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Ethanol-Induced Conditioned Place Aversion in Rats: Effect of Interstimulus Interval

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BORMANN, N. M. AND C. L. CUNNINGHAM. *Ethanol-induced conditioned place aversion in rats: Effect of interstimulus interval*. PHARMACOL BIOCHEM BEHAV **59**(2) 427–432, 1998.—The purpose of this study was to examine the effect of interstimulus interval (ISI) on ethanol-induced place aversion in rats. Six groups of rats initially received four pairings of a distinctive floor stimulus (CS+) with ethanol (1 g/kg, IP) and four pairings of a different floor stimulus (CS−) with saline. Groups −30, −15, −10, −5, 0, and 5 were injected 30, 15, 10, 5, or 0 min before, or 5 min after exposure to the 5 min CS, respectively. After testing for place aversion, all groups were exposed to an additional set of conditioning trials using a higher dose of ethanol (1.5 g/kg). During the first test, only groups 0 and −15 exhibited conditioned place aversion. However, during the second test, all groups showed conditioned aversion except group −30. The results suggest that ethanol's aversive effects dissipate by 30 min postinjection or that it is more difficult to associate those effects with short-duration external stimuli at long backward intervals. In contrast to recent findings with mice, the direction of ethanol-induced place conditioning was not altered in rats exposed to different ISIs. © 1998 Elsevier Science Inc.

Place conditioning Interstimulus interval Classical conditioning Conditioned place aversion Ethanol Locomotor activity Rats

ADMINISTRATION of ethanol by various routes (oral, IP, IV, and IG) at doses of 1 g/kg or higher in the place conditioning paradigm has most often been found to produce a conditioned place aversion in drug naive rats (6,7,14,15,23,24,26,38–43,45,46), including rats that have been selectively bred for ethanol preference (37,44). Conditioned place preference has occasionally been reported in rats, but these outcomes have required extensive exposure to ethanol before conditioning (2,24,26,30) or the coadministration of food (40,41) or other drugs (29,45) on ethanol conditioning trials. Over the past 25 years, the literature reveals only two isolated experiments in which drug-naive rats were reported to develop a conditioned place preference with ethanol (1 g/kg) (3,4). Neither finding has ever been replicated, despite an explicit attempt in one case (7).

In general, the literature supports the conclusion that ethanol-induced conditioned place aversion in rats results from learning based on the Pavlovian relationship between drug-predictive environmental stimuli (CS) and the aversive pharmacological effects of ethanol (US). For example, in accord with a Pavlovian analysis, conditioned place aversion has been shown to depend on the contingency between CS and US [e.g., (6)], and is positively related to number of trials (24,39) and to US magnitude (i.e., ethanol dose) (40,41, 44,45,46). However, there is one important class of Pavlovian manipulations that has not yet been systematically examined for its impact on the development of ethanol-induced conditioned place aversion in rats. Specifically, there have been no parametric studies of the effects of various temporal variables such as the duration of exposure to the CS, the time interval between consecutive trials, or the time interval between exposure to the CS and administration of drug (interstimulus interval or ISI) on the strength of conditioned place aversion. Examination of these temporal parameters is important not only for characterizing the Pavlovian nature of place conditioning, but also because such studies may shed new light on the factors determining whether a drug produces conditioned place preference or conditioned place aversion. The latter possibility is raised by several recent studies suggesting that the direction of place conditioning depends critically on whether the drug is administered just before the CS or shortly after its removal. In particular, whereas administration of nicotine or

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amphetamine just before CS exposure typically produces conditioned place preference, injection of these drugs after removal from the CS produces a conditioned place aversion (20–22,47). A similar finding has recently been reported in studies of ethanol-induced place conditioning in mice. Mice, which consistently display a conditioned place preference when ethanol is administered just before CS exposure [e.g., (9–13,15–18,31–36)], were found to develop conditioned place aversion when ethanol was given just after CS exposure (17). The latter finding is particularly intriguing because mice and rats show place conditioning in opposite directions when ethanol is administered under identical conditions just before CS exposure (15).

The present experiment was designed to examine systematically the effect of ISI on conditioned place aversion produced by ethanol in rats. The existing literature reveals evidence of conditioned place aversion in different studies using ISIs ranging from −10 min (i.e., administration of ethanol 10 min before CS exposure) (37,38) to +15 min (i.e., administration of ethanol beginning 15 min after the onset of CS exposure) (43), with a 0 min ISI most commonly employed [e.g.,(1,4,6,14,15,24,29,41,44,45)]. This range completely overlaps with that used in the subset of rat studies in which conditioned place preference has been reported. To date, however, different ISIs have not been directly compared within the same experiment.

In the present study, rats were injected with ethanol 30, 15, 10, or 5 min before (groups −30, −15, −10, or −5), or 5 min after (group 5) exposure to a distinctive tactile (floor) CS. To determine the effect of manipulating ISI on acquisition of place conditioning, the magnitude of place conditioning in these groups was compared to a 0 min ISI (group 0) reference group. A CS duration of 5 min was selected for this experiment for several reasons. First, previous studies have shown that CSs of similar duration can elicit either preference or aversion in mice (17) and either preference (30) or aversion (15) in rats. Second, one study in mice showed that a 5-min CS duration produced stronger place conditioning (preference) to ethanol-paired cues than a 30 min CS duration (18). Finally, by using a relatively short CS (trial) duration, we maximized our ability to associate the CS with different portions of the rapidly changing brain ethanol concentration function over time after IP injection.

Place conditioning was initiated with a dose of 1 g/kg, which has most often been reported to produce no effect or place aversion in drug naive rats [e.g., (7,37,38,40,41,44,46)], although there have been two reports of conditioned preference at this dose (3,4). We initiated conditioning with a relatively low dose to avoid ceiling effects in place aversion and thereby to increase our ability to detect ISI effects. Because the evidence of place aversion at nonzero ISIs was marginal after the first four conditioning trials, ethanol dose was increased to 1.5 g/kg on the next four trials to offset tolerance and to enhance its unconditioned effects.

METHOD

Subjects

One hundred twenty male Holtzman albino rats weighing approximately 380–450 g were obtained from Harlan–Holtzman. All rats were housed individually in stainless steel wire mesh hanging cages and were maintained on a 12 L:12 D cycle (lights on at 0700 h). Lab chow and water were available at all times in the home cage.

Apparatus

The apparatus consisted of eight place conditioning boxes enclosed in separate 71 × 58.8 × 68.4 cm (internal dimension) light- and sound-attenuating chambers (Kalt, Portland, OR). The place conditioning boxes (47.5 × 15.5 × 18 cm) were constructed from clear acrylic and aluminum with five sets of infrared light sources and photobeam detectors on the long walls of each box. The detectors were placed 5 cm above the floor with one set of photodetectors placed in the center of the walls and two additional photodetectors 7 cm apart on each side of center. Occlusion of the infrared beams was used to measure general activity and side position (left vs. right) in each box. A rat was considered to have switched sides when both of the outer photobeams on one side were released and at least one of the outer photobeams on the other side was occluded. Activity and amount of time spent on both sides of the box were collected and analyzed by microcomputer (10 ms resolution).

The floors of each box were composed of interchangeable halves of three floor types: mesh, grid, and hole. The "mesh" floor was made of galvanized-wire hardware cloth (6.5 mm squares) mounted over an acrylic frame. The "grid" floor consisted of 2.3 mm stainless steel rods mounted 13 mm apart in an acrylic frame. The "hole" floor was made of perforated stainless steel with 13 mm round holes on 19 mm staggered centers. Subjects were exposed to the mesh floor only on habituation days. The grid and hole floors were selected as CSs on the basis of previous pilot experiments in which rats showed a preference for the mesh floor but exhibited approximately equal preference between grid and hole floor types. The floors were cleaned and the litter paper was changed after each animal.

Drugs

Ethanol was made every 2 days by diluting ethyl alcohol USP (190 proof) with normal (0.9%) saline to a 15% v/v solution. Doses of ethanol injected were produced by manipulating the volume of the 15% ethanol solution injected; 8.4 ml/kg was injected for the 1.0 g/kg dose, and 12.5 ml/kg was injected for the 1.5 g/kg dose. All injections were intraperitoneal.

Procedure

The general design and procedure were similar to those used previously [e.g., (15,17)] and were approved by Oregon Health Sciences University's Animal Care and Use Committee. The study was run as two separate experiments, with groups −30, 0, and 5 trained at a different time than groups −15, −10, and −5. All training for all groups was conducted within a 3-month period. The experiments consisted of three phases: habituation, conditioning, and test phases. Training occurred 7 days per week.

Habituation (1 day). On the habituation day, subjects were placed in the conditioning boxes on the mesh floor for 5 min. The purpose of this session was to acclimate subjects to handling and to the conditioning boxes.

Conditioning (8 days). Before the conditioning phase, subjects within each of the six ISI groups (n = 20/group) were randomly assigned to one of two conditioning groups (GRID+ or GRID−). Subjects were exposed to a discriminative Pavlovian conditioning procedure in which they received four CS+ and four CS− trials, with CS+ and CS− trials occurring on alternate days (the order of stimulus presentation was counterbalanced within each conditioning group). During condi-

tioning trials, subjects had access to the entire floor of the conditioning compartment with both halves of the floor being either hole or grid. GRID+ conditioning groups in each ISI group received ethanol paired with the grid floor and saline paired with the hole floor on alternate days. GRID− conditioning groups in each ISI group received ethanol paired with the hole floor and saline paired with the grid floor on alternate days. ISI groups −30, −15, −10, −5, and 0 received an intraperitoneal ethanol injection 30, 15, 10, 5, and 0 min, respectively, before placement on the CS+ floor for 5 min. Subjects in all but group 0 were returned to their home cages during the delay. Group 5 was exposed to the CS+ floor for 5 min and received ethanol immediately upon removal from the floor. The dose used for the initial series of conditioning trials was 1 g/kg. Because subjects in the GRID+ and GRID− groups within each ISI group were matched for exposure to each CS, ethanol, and saline, differences between these groups during preference testing cannot be attributed to nonassociative effects of the injections or to differential familiarity with the CSs. Rather, differences are more likely due to learning based on the paired relationship between the CS+ floor and ethanol (8).

Test (2 days). During the test phase, subjects had access to both grid and hole floor types for 60 min on each of 2 consecutive days. Position (left vs. right) of grid and hole floors was counterbalanced within each conditioning group.

Beginning 3 days after the second test, all groups received another eight conditioning trials (four CS+ and four CS− trials) using a higher dose of ethanol (1.5 g/kg), followed by two more test trials.

RESULTS

Activity and preference data were analyzed using analysis of variance with the alpha level set at 0.05. Due to experimenter errors, one subject from each of groups −30, −15, −10, −5, and 0 was excluded from analyses of all conditioning and test data.

Conditioning Trials

Figure 1 shows activity on the first ethanol trial and first saline trial at each dose. In general, the low dose of ethanol had little effect on activity (left panel), whereas the high dose suppressed activity in all groups that received ethanol at least 5 min before placement in the apparatus (right panel). These observations were confirmed by two-way (ISI [6] × Drug [2]) analyses of variance (ANOVA) performed separately on mean activity counts per min for each of these trials. Analysis of the first trial data yielded no significant effects. However, analysis of Trial 5 data revealed a significant main effect of drug, $F(1, 109) = 53.2$, $p < 0.001$, and a significant ISI × drug interaction, $F(5, 109) = 6.5$, $p < 0.001$. Within-group comparisons of activity on the fifth saline vs. ethanol trial indicated significantly lower activity counts on ethanol trials for groups −30, −15, −10, and −5 (all ps < 0.01). With repeated exposure to the high dose of ethanol, the activity difference between ethanol and saline trials diminished, primarily as the result of habituation on saline trials (data not shown).

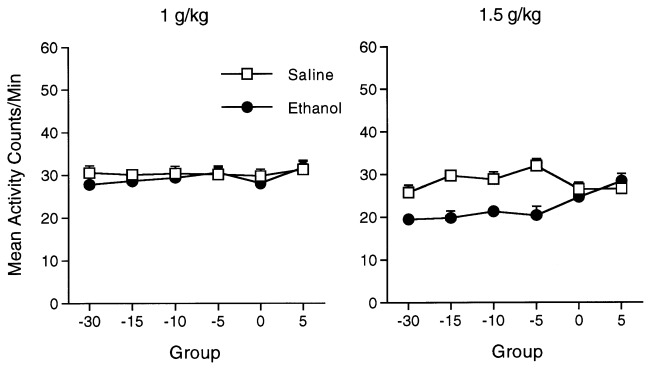

FIG. 1. Mean (±SEM) activity counts per minute during the first conditioning trials at 1 g/kg (left panel) and 1.5 g/kg (right panel). Activity data are collapsed across conditioning subgroups. Open squares indicate activity during saline (CS−) trials, while closed circles indicate activity during ethanol (CS+) trials.

Place Preference Test

Grid times. To simplify presentation of the test data, Fig. 2 depicts mean percent time spent on the ethanol-paired floor by each ISI group (averaged across conditioning group) during the preference tests given after training at each ethanol dose. At the lower dose, there was evidence of a conditioned place aversion in two of the ISI groups (0, −15). At the higher dose, all groups except −30 showed a conditioned aversion. This aversion was greatest in the group that received simultaneous exposure to ethanol and the CS (group 0). Group −30 exhibited no preference for either CS+ or CS− floor.

Evidence of place aversion in this design is provided by comparing mean time spent on the grid floor in GRID+ and GRID− conditioning groups within each ISI group at each dose (Fig. 3). For example, if ethanol produced a conditioned

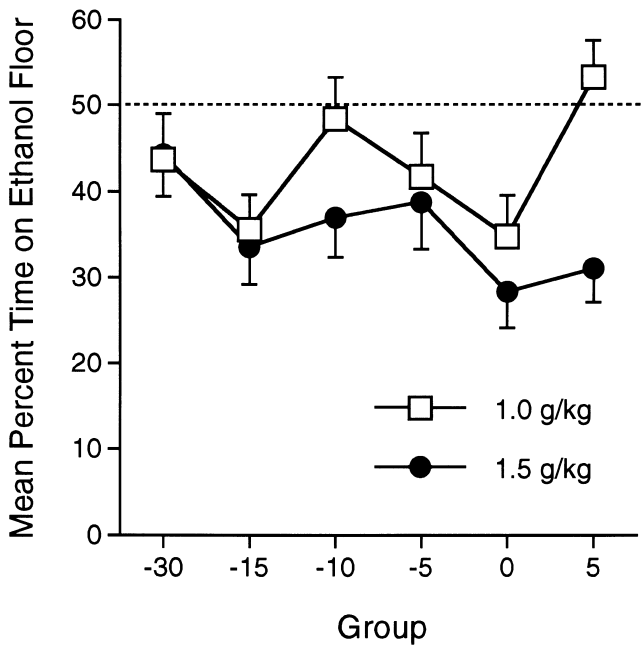

FIG. 2. Mean (±SEM) percent time spent on the ethanol-paired floor averaged across test sessions and conditioning subgroups. Open squares indicate percent time spent on the CS+ floor after four pairings with 1 g/kg ethanol. Closed circles indicate percent time spent on the CS+ floor after an additional four pairings with 1.5 g/kg ethanol.

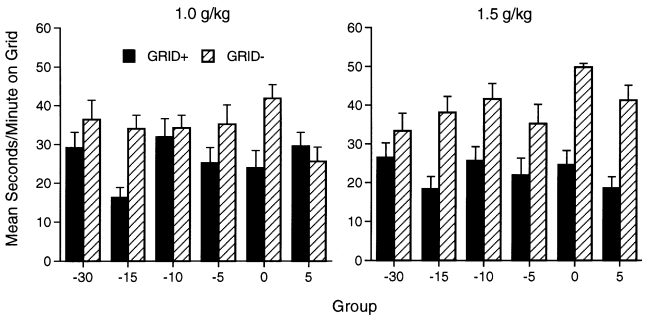

FIG. 3. Mean (±SEM) seconds/minute spent on the grid floor averaged across test sessions after conditioning with 1 g/kg ethanol (left panel) and 1.5 g/kg ethanol (right panel). GRID+ and GRID− refer to the subgroups within each ISI group that had previously received either the grid floor (GRID+) or hole floor (GRID−) and ethanol on CS+ conditioning trials. These subgroups were exposed to the opposite floor type and saline on CS− conditioning trials.

place aversion, then GRID+ subjects should have spent less time on the grid floor than GRID− subjects because ethanol was paired with the grid floor for these subjects during conditioning. Differences between GRID+ and GRID− conditioning groups were expected to vary between ISI groups. Statistically, a significant ISI × conditioning group interaction indicates that the magnitude of place aversion was dependent upon ISI. Data were collapsed across test sessions at each dose because preliminary analyses showed no differences between the two tests.

A two-way ANOVA (ISI [6] × conditioning group [2], of grid times after conditioning at the lower dose revealed no main effect of ISI, but a main effect of conditioning group, $F(1, 103) = 13.6$, $p < 0.001$, and an ISI × conditioning group interaction, $F(5, 103) = 2.3$, $p < 0.05$. Planned comparisons of GRID+ vs. GRID− conditioning groups within each ISI group showed significant place aversion in groups −15 and 0 (Bonferroni-corrected ps < 0.05). A similar two-way ANOVA of grid times from the tests conducted after conditioning at the higher ethanol dose yielded a significant main effect of conditioning group, $F(1, 103) = 61.4$, $p < 0.001$. Separate planned comparisons of GRID+ and GRID− conditioning groups within each ISI group indicated a significant place aversion in groups −15, −10, 0, and 5 (Bonferroni-corrected ps < 0.05). The place aversion in group −5 approached the criterion for significance ($0.05 < p < 0.1$, Bonferroni-corrected); however, there was no evidence of place conditioning in group −30.

Activity. One-way ANOVAs indicated that there were no differences among ISI groups in activity levels during testing. Mean activity counts per minute were 11.2 (±0.2) and 9.6 (±0.2) for the preference tests after conditioning with 1.0 and 1.5 g/kg ethanol, respectively.

DISCUSSION

This article describes the first systematic investigation of ISI effects on the direction and magnitude of ethanol place conditioning in rats. The results of this experiment are consistent with many other ethanol place conditioning studies in showing conditioned place aversion to ethanol-paired stimuli after training with moderate doses of ethanol at a 0-min ISI (6,14,15,24,26,40–42,44,45). When ISI was varied (−30 to +5), the 1.0 g/kg ethanol dose produced a conditioned place aversion at only one of the nonzero ISIs (group −15). However, with additional training at a higher dose (1.5 g/kg), all ISIs were effective at producing conditioned place aversion except the backward 30-min interval (group −30). At both doses, conditioning was strongest at the 0-min ISI, suggesting that simultaneous exposure to ethanol and the CS is optimal for producing conditioned place aversion in rats.

In the literature on ISI effects with nondrug USs, the reduction in conditioning observed at nonoptimal ISIs is often attributed to degradation in CS-US temporal contiguity or to greater interference (overshadowing) by stimuli other than the target CS (19,28). In the case of drug-induced place conditioning, however, one must also consider the fact that the US is not a punctate event with a discrete onset and termination. Rather, it is a relatively long-lasting event whose intensity varies over time, presumably as some function of brain-drug level. Moreover, it is possible that the motivational valence of the drug US changes as a function of time after injection (17). Thus, the effect of ISI on ethanol-induced place conditioning could reflect the influence of at least two variables: (a) changes in associability of the target CS as a function of time between presentation of the CS and US, and (b) changes in the quality or intensity of ethanol's motivational effects as a function of time-dependent changes in brain ethanol concentration.

The potential role played by each of these variables in the present study is illustrated in Fig. 4, which depicts hypothetical changes in blood ethanol concentration (BEC) over time after injection. The shape of the BEC curve was extrapolated from a recent study in which rats received an IP injection of 1 g/kg ethanol (25). The shaded vertical bars depict the time windows occupied by the CS+ in each of the ISI groups. Examination of this figure suggests several tentative conclusions with respect to the possible role of BEC in establishing place aversion in our study. First, it seems clear that BEC during the CS is not a direct determinant of conditioning strength. For example, the groups hypothesized to show the highest BEC during the CS (groups −10, −15) did not show the strongest

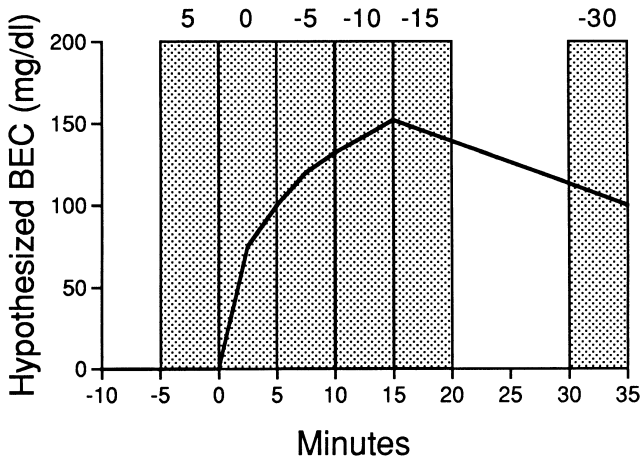

FIG. 4. This figure depicts hypothetical changes in blood ethanol concentration (BEC) over time after injection. The shape of the BEC curve was extrapolated from a recent study by Gauvin et al. (1994), in which rats received an IP injection of 1 g/kg ethanol. The shaded vertical bars depict the time windows occupied by the CS+ in each of the ISI groups (groups 5, 0, −5, −10, −15, and −30).

conditioning. Even more striking, however, is the fact that a group expected to experience a relatively high BEC during the CS showed no place conditioning (group −30), whereas a group that did not receive ethanol until after the CS displayed significant place aversion (group 5). Comparison of the aversion test data with Fig. 4 suggests that temporal proximity of the CS to the onset of ethanol intoxication (i.e., rising phase of the BEC function) may be a more critical determinant of the strength of place aversion than the absolute BEC level experienced during the CS. It is important to note, however, that ethanol's ability to affect development of conditioned aversion did not end with removal of the CS. This observation is best illustrated by considering group 5, whose conditioned aversion clearly depended on ethanol effects that were not experienced until after the CS was removed. Thus, it seems quite reasonable to suppose that conditioning observed in other groups was also influenced by effects of ethanol that continued beyond the time of CS exposure.

It has previously been hypothesized that the magnitude of ethanol's rewarding effect fluctuates with BEC, such that ethanol is most rewarding during the ascending limb, but not during the descending limb of the curve [e.g., (27)]. The results with the 1.5 g/kg dose argue against this hypothesis because place aversion was observed in groups exposed to the CS during the ascending limb, and no conditioning was observed in the group exposed to the CS while blood-ethanol levels were falling (group −30). In fact, the above results suggest the opposite conclusion: rapidly increasing levels of blood-ethanol may be more aversive to rats than slowly descending levels. Thus, we cannot rule out the possibility that differences in magnitude of place aversion with changes in ISI may have been due to qualitative changes in ethanol's motivational effects.

The finding of significant place aversion at the low dose in group −15, but not in groups −10 and −5, was not expected and is not readily explained in terms of the temporal relationship between the CS and onset of ethanol intoxication. Although one might be tempted to speculate about special motivational effects experienced at the peak of the BEC curve (see Fig. 4), the overall pattern of results from both tests suggests that the effect seen in group −15 was due to sampling error or use of an ethanol dose (1 g/kg) that has sometimes been found to be marginally effective with the optimal 0 min ISI (1,30). Although we attribute the greater consistency of effects in the second test to additional conditioning at a higher ethanol dose (1.5 g/kg), it is possible that continued training at the lower dose would have eventually produced a similar pattern of aversive conditioning.

CS duration is another variable that may have influenced the pattern of findings observed here. Although most ethanol place conditioning studies in rats have used 15 to 30 min CS durations (1,2,4,6,7,24,29,38,39,41,43,45,46), it is not known whether these durations are optimal for acquisition of place aversion. In mice, a 5-min CS duration has been shown to be more effective than 15 or 30 min in establishing ethanol-induced conditioned place preference (18). Although 5 min may not be the optimal duration for conditioning aversion in rats, the present study confirms previous results (15), demonstrating the efficacy of a 5-min CS. Nevertheless, it is quite possible that longer duration CSs would change the shape of the ISI function for conditioned place aversion. This change might occur either because longer durations of CS-US overlap improve strength of conditioning (5), or because longer CS durations reduce interference (overshadowing) by contextual stimuli that may compete with the CS for association with the US (19,28). A systematic investigation of CS duration effects on magnitude of conditioned place aversion is needed to establish the boundary conditions for rats in this paradigm.

Consistent with previous findings in rats [e.g., (15)], ethanol produced a decrease in locomotor activity during conditioning trials. However, ethanol's effect on activity during conditioning trials did not appear to be related to magnitude of conditioned place aversion. For example, although group −30 showed an ethanol-induced decrease in activity comparable to other backward ISI groups, this group did not show a conditioned place aversion. Furthermore, groups 0 and 5 showed no reduction in activity on ethanol conditioning trials, yet both showed a significant place aversion.

The results of the Cunningham et al. (17) study raised the possibility that the species difference in the direction of ethanol-induced place conditioning is related to species differences in sensitivity to temporal variables instead of an insensitivity to ethanol's rewarding effect in rats. If this were true, then rats might have exhibited conditioned place preference instead of aversion with nonsimultaneous administration of the CS and the ethanol US. However, in contrast to findings in mice (17), the direction of the conditioned response did not shift from aversion to preference in rats with changes in ISI. The present study suggests that ethanol's motivational properties are aversive for at least 15 min after injection in rats. In contrast, the mouse place conditioning literature offers many examples of conditioned place preference at ethanol doses above 1 g/kg [e.g., (9,12,13,15,17,18,33)]. Overall, these findings are consistent with the conclusion that rats are less sensitive than mice to ethanol's rewarding effects as measured by the place conditioning paradigm (15).

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