacetic acid (DOPAC) and other endogenous catechol-containing compounds produces quinones that could induce protein modification by conjugating to proteins in vivo. The DOPAC quinone produced by autooxidation is responsible for the irreversible inhibition of [^{3}H]spiperone binding to neuronal dopamine D_2 receptors. However, ascorbic acid can prevent this inhibition (3). It has been reported that systemic administration of dopamine D_2 receptor antagonists, such as haloperidol, L-sulpiride, and clozapine, largely increased the extracellular DOPAC levels (25,36). Such an increase in extracellular DOPAC could result in the inhibition of these antagonists further binding to the D_2 receptors due to DOPAC quinone conjugation. However, it can be assumed that when ascorbic acid is administered in combination with dopamine D_2 antagonists, the DOPAC quinone conjugation to the receptor proteins could be prevented, which as a consequence could enhance dopamine D_2 receptor antagonists binding to their receptors. Thus, a synergistic phenomenon between ascorbic acid and dopamine D_2 receptor antagonists is produced.

TABLE 1

EFFECTS OF ASCORBIC ACID AND DOPAMINE ANTAGONISTS ON SERUM ETHANOL CONCENTRATIONS

Group	Serum Ethanol (mg/ml)		
	15 min	30 min	60 min
Saline-ethanol	4.7 ± 0.6	4.0 ± 0.2	3.0 ± 0.2
AA-ethanol	3.2 ± 0.4*	2.4 ± 0.3*	3.3 ± 0.4
Hal-ethanol	5.3 ± 0.5	3.9 ± 0.2	3.4 ± 0.4
Sul-ethanol	6.1 ± 0.1*	4.9 ± 0.6	5.2 ± 0.2
Cloz-ethanol	5.3 ± 0.4	5.2 ± 0.1*	5.2 ± 0.3*
SCH-ethanol	5.6 ± 0.4	6.0 ± 0.1*	5.5 ± 0.2*
AA-Hal-ethanol	4.2 ± 0.6	5.1 ± 0.6*	4.3 ± 0.4
AA-Sul-ethanol	5.3 ± 0.2	5.4 ± 0.2*	4.4 ± 0.4
AA-Cloz-ethanol	3.6 ± 0.7	4.0 ± 0.4	4.6 ± 0.7*
AA-SCH-ethanol	5.3 ± 0.4	5.7 ± 0.1*	5.4 ± 0.1*

Data are expressed as mean ± SEM, n = 6. Ascorbic acid and dopaminergic antagonists are administered 30 min before ethanol 4.0 g/kg, IP. AA = Ascorbic acid 1000 mg/kg, IP; Hal = haloperidol 1.0 mg/kg, SC; Sul = L-sulpiride 80 mg/kg, SC; Cloz = clozapine 2.5 mg/kg, SC; SCH = SCH 23390 2.0 mg/kg, SC. *$p < 0.05$ compared with Saline-ethanol group.

It is known that dopamine receptor antagonists, such as the phenothiazines (26) and pimozide (1), can potentiate the sedative-hypnotic effects of ethanol. The present study, by using the selective dopamine D_1 and D_2 receptor antagonists, has shown that dopamine D_2 receptor antagonists L-sulpiride and haloperidol potentiated ethanol-induced LORR in mice. Although clozapine, at the doses used in the present study, did not affect ethanol-induced LORR, it significantly potentiated LORR at higher doses used in the preliminary tests (data not shown). All these dopamine D_2 antagonists also synergistically potentiated the effect of ascorbic acid on ethanol-induced LORR in mice. Thus from these results it is plausible to assume that the inhibition of dopamine D_2 receptors contributes to the potentiation of ethanol-induced LORR, and furthermore, ascorbic acid, possibly via a mechanism mainly linked to the inhibition of dopamine D_2 receptors, potentiates ethanol-induced LORR in mice.

Some of the dopamine antagonists used in this study also interact with other receptors. For example, haloperidol shows affinities for σ, α_1, and 5-HT_2 receptors, and clozapine for α_1, 5-HT, and H_1 receptors (23). For this reason, the possibility exists that the potentiation of ethanol-induced LORR partially results from blocking or stimulating receptors other than dopamine D_2 receptors. However, L-sulpiride, a more selective dopamine D_2 receptor antagonist among the dopamine antagonists used, also potentiated ethanol-induced LORR, providing evidence for the possible involvement of dopamine D_2 receptors in the potentiation of ethanol-induced LORR in mice.

The relative contribution of dopamine receptor subtypes in ethanol-induced central effects was investigated in recent years (6,31). It has been shown that dopamine D_2 antagonists can reduce the hyperactivity induced by low doses of ethanol (6,31) and potentiate LORR induced by high doses of ethanol (6) in mice. The effect of dopamine D_1 antagonist SCH 23390 is clearly not specific (21,31). In the present study, SCH 23390 used alone did not affect ethanol-induced LORR, even at a high dose that delayed the clearance of ethanol from the blood. This is consistent with the observation of Cohen et al.

(6) who, however, used much lower doses than we used and found that SCH 23390 inhibited the stimulated locomotor activity by ethanol but did not potentiate ethanol-induced LORR. However, in the interaction study, SCH 23390 at the dose of 2.0 mg/kg synergistically increased the effect of ascorbic acid. This may be the cause of high blood ethanol concentration maintained by the interaction of SCH 23390 and ascorbic acid, or the mega-dose of SCH 23390 being used, which may possibly produce some nonspecific actions other than acting only on D_1 receptors. In fact, the reports on the role of dopamine D_1 receptor in affecting ethanol's actions are controversial. For example, it is reported that dopamine D_1 antagonist SCH 23390 inhibits the stimulated locomotor activity by ethanol, but it has no effect on ethanol-induced LORR (6). Some reports show that SCH 23390, or disruption of D_1 receptor expression, decreases ethanol consumption (12,13), and others show that SCH 23390 has little effect on ethanol intake (22,32). These observations may suggest that dopamine D_1 receptor does not play a crucial role in affecting the hypnotic effect of ethanol, despite the fact that it may be more important in regulating other effects of ethanol than dopamine D_2 receptors (8,13) in the central nervous system.

The possible alteration in pharmacokinetic behaviors of ethanol should be taken into account for the interpretation of the interactions between ethanol, ascorbic acid, and dopaminergic antagonists in the preset study. There are some paradoxical data published regarding the effect of ascorbic acid on the pharmacokinetic process of ethanol, including increasing the blood ethanol concentration (27), no change (14), or accelerating (5,33,42) the clearance of ethanol. Ferko clearly showed that ascorbic acid potentiated ethanol-induced sleep without affecting the blood ethanol concentration (14), and in the present study ascorbic acid decreased blood ethanol concentration in mice. Thus the effect of ascorbic acid on ethanol-induced LORR should not be explained by the alteration of pharmacokinetic process of ethanol, but by their mutual interaction in the central nervous system.

Few data have been published pertinent to the effect of dopaminergic antagonists on the pharmacokinetic process of ethanol. Shen et al. (31), by determining the brain ethanol concentration of FAST mice, found no evidence to support a pharmacokinetic explanation for changes in ethanol-induced locomotor behavior produced by D_1 antagonist SCH 23390 or D_2 antagonist raclopride. In the present study, we found that L-sulpiride, clozapine, and SCH 23390 significantly increased the blood ethanol concentration, whereas haloperidol had no effect. When the dopamine antagonists were used together with ascorbic acid respectively, all four groups showed higher blood ethanol concentrations than the ethanol alone group did when compared with each other at different time points. One may speculate, then, that the reason of potentiation of ethanol-induced LORR by dopamine antagonists and/or their use together with ascorbic acid is the alteration of pharmacokinetic process of ethanol. However, a dissociation between the effect of the drugs on ethanol-induced LORR and the drug-induced changes of blood ethanol concentration can be found when the behavior data were compared with the blood ethanol concentration in each group. Haloperidol, which had no effect on blood ethanol concentration, potentiated ethanol-induced LORR, whereas clozapine and SCH 23390, which increased blood ethanol concentration, had no significant effect on ethanol-induced LORR at the same dose used. The interaction analysis showed that only L-sulpiride and SCH 23390 show some interactions with ascorbic acid in the increase in blood ethanol concentration, although all dopamine D_2 and D_1 antagonists tested in the present study potentiated the effect of ascorbic acid on ethanol-induced LORR. Thus, according to the present and other observations (31) it does not appear that interference of dopaminergic drugs with ascorbic acid on ethanol-induced LORR is the result of alteration of pharmacokinetic process of ethanol. However, the potential pharmacokinetic alteration of ethanol induced by dopaminergic drugs merits further investigation.

In conclusion, the present study demonstrates that ascorbic acid potentiates ethanol-induced LORR and dopamine receptor D_2 antagonists synergistically enhance the effect of ascorbic acid on ethanol-induced LORR. However, dopamine D_1 antagonist SCH 23390 did not affect ethanol-induced LORR, but potentiated the effect of ascorbic acid on ethanol-induced LORR only at high doses. These results suggest that ascorbic acid may modulate the sedative actions of ethanol and this effect of ascorbic acid is somewhat linked to dopamine D_2 receptors in the central nervous system.

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