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Haloperidol reduces ethanol-induced motor activity stimulation but not conditioned place preference

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Abstract. This experiment examined the impact of a dopamine receptor blocker on ethanol's rewarding effect in a place conditioning paradigm. DBA/2J mice received four pairings of a tactile stimulus with ethanol (2 g/kg, IP), haloperidol (0.1 mg/kg, IP) + ethanol, or haloperidol alone. A different stimulus was paired with saline. Ethanol produced increases in locomotor activity that were reduced by haloperidol. However, conditioned preference for the ethanol-paired stimulus was not affected by haloperidol. Haloperidol alone decreased locomotor activity during conditioning and produced a place aversion. These results indicate a dissociation of ethanol's activating and rewarding effects. Moreover, they suggest that ethanol's ability to induce conditioned place preference is mediated by nondopaminergic mechanisms.

Key words: Haloperidol – Ethanol – Conditioned place aversion – Conditioned place preference – Inbred mice (DBA/2J) – Locomotor activity – Reward – Dopamine system

Although the place conditioning procedure has been used extensively during the last 10 years to study the neural basis of the rewarding effects of many abused drugs, it has not been used to examine the neurochemical mechanisms underlying ethanol's rewarding effect (see reviews by Carr et al. 1989; Hoffman 1989; Swerdlow et al. 1989). Attempts to do so have probably been hindered by the great difficulty in producing ethanol-induced conditioned place preference in rats. Most place conditioning studies with ethanol have resulted in the development of place aversion (cf Sherman et al. 1988). Extensive pre-exposure to ethanol, a large number of conditioning trials, or the concurrent availability of food has been required in order to produce a relatively small conditioned place preference with ethanol (Stewart and Grupp 1981; Reid et al. 1985; Bozarth 1990). Recently, however, we found that several different selectively bred and inbred strains of mice readily develop a robust conditioned preference for ethanol-paired stimuli using a relatively conventional place conditioning procedure (Cunningham and Prather 1990; Cunningham and Noble 1991; Cunningham et al. 1991, 1992; Risinger and Cunningham 1992). The relative ease with which mice display ethanol-induced conditioned place preference has encouraged us to begin using this procedure to study the neuropharmacological basis of ethanol reward (e.g., Risinger et al. 1991).

The present experiment was designed to study the role of dopaminergic processes in ethanol reward using inbred mice in the place conditioning procedure. Although the dopamine system has been consistently implicated in stimulant and opiate reward (cf Carr et al. 1989), considerably less is known about its role in ethanol reward. One current theory suggests all addicting drugs, including ethanol, have both psychomotor stimulant and rewarding properties which are mediated by the same central dopamine systems (Wise and Bozarth 1987). The present study tested this hypothesis by examining the influence of a dopamine receptor blocker, haloperidol, on ethanol-induced locomotor activation and conditioned place preference. The dose of haloperidol chosen for the present study (0.1 mg/kg) was well above the dose shown to be effective in reducing operant responding for ethanol in rats (cf Pfeffer and Samson 1988). Presumably, if dopamine receptor blockade disrupts ethanol's activating effect, it should also retard the conditioning of place preference.

Materials and methods

Subjects. The subjects were 86 naive, adult male DBA/2J mice (60 days old). They were housed in groups of four with continuous access to food and water in the home cage. Experimental procedures were conducted during the light phase of a 12 : 12 light/dark cycle (lights on at 0700).

Apparatus. Twelve identical acrylic and aluminum chambers (30 × 15 cm x 15 cm high) were enclosed in separate ventilated, light

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and sound attenuating boxes (Coulbourn Model E10–20). Six sets of infrared light sources and detectors were positioned opposite each other at 5-cm intervals on the long walls of each chamber, 2.2 cm above the floor surface. Occlusion of the infrared beams was used both as a measure of general activity and to determine the animal's position (left or right side) in the chamber. Total activity counts and amount of time spent on each side of the chamber (0.01 s resolution) were recorded each minute by computer. The floor of each box consisted of interchangeable halves with two distinctive textures: "hole" floors were made from perforated stainless steel (16 gauge) with 6.4 mm round holes on 9.5 mm staggered centers; "grid" floors were composed of 2.3 mm stainless-steel rods mounted 6.4 mm apart in acrylic rails. This combination of floor textures was selected on the basis of previous studies indicating that drug-naive control groups spend about half their time on each floor type during preference tests (e.g. Cunningham et al. 1992).

Procedure. The experiment involved three consecutive phases: habituation (one session), conditioning (eight sessions), and testing (one session). Sessions were conducted 5 days a week with a 2-day break between the first four and second four conditioning sessions. The habituation session was intended to reduce the novelty and stress associated with handling, injection, and exposure to the apparatus. All subjects received saline (15 ml/kg) and were immediately placed in the conditioning box for 5 min on a smooth floor covered with paper.

During the conditioning phase, mice were randomly assigned to one of three drug treatment groups: SE (saline + ethanol), HE (haloperidol + ethanol), or HS (haloperidol + saline). Within each drug treatment group, mice were randomly assigned to one of two conditioning subgroups ($n = 13$–16/group) and exposed to a Pavlovian differential conditioning procedure. On alternate days, mice in the Grid + subgroups received drug treatment prior to placement on the grid floor (CS + trial), and saline prior to placement on the hole floor (CS − trial). In contrast, mice in the Grid − subgroups received saline before placement on the grid floor (CS − trial) and drug treatment before placement on the hole floor (CS + trial). Thus, the conditioning subgroups within each drug treatment condition were matched for exposure to each drug and floor type, and differed only in the specific floor + drug relationship (cf Cunningham 1992).

Each mouse received two IP injections before each CS + trial. The first injection contained either haloperidol (0.1 mg/kg Haldol, McNeil Pharmaceutical) or saline. The second injection, 1 h later, contained either ethanol (2 g/kg, 20% v/v) or saline. HE mice received haloperidol followed by ethanol, SE mice received saline followed by ethanol, and HS mice received haloperidol followed by saline. Mice were returned to the home cage after the first injection. After the second injection, they were immediately placed in the apparatus with the assigned CS + floor. On alternate days, all subjects received two saline injections spaced 1 h apart before exposure to the CS − floor. Subjects had access to both sides of the apparatus and floor texture was homogeneous on all conditioning trials. Each mouse received four 5-min conditioning trials of each type; order of exposure to drug treatment was counterbalanced within groups.

For preference testing, all subjects received two saline injections 1 h apart before placement in the apparatus for a 30-min session with half grid floor and half hole floor (left/right position counterbalanced within groups). Data were analyzed by analysis of variance using a 0.01 alpha level.

Results

Figure 1 depicts mean activity counts per minute (± SEM) for the first and last conditioning trials. SE subjects showed higher mean activity counts per minute on the first CS + trial than on the first CS − trial, indicating ethanol-induced locomotor activation. HE subjects were less active on their first CS + trial, demonstrating that haloperidol reduced the locomotor activating effect of ethanol. However, haloperidol did not completely eliminate ethanol's activating effect in HE mice; CS + trial activity still exceeded that seen on the first CS − trial. HS subjects displayed lower levels of activity on their CS + trial than on their CS − trial, indicating that haloperidol alone decreased locomotor activity. Two-way analysis of variance (drug treatment × trial type) yielded significant effects of drug treatment [$F(2,83) = 79.9$], trial type [$F(1,83) = 102.9$] and drug treatment × trial type [$F(2,83) = 103.3$]. Follow-up analysis of CS + trial activity indicated that the difference between groups SE and HE was significant [$F(1,57) = 76.2$]. A separate analysis of CS − trial activity showed no differences among drug treatment groups [$F(2,83) = 2.4$]. Within-group comparisons indicated that the activity difference between CS + and CS − was significant in groups SE [$F(1,31) = 256.5$] and HS [$F(1,26) = 12.9$]. However, the difference in group HE was not significant [$F(1,26) = 5.9$, $0.01 < P < 0.03$].

Activity during CS + trials increased over trials in the SE and HE groups, but declined in the HS group. Within-group analyses indicated significant trial effects for all three groups [SE: $F(3,93) = 10.4$; HE: $F(3,78) = 6.9$; HS: $F(3,78) = 12.8$].

Figure 2 depicts mean seconds per minute (± SEM) spent on the grid floor by all groups during the 30-min preference test. Magnitude of place conditioning under each drug treatment condition is represented by the dif-

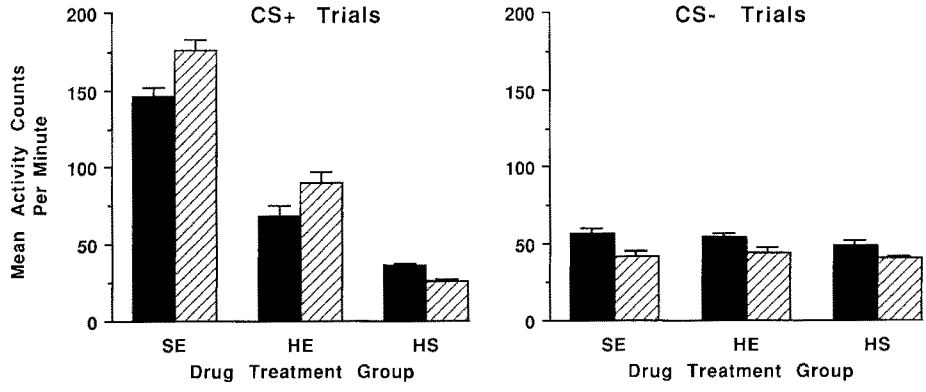

Fig. 1. Mean activity counts per minute (± SEM) during the first (■) and fourth (▨) CS + trials *(left panel)* and CS − trials *(right panel)*

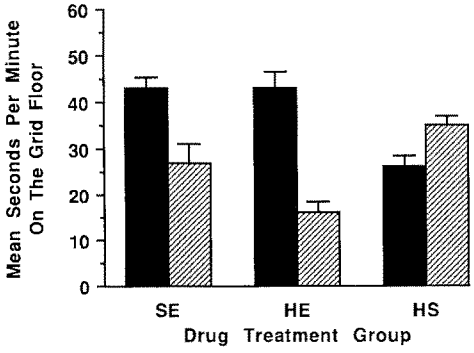

Fig. 2. Mean seconds per minute (±SEM) spent on the grid floor by each conditioning group during the 30-min preference test. On CS+ conditioning trials, HE mice had received haloperidol followed by ethanol, SE mice had received saline followed by ethanol, and HS mice had received haloperidol followed by saline. All subjects received saline injections on CS− trials and before the preference test. Grid+ groups (■) had previously received pairings of the grid floor and drug treatment, whereas Grid− groups (▨) had received pairings of the grid floor and saline

ference between conditioning subgroups (i.e., Grid+ vs Grid−). As can be seen, haloperidol did not reduce ethanol's rewarding effect; conditioned place preference was observed in both the SE and HE groups. However, haloperidol alone produced a conditioned place aversion in the HS group. Analysis of variance (drug treatment × conditioning group) supported these observations, yielding significant effects of conditioning group [$F(1,80) = 19.6$] and drug treatment × conditioning group [$F(2,80) = 17.5$]. A separate analysis comparing only the SE and HE groups also showed a significant effect of conditioning group [$F(1,55) = 40.0$], but no effect of drug treatment or drug treatment × conditioning group [both Fs < 2.6], indicating that haloperidol did not alter strength of place conditioning. Followup comparisons of the conditioning groups within each drug treatment showed reliable conditioned place preference in group SE [$F(1,30) = 10.8$] and group HE [$F(1,25) = 35.1$], and reliable conditioned place aversion in the HS group [$F(1,25) = 7.8$]. Activity levels during the preference test did not differ across drug treatment groups [$F(2,83) = 1.2$]. Mean (±SEM) activity counts per minute were 27.6±1.3, 27.7±1.3, and 29.9±0.9 for groups SE, HE and HS, respectively.

Discussion

The present study is the first to examine the role of the dopamine system in ethanol's rewarding effect using the place conditioning paradigm. Pretreatment with haloperidol on conditioning trials did not affect development of ethanol-induced conditioned place preference, even though haloperidol substantially reduced ethanol-induced locomotor activation. Thus, contrary to the prediction of the psychomotor stimulant theory of addiction (Wise and Bozarth 1987), these results suggest a dissociation between the neuropharmacological mechanisms underlying ethanol's stimulant and rewarding effects. Although ethanol's locomotor stimulant effect was altered by dopamine receptor blockade, its rewarding efficacy was not. These observations are consistent with a number of other reports showing that haloperidol can block locomotor activation produced by stimulant drugs (e.g., nomifensine, bupropion and methylphenidate), yet may fail to prevent development of conditioned place preference (cf Carr et al. 1989; Hoffman 1989).

The conclusion that the dopamine system is uninvolved in ethanol's rewarding effects must be tempered by previous findings showing that dopamine receptor blockers (haloperidol, pimozide) reduce ethanol drinking and operant self-administration of ethanol in rats (Pfeffer and Samson 1986, 1988). Although differences in species and the nature of the behavioral tasks make it difficult to reconcile these findings with those of the present study, one conclusion may be that the place conditioning task used in the present study does not provide a valid measure of ethanol's rewarding effects (e.g. Dworkin and Smith 1988). However, this conclusion seems unwarranted in as much as the literature generally provides concordance between conclusions based on studies of drug-induced place conditioning and studies using other behavioral indices of drug reward (Carr et al. 1989).

It may be that the outcome of previous drinking and self-administration studies was due more to the role played by dopaminergic systems in the expression of conditioned reward rather than to an effect on the primary rewarding properties of ethanol. Because dopamine receptor blockade in those studies was not implemented until the ethanol-reinforced behavior was well established, one might attribute the altered performance to interference with the expression of a dopamine-mediated conditioned motivational effect that normally modulates ethanol-reinforced behavior. In contrast, the present study was not designed to examine dopamine's role in the expression of an ethanol-induced conditioned motivational effect. Rather, this study attempted specifically to determine whether haloperidol would interfere with the primary rewarding effects of ethanol experienced on each conditioning trial or with the process of learning about those effects. While the present outcome clearly suggests that dopaminergic mechanisms played no role in the development of ethanol-induced conditioned motivational effects, it does not rule out a possible role of the dopamine system in the expression of such effects (see Hiroi and White 1990, for a related discussion about dopaminergic influences on the learning and expression of amphetamine-induced conditioned place preference).

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