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Place Conditioning With Alcohol in Alcohol-Preferring and -Nonpreferring Rats

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STEWART, R. B., J. M. MURPHY, W. J. McBRIDE, L. LUMENG AND T.-K. LI. *Place conditioning with alcohol in alcohol-preferring and -nonpreferring rats.* PHARMACOL BIOCHEM BEHAV 53(3) 487–491, 1996.—A place-conditioning procedure was used to examine the effect of selective breeding for ethanol preference on sensitivity to the rewarding and/or aversive effects of ethanol. On 4 alternate days, groups of seven to eight alcohol-preferring (P) and alcohol-nonpreferring (NP) rats received IP injections of 0.0 (saline controls), 0.5, 1.0, or 1.5 g ethanol/kg body wt. immediately before 15-min confinement in a novel environment. On the 4 intervening days the same rats received saline injections before 15 min confinement in a different environment. On day 9, a 15-min choice test was given with no injections, in which the rats could move freely between the ethanol and the saline-paired environments. Dose-dependent avoidance of the ethanol-paired environment was observed in both lines of rats (1.0 and 1.5 g/kg), but the magnitude of the avoidance was less in the P relative to the NP rats, indicating that ethanol was less aversive for the P rats. No evidence for a place preference was observed in either line with any of the ethanol doses. An innate reduced sensitivity to the aversive effects of ethanol in rats of the P line and/or an enhanced sensitivity to the aversive effects of ethanol in rats of the NP line may contribute to the different levels of oral ethanol self-administration observed in these selectively bred rat lines.

Alcohol-preferring rats Alcohol-nonpreferring rats Place conditioning Alcohol aversion
Alcohol reinforcement

ALCOHOL-PREFERRING (P) and alcohol-nonpreferring (NP) lines of rats were selectively bred for differences in preference for a 10% (v/v) ethanol solution over concurrently available water (11,12). The high oral ethanol intake of P rats may reflect the capacity of ethanol to function as a positive reinforcer (14,27). However, mechanisms in addition to those that subserve positive reinforcement could contribute to high or low ethanol drinking. For example, the aversive effects of ethanol may regulate ethanol intake by placing a limit on the amount of ethanol that can be consumed without ill effects (4). Froehlich et al. (8) compared P and NP rats using a conditioned taste aversion (CTA) procedure in which the aversive effects of alcohol were inferred by the avoidance of a drug-free saccharin solution that had been previously associated with ethanol administration. Ethanol injections resulted in a smaller CTA in P rats than in NP ones. This suggests that the low ethanol consumption of NP rats may be due, at least in part, to an enhanced sensitivity to the aversive effects of ethanol, and/or that the high ethanol consumption shown by P rats may result from a reduced sensitivity to the aversive effects of ethanol. The present investigation represents a replication and extension of this work by comparing P and NP rats using a different measure of ethanol-induced aversion. A place-conditioning procedure was used in which ethanol administration was paired with environmental cues and the subsequent avoidance of those cues indicated the degree of aversion to the effects of the drug. The motor activity-reducing effects of ethanol injections were also quantified during the

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place-conditioning trials to determine the extent to which line differences in place aversion are associated with changes in ethanol-induced motor impairment or sedation.

METHODS

Subjects

We used 29 female P rats and 32 female NP rats from the S-33 selected generation, with initial body weights of 223–365 and 257–347 g, respectively. The animals were individually housed in hanging wire cages, had water and Purina 5001 rodent chow (BioServ, Frenchtown, NJ) continuously available, and were maintained on a 12 L : 12 D cycle (lights on at 0600 h).

Apparatus

Conditioning/test boxes were used which were divided into two 38 × 38 × 38-cm end compartments. One end compartment was black with a smooth black floor, and the other was white with a white floor area covered by 1-cm grid hardware cloth wire screening. The two end compartments could be separated either by a 10-cm-thick solid partition (for conditioning trials) or by a partition that contained a 10 × 10 × 10-cm passageway at the center of its base to allow access to both compartments during choice tests. The passageway was grey with a sheet metal floor. For the purpose of scoring locomotor activity, the floor of each of the two end compartments was divided into four equal quadrants by 1-cm-wide painted stripes. The boxes were covered with wire screen lids. A videocamera was mounted on the ceiling above the apparatus to monitor and record the conditioning and choice test sessions for subsequent visual analysis.

Procedure

Ethanol-conditioning trials. On alternate days, separate groups of seven to eight ethanol-naive female P and NP rats received IP injections of either 0.5, 1.0, or 1.5 g ethanol/kg body wt. and were immediately confined for 15 min in one of the compartments of the conditioning/test box. The ethanol concentrations were adjusted so that a constant volume of 20 ml/kg body wt. was injected at each dose. The highest concentration was 7.5% (w/v) for the 1.5-g/kg dose. On intervening days, the same rats received saline injections (20 ml/kg body wt.) preceding 15-min confinement in the other compartment. The experimental design was counterbalanced for which compartment (black or white) was paired with ethanol and for order of treatments (whether the ethanol was given on odd- or even-numbered trials). In addition, control groups of seven to eight P and NP rats were administered saline before all conditioning trials. For the purpose of making the data from the saline control groups comparable to those from the groups that received ethanol injections, each rat in the saline control groups had one of the compartment types (black or white) and one of the treatment orders (odd- or even-numbered trials) designated as 0.0 g/kg ethanol conditioning trials.

Locomotor activity during conditioning trials was quantified by counting the number of times per 15-min trial that the rat crossed painted lines that divided the floor of each end compartment into four equal quadrants. A rat was considered to have crossed into a different quadrant when a spot (approximately 15 mm diam.), drawn between the shoulder blades of the animal with a black marker pen, crossed one of the lines.

Choice test. On the day following the four ethanol and four saline conditioning trials, a 15-min choice test was given with no injections in which the rats could move freely through the passageway between the two end compartments. At the start of the trial, the rat was placed in the passageway with its head facing the white compartment. The amount of time (s) that the animal spent in the ethanol- and saline-paired compartments was measured. Again, the location of the rat in the apparatus was defined as the location of a spot drawn between the shoulder blades of the animal.

Data Analyses

Motor activity during conditioning trials. Initial analysis of the activity scores (line crossings/15-min trial) examined each dose group [0.0 (saline-only controls), 0.5, 1.0, and 1.5 g ethanol/kg body wt.] within each line (P or NP). Two-way repeated-measures analyses of variance (ANOVA) were used with trial number and drug (ethanol trials compared with saline trials of the same animal) as within-subject factors. For most of the groups there was a small tendency for activity to increase across the four ethanol trials and across the four intervening saline trials. However, no effects of trial or interactions of trial with drug were found to indicate the development of tolerance or sensitization to the activity-altering effects of the ethanol across the conditioning trials. Thus, to simplify the presentation of the results, the factor of trial was eliminated from subsequent analyses. For each rat, a mean saline activity score and mean ethanol activity score were calculated by summing the number of line crossings per 15-min trial over the four ethanol and four saline conditioning trials and dividing each of these two sums by four. These individual-rat means were the data for a three-way split-plot ANOVA. The factors of the ANOVA were line (P and NP), dose [0.0 (saline-only controls), 0.5, 1.0, and 1.5 g ethanol/kg body wt.], and drug (ethanol trials compared with saline trials of the same animal), with repeated measures on the factor of drug. Paired Student's *t*-tests were used to compare saline and ethanol activity scores within each experimental group at each ethanol dose (four comparisons per dose group), and unpaired Student's *t*-tests were used to compare saline and ethanol activity of the P and NP rats at each ethanol dose (eight comparisons). The α-level for these comparisons was set at $p < 0.05$ with the critical levels modified to correct for multiple comparisons according to the Sidak modification of the Bonferroni critical levels tabled by Games (9).

Conditioned preference or aversion during the choice test. A difference score was calculated for each rat by subtracting the time spent in the saline-paired compartment during the 15-min choice test from that spent in the ethanol-paired compartment. Preferences would produce positive values and aversions would produce negative values. These difference scores were analyzed using a three-way ANOVA. The factors were line (P and NP), dose [0.0 (saline-only controls), 0.5, 1.0, and 1.5 g ethanol/kg body wt.], and compartment (whether the rats ethanol trials occurred in the white box with the grid floor or in the black box with the smooth floor). To determine the presence or absence of a significant preference or aversion for the compartment paired with ethanol within each of the lines of rats, unpaired Student's *t*-tests were used to compare the difference scores for each ethanol dose group to the difference scores for the corresponding saline control group (three comparisons for each line). In addition, unpaired Student's *t*-tests were used to compare the P and NP rats at each ethanol dose (four comparisons). The α-level for these *t*-tests was set at $p < 0.05$ with the critical levels modified to correct for multiple comparisons according to the Sidak modification of the Bonferroni critical levels tabled by Games (9).

RESULTS

Motor Activity During Conditioning Trials

The ANOVA of the activity scores for the ethanol-naive P and NP rats (Fig. 1) yielded a significant effect of line [$F(1, 53) = 74.89$, $p < 0.001$], indicating that overall, the activity was lower in the NP compared with the P rats. A significant effect of dose [$F(3, 53) = 6.03$, $p < 0.001$] reflected the fact that the level of activity varied with the ethanol dose received. A significant effect of drug [$F(1, 53) = 72.86$, $p < 0.001$] indicated that ethanol produced a reduction in activity when the ethanol and saline trials of same animals were compared. Significant interactions of line with drug [$F(1, 53) = 6.48$, $p < 0.02$] and dose with drug [$F(3, 53) = 13.70$, $p < 0.001$] indicated that the ethanol-produced reductions in activity varied depending on which line of rats and doses were tested. Post hoc comparisons using paired t-tests of the activity following saline and ethanol injections within each line and dose indicated significant reductions at the 1.0- and 1.5-g/kg ethanol doses for the P rats [$t(7) = 7.68$, $p < 0.01$; $t(6) = 9.74$, $p < 0.01$, respectively] and at the 1.0- and 1.5-g/kg ethanol doses for the NP rats [$t(7) = 5.38$, $p < 0.01$; $t(7) = 4.41$, $p < 0.05$, respectively]. The activities of the ethanol-naive P and NP rats were compared at each dose level using unpaired t-tests, and the NP rats usually were found to be less active than the P rats regardless of whether they were treated with ethanol [range of t values: 2.77–5.81, $p < 0.20$–0.01], i.e., the NP rats generally were less active than the P ones during ethanol and saline trials at all dose levels.

Choice Test

Unconditioned preferences/aversions. When time in the two different compartments of the apparatus was compared within the saline control groups, rats of the P line spent similar amounts of time (mean ± SEM) in the black, smooth-floor compartment (397.0 ± 38.7 s) and the white, grid-floor compartment (377.7 ± 39.1 s). However, rats of the NP line spent significantly more time in the black relative to the white compartment [538.6 ± 45.4 vs. 184.0 ± 10.4 s; $t(7) = 6.78$, $p < 0.001$].

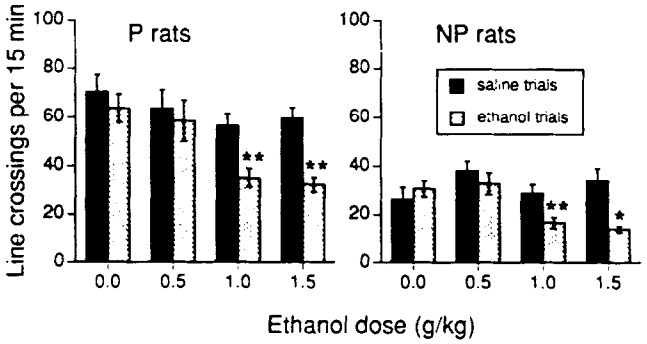

FIG. 1. Motor activity of the P and NP rats during the place-conditioning trials. Each ethanol dose is represented by a pair of adjacent bars that illustrate the mean (±SEM) line crossings per 15 min by a group of seven to eight rats during saline-conditioning trials (dark bars) and ethanol-conditioning trials (light bars). These means were derived by determining the mean activity for each rat over four conditioning trials (saline or ethanol) and then calculating the mean of these means. The standard errors shown represent between-subject variation only (based on $n = 7$–8). $^{*}p < 0.05$, $^{**}p < 0.01$ significant difference between saline and ethanol trials by paired t-test subsequent to ANOVA.

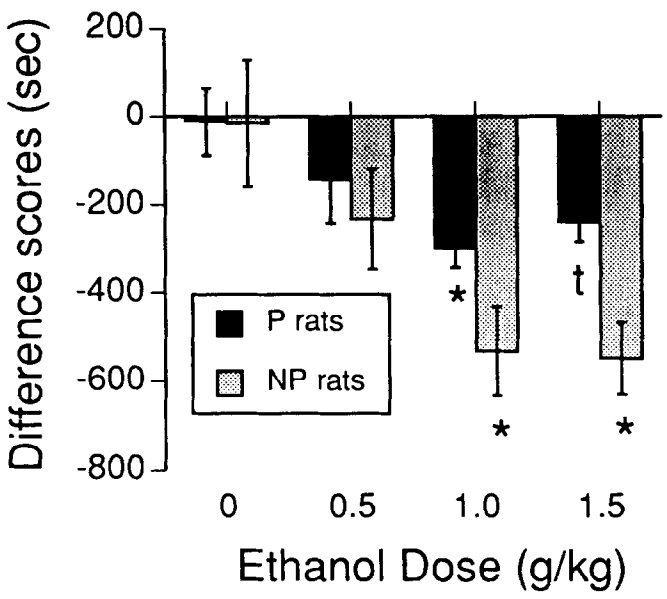

FIG. 2. Conditioned place aversions produced by ethanol injections in ethanol-preferring (P) rats and -nonpreferring (NP) rats. The mean (±SEM) difference scores (time spent in the saline-paired compartment per 15-min choice test subtracted from the time spent in the ethanol-paired compartment) for each group of seven to eight P and NP rats are shown. $^{t}p < 0.05$ significant difference between P and NP rats by t-test subsequent to ANOVA. $^{*}p < 0.05$ significant difference from the corresponding saline (0-g/kg) control group by t-test subsequent to ANOVA.

Conditioned preferences/aversions. Fig. 2 shows the place-conditioning results. The ANOVA of the difference scores (time in ethanol-paired compartment minus time in saline-paired one) yielded significant effects of line [$F(1, 45) = 9.07$, $p < 0.004$], dose [$F(3, 45) = 11.77$, $p < 0.001$], compartment [$F(1, 45) = 19.92$, $p < 0.001$], and a Line × Compartment interaction [$F(1, 45) = 7.53$, $p < 0.008$]. The significant F values with the compartment factor reflected the large preference for the black compartment seen in the NP rats regardless of drug treatment. Comparisons of the ethanol groups with the saline control groups within each line using t-tests indicated that the difference scores for the P rats receiving the 1.0-g ethanol/kg body wt. dose were significantly lower than the saline control group [$t(13) = 3.26$, $p < 0.05$]. The difference scores for the P rats at the 1.5-g ethanol/kg body wt dose. showed a nonsignificant tendency to be lower than those of the saline controls [$t(12) = 2.53$, $p < 0.10$]. The difference scores for the NP rats receiving 1.0- and 1.5-g ethanol/kg body wt. doses were significantly lower than the difference scores for the saline control rats [$t(14) = 2.94$, $t(14)$ 3.22, respectively, $p < 0.05$]. Ethanol produced conditioned aversions in both lines of rats at the two highest doses. The 0.5-g/kg ethanol dose produced no statistically significant effects. The comparison of difference scores of the P and NP rats at each dose indicated that the place aversion was significantly smaller for the P rats than for the NP rats at the 1.5-g/kg ethanol dose level [$t(13) = 3.20$, $p < 0.05$].

DISCUSSION

The administration of ethanol resulted in either no conditioned effects or the avoidance of the environmental cues asso-

ciated with the drug. No conditioned place preference was seen. Place conditioning mediated by ethanol has been extensively studied, but the factors that reliably produce ethanol-induced place preferences in rats are not well understood. A few studies have shown conditioned place preferences in rats with certain kinds of ethanol preexposure histories (10,15) or when the ethanol is combined with food (18,19), morphine (13), or an alcohol dehydrogenase inhibitor (23). However, the preponderance of place-conditioning studies (including the control groups in the experiments just listed) show no effects at low ethanol doses and conditioned place aversions at doses of 1.0 g/kg or higher (1,6,7,10,13,15,17-21,23,25). There have been only two published reports of place preferences without any ethanol preexposure or combinations of ethanol with other treatments (2,3), and these used the same route of administration and ethanol doses that resulted in either no effects or place aversions in the present investigation (Fig. 2) and in other studies (1,6,7,18,19). The present investigation indicates that with the ethanol doses and other parameters used, the testing of P rats that are selectively bred for oral ethanol preference does not result in the development of a place preference.

When ethanol-naive rats of the P and NP lines were compared, the conditioned place aversions mediated by ethanol injections were reduced in the P rats relative to the NP rats. This apparent line difference in sensitivity to the aversive effects of ethanol was accompanied by the observation of two additional behavioral differences between the P and NP rats that may be relevant to the development and manifestation of conditioned place aversions. These two differences are discussed below and include: a) less general activity in NP rats relative to P rats during saline and ethanol-conditioning trials; and b) a strong unconditioned preference for the black, smooth-floored compartment in NP but not P rats.

Investigations by Vezina and Stewart (26), Swerdlow and Koob (24), and Carr et al. (5) showed that general activity levels and exploratory behavior are factors that can alter the outcomes of place-conditioning studies. For example, restrictions in motor activity during conditioning trials can alter the strength of conditioned place preferences. In the present investigation, lower levels of motor activity were observed in the NP rats relative to P rats, even in the absence of ethanol injections. However, it is not clear how this necessarily would affect the manifestation of the ethanol-induced place aversion. One possibility is that the place aversion shown by the NP rats may have undergone a slower rate of extinction during the choice test trials: Because the NP rats appear to be generally less inclined than P rats to explore the apparatus, they would spend relatively more time in one place (the compartment that was not previously paired with ethanol).

An analysis of the saline control groups indicated that rats of the P line showed similar unconditioned preferences for the white and black compartments of the test apparatus, but the NP rats showed a strong unconditioned preference for the black compartment. However, it also is not clear how this would result in a stronger place aversion in the NP rats relative to the P rats. Two possibilities are that: a) the preference for the darker environment shown by the NP rats may reflect a line difference in the ability to discriminate the environmental cues, and/or b) the preference for the darker environment may indicate a line difference in emotionality or anxiety. The observed line differences in preference for environmental cues and locomotor activity levels (discussed earlier) are interesting in addition to their possible effects on the outcome of the place-conditioning study, because they may reflect inherited behavioral characteristics that are manifestations of physiologic mechanisms associated with selection for ethanol preference.

The observation of differences in ethanol-mediated conditioned place aversions in P and NP rats is in agreement with results from a previous study in which a conditioned taste aversion (CTA) procedure was used to evaluate the aversive effects of a similar range of ethanol doses in these rat lines (8). Because similar results were obtained with both place-conditioning and CTA procedures, it is less likely that the observed effects were dependent on idiosyncrasies of the particular behavioral tests. In the previous CTA study (8), blood alcohol concentrations were determined 15–180 min following ethanol injections, and no differences between the P and NP rats were noted. The combined findings from the CTA and place-conditioning studies suggest that different CNS sensitivities to the aversive effects of ethanol are associated with selective breeding for differences in oral ethanol preference. It remains to be determined whether the different sensitivities are specific to ethanol. It is possible that P and NP rats also may differ in sensitivity to the aversive effects of drugs in addition to ethanol.

Schechter (16) reported the results of a place-conditioning experiment in which P and NP rats were compared using a 1.0-g ethanol/kg body wt. dose. As in the present investigation, a conditioned place aversion was observed in both lines of rats but, unlike the present investigation, no significant difference between the P and NP rats was found. Schechter's methods differed from those of the present investigation in that male rats were used, the ethanol injections were given 10 min before 30-min conditioning trials (compared to immediately before 15-min conditioning trials in the present investigation), and six conditioning trials (compared to eight in the present investigation) were given. Whether any of these procedural differences account for the disparate findings of the two studies remains to be determined. Schechter also measured motor activity following ethanol injections and found that the NP rats were more impaired than the P ones at the same 1.0-g ethanol/kg body wt. ethanol dose. This finding is similar to the results of previous comparisons of ethanol-produced changes in the spontaneous motor activity of P and NP rats (28). In the present investigation, motor activity was measured during conditioning trials. Line differences were not observed at the 1.0- and 1.5-g/kg ethanol doses, perhaps as the result of a floor effect imposed by the low baseline activity levels of the NP rats.

Taken together, the present study and previous investigations (8,22) suggest that innate differences in sensitivity to the aversive effects of ethanol may play a part in determining the levels of ethanol intake seen in the selectively bred P and NP lines of rats. To gain a more complete understanding of processes that regulate ethanol consumption, both sides of the coin—ethanol reinforcement and ethanol aversion—should be considered. An important theoretical question is whether alcohol-dependent persons drink excessively because for them the drug is more reinforcing, less aversive, or both.

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