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Conditioned Place Aversion Mediated by Orally Self-Administered Ethanol in the Rat

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STEWART, R. B. AND L. A. GRUPP. *Conditioned place aversion mediated by orally self-administered ethanol in the rat.* PHARMACOL BIOCHEM BEHAV **24**(5) 1369–1375, 1986.—The hypothesis was tested that ethanol, self-administered via the oral route, would mediate a conditioned preference for the environment in which the drug was consumed. Ten rats were trained to drink an 8% (weight/volume) ethanol solution in association with one environment and had a different environment paired with the availability of water. Ten control animals had only water available in both environments. The experimental animals drank more ethanol solution than water and achieved doses in excess of their metabolic capacity as confirmed by blood ethanol levels. The drug was functioning as a positive reinforcer, yet the rats avoided the environment in which ethanol was consumed, indicating aversive properties of the drug. The control animals showed no change in preference for the environments associated with water. The conditioned place aversion observed was in accordance with previous studies in which rats were passively dosed using non-oral routes of administration but was paradoxical since the ethanol was actually self-administered.

Ethanol self-administration Place conditioning Aversion Reinforcement Rat

ATTEMPTS to model human alcohol use and abuse using rats have resulted in a divergent literature in which there appears to be some controversy concerning the stimulus properties and "abuse potential" of ethanol for this species. It is clear that rats self-administer ethanol by the oral route. Given continuous access to drinking tubes containing water and solutions of ethanol and water, rats will prefer ethanol solutions up to concentrations of about six percent (weight/volume, w/v) [32] but typical daily drug consumption is low compared to the rat's metabolic capacity [46]. Various procedures have been employed to achieve higher levels of oral ethanol consumption including the intermittent delivery of food pellets [11], weight reduction [24], limiting temporal access to the drug [36] and presenting the drug in a series of ascending concentrations ([45]; see [23] for review). The efficacy of such procedures has been demonstrated in studies in which rats lever-press on very high fixed ratio schedules for access to the drug [24], will prefer concentrations as high as 32 percent w/v [25] and will drink in excess of their metabolic capacity so that pharmacologically relevant blood ethanol levels can be measured [42].

Although there is little doubt that orally-consumed ethanol can act as a reinforcer for rats, the use of other routes of administration has produced divergent and less clear-cut results. Rats will self-administer ethanol by the intravenous (IV) route if infusions are contingent upon lever presses [38]. However, the doses achieved are very low (e.g., 62.5 mg/kg/day) [37], self-administration deteriorates when modest fixed-ratio schedules are imposed [13] and self-administration is not always attained [29], even under identical conditions to those under which rats readily self-administer other drugs [8,13]. The intragastric (IG) route has also been used in lever-press experiments, but the amounts self-infused by rats are also very low [39]. Rats will show a conditioned taste aversion (CTA) to a previously neutral flavour that has been associated with either intraperitoneal (IP) or IG infusions of ethanol [6,18] and IV infusions of ethanol have been used to motivate rats to jump a hurdle in a shuttlebox or refrain from entering the goalbox of a straight maze in order to avoid the drug [15]. Thus, there is evidence that ethanol can also act as an aversive stimulus or punisher for rats.

Another method which has been used to evaluate the motivational properties of ethanol has been the place conditioning procedure [1,12] which involves exposing an animal to the effects of a drug while in a novel or distinctive environment. Subsequent avoidance or preference for that environment in the absence of the drug is indicative that the rat has come to associate either aversive or rewarding aspects of the drug with the location in which it was experienced. Using this technique, preferences have been demonstrated for environments paired with drugs of abuse such as morphine [1], heroin [4], amphetamine [31], and cocaine [40]. Indeed, Black *et al.* [3] reported that rats would develop a preference for an environment that had previously been associated with ethanol, administered by the IP route. However, such a preference has not been replicated. Cunningham [9,10], on the other hand, used nearly identical procedures and the

same dose as Black *et al.* and found that rats would avoid an environment previously paired with ethanol. Extensive dose-response studies have since been done using IP [41,43], IG [34,44] and IV [44] routes of administration. The general finding has been no effects at low doses and aversion at high ethanol doses.

Why do other drugs of abuse produce conditioned place preferences while ethanol does not? An overview of the literature on the reinforcing and aversive stimulus properties of ethanol for rats provides a possible explanation. In all previous place conditioning experiments, ethanol was administered either by injection or infusion. The oral route has not been used. However, as discussed previously, oral consumption of the drug can be high and robust (e.g., [25]) while the use of other routes produces either self-administration that is not robust (e.g., [36]) or evidence that the drug is aversive (e.g., [15]). These observations, together with the observation that alcohol is consumed orally by humans, encouraged the hypothesis that ethanol, self-administered by the oral route, may mediate a conditioned preference for an environment associated with the drug.

To test this hypothesis, the present experiment used a procedure [42] adapted from the operant conditioning technique of Meisch and others [22,26] which achieves substantial and selective ethanol intake by rats and results in pharmacologically relevant blood ethanol levels during relatively short experimental sessions. Briefly, this procedure takes advantage of the rat's propensity to eat and drink at the same time. Thus, if water is offered to food-deprived rats in conjunction with a measured amount of food, substantial amounts of the fluid will be consumed in a relatively brief period of time. This pattern is not disrupted if solutions with increasingly higher concentrations of ethanol are substituted for the water, even when they are of the order which animals otherwise would avoid. When ethanol is later offered in the absence of food, drinking remains elevated. The following experiment juxtaposed ethanol drinking engendered in this manner with a standard place conditioning procedure in which the ethanol self-administration was paired with one environment and the availability of water, the drug vehicle, was paired with a different environment.

METHOD

Subjects

Twenty male Long Evans hooded rats (Charles River, Québec), 346–391 g, were housed individually and kept on a 12/12 hr light/dark cycle with lights on at 7:00 a.m. All animals were weight-reduced and kept at 80% of their pre-experimental free-feeding weights for the duration of the study, including both choice tests. The rats were fed only sufficient Purina lab chow in the home cages to maintain their reduced weights and this feeding took place approximately two hours after conditioning trials and choice tests. Water was available at all times in the home cages.

Drug Preparation

Solutions of 2, 4 and 8% ethanol (w/v) were prepared in tap water. For example, the 8% solution was made by adding 10.14 ml of absolute ethanol to a volumetric flask with sufficient tap water to make a total volume of 100 ml.

Apparatus

The apparatus consisted of two kinds of conditioning boxes and a test box of plywood construction except where noted. One conditioning box, measuring 38×38×38 cm, was white with the floor area covered with a wire screen grid. The other conditioning box, also measuring 38×38×38 cm, was painted black and had a smooth plywood floor. The test box was rectangular, measuring 86×38×38 cm, and resembled the two different conditioning boxes laid side by side but with no partition to separate them. Between the black and the white compartments of the test box was a 10 cm wide grey area which had a sheet metal floor. The conditioning boxes were equipped with single graduated drinking tubes. To assure that the animals remained inside, all boxes were covered with wire screen lids.

Pre-Conditioning Choice Test

For three consecutive days, all animals were placed individually in the grey "choice point" area of the text box and then allowed to shuttle freely among the black, white and grey areas for 15 min. The first two days served to familiarize the rats with the apparatus and on the third day the amount of time spent in each compartment of the test box was measured. Choice tests were monitored using a remote video camera.

Experimental Groups

The assignment of the 20 animals to two experimental groups of ten rats each was based on the results of the pre-conditioning choice test. These two groups were designated the Ethanol self-administration group (Ethanol-SA group) and the Water-only group (H_2O group). Half of the animals in the Ethanol-SA group were designated to have access to ethanol in the type of conditioning box which corresponded to the compartment of the test box which they did not prefer in the pre-conditioning choice test. The remaining rats in the Ethanol-SA group were to receive ethanol in the conditioning box for which they indicated preference in the pre-conditioning test. Similarly, the H_2O group was subdivided so that for five animals their less preferred compartment was designated as the "control" compartment for the purpose of statistical analysis while for the other five animals their more preferred compartment was designated as the "control." The groups were matched so that the mean time spent in the ethanol compartment during the pretest by the Ethanol-SA group and the mean time spent in the "control" compartment by the H_2O group were similar.

Place Conditioning Trials

Immediately following the pre-conditioning choice test, daily place conditioning trials were instituted. The first 46 trials comprised the procedure for establishing ethanol as a reinforcer [25,41] and drinking was elicited by the eating of 6 g of Purina lab chow which was always placed in the conditioning boxes. For the first ten of these trials the animals of the Ethanol-SA group were removed from their home cages and placed individually into a conditioning box for 90 min during which water was the only available liquid. The type of conditioning box was alternated daily so that each rat was given five trials in both the black and the white boxes. Beginning on the 11th day every second day was designated an ethanol trial and the water was replaced by 2% ethanol for two trials, then 4% ethanol for 4 trials, and finally 8% ethanol for 12 trials. On intervening days a water trial was given and the same rats were placed in the other conditioning box for

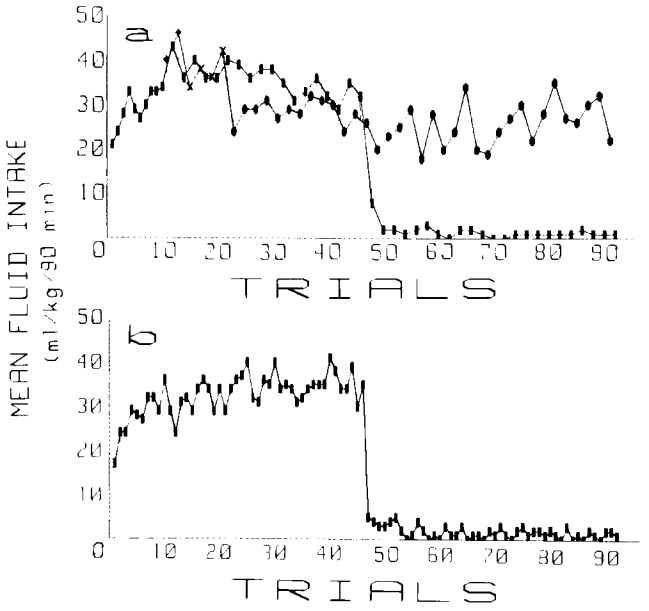

FIG. 1. Mean fluid consumption (ml/kg) consumed during 92 daily 90 min place conditioning trials for (a) the ten animals in the Ethanol-SA group and (b) the ten animals in the H_2O group. For each of the first 46 trials 6 g of food was available and for the last 46 trials no food was given to the animals. Vertical lines indicate standard error. (■) H_2O, (◆) 2% w/v ethanol, (×) 4% w/v ethanol, (●) 8% w/v ethanol.

90 min during which water was the available liquid. In this way ethanol and water trials alternated throughout, with ethanol always paired with one environment and water always paired with a different environment. For example, if a black box was used for an animal's ethanol place conditioning trials then a white box would be used for its water trials. Following the first 46 trials the procedure for establishing ethanol as a reinforcer was complete and food was no longer placed in the conditioning boxes. Forty-six additional place-conditioning trials were then given with 8% ethanol and water continuing to be alternated daily, each fluid paired with its distinctive conditioning box environment.

The 10 animals in the H_2O group were treated identically to the animals in the Ethanol-SA group except that water was the only available liquid during all the place-conditioning trials. The amount of liquid consumed during each place-conditioning trial was measured.

Post-Conditioning Choice Test

After a total of 92 place conditioning trials a second 15 min test trial was given in which the amount of time spent in each compartment of the test box was again measured. No ethanol or water was available during the post-conditioning choice test. Of interest was the amount of time spent in the compartment which was associated with the availability of ethanol for the Ethanol-SA group and the amount of time spent in the compartment designated as the "control" compartment for the H_2O group.

Blood Sampling and Analysis

Three days after the post-conditioning choice test, the animals of the Ethanol-SA group were placed in conditioning

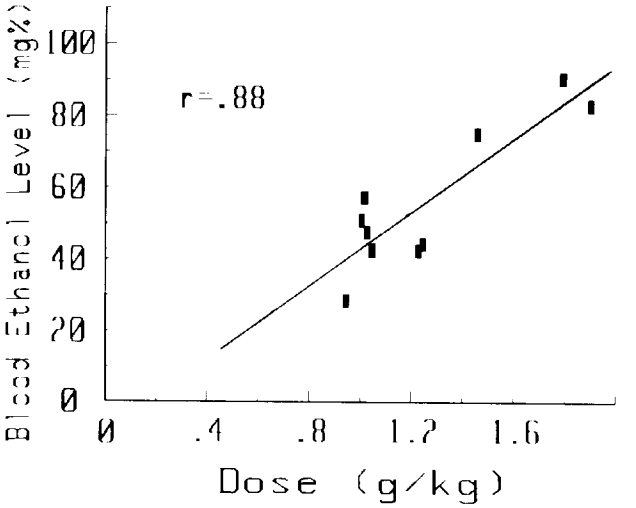

FIG. 2. Blood ethanol levels (mg %) from samples obtained 60 min after the initiation of drinking plotted as a function of dose (ml 8% ethanol consumed converted to g/kg). The points represent individual samples obtained from each of the ten animals in the Ethanol-SA group.

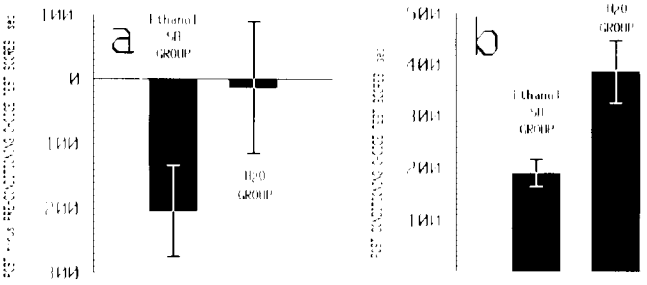

FIG. 3. (a) Mean change in time (sec) spent in the ethanol-paired compartment of the choice test box for animals in the Ethanol-SA group and in the "control" water-paired compartment for the animals in the H_2O group. The numbers were obtained by subtracting each animal's pre-conditioning choice test time from its post-conditioning choice test time. Vertical lines indicate standard error. (b) Mean times (sec) that animals in the Ethanol-SA and H_2O groups spent in the ethanol-paired and "control" compartments respectively during the 15 min post-conditioning choice test. Vertical lines indicate standard error.

boxes in the usual manner and were allowed to drink 8% ethanol solution for 60 min. They were then removed from the boxes and had 50 μl samples of blood drawn from the cut tip of the tail. The amount of ethanol consumed during that session was noted. Blood samples were prepared and analyzed chromatographically according to the method of LeBlanc [18].

RESULTS

Ethanol and Water Consumption

Figure 1a shows the mean amount of fluid consumed during each place conditioning trial for the ten animals in the

Ethanol-SA group. For the first 46 trials 6 g of food was always placed in the conditioning boxes during both ethanol and water trials and consumption of these two fluids did not differ. However, during the last 46 trials (trials 47–92) food was no longer available in the conditioning boxes and 8% ethanol consumption remained elevated while water drinking was reduced to very low levels. For the purpose of statistical analysis the mean fluid consumption for each rat for the last 23 ethanol trials and the last 23 water trials was calculated. Mean ethanol consumption for individual animals ranged from 13.73 to 49.66 ml/kg/trial (1.10–3.97 g/kg/trial) with a group mean of 25.45 ml/kg/trial (2.04 g/kg/trial). Mean water consumption for individual animals ranged from 0.28 to 3.18 ml/kg/trial with a group mean of 1.39 ml/kg/trial. Ethanol drinking statistically exceeded water intake during the last 46 trials, $t_9=7.35$, $p<0.01$.

Figure 1b shows the mean amount of water consumed during each place conditioning trial for the 10 animals in the H_2O group. Water intake for this group was similar to the water consumption observed in the Ethanol-SA group's alternate-day water trials, i.e., water drinking was elevated for the first 46 trials during which 6 g of food was available and then dropped off sharply during the last 46 trials when food was no longer present.

Blood Ethanol Analysis

Figure 2 shows the blood ethanol levels from samples obtained 60 min after the initiation of drinking plotted as a function of dose (ml 8% ethanol consumed converted to g/kg). Dose and blood ethanol levels were positively correlated, $r(8)=0.88$, $p<0.01$, two-tailed. The mean blood ethanol level was 56.2 mg% with a range from 28.4 to 90.3 mg%. It should be noted that the mean dose for the separate blood analysis session (which took place when the rest of the experiment was completed) was 1.26 g/kg. This was considerably less than the mean (2.04 g/kg) dose reported previously for the actual conditioning sessions. Therefore it is likely that these blood ethanol levels underestimate the values actually achieved during the place conditioning trials.

Place Conditioning Results

Figure 3a shows the mean change in the time spent in the ethanol-paired compartment of the test box for animals in the Ethanol-SA group, calculated by subtracting each animal's pre-conditioning choice test from its post-conditioning choice test time. The Ethanol-SA group showed a significant, $t_9=2.94$, $p<0.02$, reduction in the time spent in the compartment associated with the consumption of the drug. Figure 3a also shows no difference, $t_9=0.13$, N.S., in the time that rats of the H_2O group spent in the "control" compartment of the test box when pre- and post-conditioning choice test trials were compared. The mean change in time for the Ethanol-SA group was different from the mean change in time for the H_2O group only at the 0.10 significance level, $t_{18}=1.75$, N.S.

Figure 3b shows the mean times that animals in the Ethanol-SA and H_2O groups spent in the ethanol-paired and "control" compartments respectively during the post-conditioning choice test. The Ethanol-SA group spent significantly, $t_{18}=3.07$, $p<0.01$, less time in the ethanol-paired compartment than the H_2O group spent in the "control" compartment, again indicating that the animals were avoiding the location in which they self-administered the drug.

General Observations

Although activity levels of the animals during the post-conditioning choice test were not systematically measured, there appeared to be no difference between the experimental and control rats nor did the Ethanol-SA group manifest any overt signs of withdrawal or distress.

DISCUSSION

The finding of an aversion for environmental stimuli associated with ethanol is in accordance with previous place conditioning experiments in which this drug was used [10, 34, 42, 44]. However, the obvious difference is that in the present study the drug was self-administered. Ethanol intake clearly exceeded water consumption. The doses achieved resulted in measurable blood ethanol levels, indicating that the animals probably experienced some pharmacological (i.e., CNS) effects of the drug. Ethanol was acting as a positive reinforcer, yet, paradoxically the rats avoided the location in which they consumed the drug.

Paradoxical findings are not unknown in studies in which preference or aversion for a drug are assessed indirectly by pairing the drug with a neutral stimulus. Other drugs of abuse such as morphine and amphetamine have been used to produce conditioned taste aversions [6,21] yet conditioned place preferences have been demonstrated with the same drugs [1,31], even when the same animals are simultaneously tested with both CTA and place conditioning procedures [31,35]. Such results suggest that there may be some predisposition in the CTA and place conditioning techniques to show aversion and preference respectively for drugs of abuse. Ethanol seems to be exceptional since both taste and place conditioning studies are fairly consistent in indicating aversion for the drug. However, if the self-administration of the ethanol in the present study was to be interpreted as a conditioned taste preference, it would constitute a curious demonstration of a taste preference occurring simultaneously with a conditioned place aversion. A relevant investigation in this regard is one by Sherman *et al.* [34] in which food deprived rats were administered ethanol (0.5, 1.0 or 2.0 g/kg by gastric intubation) in one environment with access to a flavoured solution. On control trials, water was administered and the animals were placed in a different environment with a different flavoured solution. Aversion was later found for the ethanol-associated environment at all three doses. However, flavour choice tests showed a CTA at the 2.0 g/kg dose, no effects at the 1.0 g/kg dose and, of particular interest, a flavour preference at the 0.5 g/kg dose. Thus, at the 0.5 g/kg dose the same animals indicated a conditioned taste preference and a conditioned place aversion, a result that parallels the present experiment except that the putative flavour preference in our study is for the taste of the ethanol solution itself which was self-administered rather than given by intubation. In a second experiment Sherman *et al.* [34] substituted an isocaloric glucose solution for the ethanol in one group of animals and for a second group isocaloric glucose was substituted for the water on control trials. They found that the isocaloric glucose solution conditioned a flavour preference of the same magnitude as that obtained with ethanol and that when ethanol provided no caloric advantage, the associated flavour was less preferred than a flavour associated with an isocaloric glucose solution. They concluded that perhaps caloric restoration served as the reinforcing mechanism for the conditioned flavour preference that they obtained with ethanol. The animals in the present

experiment were maintained at 80% of their free-feeding body weights. In this chronically hungry state it is plausible that the animals were self-administering ethanol for its caloric content rather than for its pharmacological effects. Such a possibility has been the subject of critical debate concerning animal models in which food deprivation is used as a manipulation and has been discussed extensively elsewhere [2, 7, 19, 23]. Nevertheless, a compelling interpretation of the present results is that caloric restoration provided the impetus to maintain the ethanol drinking in the face of aversive post-ingestional effects which were conditioned to the environment in which the drug was consumed.

An alternative interpretation is that the drug has both reinforcing and aversive pharmacological effects. This is not a new concept and it has been incorporated into a theory of aversive control of drug-taking behavior [5]. According to this theory, the reinforcing properties of a drug motivate the initiation and maintenance of its intake while the aversive effects play a regulatory role to modulate or stop the drug self-administration in a similar manner to the way that satiation mechanisms modulate the intake of food. In the present study and in other experiments which used the same techniques to engender drinking [25,41] it was observed that the rats consumed most of the ethanol during the first 10 or 15 min of a drinking session. It is possible that during this initial drinking bout the ethanol is reinforcing but that as more of the drug is absorbed and blood ethanol levels rise, the final effect of the drug is aversive. This idea is amenable to experimental investigation by simply varying the conditioning session length so that it encompasses only the initial, putatively reinforcing, part of the drinking session.

The question still may be begged as to why the animals continue to drink if the ethanol has aversive consequences. Figure 1 shows no trend or tendency for ethanol consumption to decrease as a function of trial. Yet the literature on the conditioned taste aversion phenomenon suggests that rats are genetically predisposed or "prepared" to avoid the consumption of a substance if its consumption is followed by aversive post-ingestional effects [33].

On the other hand, it is possible that the aversive effects of ethanol that were indicated by the avoidance of the environment in which the drug was consumed are, in a manner of speaking, irrelevant to whether the drug continues to be self-administered. Some theorists [27,28] have cited such phenomenon as the self-administration of painful electric footshocks [17] and response-produced opiate antagonist administration by opiate-dependent animals [16] and have concluded that reinforcement and punishment are not the inherent properties of a stimulus but rather are descriptions of functional relationships between stimuli and behaviour. Preconceived notions about hedonic qualities of a drug stimulus, i.e., whether a drug effect is subjectively "pleasant" or "unpleasant," are not as relevant to predicting the abuse potential of a drug as are such factors as the behavioral history of the organism, the schedule of presentation of the drug stimulus, and the ongoing behavior at the time of the presentation of the drug. In the case of ethanol, there is experimental evidence which suggests that the drug can function as an aversive stimulus [10, 15, 20]. Furthermore, robust ethanol self-administration by rats is usually only achieved after the use of such procedures as schedule-induced polydipsia [11] or other methods such as the one described in this paper. Electric shock can also function as an aversive stimulus, yet animals will also self-administer footshocks if appropriate experimental procedures are instituted. This parallelism suggests that the self-administration of ethanol may share some common characteristics with the self-administration of "noxious" stimuli which is rather dramatically illustrated by the response-produced electric shock phenomenon [14]. Other drugs such as morphine and cocaine appear to be readily self-administered by rats even in the absence of special procedures [30]. It may be that drugs of abuse differ, perhaps along a continuum, in the extent to which other factors (environmental conditions, schedules of reinforcement, drug-taking history) are important in determining whether the drug will function as a positive reinforcer. The discrepancy between the widespread use of alcohol by man and the reluctance of the naive laboratory rat to consume "abusive" quantities of the drug might best be resolved with reference to the presence or absence of environmental conditions which foster the self-administration of the drug.

The finding that rats will avoid an environment in which they had voluntarily consumed ethanol seems contradictory, but the self-administration of this drug by humans is no less paradoxical. It is well known that alcoholics will persist in drinking even though this behavior often results in aversive consequences such as nausea, hangover or withdrawal symptoms, morbidity due to cirrhosis, economic loss and social disruption. To the extent that the results of the present experiment may illustrate the persistent consumption of a drug with aversive consequences, they may accurately reflect the human condition.

ADDENDUM

While this manuscript was under editorial review, a paper was published by Reid *et al.* (Reid, L. D., G. A. Hunter, C. M. Beaman and C. L. Hubbell. Toward understanding ethanol's capacity to be reinforcing: A conditioned place preference following injections of ethanol. *Pharmacol Biochem Behav* **22**: 483–487, 1985). They report obtaining a conditioned place preference following 1.0 g/kg IP injections of ethanol. It was necessary for their experimental animals to have consumed a 6% ethanol solution for 26 days (1 hr daily access motivated by 20 hr of fluid deprivation) and only a *very short* (4 to 8 min) conditioning session length yielded the preference. This work adds some support to our suggestion that the ethanol, as self-administered in our experiment, may have been reinforcing during the initial few minutes of a conditioning session, but that as more of the drug was absorbed and the blood ethanol levels increased, the final and net effect of the drug was aversive.

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