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Plus-Maze Behavior and Susceptibility to 3-Mercaptopropionate-Induced Seizures in Rat Lines Selected for High and Low Alcohol Sensitivity

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TUOMINEN, K., K. HELLEVUO AND E. R. KORPI. *Plus-maze behavior and susceptibility to 3-mercaptopropionate-induced seizures in rat lines selected for high and low alcohol sensitivity.* PHARMACOL BIOCHEM BEHAV **35**(3) 721–725, 1990.— Selective outbreeding for high and low acute alcohol sensitivity has produced two rat lines (alcohol-sensitive ANT and alcohol-insensitive AT lines) that also differ in their sensitivity to GABAergic drugs, benzodiazepines and barbiturates. These rats were now compared in two behavioral tests believed to involve central GABAergic mechanisms, in elevated plus-maze test and in 3-mercaptopropionate-induced seizure test. The AT animals spent more time in the open arms of the plus-maze than the ANT rats, suggesting that the AT's behave less anxiously. The ANT's were more susceptible to seizures induced by 3-mercaptopropionate (50 mg/kg, IP) than the AT's, suggesting the ANT's having greater sensitivity to a decrease in brain GABA concentration. At the time of the first seizure signs, there was a tendency, though a nonsignificant one, to greater decreases in brain GABA in the ANT's than AT's. These results suggest that there are differences in GABA-related behaviors between ethanol-naive rats of the lines produced by selective outbreeding for differences in alcohol sensitivity. In theory, these behavioral line differences might physiologically counteract alcohol effects in the ANT's and enhance them in the AT's. In elevated plus-maze test, however, an acute dose of ethanol (1 g/kg, IP) significantly changed the behavior of the ANT animals, but only up to level of the AT rats. The apparent sensitivity to ethanol may thus be dependent on the naive behavior of the alcohol-insensitive AT and alcohol-sensitive ANT rats.

Elevated plus-maze 3-Mercaptopropionic acid Seizure susceptibility Alcohol-sensitivity Selected rat lines

THE major central inhibitory neurotransmission system, using gamma-aminobutyric acid (GABA) as its transmitter, influences a number of various behaviors. GABA mechanisms are involved, among others, in the expression of seizures, anxiety and sedation (7, 13, 17, 21), with a high GABA tone decreasing seizure susceptibility and anxiety, and increasing sedation. All of these behaviors can be studied in rodents. Seizure activity can be assessed, e.g., after chemical depletion of brain GABA by 3-mercaptopropionic acid (3-MPA) that inhibits the GABA synthesizing enzyme glutamate decarboxylase (15,33). An elevated plus-maze test can be used to assess aspects of fear and anxiety in approach-avoidance conflict situation. In this test, drugs enhancing the GABA effects, benzodiazepines and barbiturates, cause the animals to spend more time in the open arms of the plus-maze supposedly because they decrease fear and anxiety (28).

There is evidence that the expressions of seizures, anxiety and sedation are under genetic influence in rodents. Genetic factors are at least partly responsible for the susceptibility to seizures (26), as well as the sensitivity to drug-induced sedation (6, 8, 11, 23, 24). They also play a role in determining the emotional responses, such as fear (3).

Our laboratory has produced alcohol-sensitive ANT (*A*lcohol *N*on-*T*olerant) and alcohol-insensitive AT (*A*lcohol *T*olerant) rat lines by selective outbreeding, avoiding sib-mating, using the degree of impairment in motor behaviors at the same blood alcohol concentration after an acute alcohol challenge as the selection criteria (6). These rat lines differ also in their sensitivity to GABAergic drugs in a similar fashion as to ethanol (11,29).

These lines also differ in some sober behaviors, brain metabolism and neuronal functions in different brain regions (14, 20, 25, 30). It is not known whether these differences have developed by chance during the selection or whether they are related to the mechanisms controlling ethanol sensitivity. Since the GABAergic system seems to be mediating at least partly the intoxicating actions of alcohol (12,31), we wanted to compare AT and ANT rats in seizure sensitivity and plus-maze behavior to get an idea whether there is a more generalized difference between these rat lines in their GABAergic behaviors. Our hypothesis was that

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features in GABAergic behaviors that might be expected to oppose alcohol intoxication, i.e., seizure susceptibility to lowered brain GABA and the level of anxiety, would be more pronounced in the sober alcohol-insensitive AT rats than in the alcohol-sensitive ANT rats.

METHOD

Animals

Altogether 53 AT and 53 ANT male rats from the F_{33} generation and 15 AT and 15 ANT male rats from the F_{34} generation (Experiment 3 in Table 1) were used. The animals were housed in stainless steel wire cages in groups of 4–6 rats with rat chow (R3 pellets, Ewos AB, Södertälje, Sweden) and tap water freely available. The ambient temperature was maintained at 22 ± 2°C, the relative humidity at 50 ± 5%, and the light/dark cycles at 12 hr (lights on at 6:00 a.m.). No significant line differences in body weights were found in any of the experiments. At the time of Experiment 1, the mean ± SEM ($n = 20$) weight of the AT's was 197 ± 9 g and that of the ANT's 197 ± 4 g.

Elevated Plus-Maze Test

The plus-maze was constructed according to the measures given by Pellow *et al.* (28) from transparent Plexiglas. The floors and closed arm walls were covered with black contact tape. The tests were carried out between 9:00–11:00 a.m. with normal artificial lighting. Six to eight rats were tested daily (only one from each cage).

The test was started by placing the animals in the center of the maze with its head towards an open arm. The behavior of the animals was recorded on a videotape for 5 min. The maze was cleaned after every animal. The total time spent in open and closed arms (all feet within the area), the frequency of arm changes, the latency of going into an arm, and the choice (open or closed) of the 1st arm entry were analyzed from the video recordings.

Tilting Plane Test

The effect of acute ethanol [2 g/kg, IP, as 12% (w/v) solution in saline] on the motor coordination was tested on a tilting plane (1,11). Each rat was given a test before ethanol injection, and another test 30 min after the injection. The change of the sliding angle was taken as a measure of motor impairment by ethanol. Immediately after the test, tail tip blood samples were drawn and analyzed for ethanol concentration by head space gas chromatography (5).

Seizures Induced by 3-Mercaptopropionic Acid (3-MPA)

The rats were injected IP with 3-MPA (Fluka, Buchs, Switzerland) at two dose levels (35 and 50 mg/kg; dissolved in saline and injected in a volume of 2.5 ml/kg). The seizure activity was scored by two observers using a scoring system modified from Löscher (22) as follows:

0—no seizures
1—clonic jerks, muscle twitches
2—wild running
3—clonic seizure with loss of righting reflex
4—tonic forelimb extension
5—tonic hindlimb extension

Immediately after the injection, the animals were placed in a Plexiglas cage and observed for 30 min or until they reached the score 5. The animals were killed by inhalation of CO_2. The highest score of each animal was recorded. In a pilot experiment, the rats ($n = 10$ for both lines) received 75 mg/kg of 3-MPA, and all rats went quickly to tonic hindlimb extensions after the first seizure signs. There were no line differences in the latencies after this dose (data not shown).

Analysis of GABA After 3-MPA

Rats were treated with 3-MPA (50 mg/kg, IP), and then 5 min later killed by microwaves focused to their brains (New Japan Radio, model NJE 2603, Tokyo, Japan; power 8.9 kW for 1.75 sec). The heads were cooled in crushed ice, and cerebral cortex, hippocampus, hypothalamus and cerebellum carefully dissected. GABA concentrations were determined using precolumn derivatization with *o*-phthalaldehyde (OPA)/2-mercaptoethanol solution followed by HPLC on a reversed phase column and fluorescence detection using a gradient run with phosphate- and phosphate-acetonitrile buffers (10,18). Briefly, tissue samples were sonicated in perchloric acid, and centrifuged. Supernatants were taken, the internal standard norvaline added, and the samples diluted with methanol to fit the linear range of the fluorescence detector (10–600 pmol/amino acid/injection). The derivatization of the samples and the constructed GABA standards was made by the sample processor. The OPA reagent, stored in −20°C, was made weekly from 50 mg OPA, 5 ml absolute methanol, 5 ml saturated H_3BO_3-buffer pH 9.5 and 50 μl 2-mercaptoethanol. The chromatograph system consisted of a WISP 710B sample processor, equipped with an OPA valve, two Model 510 pumps controlled by an Automated Gradient Controller (Waters Associates, Milford, MA), a glass-bead column, a Waters Bondapak C18 precolumn, an Altex Ultrasphere ODS 5 μm (250 × 4.6 mm i.d.) column (Beckman Instruments Inc., San Ramon, CA) and a Waters 420AC Fluorescence Detector.

Statistical Analysis

The AT and ANT lines were compared with Student's *t*-test or with analysis of variance followed by *t*-test as a post hoc test. When parametric tests could not be used, the Fisher's four-fold table test was done (16).

RESULTS

Elevated Plus-Maze Test

The alcohol-insensitive AT animals spent significantly ($p < 0.001$) more time in the open arms of the plus-maze than the alcohol-sensitive ANT animals (Experiment 1 in Table 1). They also made more arm entries and chose the open arm more frequently as their first choice than the ANT's. The time spent in the closed arm and the latency to the first arm entry tended to be shorter in the AT's than ANT's.

The line differences found in naive rats in Experiment 1 in the open arm times and the number of arm entries were not seen in the ethanol-treated rats (Experiment 2 in Table 1). With ethanol the alcohol-sensitive ANT's decreased their closed arm times more than the alcohol-insensitive AT's. Ethanol increased the number of arm entries in both lines. The saline-treated ANT's had a longer latency to the first arm entry than the AT's, suggesting an effect by the injection.

In Experiment 3 (Table 1) the naive alcohol-sensitive ANT's again had significantly lower open arm times, when the closed arms were covered with black tape. Removing the tape increased the variability and the line difference was no longer significant. It also reduced the time the rats spent in the closed arms, the effect being significant within the AT's ($p < 0.01$). The AT's had a

TABLE 1

BEHAVIOR OF THE ALCOHOL-INSENSITIVE AT AND ALCOHOL-SENSITIVE ANT RATS IN AN ELEVATED PLUS-MAZE TEST

	Rat Line	Treatment/ Condition	n	Open Arm Time (sec)	Closed Arm Time (sec)	Number of Arm Entries During 5 Min	Latency to the 1st Arm Entry (sec)	1st Choice Open Arm
Experiment 1	AT	naive	20	14.2 ± 3.5	250 ± 7	4.9 ± 0.6	1.7 ± 0.4	13/20
	ANT	naive	20	0.7 ± 0.7‡	262 ± 5	2.5 ± 0.4†	7.0 ± 2.7	1/20†
Experiment 2	AT	ethanol	10	16.0 ± 8.5	230 ± 13^{L}*	6.7 ± 1.0^{C}†	7.5 ± 2.9^{L}†	5/10
	ANT	ethanol	10	13.6 ± 6.1	192 ± 10*	5.7 ± 0.8	12.7 ± 4.1	4/10
	AT	saline	10	12.7 ± 4.8	234 ± 16	3.9 ± 0.9^{a}	7.4 ± 2.8	5/10
	ANT	saline	10	1.7 ± 0.8	244 ± 8^{c}	3.0 ± 0.3^{b}	21.0 ± 4.0*	3/10
Experiment 3	AT	naive, black closed arms	7	12.6 ± 4.6^{L}*	216 ± 9^{C}‡	5.4 ± 1.1^{L}*	4.1 ± 2.0^{L}*	4/7
	ANT	naive, black closed arms	7	0.0 ± 0.0*	203 ± 11	3.6 ± 0.8	12.9 ± 4.2	0/7*
	AT	naive, transparent closed arms	8	21.8 ± 9.8	167 ± 10^{b}	7.5 ± 1.0	8.5 ± 2.7	4/8
	ANT	naive, transparent closed arms	8	4.5 ± 3.6	179 ± 8	4.4 ± 1.0*	16.6 ± 4.6	1/8

Experiment 1: Naive rats were individually taken from the maintenance cages and immediately placed on the plus-maze for 5 min. Experiment 2: The rats from Experiment 1 were divided into 4 groups, and injected intraperitoneally either with ethanol [1 g/kg, IP as 12% (w/v) solution] or saline (8 ml/kg, IP) 30 min before they were placed in the plus-maze for 5 min. Experiment 3: Naive rats were placed for 5 min in plus-maze with either transparent or black closed arms. Open and closed arm times are the lengths of time the animals spent in open or closed arms, respectively. Results are given as means ± SEM for n rats. Statistical comparisons were made with Student's *t*-test (naive rats), or Fisher test (1st choices) or with two-way analysis of variance followed by post hoc *t*-tests. Post hoc: Significance of the difference from AT line: *$p<0.05$, †$p<0.01$, ‡$p<0.001$. Significance of the difference between conditions within the same line: $^{a}p<0.05$, $^{b}p<0.01$, $^{c}p<0.001$.

Analysis of variance: L, line effects; C, treatment or condition effects; there were no significant L × C interactions.

higher frequency of arm entries than the ANT's in the plus-maze with transparent walls.

Tilting Plane Test

Two weeks after the plus-maze test (Experiment 1), the alcohol sensitivity of the animals was tested using the tilting plane. The alcohol-sensitive ANT rats were more impaired ($p<0.001$) by ethanol (2 g/kg, IP, 30 min) than the alcohol-insensitive AT rats. The decrease in the sliding angle was 19.5 ± 1.4° (mean ± SEM, n = 20) and 1.2 ± 1.5° for the ANT's and AT's, respectively. There was no difference ($p>0.05$) between the lines in blood ethanol concentrations, the ANT's having 46 ± 1 and AT's 48 ± 1 mmol/l.

Seizures Induced by 3-Mercaptopropionic Acid

There were no significant differences between the lines in the seizure behavior after 35 mg/kg 3-MPA, but after 50 mg/kg, a significantly ($p<0.05$) greater proportion of the alcohol-sensitive ANT than alcohol-insensitive AT rats reached the highest behavioral score (Table 2). The mean seizure scores were also higher in the ANT's than AT's after 50 mg/kg 3-MPA, but there were no line differences in the latencies to the first seizure signs. There

TABLE 2

COMPARISON OF SEIZURES INDUCED BY 3-MERCAPTOPROPIONIC ACID IN THE ALCOHOL-INSENSITIVE AT AND ALCOHOL-SENSITIVE ANT RATS

Rat Line	Dose of 3-MPA (mg/kg, IP)	n	n Reaching Score 1 or 2	Latency for Score 1 or 2 (sec)	Mean Final Seizure Score	n Reaching Score 5
AT	35	9	4	340 ± 47	1.2 ± 0.5	0
ANT	35	9	6	397 ± 33	1.8 ± 0.7	2
AT	50	10	7	273 ± 47	2.6 ± 0.6	3
ANT	50	10	9	293 ± 22	4.5 ± 0.5*	9*

The rats were injected intraperitoneally with one of the two doses of 3-mercaptopropionic acid (3-MPA), placed in transparent Plexiglas cages, and observed for 30 min or until they reached the score 5. All rats receiving the same dose were tested on the same day. About half of the rats were used only in this experiment (11 out of 19 in both lines), the rest were used earlier in Experiment 1 and Experiment 2. Results are given as means ± SEM. Analysis of variance indicated a significant ($p<0.05$) line difference in the mean final seizure scores, but not in the latencies to scores 1 or 2. Post hoc *t*-test: *$p<0.05$ from the corresponding AT value. A higher number of the ANT than AT rats reached the highest seizure score of 5 (Fisher test, *$p<0.05$).

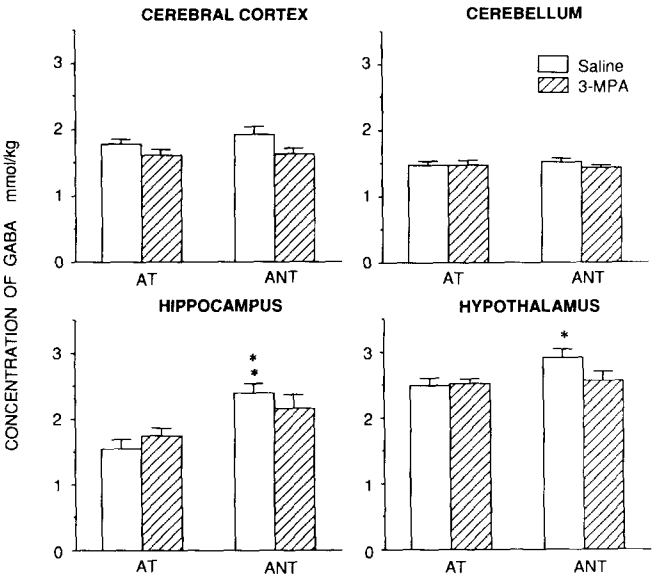

FIG. 1. GABA concentrations in different brain regions of alcohol-insensitive AT and alcohol-sensitive ANT rats treated with 3-mercapto-propionic acid (3-MPA; 50 mg/kg, IP, 5 min before sacrifice). The columns are means ± SEM for 5–6 rats per group. Significance of the difference from the corresponding value of the AT line (Student's *t*-test): $*p<0.05$, $**p<0.01$. There was no significant ($p>0.05$) difference between saline and 3-MPA treatments within either rat line, but a tendency for rat line × treatment interaction was observed in analysis of variance repeated over all brain regions, $F(1,18)=3.66$, $p=0.0718$.

were no differences within the lines, whether the rats had or had not been used earlier in plus-maze tests (data not shown).

Brain regional concentrations of GABA were determined to see whether 3-MPA (50 mg/kg, IP) differently affects them in the AT's and ANT's. An early time point (5 min) after 3-MPA injection was chosen for analyses because the differential seizure behavior itself might affect the brain GABA differently in the AT and ANT lines. No effects could be found in the AT's, whereas a tendency to decreased GABA in all brain regions was found in the ANT's (Fig. 1). In addition, the saline-treated AT's had lower GABA concentrations in the hippocampus and hypothalamus than the ANT's.

DISCUSSION

The rat lines produced by selective outbreeding for low (AT) and high (ANT) sensitivity to moderate alcohol doses also differ in a similar fashion in their sensitivity to a benzodiazepine and barbiturate (11,29). This suggests that the GABA/benzodiazepine receptor complex is involved in the differential sensitivity of the lines. Ethanol-naive animals from these alcohol-insensitive AT and alcohol-sensitive ANT lines behaved differently in two tests—the elevated plus maze test and seizure susceptibility test—which are believed to reflect brain GABAergic activity.

Line differences in sober animals had previously been found with a modified swimming test, but the relation of this test to GABAergic mechanisms was unknown and it was possible that the line difference was due to accidental gene drift and was not related to the mechanisms controlling alcohol sensitivity [see (30)]. The present results suggest, however, that the behavioral differences seen between the lines in the absence of alcohol may in fact be caused by differences in their GABA systems.

It should be mentioned, however, that although GABA-enhancing drugs increase open arm time (28) and benzodiazepine withdrawal decreases it (2), other classes of drugs, e.g., 5HT-IA agonists (32) also have anxiolytic effects. Similarly, although 3-MPA is known to inhibit the GABA synthesizing enzyme (15,33), its exact mechanism of action in inducing convulsive behavior is not entirely known, and a general increase in brain GABA concentration does not abolish seizures by 3-MPA (22). (In our study, we did not observe any marked reductions of brain GABA, probably because of the early time point chosen for analysis.) Nevertheless, we feel that a major component in both of these tests is a GABAergic one.

In the elevated plus-maze test, the AT rats spent more time in the open arms than the ANT rats, which suggests that the activity of the GABAergic neurons is greater in naive AT's than ANT's. This contrasts with reports on other rat and mouse strains, which indicate accentuation of ethanol effects by increased GABAergic activity and attenuation of the effects by blockade of GABA actions (4, 9, 19, 27). Thus, considering our selection program, the present finding may illustrate an adaptation of the GABA system in a way that anxiolytic and sedative mechanisms have diverged in the lines. Similar divergence can be postulated to have taken place between sedative and convulsive mechanisms, since the alcohol-sensitive ANT rats were more susceptible to 3-MPA-induced seizures than the alcohol-insensitive AT rats. These suggestions are against the coselection of high alcohol sensitivity with low anxiety and low seizure susceptibility in naive rats.

Even if the above simple divergence hypothesis were wrong, and the present behavioral differences somehow associated with alcohol sensitivity, the effects of a low ethanol dose on the plus-maze behavior suggests that the effect of ethanol may be dependent on the naive behavior of the rats. Ethanol at the dose of 1 g/kg seemed to affect mainly the ANT's, but it actually "normalized" their behavior roughly to the level of the AT's. Since only one dose of ethanol was used, it is premature to conclude that ethanol differentially affected the anxiety or fear of the AT's and ANT's in the plus-maze test.

In conclusion, the present study provides evidence that the rat lines selectively outbred for differential sensitivity to moderate doses of alcohol, differ in their nonintoxicated state in behaviors believed to reflect at least partly the brain GABAergic activity. Until the associations of these behavioral differences with alcohol sensitivity differences will be confirmed by genetic experiments in the AT and ANT rats, the behavioral differences between naive rats should be taken into consideration, when interpreting the role of the GABAergic mechanisms in the alcohol actions.

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