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Absence of Reinforcement With Low Dose Intravenous Ethanol Self-Administration in Rats[1]

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NUMAN, R., A. M. NAPARZEWSKA AND C. M. ADLER. *Absence of reinforcement with low dose intravenous ethanol self-administration in rats.* PHARMACOL BIOCHEM BEHAV 21(4) 609–615, 1984.—Male hooded rats were implanted with intravenous cannulas and housed in operant chambers supplied with 2 levers and enclosed in sound-attenuating cubicles. In Experiment 1, seven rats received a 1.0 mg/kg infusion of ethanol for each press on the previously determined non-preferred lever. The other lever served to count "activity lever presses." An additional 7 rats served as controls and were treated identically except that each press on the non-preferred lever led to an infusion of saline, isovolumetric to the ethanol infused in the experimental subjects. The rats were tested under these conditions of continuous reinforcement for 9 days. Throughout this period, self-infusions and "activity lever presses" did not differ between the groups, suggesting that ethanol was not reinforcing at a dose of 1.0 mg/kg. These results were replicated, and extended to other low doses of ethanol in Experiment 2. Here, we employed a design where depression of either lever, under conditions of continuous reinforcement, led to the infusion of a solution. Fifteen rats were randomly assigned to one of three groups (5 rats/group). In one group, depression of the previously determined non-preferred lever led to an infusion of 16.0 mg/kg of ethanol, while depression of the other lever led to an infusion of isocaloric glucose. For the other two groups, depression of the non-preferred lever led to an infusion of 4.0 and 1.0 mg/kg ethanol respectively, and depression of the other lever led to a glucose infusion. The animals were tested for 9 days, and in each case, ethanol self-infusions did not differ significantly from glucose self-infusions. These data confirm the absence of reinforcement with low doses of ethanol. Additional data are presented to support these findings, and we conclude that previous reports of reinforcing effects for low doses of ethanol self-administered intravenously by rats were probably due to the non-specific effects of ethanol.

Alcohol reinforcement Non-specific effects of ethanol Ethanol self-administration Rats Intravenous infusion

WHILE ethanol has been shown to serve as a reinforcer when self-administered by various routes in a number of species [1, 2, 7, 14, 17, 21, 22, 23, 33], the experimental procedures involved are often lengthy and complex. Further, even in the experimental paradigms that are successful, some animals will nonetheless refrain from the self-administration of ethanol, and some will discontinue self-administration, even in the face of withdrawal distress [1, 2, 7, 15, 21, 23, 33, 34]. These results suggest that, at best, ethanol is a rather weak and inconsistent reinforcer, especially compared to other drugs of abuse [12, 13, 16, 29, 34]. These studies also suggest that ethanol may not be a primary reinforcer for the ethanol naive animal and that experience, of one type or another, with the drug is necessary to establish its reinforcing capacity. This viewpoint is supported by several recent studies showing that initially non-preferred doses of ethanol acquire reinforcing properties after a period of passive exposure to the drug [9, 15, 19, 23].

A few laboratories, however, have presented data showing that extremely low doses of ethanol (1 mg/kg or less) are reinforcing to alcohol naive rats when self-administered intragastrically [28] or intravenously [26,28]. Most recently, Sinden and Le Magnen [26] found that ethanol at a dose of 1 mg/kg (but not 0.5 or 5 mg/kg) served as a reinforcer for alcohol naive rats when self-administered intravenously. In each of these positive studies, self-administration was tested in cylindrical operant chambers (25 cm diameter) with only a single lever available; the rats were not pretrained or shaped to press the lever, and the reinforcing properties of ethanol were observable within a few days.

A potential problem with these studies is that only a single lever was employed, making it difficult to differentiate the locomotor excitatory effects of ethanol [24] from a reinforcing effect. The size and cylindrical shape of the operant chambers, and the fact that in one of the studies [26], they were apparently not sound-attenuated, may have compounded this problem. This contention is supported by the recent work of Grupp [12]. Using a fixed ratio, small-N design, and rectangular operant chambers with two levers (one for food delivery, and one for ethanol delivery) he was unable to demonstrate a reinforcing effect for various doses of ethanol (1–180 mg/kg) self-administered intravenously by

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rats. He did, however, show that cocaine was clearly reinforcing under identical conditions. Further, in three recent studies [3, 6, 29] ethanol, administered (IP, IV, or IG) to rats in various doses (1–5,000 mg/kg) was found to be either neutral (low doses) or aversive (high doses) when tested in a conditioned place preference paradigm. It has also been shown [13] that rats will learn to perform various responses to *avoid* intravenous infusions of ethanol (200–800 mg/kg, one should, however, interpret these data with caution as the volume of the infusion may have had aversive properties). These studies, taken together, suggest, at least for the alcohol naive rat, that low doses of ethanol (<100 mg/kg) are neutral (i.e., without reinforcing or aversive properties) and relatively larger doses (≥100 mg/kg) have aversive properties. In agreement with the above findings, our own work [23] has shown that, in alcohol naive rats, ethanol at a unit dose of 100 mg/kg has aversive properties when self-administered intravenously. In the present experiments we carried out further tests for the reinforcing capacity of low doses of intravenous ethanol in 2-lever rectangular operant chambers. Our findings, taken together with those reported above, show that low doses of ethanol are *not* reinforcing to alcohol naive rats when self-administered intravenously, and suggest that early reports of such reinforcing properties were probably due to non-specific effects of the drug.

EXPERIMENT 1

In this study we attempted to replicate the findings of Sinden and Le Magnen [26] showing the reinforcing properties of intravenous ethanol at a dose of 1 mg/kg. The main difference between this report and theirs is that we used standard rectangular operant chambers housed in sound attenuating cubicles, and the chambers were equipped with 2 levers rather than 1. We also tested the animals for 9 days rather than 5.

METHOD

Animals and Apparatus

Fourteen male hooded rats of the Long-Evans strain (Simonsen Labs, Gilroy, CA) were used. All rats were acclimated to laboratory conditions for approximately one week prior to surgery; during this time they were housed in pairs in solid bottom box cages with a contact bedding. Food and water were freely available, and temperature and lighting conditions were controlled as described below. On the day of surgery, the rats weighed between 263–376 g (mean, 320 g), and each was implanted with a chronic indwelling jugular cannula while under Nembutal anesthesia (50 mg/kg). The cannula was passed from the jugular vein, subcutaneously, to exit at the dorsal region of the animal's neck. The rat was then placed in a harness which had a 40 cm length of spring attached to it, and the cannula was passed through this protective spring. Each rat was then individually housed in an operant chamber (30×25×27 cm) that was enclosed in a sound attenuating cubicle (both from BRS/LVE, Laurel, MD). The spring and cannula tubing were attached to a Small Animal Infusion Swivel (Harvard Apparatus, Ealing Co., South Natick, MA) positioned above the center of the sound attenuating cubicle. The swivel, in turn, was connected by way of polyethylene tubing to an injection system (Harvard Apparatus Compact Syringe Pump, Model 975) located outside of the sound attenuating cubicle. The one-way cannula, itself, was constructed of polyethylene tubing (PE 50) with a silastic tubing tip (0.037 in. o.d.). A more detailed description of the surgical procedures, and directions for cannula and harness construction can be found elsewhere [27].

The animals remained in the behavioral chambers 24 hr a day throughout the entire experiment. Food (granulated Wayne Lab Blox) was supplied in spill-proof jars, and water (with 50 mg oxytetracycline/100 ml of water) was available in calibrated drinking tubes. The chambers were well ventilated, temperature controlled (23±1°C), and internal lighting alternated on a 12 hr day-night (0800–2000 hr) cycle. All programming was carried out with electromechanical circuitry.

Procedure

During the first 24 hr following surgery, depression of either the left or right lever led to an infusion of sterile isotonic saline (0.1 ml administered over a 1 sec period) for all rats. Lever presses during this period allowed us to determine the preferred (higher number of lever presses) and non-preferred levers for each rat. For each rat, on subsequent days, only activation of the non-preferred lever led to an infusion, depression of the other lever had no effect, but these lever presses were counted. We followed this procedure under the assumption that preferred lever presses during the first 24 hr represent non-specific effects, and we wanted to minimize this influence on subsequent data.

Following this 24 hr lever preference period, the rats were randomly assigned to one of two groups. For 7 rats, depression of the non-preferred lever led to a 1.0 mg/kg infusion of ethanol (0.5% v/v solution prepared from 95% ethanol and sterile saline). Depending upon the weight of the animal, the infusion duration ranged from 0.5 sec to 1.2 sec, and the volume infused ranged between 0.06–0.10 ml. For the other 7 rats, isovolumetric amounts of sterile isotonic saline were delivered for each depression of non-preferred lever. For all rats, lever presses that occurred during an infusion were counted, but had no other consequences. The rats remained in the operant chambers, under these conditions of continuous reinforcement 24 hr/day for a period of 9 days.

Each day, at approximately 1000 hr, total lever presses and infusions were recorded (we also recorded lever presses on the previously preferred lever as an indicator of "activity lever presses"—these lever presses had no effect). At this time we also weighed the animals (and adjusted the time of infusion, if necessary, to maintain a 1 mg/kg dose/infusion) and recorded food and water intake.

RESULTS AND DISCUSSION

Table 1 shows that all animals consumed adequate food and water each day, and gained weight. These data demonstrate that the animals were healthy throughout the experimental period. The ethanol and saline rats did not differ on any of these measures (t-test, all $p>0.10$).

Figure 1 presents the mean number of infusions received, over 3-day blocks, by the saline and ethanol animals during the experimental period (upper graph—A) and the mean number of "activity lever presses" as well (lower graph—B). For both measures, the ethanol rats tended to have lower response rates than the saline rats, but because of inter-animal variability, the difference was not statistically significant. Analysis of variance on the infusion data (Fig. 1A) showed no effect of drug condition, $F(1,12)=1.08$, $p>0.10$. However, both groups tended to increase self-administrations over days, $F(2,24)=5.14$, $p<0.025$, but there was no drug × day interaction, $F(2,24)=2.00$, $p>0.10$. For

TABLE 1

FOOD AND WATER INTAKE, AND BODY WEIGHTS FOR ETHANOL AND SALINE RATS

		Mean ± S.E.			
Group	N	Initial Wt (g)	Terminal Wt (g)	Food Intake (g/day)	Water Intake (ml/day)
Ethanol	7	322.5 ± 16.9	332.7 ± 16.1	20.2 ± 0.6	31.9 ± 0.9
Saline	7	316.7 ± 14.9	324.0 ± 12.0	19.9 ± 1.2	34.9 ± 2.1

"activity lever presses" (Fig. 1B), there were no significant drug, $F(1,12)=0.77$, $p>0.10$, days, $F(2,24)=0.74$, $p>0.10$, or drug × days interaction effects, $F(2,24)=0.54$, $p>0.10$.

These data suggest that ethanol, at a dose of 1 mg/kg, is *not* reinforcing for ethanol naive rats. These findings agree with those of Grupp [12], and Asin *et al.* [3] but not with those of Smith *et al.* [28] or Sinden and Le Magnen [26]. As suggested earlier, this difference may be procedural. The cylindrical, single lever operant chambers, employed in the positive studies, may have led to non-specific effects. Alternatively, this type of chamber may have facilitated contacts with the lever, initially via non-specific effects; however, after a sufficient number of lever presses, perhaps a threshold level of ethanol in brain and blood was achieved to produce a reinforcing effect [33,34]. However, this alternative seems unlikely as Sinden and Le Magnen [26] found that a 5 mg/kg dose of ethanol/self-infusion tended to have aversive effects.

Nonetheless, one might still speculate that the response rates of the rats, in the current experiment, were too low to uncover a reinforcing effect. It should be noted, however, that for many other drugs of abuse, under similar experimental conditions, intravenous self-administration is rapidly acquired [12, 16, 34]. In addition, Asin *et al.* [3] found that there were detectable levels of ethanol in the blood and brain following a single intravenous infusion of 2 mg/kg ethanol. These data, taken together, suggest that if the ethanol in the current experiment was reinforcing, the ethanol rats should have performed the lever-press response at a higher rate than the saline rats, but they did not. Further, while the mean response rates were low in our experiment, a few animals in the ethanol (and saline) group self-administered as many as 60 infusions of ethanol in some of the 24 hr periods, yet a reinforcing effect was not discernable when these rats were tested further. The data for one of these rats is shown in Fig. 2. Here, following 10 days of ethanol self-administration, the syringe was filled with isotonic saline for 6 days, followed by additional 6-day periods with ethanol and saline again. In general, this rat increased lever presses over days, but there was no difference in ethanol (1 mg/kg) preference over saline. Thus, even here, where relatively large amounts of ethanol were self-administered, a reinforcing effect was not observed. During the last 12 days, when infusion rates for this rat were relatively stable, the mean number of infusions/2 day block varied between 43 and 67, and the mean number of infusions during the ethanol period was 57.5 (SE=4.77) and during the saline period it was 51.33 (SE=4.26).

Our data, therefore, show that ethanol, self-administered intravenously at a dose of 1 mg/kg, is not reinforcing for alcohol naive rats. The results of Experiment 2 systematically replicate this effect, and extend this finding to other low doses of ethanol.

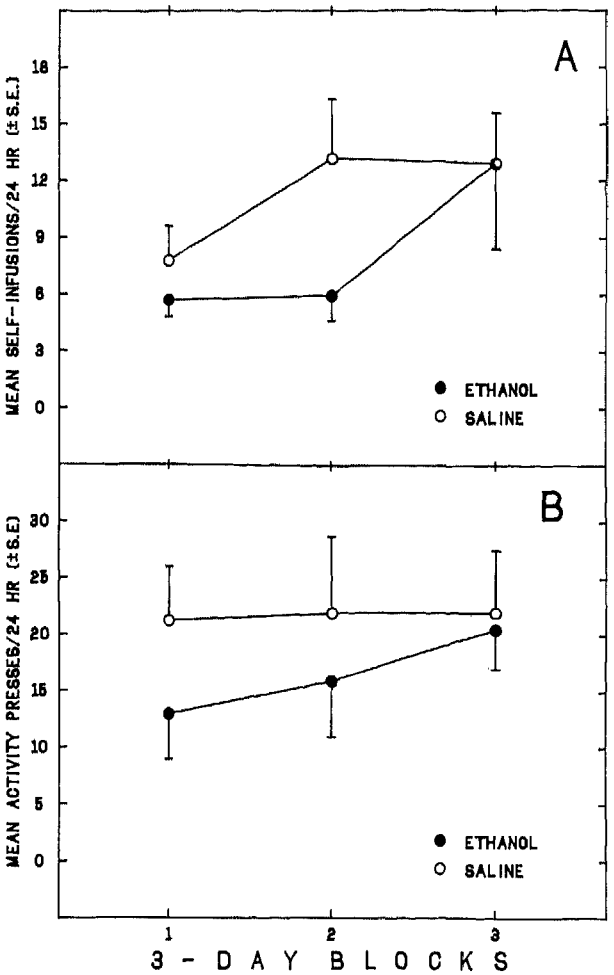

FIG. 1. Mean number of daily self-infusions (upper graph A) and "activity lever presses" (lower graph B) made by ethanol and saline rats during the 9-day testing period. Each infusion led to a 1 mg/kg dose of ethanol for the ethanol rats, or an equivolumetric infusion of saline for the saline animals. There were 7 rats in each group.

EXPERIMENT 2

Since we did not uncover a reinforcing effect for ethanol at a dose of 1 mg/kg, we assessed the effects of other ethanol

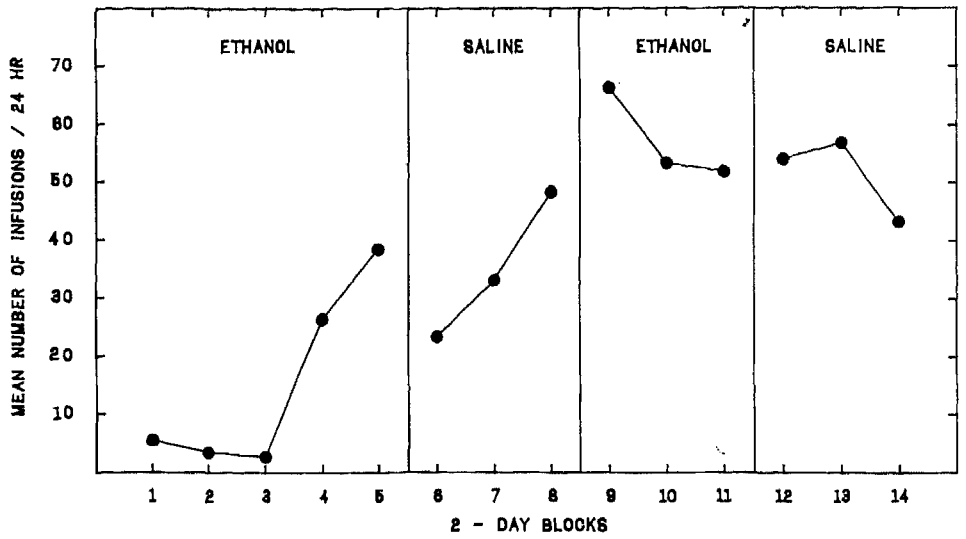

FIG. 2. Data for one rat showing high rates of ethanol self-administration during initial testing. Subsequent testing with saline and ethanol (1 mg/kg) shows no difference in the rates of self-administration for these substances.

doses in this experiment. The procedure was modified so that each animal could serve as its own control, and we tested the following ethanol doses: 1, 4 and 16 mg/kg.

METHOD

Animals and Apparatus

Fifteen male hooded rats of the Long-Evans strain weighing between 271–452 g (mean 338 g) at the time of surgery were used. The surgical procedures, apparatus, and housing conditions were identical to those described in Experiment 1.

Procedure

During the first 24 hr following surgery, depression of either the left or right lever led to an infusion of sterile isotonic saline (0.1 ml infused over a 1 sec period) for all rats. As in Experiment 1, these data allowed us to determine the preferred and non-preferred levers for each rat. For each rat, on subsequent days, only activation of the non-preferred lever led to an infusion of ethanol. In contrast to Experiment 1, however, depression of the preferred lever led to an infusion of isotonic glucose (5.0%) isocaloric to the ethanol dose being employed (except for the 1 mg/kg rats; see below). The rationale for this procedure was described in Experiment 1, and we used glucose to assure that presses for ethanol were not motivated by its caloric content.

Therefore, following the 24 hr preference test, the rats were randomly assigned to 3 groups (5 rats/group). One group received an infusion of 16 mg/kg ethanol (5% v/v) following each press on the non-preferred lever, and an infusion of isocaloric glucose for each depression of the other lever. A second group was treated similarly, receiving 4 mg/kg ethanol (1% v/v) and isocaloric glucose for its lever presses. The third group received 1 mg/kg ethanol (0.5% v/v) and *isovolumetric* glucose (the volume and time parameters necessary for an isocaloric infusion were too small to be handled by our infusion pump) for its lever presses. All ethanol solutions were prepared from 95% ethanol and sterile saline. No infusion lasted more than 2.5 sec, and the amount infused/

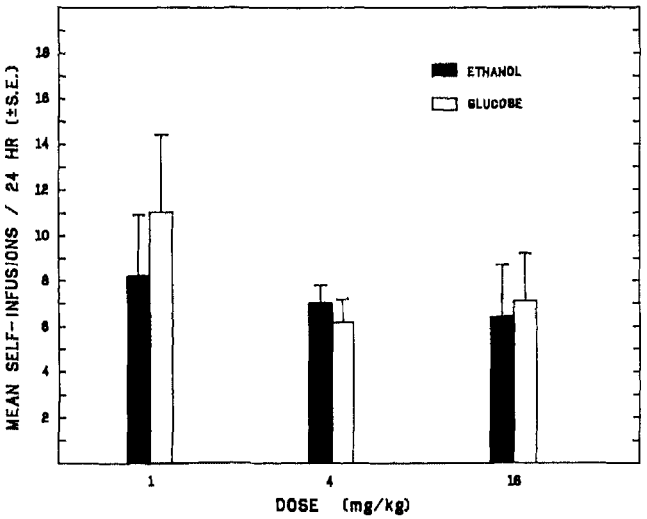

FIG. 3. Mean number of daily self-infusions for ethanol or glucose during the 9-day test period in the two-lever experiment. Depression of one lever led to an infusion of ethanol, while depression of the other lever led to an infusion of isocaloric glucose (except for the 1 mg/kg group; see text). Ethanol doses tested for each group, consisting of 5 rats each, are indicated.

infusion did not exceed 0.25 ml. As in the previous experiment, lever presses made during an infusion were counted, but had no other consequences. The animals were tested under these conditions of continuous reinforcement for 9 days (24 hr/day).

Each day, at approximately 1000 hr, total lever presses and infusions (for each solution) were recorded, the animals were weighed, and food and water intake were determined. Also, the amount of solution infused/infusion was adjusted each day to maintain the required doses.

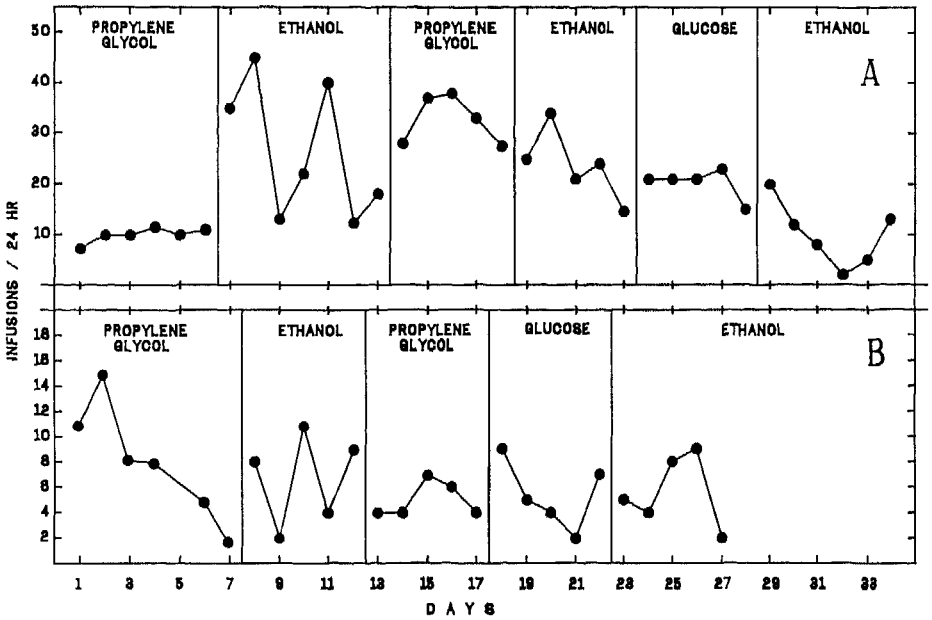

FIG. 4. Small-N experiment for two rats one self-infusing 4 mg/kg ethanol (upper graph A) and the other 16 mg/kg ethanol (lower graph B). Periods of ethanol availability alternate with periods of access to isocaloric control solutions (either glucose or propylene glycol). The figure shows that ethanol is not preferred over these control solutions for either rat.

RESULTS AND DISCUSSION

As in Experiment 1, the rats remained healthy throughout the experimental period, they consumed normal amounts of food and water, and gained weight. The average weight of the rats at the end of the experiment was 351 g, and there were no significant weight differences between the groups.

Figure 3 shows the mean number of infusions for both ethanol and glucose during the 9-day testing period. Within group (dependent t-test, two-tailed) analysis showed no difference between ethanol and glucose self-administrations for any of the groups (all $t(4)<2.00$, $p>0.10$). One-way analysis of variance showed no difference between the groups for the number of ethanol infusions self-administered, $F(2,12)=0.19$, $p>0.10$.

The finding for the 1 mg/kg group replicates our findings from Experiment 1. These data also show that neither 4 nor 16 mg/kg ethanol serves as a reinforcer for ethanol naive rats.

To further support these data, we carried out a few additional observations in a small number of rats. In one case (Fig. 4) we tested two rats, one at 4 mg/kg ethanol (Fig. 4A) and the other at 16 mg/kg ethanol (Fig. 4B). In these cases, only depression of the non-preferred lever led to an infusion of solution. Periods of isocaloric control solution availability alternated with periods of ethanol availability (each, at least 5 days). As can be seen from Fig. 4, in one animal (4 mg/kg ethanol), overall response rate was high, while in the other animal (16 mg/kg ethanol) response rate was low. However, in neither case did self-infusions of ethanol clearly differ from self-infusions of the isocaloric control solutions—either isotonic (5%) glucose, or propylene glycol (1% v/v ethanol and 0.95% v/v propylene glycol were used for the 4 mg/kg ethanol rat, and 5% v/v ethanol and 4.8% v/v propylene glycol were used for the 16 mg/kg ethanol rat, and infusion parameters were similar to those reported above).

Finally, in 4 rats, we tested ethanol at 1, 4, 16, and 64 mg/kg (each dose was assigned to only 1 rat). This was a 2-lever experiment in which depression of the preferred lever led to an intravenous infusion of isotonic saline (equivolumetric to the ethanol dose being tested), while depression of the other lever led to an infusion of ethanol at one of the above doses. Infusion parameters and solution concentrations were similar to these described above. The animals were tested for 10 days. On each day, infusions were available from one lever at a time for a 2 hr period, then from the other lever for the next 2 hr period, and so on. This alternation procedure continued 24 hr each day throughout the 10 day test period. A cue light was always illuminated above the currently active lever. Here again, the number of ethanol infusions, at each dose, across the 10 day test period, were always lower than the number of saline infusions self-administered. These data confirm the absence of a reinforcing effect for ethanol at any of these doses.

GENERAL DISCUSSION

These data clearly show that low dose intravenous infusions of ethanol are not reinforcing for ethanol naive rats. We controlled for both the non-specific motor excitatory effects of low doses of ethanol and for the caloric content of ethanol. These control procedures were not employed in the earlier studies showing a reinforcing effect for low doses of ethanol [26,28]. Therefore, we conclude that those positive reports were probably due to the non-specific effects of ethanol, rather than some reinforcing property of the drug. Further arguments in favor of this point of view were discussed above. Our findings agree with those of Grupp [12], and Asin *et al.* [3] who, using different but complementary procedures, also failed to uncover a reinforcing effect for low doses of ethanol.

Alcohol is therefore an anomalous drug compared to

other substances of abuse. As pointed out above, most other drugs of abuse are readily self-administered by the drug naive animal using procedures similar to those reported here.

However, alcohol is often abused by people. How does this reinforcing capacity develop? While predisposing genetic factors certainly play a role [11, 20, 25, 31], it seems to us, that a history of prior exposure to ethanol is also critical for the development of its reinforcing properties. This contention is supported by a number of studies in a variety of species, and using many different procedures [1, 9, 15, 19, 23, 30, 34]. In our own work [23] we have found that an initially aversive dose of ethanol acquires reinforcing properties following multiple periods of exposure to dependence inducing doses of ethanol. It was not clear however, in that study, whether the rats "learned" to intravenously self-administer ethanol to block withdrawal distress, or if tolerance developed to the initially aversive properties of the drug, unmasking a reinforcing capacity, or some combination of the two.

The idea that a history of exposure to ethanol might unmask its reinforcing property in animals is not new [4,13]. In fact, data in monkeys and rats suggest that even ethanol experienced animals will regulate their self-administration based on blood alcohol levels, decreasing their rate of self-administration when blood alcohol concentrations reach certain levels [14, 17, 32, 33]. These data imply some type of self-regulatory feedback system. These findings, in conjunction with the data in humans and monkeys [33,34] showing a cyclic pattern of ethanol intake and withdrawal suggest that, at least for early exposures to ethanol, high blood alcohol levels may be aversive or even toxic, so much so, that the subject will discontinue self-administration even in the face of withdrawal distress. Further, the fact that Winger *et al.* [34] report that monkeys, after prolonged experience with ethanol, will no longer exhibit these voluntary withdrawal episodes, suggests that perhaps some CNS or biochemical change induced by ethanol occurs over time which diminishes the aversive/toxic effects of ethanol. One might speculate that the animal now self-administers ethanol both for its unmasked reinforcing properties, and to block withdrawal distress. This line of reasoning is corroborated by taste conditioning studies showing that ethanol paired with flavors, in the ethanol naive animal, leads to an aversion for the paired flavor; an aversion does not develop, however, in the ethanol experienced animal, and a preference for the flavor may even occur under some circumstances [5, 8, 10, 18]. Further investigations along these lines should prove fruitful.

ADDENDUM

While our manuscript was under editorial review, an important paper was published by Collins *et al.* (Collins, R. J. J. R. Weeks, M. M. Cooper, P. I. Good and R. R. Russell. Prediction of abuse liability of drugs using IV self-administration by rats. *Psychopharmacology* **82:** 6–13, 1984). This work tested for the reinforcing effects of a number of drugs including ethanol, administered intravenously by rats in an operant lever-press paradigm. They tested several doses of ethanol (0.12–320 mg/kg) and, as in our work, found that none were reinforcing for rats when self-administered intravenously.

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