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BRIEF COMMUNICATION

Evidence for the Rewarding Effects of Ethanol Using the Conditioned Place Preference Method

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BOZARTH, M. A. *Evidence for the rewarding effects of ethanol using the conditioned place preference method.* PHARMACOL BIOCHEM BEHAV **35**(2) 485–487, 1990.—Rats were tested for the rewarding effects of ethanol using a place preference conditioning procedure. After receiving a total of 15 daily conditioning trials under 1.0 g/kg ethanol (IP), a significant place preference was produced. Subjects conditioned using saline or 0.5 g/kg ethanol showed no changes in place preference. This study suggests that failures to demonstrate rewarding effects from ethanol with the conditioned place preference method may be due to an insufficient number of conditioning trials or to an inadequate exposure to the drug. The fact that place preference conditioning was effective in demonstrating ethanol reward while other methods have been equivocal suggests that this method may be a valuable technique for studying the mechanisms of ethanol reward.

Conditioned place preference Drug reward Ethanol

ETHANOL abuse aptly attests to the reinforcing effects of ethanol in humans. Animal models of ethanol reward, however, have not been consentaneously established. Animals self-administer ethanol only reluctantly. Oral ethanol self-administration usually relies on consumption of a sweetened ethanol solution, and this procedure is controversial [see (6)]. Furthermore, most laboratories have been unable to establish intravenous ethanol self-administration [e.g., (7, 9, 11, 14)], despite the fact that other addictive drugs are readily self-administered by laboratory animals [e.g., (7)]. The failure to develop widely accepted methods of studying ethanol reward in laboratory animals has severely limited research concerning the biological mechanisms of ethanol reinforcement.

Place preference conditioning has been suggested to measure the rewarding effects of a drug (17). This technique assesses drug reward by measuring the association developed between certain environmental stimuli and the drug effect. After several conditioning trials, animals reliably increase the amount of time spent in the compartment associated with the effects of rewarding drugs such as heroin (4) and cocaine (12,18). Most attempts to establish a conditioned place preference using ethanol have not been successful. Investigators usually test experimentally naive subjects following several conditioning trials, and this procedure does not produce a conditioned place preference from ethanol (1, 8, 19, 20). Because it may require repeated exposure to ethanol for the rewarding effects of this drug to develop, place preference conditioning was tested following extended drug conditioning.

METHOD

The apparatus used for measuring place preference consisted of a shuttle box (25 × 36 × 35 cm) with a smooth Plexiglas floor on one side and a tubular stainless steel floor on the other. The amount of time spent on each side of the apparatus and the number of crosses were automatically recorded using a microcomputer (2). Rats were allowed free access to the entire shuttle box for 15 minutes a day during the first 5 days of testing. The last day of this series served as a measure of each animal's preconditioning place preference. Next, they were conditioned for 15 days; during each conditioning trial, animals were intraperitoneally injected with drug (10 ml/kg), and a barrier was inserted to restrict the animals to the conditioning side for 30 minutes following injections. All animals were conditioned on their nonpreferred side of the apparatus. Conditioning trials were conducted in 5-day blocks with two no-treatment days between blocks.

Thirty male, Long-Evans rats (325–375 g) were randomly divided into three groups. One group received drug vehicle (isotonic saline, 10 ml/kg), another group received 0.5 g/kg ethanol, and the final group received 1.0 g/kg ethanol. Three days after the last conditioning trial, all animals were injected with drug vehicle and place preference remeasured during a single 15-minute trial when the subjects had free access to the entire shuttle box. All

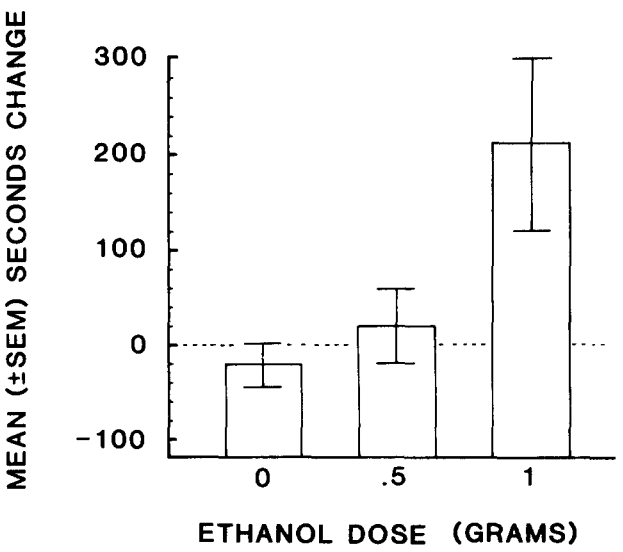

FIG. 1. The figure depicts the mean (±SEM) changes in place preference following conditioning with saline (10 ml/kg) or ethanol (0.5 and 1 g/kg). Positive scores indicate a place preference, while negative scores indicate a place aversion.

behavioral testing occurred during the light phase of a 12-hour light/dark illumination cycle.

RESULTS AND DISCUSSION

The data were analyzed by subtracting each subject's preconditioning score from the amount of time spent on the side of putative conditioning following the 15 conditioning trials (see Fig. 1). This procedure compensates for individual differences in the rats' preconditioning place preferences. A difference score of zero indicates no change in place preference following conditioning, while positive and negative scores indicate place preferences and place aversions, respectively. A one-way analysis of variance revealed a significant place preference for the group conditioned with 1.0 g/kg ethanol, while neither saline nor 0.5 g/kg ethanol produced a significant change in place preference, $F(2,27) = 4.205$, $p<0.05$. No significant changes in locomotor activity were found, $F(2,27)=0.019$, $p>0.25$.

This study indicates that the rewarding properties of ethanol can be demonstrated with the conditioned place preference method. Because the doses tested were the same as have been unsuccessfully used in other studies (1, 8, 19, 20), it would appear that past failures to demonstrate an ethanol-induced conditioned place preference may have simply involved too few conditioning trials. It is not surprising that extensive conditioning trials are necessary to establish an ethanol-induced place preference, whereas heroin-conditioned place preference is demonstrable after even a single trial (5,12); few laboratories have been able to establish intravenous ethanol self-administration in laboratory rats, although opiates and psychomotor stimulants are readily self-administered [e.g., (7)]. Furthermore, ethanol has equivocal effects on brain stimulation reward, while opiates and psychomotor stimulants produce robust enhancement of the rewarding effects of electrical brain stimulation (21); this test has been proposed as another measure of a drug's rewarding properties (10,15). Thus, the present data are consistent with other measures suggesting that ethanol is a weak but positive reinforcer in the rat.

Whether the ethanol-induced conditioned place preference resulted from the repeated conditioning trials (i.e., repeated pairings of drug effect and environmental cues) or from the repeated exposure to ethanol cannot be discerned with the present data. Reid, Hunter, Beaman and Hubbell (16) have reported that rats that orally self-administered ethanol for 30 days prior to conditioning developed a place preference, while subjects that failed to drink ethanol did not. This finding, combined with the present study, suggests that repeated exposure to ethanol may be the critical factor. Also, Numan (13) has reported that repeated exposure to ethanol facilitates intravenous ethanol self-administration. One possible explanation of this effect is that initial ethanol administration has strong aversive as well as appetitive effects. With repeated ethanol exposure, tolerance may develop to the aversive consequences unmasking the rewarding effects of ethanol. The present study used a total of 15 ethanol injections (compared with 3 or 4 used with most other conditioned place preference studies), while the Reid *et al.* (16) study preexposed the subjects through voluntary oral self-administration. Both approaches may have permitted the development of tolerance to the aversive effects of ethanol prior to conditioning, thereby revealing a net rewarding action of ethanol.

The conditioned place preference method has received a great deal of recent attention. It appears to be an easy and reliable method for assessing drug reward, and a number of laboratories have begun using this technique. Drugs with well established rewarding actions consistently produce a conditioned place preference despite pronounced differences in the conditioning and testing procedures used by various laboratories [see (3)]. The present study, showing a significant conditioned place preference with ethanol, demonstrates the utility of this technique in studying reward from a drug that has been elusive to other measures of drug reward. Thus, conditioned place preference may be uniquely valuable for studying the mechanisms underlying ethanol reward where most other methods have failed.

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