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BRIEF COMMUNICATION

Conditioned Activation Induced by Ethanol: Role in Sensitization and Conditioned Place Preference

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CUNNINGHAM, C. L. AND D. NOBLE. *Conditioned activation induced by ethanol: Role in sensitization and conditioned place preference.* PHARMACOL BIOCHEM BEHAV **43**(1) 307-313, 1992.—Previous studies of ethanol-induced activation and place preference conditioning have shown that repeated exposure to ethanol produces sensitization to ethanol's locomotor activating effect in mice. This experiment was designed to determine whether the behavioral sensitization to ethanol that occurs during place preference conditioning is due to development of a Pavlovian conditioned activity response. Mice (DBA/2J) in the experimental group (BEFORE) received four pairings of a distinctive floor stimulus with ethanol (2 g/kg, IP); a different floor stimulus was paired with saline (counterbalanced). Mice in two control groups were exposed equally to each floor stimulus and were handled and injected as often as experimental mice. One control group (AFTER) always received ethanol in the home cage 1 h after exposure to the floor stimulus, while the other control group (NO-DRUG) never received ethanol during conditioning. BEFORE group mice showed a significant conditioned place preference, whereas control mice did not. Activity tests after saline or ethanol indicated higher activity levels in BEFORE mice compared to control mice, regardless of floor stimulus. Moreover, BEFORE mice were more active on their CS+ floor than on their CS− floor during saline tests; activity was equally elevated on both floors during ethanol tests. These results support the hypothesis that sensitization to ethanol's activating effect is mediated by Pavlovian conditioning. Further, they suggest that place conditioning established associative control by two kinds of stimuli; the specific tactile cues serving as CS+ and CS− and the general environmental cues common to both CS+ and CS− trials. Finally, these data suggest that ethanol-induced conditioned place preference and behavioral sensitization to ethanol may be mediated by a common learning process.

Ethanol Conditioned place preference Conditioned activation Sensitization Locomotor activity Inbred mice (DBA/2J)

REPEATED exposure to opiate and stimulant drugs often results in sensitization to their locomotor-activating effects (1,26,31). In light of theories postulating a biologic relationship between the activating and rewarding effects of addictive drugs (40), delineation of the mechanisms underlying behavioral sensitization may be useful in understanding drug-seeking behavior and relapse [cf.(33)]. One important determinant of sensitization to drug effects is the Pavlovian relationship between environmental stimuli and drug delivery. A positive correlation between these events can produce an association capable of mediating the development of sensitization [see reviews by (23,32,33)]. Evidence of this association has been provided most often by tests showing that expression of sensitization is specific to the environment in which the drug was originally received (17,27). In some cases, however, drug-paired environmental stimuli have also been shown to acquire the ability to evoke a conditioned activity response in the absence of drug (37).

Although sensitization and conditioned activity responses have been well described for opiate and stimulant drugs, the literature on sensitization to ethanol's locomotor-activating effect is rather sparse and there is no information on the role played by conditioning in the development of ethanol-induced sensitization. The paucity of data in this area is due, in part, to species and strain differences in sensitivity to the acute stimulating effect of ethanol and in the effect of chronic ethanol exposure. Although there are some reports of ethanol-induced hyperactivity in rats (18), the more commonly ob-

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served outcome is a depression of locomotor activity (15,22). There appear to be no studies indicating that chronic ethanol exposure produces sensitization to ethanol-induced hyperactivity in rats. Ethanol-induced stimulation has been reported much more frequently in mice, but this effect depends greatly upon dose and genotype (4–7,14,15,25,36). In many instances, inbred or selectively bred mice that are initially stimulated by ethanol have shown behavioral sensitization following chronic exposure to ethanol (6,20–22,24). It is not known, however, whether development of sensitization to ethanol's activating effect is influenced by Pavlovian conditioning or whether it is accompanied by changes in ethanol's rewarding properties.

Recent studies in this lab have shown that repeated injections of ethanol produce sensitization to its activating effect in inbred (DBA/2) mice during conditioning trials that produce conditioned preference for ethanol-paired environmental stimuli (11,13,29,30). These observations raise the interesting possibility that the learning process that mediates the conditioning of ethanol's motivational effect also mediates the expression of sensitization to ethanol's locomotor-activating effect. As a first step toward evaluating this possibility, the present experiment was designed to determine whether a place conditioning procedure known to produce preference for ethanol-paired stimuli would also endow those stimuli with the ability to evoke a conditioned activity response or to control the expression of sensitization to ethanol's locomotor-activating effect.

METHOD

Subjects

Seventy-two adult, male, inbred mice (DBA/2J) were obtained from the Jackson Laboratory (Bar Harbor, Maine) at 6 weeks of age and allowed to acclimate to the animal colony for 2 weeks before training. They were housed in groups of four in polycarbonate cages (27.9 × 9.5 × 12.7 cm) with cob bedding at an ambient temperature of 21 ± 1°C. Water and lab chow were available at all times in the home cage. Experimental procedures were conducted during the light phase of a 12 L:12 D cycle (lights on at 0700 h).

Apparatus

The apparatus consisted of eight identical acrylic and aluminum boxes (30 × 15 × 15 cm) enclosed in separate ventilated, light- and sound-attenuating enclosures (Coulbourn Instruments, Lehigh Valley, PA, Model E10-20). Infrared light sources and photodetectors (total of six sets) were mounted opposite each other at 5-cm intervals on the long walls of each box, 2.2 cm above the floor. Occlusion of the infrared light beams was used both as a measure of general activity and to detect the animal's position (left or right side) within the box. Three photodetectors monitored activity on one side of the apparatus, while the other three detected activity on the opposite side. A change in sides was recorded when all photobeams on one side were inactivated and at least one beam on the opposite side was occluded. Total activity counts and amount of time spent on each side of the chamber were recorded every minute by an Apple II microcomputer (10-ms resolution).

The floor of each box consisted of interchangeable halves made of one of two textures. The "grid" (G) floor was composed of 2.3-mm stainless steel rods mounted 6.4 mm apart in acrylic rails. The "hole" (H) floor was made from perforated stainless steel (16 ga) with 6.4-mm round holes on 9.5-mm staggered centers. This combination of floor textures was selected on the basis of previous studies showing that drug-naive control groups spend about half their time on each floor type during preference tests (11,12). The floors and inside of the box were wiped with a damp sponge and the litter paper beneath the floors was changed after each mouse.

Procedure

The experiment included four main phases: habituation (one session), conditioning (eight sessions), activity testing (four sessions), and preference testing (one session). Sessions were conducted on consecutive days except as noted below. Each mouse was weighed and injected (IP) immediately before being placed in the center of the apparatus for each session. The habituation was intended to reduce the novelty and stress associated with handling, injection, and exposure to the apparatus. All mice were injected with saline and placed in the conditioning box for 30 min on a smooth floor covered with paper. Subjects were not exposed to the distinctive floor textures to avoid latent inhibition (19).

Conditioning. The experimental design during the conditioning phase is outlined in Table 1. Mice were randomly assigned to conditioning subgroups within one of three main treatment groups. Mice in the BEFORE group subgroups were exposed to a Pavlovian discrimination conditioning procedure that was expected to produce preference for the ethanol-paired floor texture. On all conditioning trials, subjects had access to both sides of the apparatus and floor texture was homogeneous [cf.(38)]. On alternate days, mice in the G+/− subgroup were injected with ethanol (2 g/kg, 20% v/v) just before placement on the grid floor, whereas mice in the H+/− subgroup received ethanol before placement on the hole floor (CS+ trial). On intervening days, all subjects were injected with saline before exposure to the other floor texture (CS− trial). All mice also received a saline injection in the home cage about 1 h after each conditioning trial injection. This second injection was given as a control for nonpharmacological aspects of the treatment administered to mice in the AFTER group (see below). Four 5-min conditioning trials of each type were given over an 8-day period; order of exposure to CS+ and CS− was counterbalanced within each subgroup. Mice in the two BEFORE group subgroups were matched for overall exposure to each floor type, ethanol, and saline, and differed only in the floor-drug contingency. Thus, any differences between these subgroups during activity or preference tests can be attributed to development of a Pavlovian association between the CS+ floor and ethanol [cf.(9)].

Mice in the AFTER group subgroups were exposed to each floor type, ethanol, and vehicle as often as subjects in the BEFORE group; however, ethanol injections were always given in the home cage about 1 h after the conditioning trial. Whenever a CS+ trial was scheduled for the BEFORE group subgroups, mice in the G−/+ and H−/+ AFTER group subgroups received a saline injection before the conditioning trial and an ethanol injection afterward in the home cage. When CS− trials were scheduled, these subgroups received saline injections both before and after the trial. In Pavlovian conditioning terms, the AFTER group is an "unpaired" learning control. Because it received the same number of ethanol and saline injections as the BEFORE group, it was expected to show the same degree of nonassociative tolerance or sensitization to ethanol's effects as the BEFORE group. Any test session differences between the AFTER group and either of the BEFORE group subgroups can be attributed to the development of a floor–ethanol or apparatus–ethanol association

TABLE 1

EXPERIMENTAL DESIGN AND PREFERENCE TEST RESULTS

Group	Conditioning Subgroup	Conditioning: Odd Days* (apparatus/home cage†)	Conditioning: Even Days (apparatus/home cage)	Preference Test [mean (±SEM) s/min spent on grid floor]
BEFORE	G+/− (n = 12)	Grid → EtOH/saline	Hole → saline/saline	37.2 ± 3.2
	H+/− (n = 12)	Hole → EtOH/saline	Grid → saline/saline	17.6 ± 2.4
AFTER	G−/+ (n = 11)	Grid → saline/EtOH	Hole → saline/saline	23.9 ± 3.8
	H−/+ (n = 11)	Hole → saline/EtOH	Grid → saline/saline	25.4 ± 4.2
NO-DRUG	−/− (n = 24)	Grid → saline/saline	Hole → saline/saline	28.2 ± 2.5

*Order of exposure to conditioning day treatments was counterbalanced within each subgroup.

†Apparatus injections were given just before placement on the assigned floor; home cage injections were given 1 h after the conditioning trial.

in the BEFORE groups [cf.(9)]. The AFTER group subgroups were not expected to develop an association between the apparatus or either floor type and ethanol because of the long delay between exposure to these events. The design permitted this assumption to be evaluated because mice within each AFTER group subgroup were consistently exposed to the same floor on every delayed ethanol injection trial (i.e., mice in the G−/+ subgroup always received ethanol 1 h after exposure to the grid floor whereas mice in the H−/+ subgroup always received ethanol 1 h after exposure to the hole floor). The development of any association between the floor cue and delayed injection of ethanol would presumably be evidenced by differences between these two subgroups during testing.

Mice in the NO-DRUG group were exposed to the apparatus, floors, and injection procedures under the same general conditions described for the other groups. However, saline was administered in place of ethanol. These animals were not expected to develop any conditioned responses or become tolerant/sensitized to ethanol's effects. They served as a control for nonpharmacological effects of repeated exposure to the apparatus, floor types, handling, and injection.

Activity tests. To assess the effects of the conditioning procedures under comparable conditions, all mice received a series of four activity tests beginning 48 h after the last conditioning trial. Saline was administered in the first two test sessions to determine whether environmental stimuli had acquired control over activity in the absence of drug. Ethanol was given in the next two test sessions to determine whether environmental stimuli had acquired control over drug-induced activation. Each activity test was conducted like a conditioning trial in that all mice received the test injection just before a 5-min placement in the apparatus on one of the two floor types. However, no injections were given in the home cage after these tests. Half the subjects in each subgroup were tested on the grid floor during the first test session under each drug condition. The remaining subjects were tested first on the hole floor. These conditions were reversed for the second test under each drug condition. Thus, each mouse was tested once on its CS+ floor and once on its CS− floor, both in the presence and in the absence of ethanol. The primary dependent variable was the number of activity counts measured during each of the test sessions. Successive test sessions occurred at 24-h intervals with the exception of the second ethanol test, which was given 48 h after the first ethanol test to minimize the possibility that performance on the second test was affected by long-lasting compensatory responses to the first ethanol injection [cf.(16)]. Mice remained undisturbed in their home cages on days when no sessions were conducted.

Place preference test. The floor preference test was given 48 h after the last activity test. All subjects received a saline injection before placement in the apparatus with half grid floor and half hole floor. Relative position of the floors (i.e., left vs right) was counterbalanced within each subgroup. The primary dependent variable was the amount of time spent on the grid floor during the 60-min test session.

Data Analysis

A procedural error during the conditioning phase required the elimination of two subjects from the AFTER group. The final number of subjects in each subgroup is shown in Table 1. In addition, a computer problem during the first ethanol activity test resulted in the loss of data from eight mice. Thus, analyses reported below for the ethanol test are based upon data obtained from the remaining subjects. The α level for all analyses was set at 0.05.

RESULTS

Conditioning

Figure 1 depicts the mean (±SEM) activity counts per minute during each of the conditioning trials for all groups. As shown in the left panel, ethanol produced a relatively high level of activity in BEFORE group mice on CS+ trials. Moreover, ethanol-stimulated activity increased over trials in contrast to the decrease in activity seen in control groups that received saline on those trials. Two-way analysis of variance (ANOVA) (groups × trials) of activity on CS+ trials yielded significant effects of groups [$F(2, 67) = 282.2$], trials [$F(3, 201) = 3.1$, and groups × trials [$F(6, 201) = 8.6$]. Separate within-group analyses confirmed the reliability of the increase in activity over trials in the BEFORE group [$F(3, 69) = 3.0$] and the decreases over trials in groups AFTER [$F(3, 63) = 15.6$] and NO-DRUG [$(3, 69) = 13.1$]. A follow-up comparison indicated no significant difference between groups AFTER and NO-DRUG [$F(1, 44) < 1$].

The right panel of Fig. 1 shows that although all three groups displayed similar activity levels after saline injection on the first CS− trial the decrease in activity over successive trials was retarded in the BEFORE group relative to the two control groups. Two-way ANOVA (groups × trials) of activ-

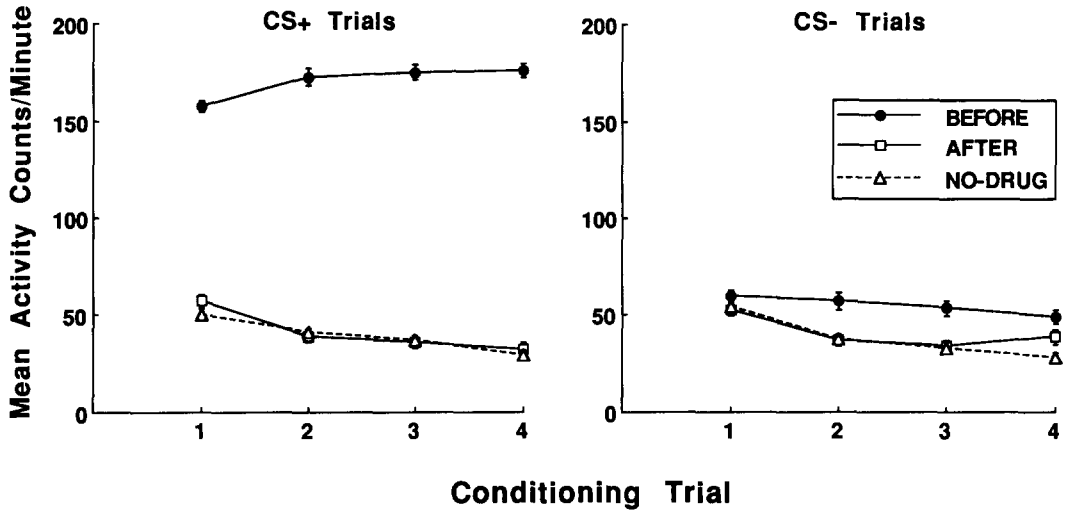

FIG. 1. Mean (±SEM) activity counts per minute during each 5-min CS+ (left panel) and CS− (right panel) conditioning trial. The BEFORE group received ethanol (2 g/kg, IP) on each CS+ trial and saline on each CS− trial. The other groups received saline on both types of trials. Data are averaged over conditioning subgroups.

ity on CS− trials revealed reliable effects of groups [$F(2, 67) = 15.4$], trials [$F(3, 201) = 26.6$], and groups × trials [$F(6, 201) = 3.2$]. Follow-up comparisons indicated a significant difference between the BEFORE group and each of the two control groups [vs. AFTER; $F(1, 44) = 16.2$; vs. NO-DRUG, $F(1, 46) = 24.2$]. There was no significant difference between groups AFTER and NO-DRUG [$F(1, 44) < 1$]. Separate within-group analyses indicated the decrease in activity over trials was reliable in all three groups [BEFORE, $F(3, 69) = 3.0$; AFTER, $F(3, 63) = 8.0$; NO-DRUG, $F(3, 69) = 30.5$].

Activity Tests

Figure 2 shows mean (±SEM) activity counts per minute for each group averaged over the two ethanol tests (left panel) and two saline tests (right panel). Activity levels on the CS+ and CS− floors are shown separately for the BEFORE group. The BEFORE group showed higher levels of activity than either control group during both the ethanol [vs. AFTER, $F(1, 40) = 13.4$; vs. NO-DRUG, $F(1, 42) = 14.7$] and saline tests [vs. AFTER, $F(1, 44) = 23.0$; vs. NO-DRUG, $F(1, 46) = 34.4$], whereas the control groups did not differ in either test (both $F < 1$). Although group BEFORE mice were more active on CS+ than on CS− in the saline tests [$F(1, 22) = 9.8$], there was no effect of CS during the ethanol test [$F(1, 22) = 2.6$]. Control group mice showed no significant differences in activity on the two floor types during either test (data not shown).

Place Preference Test

Table 1 lists the mean (±SEM) number of seconds per minute spent on the grid floor by each group during the 60-min preference test. As expected on the basis of previous stud-

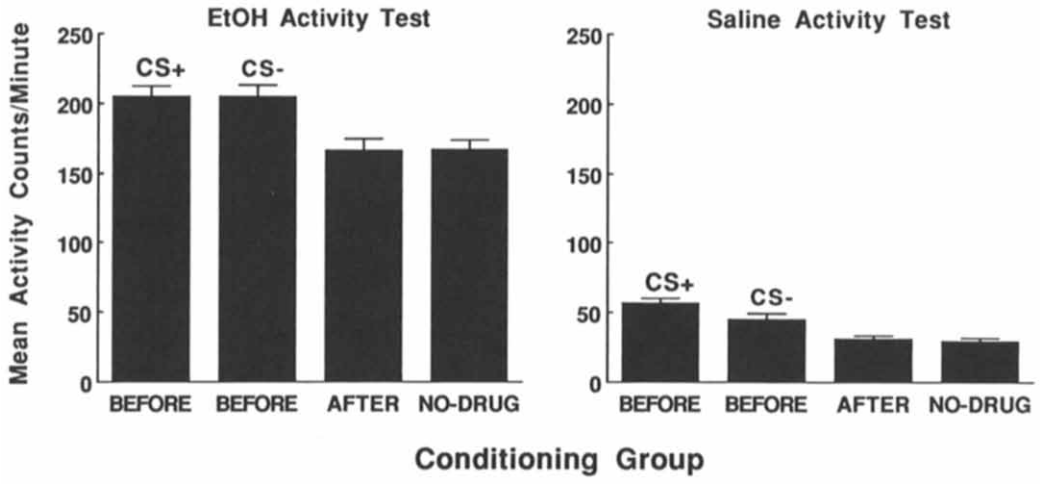

FIG. 2. Mean (±SEM) activity counts per minute during the 5-min ethanol (EtOH) (left panel) and saline (right panel) activity tests. Activity levels on the CS+ and CS− trials are shown separately for the BEFORE group (collapsed over conditioning subgroup). Activity levels did not differ as a function of floor type in the control groups; the data shown here are collapsed over floor type.

ies using these tactile stimuli, time spent on the grid floor by mice in the NO-DRUG control group (28.2 s) was nearly equal to the value expected on the basis of chance (i.e., 30 s). In contrast, experimental mice previously exposed to grid–ethanol pairings (G+/−) spent more time on grid, whereas experimental mice previously exposed to hole–ethanol pairings (H+/−) spent less time on grid. This difference between the BEFORE group subgroups indicates development of a conditioned preference for the ethanol-paired floor [$F(1, 22) = 23.5$]. The AFTER group subgroups showed a mild bias against the grid floor, but there was no significant difference between the two subgroups ($F(1, 20) < 1$], suggesting no association has been formed between floor stimuli and delayed injection of ethanol. A comparison of the two control groups showed no significant difference [$F(1, 44) = 0.9$]. However, the combined control groups were reliably different from each of the BEFORE group subgroups [both $F(1, 56) > 5.2$], providing additional evidence of conditioned place preference (2,3,34). There were no group differences in activity levels during the preference test. Mean activity counts per minute were 36.1, 33.3, and 32.5 for groups BEFORE, AFTER, and NO-DRUG, respectively.

DISCUSSION

This experiment provided several kinds of evidence implicating Pavlovian conditioning in the development of behavioral sensitization to ethanol. In accord with previous studies, ethanol increased locomotor activity in DBA/2J mice (7,15) and repeated ethanol exposure on conditioning trials augmented this excitatory effect (6,11,13,29,30), providing within-group evidence of sensitization. In contrast, activity measured after saline injections decreased over trials, suggesting development of habituation to the novelty-stress of the conditioning procedure. The greater activity of BEFORE group mice on later saline (CS−) trials is most likely due to a conditioned activity response evoked by apparatus cues that were present on both CS+ and CS− trials (see below). The lack of differences between the two control groups during conditioning indicates that home cage injections of ethanol (AFTER) had no effect on activity measured in the test chamber.

More definitive evidence of the role played by Pavlovian conditioning was provided by the between-groups demonstration of sensitization in the postconditioning ethanol activity tests. Regardless of floor stimulus, BEFORE group mice were more active after injection of ethanol than control mice that had previously received unpaired injections of ethanol in the home cage (AFTER) or no previous ethanol injections (NO-DRUG). The difference between the BEFORE and AFTER groups supports the conclusion that sensitization was mediated by a Pavlovian association between environmental cues and ethanol. In fact, the lack of difference between the AFTER and NO-DRUG groups suggests that sensitization in the BEFORE group was mediated entirely by associative mechanisms. Although between-groups evidence of sensitization has been reported previously (6,24), this is the first study showing environmental specificity of behavioral sensitization to ethanol.

Postconditioning saline activity tests indicated that ethanol-paired stimuli also acquired the ability to evoke a conditioned increase in activity in the absence of ethanol. Thus, context-dependent sensitization of ethanol's activating effect might be due to an interaction between the conditioned and unconditioned activity responses [cf.(32,33)]. In contrast to the ethanol tests, the results of the saline activity tests revealed two sources of stimulus control over activity. The difference in activity elicited by CS+ and CS− in the BEFORE group showed control by tactile floor stimuli, whereas the difference between BEFORE and AFTER groups showed control by general environmental cues common to both CS+ and CS− trials (e.g., light- and sound-attenuating enclosure, ventilation fan noise, Plexiglas and aluminum walls, handling/injection). This pattern of results might indicate that the place conditioning procedure established two separate associations capable of controlling conditioned changes in activity: a specific association between ethanol and the paired floor stimulus and a more general association between ethanol and nonspecific contextual stimuli. Alternatively, floor stimuli may have acquired the ability to "modulate" the activity response elicited by the context–ethanol association [cf.(28,39)].

There are several reasons why BEFORE group mice might have shown an effect of the floor CS in the saline tests but not in the ethanol tests. One possibility is that the influence of the floor CS was obscured during the ethanol test due to a "ceiling" effect. In other words, the relatively high level of unconditioned activation induced by ethanol may have made it too difficult to detect relatively small effects of the CS on activity. Alternatively, it may be that CS differences during the ethanol test were diminished by extinction that occurred as a result of presenting the CS+ floor without ethanol during the saline tests (which were given to all mice before the ethanol tests). Finally, it is also possible that ethanol interfered somehow with retrieval of the floor–ethanol association, even though it had no apparent effect on the context–ethanol association.

As expected on the basis of other recent studies (8,10, 11,13,29,30), BEFORE group mice displayed a conditioned preference for an ethanol-paired tactile floor stimulus. Although the saline activity test data indicate the BEFORE treatment gave associative value to both tactile floor cues and nonspecific contextual cues, the exact role played by the context–ethanol association in the expression of conditioned place preference is unclear. Conditioned place preference may result from the summation of conditioned motivational effects controlled separately by tactile and contextual cues. Alternatively, floor cues may have acquired the ability to modulate the motivational response elicited by the context–ethanol association (28,39).

The finding of preference for a drug-paired stimulus that elicits a conditioned increase in activity might be construed as supporting theories that link ethanol's activating and rewarding effects (40). It is important to note, however, that the present study merely indicates that exposure to this particular Pavlovian drug conditioning procedure simultaneously produced a conditioned activity response and a conditioned motivational effect. While this finding suggests that behavioral sensitization and conditioned preference are mediated by a common learning process, it does not mean that these conditioned changes are causally related or that they are determined by the same neural mechanisms. At least one place conditioning study provides evidence of dissociation between conditioned activity and conditioned motivational effects using *d*-amphethamine (35). In that study, a manipulation that eliminated conditioned place preference (i.e., restraint during conditioning trials) did not alter the ability of drug-paired environmental cues to increase activity. This finding indicates that presence of a conditioned activity response is not sufficient to produce a conditioned place preference. It is not known whether a conditioned activity response is necessary for the expression of conditioned preference.

Although the neuropharmacological mechanisms underlying sensitization of ethanol's activating effects are unknown,

the recent findings of Risinger et al. (29) suggest an interesting possibility. Using conditioning procedures nearly identical to those used in the BEFORE groups, these investigators found that dopamine receptor blockade by haloperidol greatly reduced ethanol-induced stimulation but did not affect development of within-group sensitization. If, as the present findings suggest, sensitization to ethanol was mediated by Pavlovian conditioning, Risinger et al.'s findings might be viewed as support for the suggestion that *unconditioned* psychomotor stimulant effects are meditated by the dopamine system, whereas *conditioned* stimulant effects are mediated by nondopaminergic mechanisms (cf. (40, p. 484)]. Because haloperidol also failed to alter the acquisition of ethanol-induced conditioned place preference, one might speculate that conditioned motivational effects induced by ethanol are mediated by the same (nondopaminergic) neurochemical mechanisms underlying environmental specificity of sensitization to ethanol.

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