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Voluntary Ethanol Drinking Increases Locomotor Activity in Alcohol-Preferring AA Rats

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PÄIVÄRINTA, P. AND E. R. KORPI. *Voluntary ethanol drinking increases locomotor activity in alcohol-preferring AA rats.* PHARMACOL BIOCHEM BEHAV **44**(1) 127–132, 1993.—This study explored, first, whether voluntary ethanol consumption produces locomotor stimulation in ethanol-preferring AA rats. Rats had continual access to water but access to a second bottle containing 10% ethanol, 0.1% saccharin, or water only for 10 min/day. Locomotor activity was significantly increased after the drinking in the ethanol group. Second, we compared the locomotor responses of AA and ANA (ethanol-avoiding) rats to IP ethanol (0.6 and 1.0 g/kg). Rats habituated to test cages showed no effects, but on a modified open field novel to animals there was a short increase in activity without any rat line difference. This activity increase might have resulted from a weak anxiolytic action of ethanol, indicated by the finding in the elevated plus-maze where IP ethanol (1.0 g/kg) increased the number of crosses from a closed arm to another in both AA and ANA rats. The results suggest that ethanol has reinforcing effects in AA rats when drunk but not when injected IP.

AA and ANA rats Alcohol preference Locomotor activity Voluntary ethanol drinking
Anxiety Elevated plus-maze Modified open field Reinforcement

IT has become increasingly popular to suggest that the stimulation of locomotor activity, seen in laboratory rodents after administration of low ethanol doses, is an expression of the reinforcing properties of ethanol (1,5,14,15,21,23). Reinforcement plays a fundamental role in addiction and, thus, probably in the etiology of alcoholism (10).

Ethanol-preferring and -avoiding lines of rats, such as the AA/ANA lines, are widely used as models of human drinking and alcoholism (19). In ethanol-preferring AA rats, orally self-administered ethanol has been established as a reinforcer in operant conditioning studies (17,18). Therefore, according to the hypothesis above, AA rats should exhibit locomotor stimulation after voluntary ethanol drinking. In the present study, we measured the locomotor activity of AA rats after a short period of voluntary ethanol drinking, with saccharin and water controls.

We also wanted to find out if ethanol preference in AA and ANA rats differ in ethanol-induced behavioral stimulation, as has been demonstrated with the P and NP lines of rats (21). Because ANAs do not voluntarily drink ethanol, we compared the locomotor activities of rats after an IP administration of ethanol. An earlier study done in an open field demonstrated that both AA and ANA rats show locomotor stimulation after an IP injection of 1.0 g/kg ethanol (9). However, in that study animals were not habituated to the test arena. Because an activity increase in a novel arena can reflect anxiolysis and not a psychomotor stimulatory (psychostimulatory) effect of a drug (4), we decided to run a series of tests designed to separate ethanol's possible psychostimulatory and anxiolytic effects. First, a cage to which rats were habituated was used to find psychostimulatory properties of ethanol (6). Second, a modified open field was used to redo the former open-field experiment (9) with a wider range of doses and with anxiolytic measures taken. Third, a specific test of anxiety, the elevated plus-maze, was used to see more clearly whether ethanol has anxiolytic properties that could lead to behavioral stimulation on a novel arena.

METHOD

Subjects

Subjects were 73 AA and 77 ANA adult, male rats of the F_{61} generation. Animals were housed in stainless steel/metal wire cages in groups of five animals. Food (R3 powder, Ewos Ab, Södertälje, Sweden) and water were available ad lib. The animal room had a temperature of 22–26°C and a relative humidity of 40–60%. Rats were maintained in a reversed 12 L : 12 D cycle with lights off at 11:30 a.m. (a red 25-W lamp

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was on during the dark period) except the 16 AA and 16 ANA rats used in the elevated plus-maze test, which were kept with a normal light/dark cycle (lights on at 6:00 a.m.).

Apparatus for Recording Locomotor Activity

Automatic locomotor activity recordings were done with a static charge-sensitive bed (SCSB) system, as described in more detail elsewhere (11,12). In short, the method uses a movement-sensitive electrical mattress to detect vertical body movement, interfaced to a microcomputer for data acquisition and analysis. The system was set to measure activity scores as the seconds of locomotor activity in each 1.5-min interval for 1 h. The mattresses were calibrated so that grooming or other small movements by animals did not elicit a locomotor activity signal but moving from one place to another did.

Locomotor Activity of AA Rats After Voluntary Ethanol Drinking

The 27 AA rats for this experiment were formerly used in the modified open-field experiment. Animals were taken from the group cages and distributed into three treatment groups—ethanol (n = 9), saccharin (n = 9), and water (n = 9)—and housed individually in stainless steel/metal wire cages. At the beginning of the tests, the weights (±SD) of rats were as follows: ethanol 376 ± 32 g, saccharin 374 ± 59 g, and water 373 ± 43 g. All animals received two bottles of drinking fluid. One bottle was always water and the other was either 10% (v/v) ethanol, 0.1% (w/v) saccharin, or water, according to the group. The drinks were continuously available for 3 weeks, during which time rats learned reliably to prefer ethanol or saccharin to water. During the next 2 weeks, water was always available but the availability of the other drink was limited, first, to 2 h per day, then shortened progressively, eventually to 10 min beginning at 1:00 p.m.

Locomotor activity testing (conducted in the same room where animals were housed) was done as follows: At 12:00 p.m., the water bottle of a rat was taken away, the rat in its cage was put on an SCSB mattress, and a styrofoam lid was attached on top of the cage. Baseline locomotor activity was recorded for 1 h. After this, each animal received a bottle containing the drink corresponding to its group for 10 min (the other bottle, water, was not given). After the 10-min drinking period, the drinks were taken away and locomotor activity was recorded for another hour. This procedure was repeated three times, once a week per animal. The first two trials were intended only to make the test situation more familiar and were not recorded.

Locomotor Activity and Anxiety of AA and ANA Rats After IP Injection of Ethanol

Activity in a cage. Ten AA and 10 ANA rats were used. Tested animals were housed in group cages with untested rats. There were four cages of AA rats and five cages of ANAs, each with five animals/cage. At the beginning of the tests, AA rats weighed 385 ± 27 g and ANA rats 382 ± 23 g. The tests were conducted in the same room where animals were housed. Each animal was treated and tested three times, once with 1.0 g/kg ethanol, once with 0.6 g/kg ethanol, and once with saline, in a random order. Each animal received one test session per week. Ten animals were tested at a time. Solutions were administered IP in a volume of 1 ml/100 g body weight. At 12:00 p.m., a clean cage (Macrolon size III) was put on an SCSB mattress, a rat put into the cage, and a perforated styrofoam lid attached on top of the cage. In the few cases in which rats started eating the styrofoam lid, a metal-wire lid was substituted. Baseline locomotor activity was measured for 1 h (=habituation); animals were then injected and put back into the cages for recording activity for another hour.

Activity and anxiety on the modified open field. The modified open field (24) was made from clear acrylic painted white on the outside. It measured 110 × 110 × 35 cm, and its floor was marked with 22 × 22-cm squares. A cylindrical chamber or container, open at one end, 15 cm deep and 13 cm in diameter, was made from steel and painted black on the outside. The container was placed lengthwise to a wall of the open field so that it laid on the floor, the open end of it being 40 cm away from the facing corner. The container was made easily removable by securing a magnetic holder to the wall. A videocamera was placed above the open field for recording the tests. A stopwatch was placed above the field so that it was included in the video picture for timing the behavioral measures. The tests were conducted at 1:30–4:30 p.m. in ordinary fluorescent laboratory lighting.

Thirty-one AA rats and 35 ANA rats were used. AA rats weighed 313 ± 42 g and ANAs 405 ± 43 g. Housed in group cages, animals were divided into six groups: AA saline (n = 11), AA ethanol 0.6 g/kg (n = 10), AA ethanol 1.0 g/kg (n = 10), ANA saline (n = 12), ANA ethanol 0.6 g/kg (n = 12), and ANA ethanol 1.0 g/kg (n = 11). Twelve ± 2 min after an IP injection, the rat was put into the container on the open field so that its head faced the closed end. The following behavioral measures were analyzed from the video-recordings during 15 min: a) locomotor activity in each minute (measured as the distance traveled in cm), b) the total locomotor activity in all 15 min, c) latency to leave the container (all paws outside the container, seconds), d) total time spent in the container (seconds), and e) number of visits into the container (all paws inside the container). The 22-cm squares on the open field were utilized to measure the distance traveled. After each animal was tested, the container was washed with water and soap and the open field with ethanol.

Anxiety in the Elevated Plus-Maze

The plus-maze was constructed from transparent acrylic according to the measures given by Pellow et al. (13) as described in detail in (20). The tests were carried out at 2:00–6:00 p.m. under normal fluorescent laboratory lighting.

Sixteen AA and 16 ANA rats were used. AA rats weighed 293 ± 28 g and ANAs 350 ± 35 g. Subjects were distributed into four groups: AA saline, AA ethanol 1.0 g/kg, ANA saline, and ANA ethanol 1.0 g/kg; n = 8 in each group. Fifteen minutes before testing, rats were injected IP with ethanol or saline. Testing started by placing a rat in the center of the maze with its head facing an open arm. During the next 5 min, the behavior of the animal was recorded on videotape. The following measures were scored from videotape: a) latency to enter either an open or closed arm (all four paws inside the same arm, seconds), b) number of entries into open arms, c) number of entries into closed arms, d) time spent in the open arms (seconds), and e) time spent in the closed arms (seconds).

Statistics

The data from the locomotor activity studies were analyzed with a one- or two-way analysis of variance (ANOVA) followed by Fisher's least significant differences (LSD) test. The modified open-field data was analyzed similarly, but a signifi-

cant finding with ANOVA was rechecked with the Kruskall-Wallis test because of a lack of homogeneity in the variances of some measures. The plus-maze data was analyzed with a two-way ANOVA followed by Students *t*-test with Bonferroni correction.

RESULTS

Locomotor Activity of AA Rats After Voluntary Ethanol Drinking

During the 10-min drinking period prior to activity testing, animals consumed (mean ± SD) 11.8 ± 3.7 ml/kg of the 10% ethanol solution, 14.3 ± 7.7 ml/kg of saccharin solution, and 4.7 ± 2.8 ml/kg of water in the respective groups. The ethanol ($p < 0.01$) and saccharin ($p < 0.001$) intakes were significantly higher than the water consumption, $F(2, 24) = 26.9$, $p = 0.0017$. The mean ± SD dose of ethanol drunk was 0.9 ± 0.3 g/kg. The subsequent locomotor activity was higher after voluntary ethanol drinking than after voluntary saccharin or water drinking. This increase was statistically significant from minute three to minute nine after the end of the drinking period (Fig. 1).

Locomotor Activity and Anxiety of AA and ANA Rats After IP Injection of Ethanol

Activity in the cage. Ethanol injections of 0.6 or 1.0 g/kg had no statistically significant effect on locomotor activity relative to that after saline injection either in AA or ANA rats (Figs. 2A and 2B).

Activity and anxiety on the modified open field. A general effect of ethanol to increase locomotor activity during the first minute was found, $F(2, 59) = 5.31$, $p = 0.0076$. Within the lines, the increase in activity was significant only in the AA line, $F(2, 28) = 3.41$, $p = 0.047$ (Figs. 3A and 3B). No significant treatment or rat line effect nor interactions between the lines and treatments in any other of the measures were found (Table 1). A separate analysis omitting the scores of those rats that did not come out of the container at all (AA saline, three rats; AA ethanol 0.6 g/kg, two; AA ethanol 1.0 g/kg, one; ANA saline, three; ANA ethanol 0.6 g/kg, none; ANA ethanol 1.0 g/kg, none) produced similar results (see Table 1). Although there seemed to be differences in some cases between groups, they were not statistically significant due to the large interindividual deviation.

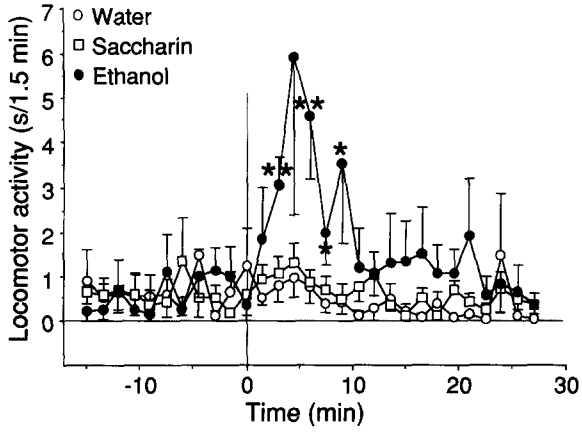

FIG. 1. Effect of a 10-min period of voluntary ethanol (10%), saccharin (0.2%), or water drinking on locomotor activity in ethanol-preferring AA rats ($n = 9$/group). Significance of difference from the saccharin group (Fisher's least significant differences): $*p < 0.05$, $**p < 0.01$. At time = 0, there is a nonrecorded interlude of 10 min during which time drinking took place. SEMs are indicated.

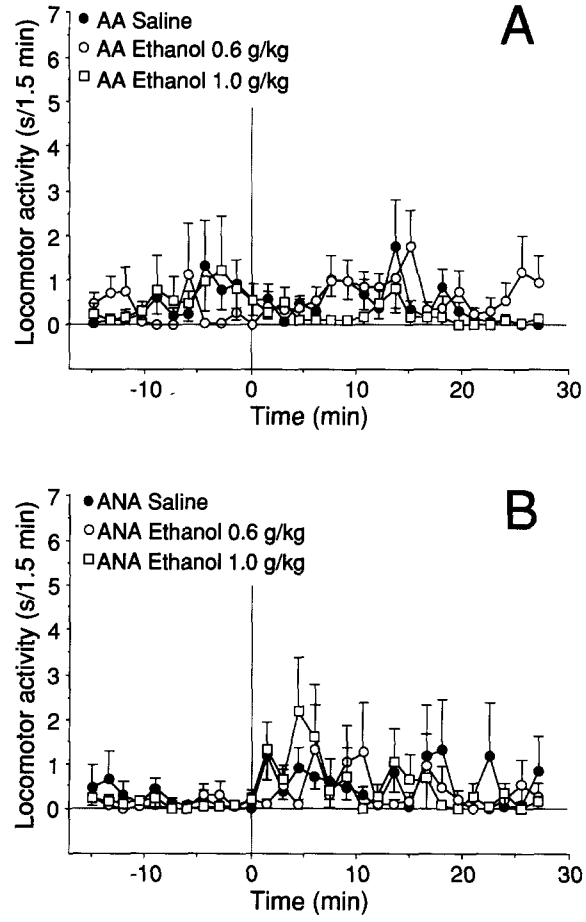

FIG. 2. Lack of effect of IP administration of 0, 0.6, and 1.0 g/kg ethanol on locomotor activity in ethanol-preferring AA rats (A) and ethanol-avoiding ANA rats (B). A repeated-measures design with 10 animals per rat line. At time = 0, there is a nonrecorded interlude of 2 min during which time injections were given. SEMs are indicated.

Anxiety in the elevated plus-maze. Significant rat line, $F(1, 28) = 5.85$, $p = 0.022$, and treatment, $F(1, 28) = 17.26$, $p = 0.0003$, effects on the number of entries to closed arms were found, but no line × treatment interaction. There were no significant changes in other measures (Table 2).

DISCUSSION

Ethanol-preferring AA rats increased their locomotor activity for a period of 6 min after a 10-min period of voluntary ethanol consumption (0.9 ± 0.3 g/kg), as compared to either water- or saccharin-consuming rats. The saccharin group provided a control for any arousal effects produced by obtaining a preferred solution during the limited access period. It has in general been found that rats become active and start drinking immediately when ethanol or saccharin is returned. In the present experiment, the saccharin group consumed more fluid during the 10-min access period than the ethanol group, and

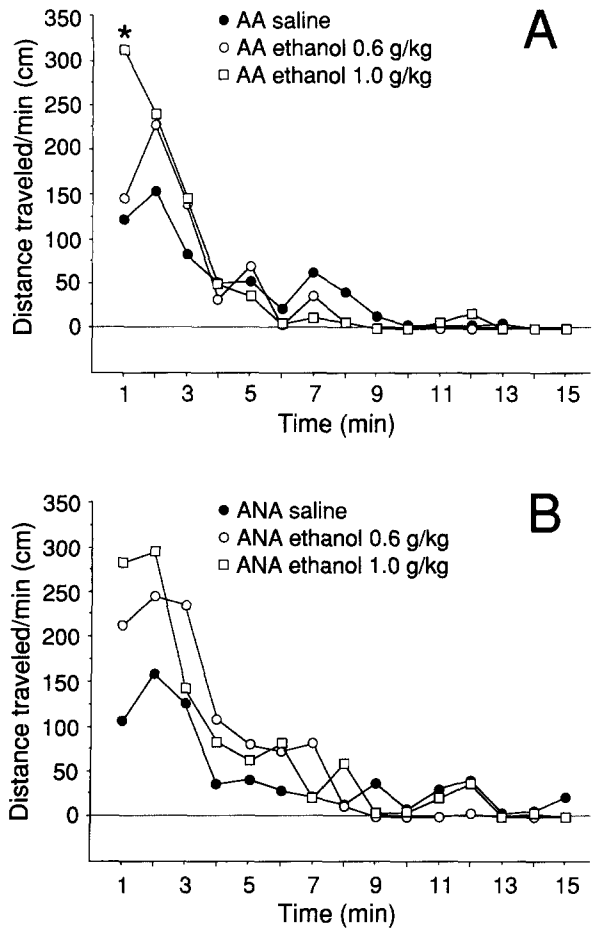

FIG. 3. Effects of IP administration of 0, 0.6, and 1.0 g/kg ethanol on exploratory locomotor activity of ethanol-preferring AA rats (A) and ethanol-avoiding ANA rats (B) on the modified open field. See Table 1 for number of animals. Significance of difference from saline treatment (Fisher's least significant differences): $*p < 0.05$.

the water group drank less than the ethanol group. Neither the saccharin nor the water group showed any noticeable change in subsequent activity but the ethanol group showed a large increase. Therefore, it is possible that the psychostimulatory effects from the gradually absorbed ethanol were involved in the locomotor stimulation. We suggest that this is a demonstration of the delayed reinforcing properties of voluntary ethanol drinking in AA rats. The results are consistent with findings that Long Evans rats increase their activity on the holeboard after voluntary ethanol drinking of about 0.7 g/kg (7). We did not measure the blood ethanol levels corresponding to the increased activity, but it has been demonstrated in our laboratory that oral administration of ethanol at 0.9 g/kg results in half maximum blood ethanol levels in 5 min, peaking (0.75‰) at 35 min. Also, voluntary drinking of ethanol (1 g/kg) in conditions comparable to those used in our experiment resulted in a blood ethanol level of 0.5‰ as measured 30 min after the start of the drinking period (Petri Hyytiä, personal communication). Thus, it is possible that the stimulation of the locomotor activity coincides with rising blood ethanol levels. AA rats used in this experiment were used in the open field test before, that is, each rat had undergone one injection with saline or ethanol (0.6 or 1.0 g/kg) and been tested once in the modified open field. Open-field rats were randomly distributed to the water, ethanol, and saccharin groups and tested for their locomotor activity several weeks after the open field test, and, therefore, we think that prior open-field exposure did not have any significant impact on the results under discussion.

IP administration of ethanol (0.6 and 1.0 g/kg) did not stimulate the activity of AA or ANA rats in the cage to which they were habituated but increased their activity (without a line difference) in the modified open field novel to animals. The latter result confirms a stimulatory finding reported before on a somewhat different open-field situation (9). The fact that the stimulation was of such a short duration (observed only during the first minute) suggests other than a psychostimulatory origin, and the fact that it did not differ in rat lines suggests that it was not related to reinforcement. Although the anxiolytic behaviors on the modified open field were not significantly increased by ethanol, in the elevated plus-maze IP ethanol increased the number of entries into the closed arms, which might be interpreted as a sign of weak anxiolytic effect. It should be noted that under these conditions ethanol failed to produce any pronounced anxiolysis because the time

TABLE 1

EFFECTS OF IP ETHANOL TREATMENT ON LOCOMOTOR ACTIVITY AND ANXIETY-RELATED BEHAVIOR IN THE MODIFIED OPEN-FIELD TEST

Measure of Behavior/Treatment	AA Rats (ethanol preferring)	ANA Rats (ethanol avoiding)
Locomotor activity during the first minute (distance traveled in cm)		
Saline	122 ± 47.3	106 ± 35.6
Ethanol 0.6 g/kg	145 ± 64.5	213 ± 67.8
Ethanol 1.0 g/kg	310 ± 54.3*	310 ± 87.2
Total locomotor activity (cm, distance traveled in 15 min)		
Saline	605 ± 205	669 ± 243
Ethanol 0.6 g/kg	656 ± 220	1,045 ± 289.5
Ethanol 1.0 g/kg	823 ± 216	1,192 ± 346.1
Latency to leave the container (seconds)		
Saline	263 ± 124	240 ± 115
Ethanol 0.6 g/kg	200 ± 117	28.3 ± 8.0
Ethanol 1.0 g/kg	98 ± 89	18.1 ± 4.9
Time spent in the container (seconds)		
Saline	707 ± 84	665 ± 99.6
Ethanol 0.6 g/kg	675 ± 108	776 ± 33.1
Ethanol 1.0 g/kg	652 ± 101	684 ± 81.9
Number of visits into the container		
Saline	3.15 ± 0.95	3.5 ± 1.55
Ethanol 0.6 g/kg	4.0 ± 1.27	4.67 ± 1.03
Ethanol 1.0 g/kg	2.72 ± 0.86	3.2 ± 0.73
% of animals not leaving the container at all		
Saline	27.3	25
Ethanol 0.6 g/kg	20	0
Ethanol 1.0 g/kg	10	0

Number of animals in each group: AA saline, $n = 11$; AA ethanol 0.6, $n = 10$; AA ethanol 1.0, $n = 10$; ANA saline, $n = 12$; ANA ethanol 0.6, $n = 12$; ANA ethanol 1.0, $n = 10$. Means and SEMs are given.

$*p < 0.05$, significance of difference (Fisher's LSD) as compared to saline treatment in the AA line.

TABLE 2

EFFECTS OF IP ETHANOL TREATMENT ON ANXIETY-RELATED BEHAVIOR IN THE ELEVATED PLUS-MAZE TEST

Rat line	Treatment	Latency to First Arm Entry (seconds)	Number of Entries to Open Arms	Number of Entries to Closed Arms	Time Spent in Open Arms (seconds)	Time Spent in Closed Arms (seconds)
AA	Saline	6.0 ± 4.2	0.4 ± 0.3	7.0 ± 1.0	3.1 ± 2.7	203 ± 17
AA	Ethanol 1.0 g/kg	1.4 ± 0.7	0.8 ± 0.4	10.9 ± 1.0	9.5 ± 6.5	218 ± 10
ANA	Saline	2.5 ± 1.1	1.3 ± 0.6	9.1 ± 0.8	11.6 ± 7.0	215 ± 13
ANA	Ethanol 1.0 g/kg	2.4 ± 1.4	1.8 ± 0.9	13.6 ± 1.2*	28.9 ± 15	192 ± 15

Means ± SEMs are indicated. $n = 8$/group.
*$p < 0.05$, student's t-test with Bonferroni correction for the significance of the difference from saline treatment.

animals spent in the open arms was not altered (13). It seems likely, however, that IP ethanol does not have a psychostimulatory effect under these experimental conditions and the short stimulatory effect seen on the modified open field results from ethanol's weak anxiolytic action, also suggested by related findings by others (3,8).

There may be several possible reasons for the lack of locomotor stimulation in the habituated cage situation (IP ethanol) as compared to the stimulation seen with the voluntary ethanol drinking in AA rats. First, the doses injected may have been too large, as suggested by the finding that ethanol-preferring P rats have been shown to increase their locomotor activity at 0.12 and 0.25 g/kg IP with little effect at higher doses (21). Second, the stress from injection might have masked ethanol's stimulatory effects because stress is known to counteract some of ethanol's behavioral effects (2,16,22). Third, the housing difference could have influenced the results. IP-injected rats were group housed, whereas voluntary drinking AA rats were singly housed. We have demonstrated that single-housed mice show striking locomotor stimulation to low ethanol doses (11). It is possible that social isolation augments ethanol's ability to increase locomotor activity also in AA rats.

In conclusion, the results show that in ethanol-preferring AA rats a brief voluntary ethanol drinking session is followed by elevated locomotor activity. Ethanol, injected IP, did not have a locomotor activity-stimulating effect on a familiar arena in either line but had a short stimulating effect unrelated to rat line on exploratory activity on a novel arena resulting possibly from anxiolysis. The results suggest that under these conditions ethanol, when drunk voluntarily, but not when administered IP, is reinforcing for AA rats.

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