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D-Cycloserine Enhances Rapid Tolerance to Ethanol Motor Incoordination

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KHANNA, J. M., G. S. MORATO, A. CHAU AND G. SHAH. *D-Cycloserine enhances rapid tolerance to ethanol motor incoordination.* PHARMACOL BIOCHEM BEHAV 52(3) 609-614, 1995.—In a recent study, we showed that D-cycloserine, an agonist at the glycine site of the NMDA receptor, enhances the development of rapid tolerance to ethanol. In the present study, we report that the acquisition of rapid tolerance to the motor incoordination effect of ethanol (tilt-plane test) was increased only when D-cycloserine was injected before, but not after, the intoxicated practice under ethanol. The effect of D-cycloserine on tolerance when this agonist was administered in divided doses before and after test was similar to that obtained when D-cycloserine was injected before test. Higher doses of D-cycloserine did not produce a further enhancement of rapid tolerance. Moreover, when the dose of ethanol on day 1 was large enough to induce rapid tolerance per se, D-cycloserine did not further enhance the tolerance. The enhancement of tolerance by D-cycloserine was antagonized by previous administration of ketamine. The enhancement of ethanol tolerance by D-cycloserine and the antagonism of this effect by ketamine cannot be attributed to changes in pharmacokinetics of ethanol. Taken together, these results confirm the participation of the NMDA receptor system in the development of tolerance to ethanol, and reinforce earlier findings about the involvement of learning in tolerance.

Ethanol Rapid tolerance D-Cycloserine Ketamine NMDA receptor system

THE involvement of NMDA receptors in the development of tolerance to ethanol has been suggested by the results of different studies from our laboratory. The NMDA antagonists (+)MK-801 and ketamine inhibited the development of rapid tolerance to ethanol in the tilt-plane and hypothermia tests, whereas (−)MK-801, the inactive isomer, was ineffective (12,15,18). Moreover, the antagonists of NMDA receptor were also shown to retard chronic tolerance to motor incoordination, hypothermia, and hypnosis produced by ethanol (14,17,24,28).

It is well established that NMDA receptors are implicated in learning and memory, and the noncompetitive NMDA receptor antagonists (+)MK-801 and ketamine prevent one form of long-term potentiation considered to be an essential synaptic substrate for learning and memory (3,4,19-23,27,29). As the development of tolerance to ethanol's effects shares many characteristics with learning (7,9,10), it has been suggested that the role of the NMDA system in ethanol tolerance may be similar to its role in learning. Recently we demonstrated that D-cycloserine, an agonist at the glycine site of the NMDA receptor that improves learning (21,26), enhances the development of rapid tolerance to ethanol (13). Animals pretreated with D-cycloserine acquired rapid tolerance to a dose of ethanol that was insufficient to induce tolerance per se. In that study it was not possible to state whether the enhancement of tolerance development by D-cycloserine depended on intoxicated practice by the animals. Moreover, we do not know whether D-cycloserine would enhance tolerance to a dose of ethanol that was large enough to induce tolerance by itself. Thus, the first purpose of the present study was to compare the effect of D-cycloserine on tolerance development when this agonist was administered before or after the intoxi-

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cated practice under ethanol. Second, to investigate whether tolerance to ethanol could be further increased by D-cycloserine, we examined the effect of D-cycloserine on tolerance production by different doses of ethanol. Finally, we verified whether the enhancing effect of D-cycloserine on tolerance could be antagonized by the previous administration of ketamine.

METHODS

Animals

Male Sprague–Dawley rats obtained from Charles River Canada, Ltd. (Montreal, Quebec) had initial body weights of 150–200 g. They were individually housed in a colony room maintained at 21 ± 1°C with lights on from 0700 to 1900 h, and were fed standard laboratory rat chow in a daily ration that was adjusted to maintain comparable body weights in the various groups. Tap water was available ad lib.

Test Procedures

Tilt-plane test. The tilt-plane test was used as a measure of motor impairment (1,6). The apparatus consisted of a plane hinged at one end, around which it could be inclined at a fixed angular velocity through a range of 55° above the horizontal axis. The animal was placed on the slightly roughened surface of the plane, which was then tilted until the animal began to slide. The sliding angle was measured before and 30, 60, and 90 min after the injection of ethanol. The degree of postdrug ataxia was assessed as the percent change in sliding angle, compared to the same animal's predrug value. Maximum impairment, regardless of the time of its occurrence, was employed as the measure of ethanol effect. This generally occurred about 30 min after injection (11).

Experimental Procedure

Experiment 1: Effect of D-cycloserine on the development of rapid tolerance to ethanol (before/after design). We randomly divided 60 rats into four groups (n = 14 or 16 each), namely: control, divided doses, and before and after groups, depending on the method of D-cycloserine administration. On day 1 at zero time, the control and after groups were injected with saline, whereas the before group received D-cycloserine (6 mg/kg, IP) and the divided doses group was injected with D-cycloserine (3 mg/kg, IP), all in equal volumes. Then, 30 min later, half of the rats in each group (n = 7 or 8 each) received ethanol (2.3 g/kg, IP) and the other half saline. Before the experiment and at successive 30-min intervals up to 90 min after ethanol or saline injection, the degree of motor impairment was assessed (tilt-plane test) in all animals. Immediately after the 90-min measurement, the control and before groups were injected with saline. whereas the after group received D-cycloserine (6 mg/kg, IP) and the divided doses group again received D-cycloserine (3 mg/kg, IP), all in equal volumes. At 120 min after initial ethanol or saline administration, another IP injection of ethanol (0.7 mg/kg) or saline was given. This procedure of giving ethanol in two doses was employed because earlier work had suggested that a total dose of 3 g/kg might be just below the threshold for producing rapid tolerance, but doses >2.3 g/kg may not always fall in the linear part of the acute-dose response curve. Rats were then returned to their home cages. On day 2, all animals received a challenge dose of ethanol (2.3 g/kg, IP) and no pretreatments were given. The animals were tested for rapid tolerance to ethanol as described earlier. Tail blood samples (50 μl) for ethanol measurement were taken on day 2 at 120 min, immediately after the last measurement of motor impairment. Blood ethanol was analysed by the enzymatic method described previously (8).

Experiment 2: Does ketamine block the effect of D-cycloserine on rapid tolerance to ethanol? We randomly divided 64 rats into eight groups (n = 8 each). On day 1, four groups were injected with ketamine (1 mg/kg, IP), whereas the other four groups received saline. Then, 30 min later, rats from two of the ketamine and two of the saline groups were injected with D-cycloserine (3 mg/kg, IP) and the remaining four groups were again administered saline, resulting in two groups with each pretreatment (saline–saline, ketamine–saline, saline–D-cycloserine, or ketamine–D-cycloserine). Sixty minutes after the first injections, one of each pair of pretreatment groups was given IP ethanol (2.3 g/kg) and the other group was given saline. Before the experiment, and at successive 30-min intervals up to 90 min after ethanol or saline injection, the degree of motor-impairment was assessed (tilt-plane test) in all animals. Immediately after the last measurement, a second IP injection of D-cycloserine (3 mg/kg) or saline was given. At 120 min after the first ethanol or saline injections, another IP injection of ethanol (0.7 g/kg) or saline was given. Rats were then returned to their home cages. On day 2, all animals received a challenge dose of 2.3 g/kg ethanol and tolerance was assessed on the tilt-plane as described earlier. No ketamine, D-cycloserine, or saline pretreatment was given on day 2.

Experiment 3: Effect of different doses of D-cycloserine on rapid tolerance to ethanol. We randomly divided 48 rats into four groups (n = 12 per group). On day 1, three groups were injected with D-cycloserine doses of 10, 30, or 90 mg/kg, IP, respectively, and one group received saline. Then, 30 min later, half of each group received ethanol (2.6 g/kg, IP) and the other half received saline. Before the experiment, and at successive 30-min intervals up to 90 min after ethanol or saline injection, the degree of motor impairment was assessed (tilt-plane test) in all animals. Rats were then returned to their home cages. On day 2, all animals received a challenge dose of 2.3 g/kg ethanol, and no D-cycloserine or saline pretreatment was given.

Experiment 4: Effect of D-cycloserine on the enhancement of tolerance induced by different doses of ethanol. We randomly divided 64 rats into two groups (n = 32 each). On day 1, one group was injected IP with D-cycloserine (10 mg/kg), whereas the other group received saline. Then, each group was subdivided into four subgroups (n = 8 each). Thirty minutes later, three D-cycloserine subgroups and three saline subgroups were injected IP with ethanol at doses of 2.6, 2.9, or 3.2 g/kg, respectively, and the remaining two subgroups received saline. Before the first injection and at successive 30-min intervals up to 90 min after ethanol or saline injection, the degree of motor impairment was assessed in all animals. Rats were then returned to their home cages. On day 2, all animals received a challenge dose of 2.3 g/kg, IP, ethanol, and tolerance was assessed on the tilt-plane as described before. No D-cycloserine or saline pretreatment was given on day 2.

RESULTS

Experiment 1: Effect of D-Cycloserine on the Development of Rapid Tolerance to Ethanol (Before/After Design).

The effect of D-cycloserine on the development of rapid tolerance to ethanol using the before/after design is shown in

Fig. 1. On day 1, all animals showed expected motor impairment after ethanol, and D-cycloserine pretreatment did not affect motor impairment. A general linear model (GLM-ANOVA) of day 1 maximum percent impairment scores showed no significant main effect of groups [$F(3, 52) = 1.86$, $p > 0.14$, NS]. The results of the rapid tolerance test on day 2 showed a significantly lower motor-impairing effect of ethanol (saline/ethanol vs. ethanol/ethanol comparison) in the before group [$t(14) = 4.234$, $p < 0.01$] and the divided doses group [$t(12) = 4.230$, $p < 0.01$]; there was no difference for the control group [$t(12) = 0.974$, $p > 0.40$] or the after group [$t(14) = 0.251$, $p > 0.90$]. A GLM-ANOVA of maximum percent impairment values on day 2 showed a significant difference among groups [$F(3, 52) = 4.64$, $p < 0.006$]. There was a significant Group × Treatment interaction [$F(3, 52) = 8.69$, $p < 0.0001$], suggesting that rapid tolerance to ethanol did not develop in all groups. A posthoc Duncan's range test for main effects of group showed that the control group had significantly higher maximum percent impairment due to ethanol than the before or divided doses groups ($p < 0.05$), suggesting that these groups had developed rapid tolerance, but there was no difference between control and after groups. There was no difference in the extent of rapid tolerance development whether D-cycloserine was given before (6 mg) or in divided doses, as the before and divided doses groups were not different. The mean blood ethanol concentrations on day 2 are shown in Table 1. There was no significant difference in blood alcohol levels among the various groups.

Experiment 2: Does Ketamine Block the Effect of D-Cycloserine on Rapid Tolerance to Ethanol?

The effect of ketamine on the enhancement of tolerance produced by D-cycloserine is presented in Fig. 2. On day 1, rats injected with ethanol showed expected motor impairment responses, and pretreatment with D-cycloserine had no effect on maximum percent impairment responses for both ketamine and saline groups of animals. On day 2, maximum percent impairment responses for all saline/ethanol vs. ethanol/ethanol treatment groups were subjected to an overall GLM-ANOVA comparison. Administration of ketamine on day 1

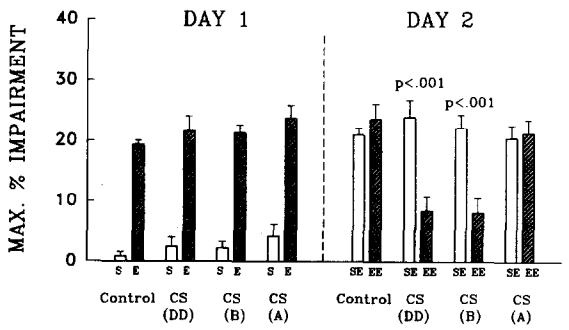

FIG. 1. Effect of D-cycloserine (CS) given before (B) after (A) or in divided doses (DD) before and after the test (tilt-plane) on the development of tolerance to ethanol (E). On day 1, six groups received CS [with E or saline (S) in different schedules (see Methods for details)], and two groups (control) received S (with E or S). Rapid tolerance to E-induced motor impairment was assessed on day 2, when all groups received a challenge dose of E. Groups EE received ethanol on day 1 and on the test day, whereas the SE groups received saline on day 1 and ethanol on the test day. Results shown are means ± SEM of seven or eight animals.

TABLE 1

BLOOD LEVELS AT 120 MIN AFTER ETHANOL (2.3 g/kg, IP) ADMINISTRATION ON DAY 2 IN RATS PRETREATED WITH EITHER D-CYCLOSERINE IN DIFFERENT SCHEDULES OR SALINE (CONTROL WITH ETHANOL OR SALINE) ON THE PREVIOUS DAY (EXPERIMENT 1)

Groups	Blood Alcohol Level (mg/dl)
Control: saline/ethanol	182.0 ± 3.4
Control: ethanol/ethanol	182.6 ± 2.9
D-Cycloserine (before + after): saline/ethanol	174.4 ± 3.2
D-Cycloserine (before + after): ethanol/ethanol	169.4 ± 7.9
D-Cycloserine (before): saline/ethanol	180.2 ± 2.9
D-Cycloserine (before): ethanol/ethanol	188.8 ± 4.3
D-Cycloserine (after): saline/ethanol	174.1 ± 4.9
D-Cycloserine (after): ethanol/ethanol	176.9 ± 2.9

Before, after and before + after refer to groups receiving D-cycloserine before, after, or both before and after, respectively. Groups saline/ethanol received saline on day 1 and ethanol on the test day, and groups ethanol/ethanol received ethanol on day 1 and also on the test day. Results shown are means ± SEM of seven or eight animals.

had no effect on response to ethanol, because there was no significant difference between ketamine vs. saline groups [$F(1, 56) = 0.00$ $p > 0.99$]. The nonsignificant main effect of D-cycloserine vs. saline pretreatment [$F(1, 56) = 0.04$, $p > 0.84$] suggested that D-cycloserine pretreatment did not enhance effect of ethanol when compared with controls (saline-pretreated group). The effect of treatment (saline/ethanol vs. ethanol/ethanol) was significant [$F(1, 56) = 5.25$, $p < 0.0257$]. The Group × Pretreatment interaction was not significant [$F(1, 56) = 0.41$, $p > 0.5257$], but the Pretreatment

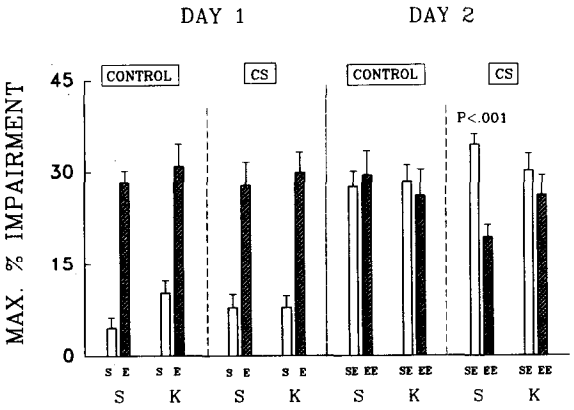

FIG. 2. Effect of ketamine (K) and D-cycloserine (CS) treatment on rapid tolerance development to ethanol (E). On day 1, two groups received CS [with E or saline (S)], two groups received saline (with E and S), another two groups received K and CS (with E and S), and the last two groups received K (with E or S). Ketamine was given 30 min before CS, and the other groups received vehicle (saline) at this time. Ethanol or saline injections were given at 60 min on day 1 in each group. Rapid tolerance to ethanol was assessed on day 2, when all animals received a challenge dose of ethanol. Group EE received ethanol on day 1 and on the test day, whereas the SE group received saline on day 1 and ethanol on the test day. Results shown are means ± SEM; $n = 8$ animals per group.

TABLE 2

BLOOD LEVELS AT 120 MIN AFTER ETHANOL (2.3 g/kg, IP) ADMINISTRATION ON DAY 2 IN RATS PRETREATED WITH EITHER KETAMINE OR SALINE PLUS EITHER D-CYCLOSERINE OR SALINE, AND GIVEN ETHANOL OR SALINE, ON THE PREVIOUS DAY (EXPERIMENT 2)

Groups	Blood Alcohol Level (mg/dl)
Ketamine + D-cycloserine: saline/ethanol	218.1 ± 7.4
Ketamine + D-cycloserine: ethanol/ethanol	207.8 ± 8.1
Ketamine + saline: saline/ethanol	214.8 ± 5.9
Ketamine + saline: ethanol/ethanol	219.4 ± 6.6
Saline + D-cycloserine: saline/ethanol	211.4 ± 4.5
Saline + D-cycloserine: ethanol/ethanol	219.4 ± 5.1
Saline + saline: saline/ethanol	211.6 ± 6.5
Saline + saline: ethanol/ethanol	207.4 ± 8.2

Results shown are means ± SEM of 8 animals/group.

× Treatment interaction was significant [$F(1, 56) = 4.81$, $p < 0.0324$], suggesting that rapid tolerance developed in the group that received saline followed by D-cycloserine pretreatment and ethanol, but administration of ketamine before D-cycloserine pretreatment blocked rapid tolerance development.

Table 2 shows blood ethanol levels on day 2 at 120 min after the administration of ethanol in various groups. A GLM-ANOVA showed no significant main effect of the ketamine vs. saline groups [$F(1, 56) = 0.29$, $p > 0.59$], D-cycloserine vs. saline pretreatment [$F(1, 56) = 0.03$, $p > 0.85$), saline/ethanol vs. ethanol/ethanol treatment [$F(1, 56) = 0.01$, $p > 0.92$], nor a significant Pretreatment (D-cycloserine vs. saline) × Treatment (saline/ethanol vs. ethanol/ethanol) interaction [$F(1, 56) = 0.02$, $p > 0.88$].

Experiment 3: Effect of different doses of D-cycloserine on rapid tolerance to ethanol. On day 1, rats injected with ethanol showed expected motor impairment responses. A GLM-ANOVA of day 1 maximum percent impairment data showed that pretreatment with different doses of D-cycloserine (Fig. 3) did not significantly affect the impairment due to ethanol [$F(3, 40) = 2.52$, $p > 0.07$]. A GLM-ANOVA of maximum percent impairment values on day 2 showed there was no difference among all dose groups [$F(3, 40) = 1.10$, $p > 0.3608$]. There was a significant main effect of ethanol treatment [$F(1, 40) = 23.08$, $p < 0.0001$], but the Group × Treatment interaction was not significant [$F(3, 40) = 0.90$, $p > 0.4517$], suggesting there was no difference in enhancement of rapid tolerance among all three doses employed.

Experiment 4: Effect of D-cycloserine on the enhancement of tolerance induced by different doses of ethanol. On day 1, rats injected with different doses of ethanol (Fig. 4) showed expected motor impairment responses, and administration of D-cycloserine did not affect the magnitude of these responses. The results of the rapid tolerance test on day 2 showed significantly lower motor-impairing effects of ethanol in the D-cycloserine-ethanol group than in the saline-ethanol group for the 2.6-g/kg ethanol dose (i.e., in rats injected with 2.6 g/kg ethanol, 24 h earlier) [$t(14) = 3.32$, $p < 0.01$]. Similar comparisons for the other doses showed no difference, [for 2.9 g/kg ethanol, $t(14) = 1.15$, NS, and for 3.2 g/kg ethanol, $t(14) = 1.20$, NS]. There was no difference in baseline effect when saline-saline/ethanol was compared with D-cycloserine-saline/ethanol [$t(14) = 1.68$, NS]. The day 2 maximum percent impairment scores for different dose groups were subjected to a GLM-ANOVA. There were significant main effects of D-cycloserine pretreatment [$F(1, 42) = 13.26$, $p < 0.0007$] and of day 1 ethanol doses [$F(2, 42) = 16.34$, $p < 0.001$], and a significant Pretreatment × Dose interaction [$F(2, 42) = 3.33$, $p < 0.05$]. These results suggested that the extent of tolerance development was significantly different for different ethanol doses, but that D-cycloserine enhanced rapid tolerance only for the group receiving the threshold dose of 2.6 g/kg ethanol on day 1. There was no significant difference in blood ethanol levels taken on day 2 at the end of motor impairment measurement among the various groups (data not shown).

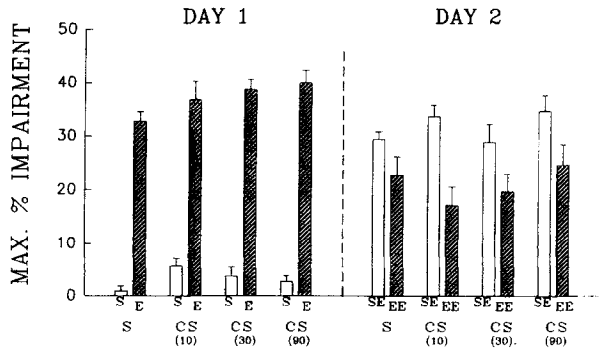

FIG. 3. Effects of different doses of D-cycloserine (CS) on the development of rapid tolerance to ethanol (E). Three groups received CS [with saline (S) or E], whereas one group (control) received saline (with S or E). Rapid tolerance was assessed on day 2, when all groups received a challenge dose of ethanol (2.3 g/kg). Group EE received ethanol on both days of the experiment, whereas SE groups received saline on day 1 and ethanol on day 2. The doses of CS on day 1 were: 10, 30, and 90 mg/kg. Results are means ± SEM of eight animals.

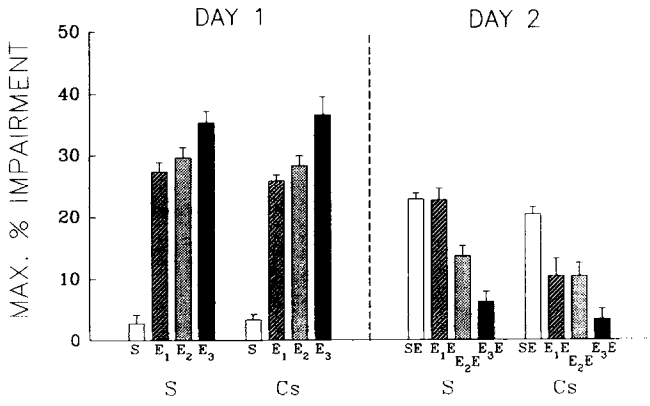

FIG. 4. Effect of D-cycloserine (CS) on the enhancement of tolerance induced by different doses of ethanol. Four subgroups received CS (with either S or E) and other four received S (with either S or E) on day 1. Rapid tolerance to ethanol-induced motor impairment was assessed on day 2. Group EE received ethanol on both days of the experiment, whereas SE groups received saline on day 1 and ethanol on day 2. The doses of ethanol on day 1 were 2.6 g/kg (E1), 2.9 g/kg (E2), and 3.2 g/kg (E3). The test dose of ethanol for assessing tolerance on day 2 was 2.3 g/kg.

DISCUSSION

The results obtained in the present study confirm our previous data on the enhancing effect of D-cycloserine on tolerance to ethanol (13). Thus, the administration of D-cycloserine with a dose of ethanol that was insufficient to produce tolerance per se did result in the development of rapid tolerance to ethanol motor incoordination in the tilt-plane test. Although the administration of the NMDA agonist before behavioral testing on day 1 enhanced the development of tolerance, the injection of D-cycloserine after the behavioral testing on day 1 did not increase the tolerance development. It is known that the facilitatory effect of D-cycloserine on glutamatergic transmission occurs through an action involving the glycine recognition site of the NMDA receptor. Moreover, D-cycloserine was found to bind with high affinity to the glycine-binding site of the NMDA receptor and improve learning of two types of learning tasks (21). As learning can play a major role in rapid tolerance (2), our data suggest that D-cycloserine may enhance the acquisition of tolerance by increasing some adaptations that occur during the intoxicated practice on day 1. The administration of D-cycloserine in divided doses both before and after the testing period on day 1 resulted in increased tolerance similar to that produced by the injection of D-cycloserine only before the test. Thus, it can be suggested that D-cycloserine affects the retention phase, but not the consolidation phase of the learning that may occur during behavioral testing.

The present study shows that D-cycloserine increases the acquisition of rapid tolerance only when the dose of ethanol is insufficient to produce tolerance by itself. Thus, we did not observe further enhancement of rapid tolerance in animals treated with higher doses of ethanol on day 1. The lack of effect of D-cycloserine in this experiment did not seem to be a consequence of insufficient dose of D-cycloserine, as increasing the dose of D-cycloserine did not produce an additional effect. At least two possibilities can explain these results. First, as D-cycloserine is a co-agonist of the NMDA receptor (5,25), this drug could enhance tolerance only when the system is not activated enough to produce tolerance. Second, it is known that there is a maximum degree of tolerance to ethanol's effect (16). Thus, D-cycloserine could not further increase tolerance once it reached that maximum level. The present study cannot distinguish between these possibilities. Experiments with other drugs to which tolerance can be completely developed (e.g., morphine) will clarify this issue. A previous study had shown that administration of (+)MK-801 on day 1 before D-cycloserine prevented enhancement of the rapid tolerance to ethanol (13). The results of the present study confirm and extend these observations with another NMDA antagonist. Ketamine clearly blocked the ability of D-cycloserine to promote rapid tolerance to a low dose of ethanol without affecting the performance of the control group on day 1.

The enhancement of ethanol tolerance by D-cycloserine and the antagonism of this effect by ketamine cannot be attributed to changes in the pharmacokinetic properties of ethanol, as the blood ethanol concentrations on day 2 at 120 min were similar in all groups (Tables 1 and 2). Taken together, the results of the present study give additional support to the findings that the NMDA receptor system participates in the development of tolerance to ethanol, and that learning and tolerance to ethanol are related.

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