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The effects of novelty, isolation, light and ethanol on the social behavior of mice

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Abstract. The social behavior of pairs of male NIH Swiss mice was assessed under a variety of experimental conditions. Increasing periods of isolation increased both the total time spent in social interaction and also increased the incidence of aggressive behavior. Familiarity with the testing arena tended to increase social behavior, but the magnitude of this effect was considerably less than that previously observed in rats. High light levels reduced social interaction. Ethanol (0.8–2.4 g/kg) caused a dose-related decrease in the total time spent in social interaction, a biphasic effect on aggressive behavior and a dose-related increase in locomotor activity. While the social interaction test in this form may not be a suitable model of anxiety in NIH Swiss mice, it should provide a useful method of assessing drug effects and investigating genetic influences on social and aggressive behavior.

Key words: Social behavior – Aggression – Isolation – Ethanol – Light – Motor activity – Mouse – Novelty

The social and aggressive behavior of mice can be studied in a number of ways (for references, see Miczek 1987). The most often used behavioral method to study aggression is to isolate a mouse and, subsequently, examine its interaction with a conspecific stimulus animal. Isolation will increase aggression in otherwise non-aggressive laboratory mice, and the isolated male mouse will then chase, threaten, and attack the opponent or, alternatively, engage in defensive and flight reactions (Brain and Nowell 1970; Krsiak 1975). To further increase aggressive behavior the test is generally performed in the home cage of the isolated mouse (Miczek 1987); the intruder is group-housed, and possibly made non-aggressive by rendering it anosmic by nasal perfusion with zinc sulphate (Parmegiani and Brain 1983).

A diminished level of aggression is seen if the mice are tested in a neutral cage, or a cage in which the test males are communal residents (see Miczek 1987). Our goal was to establish a paradigm in which basal levels of aggression are low. If a dramatic increase in spontaneous aggressive behavior was observed as a result of some pharmacological treatment, or by using a particular strain of mouse, we felt we might be able to observe a pattern of behavior similar to the impulsive type of aggression seen in some humans (Linnoila et al. 1983). Paradigms in which basal levels of aggression are high seemed less likely to us to help to identify a subpopulation of individuals which exhibit abnormally high aggressive behavior. Clearly a considerable amount of further work would be needed to substantiate any claims that the test provided a model of impulsive aggression. However, this was our starting hypothesis. Therefore, we selected a paradigm in which the social behavior of pairs of male mice was tested in a novel environment, rather than a resident-intruder situation. File (1980) has used such a paradigm to investigate the social behavior of pairs of male rats, and the test has been used as a model of anxiety. In rats severe forms of aggression such as biting are only rarely seen in the social interaction test. In contrast, preliminary studies with different strains of mice indicated a greater incidence of aggressive behavior (File 1980).

The aim of the present study was to investigate the social behavior of mice using the social interaction paradigm. The effects of isolating the mice for varying periods of time, of differing degrees of familiarity with the testing arena, of varying the ambient light level, and of a pharmacological manipulation (treatment with ethanol) were examined in separate experiments. Alcohol was chosen in view of the extensive literature already available on the effects of this compound on social and aggressive behavior (Krsiak 1976; Lagerspetz and Ekqvist 1978; Miczek 1987). This would allow a comparison of the effects observed in the present paradigm with those observed using other methods.

Methods

Animals. Male NIH Swiss [Cr: NIH(S)] mice, weighing approximately 22 g were housed individually for different time periods, depending on the experiment. They were maintained on a 12 h light: 12 h dark cycle and allowed ad lib access to food and water. The mice were assigned test partners on the basis of unfamiliarity to each other and of their weight, so that members of a pair did not differ by more than 1 g. All mice were naive to the testing apparatus, except in the experiments in which familiarity was an experimentally controlled variable (experiments 2, 3 and 4).

Apparatus. The test apparatus was made of Plexiglas (40 × 40 × 30 cm), with a solid floor and four infra-red photocells in the walls that provided an automated measure of motor activity from the number of beam breaks. The

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light level was 0.32 candelas m^{-2} in the low lighting conditions, and 12.3 candelas m^{-2} in the high lighting condition.

Experiment 1. The effect of isolation time on social behavior was studied in the first experiment. Mice were isolated for 20 (number of pairs = 12), 10 ($n=13$), 5 ($n=19$), 2 ($n=19$), 1 ($n=16$), or 0 ($n=18$) days. On the test day each pair of mice was placed in the center of the unfamiliar testing arena which was under a low level of illumination, and their social behavior scored for 7.5 min. The incidence and duration of the following behaviors were scored using a keyboard interfaced with a PDP-11 microcomputer running SKED-11 software (State Systems, Kalamazoo): active social interaction (sniffing, following, grooming), overt aggressive behavior (fighting and biting), and threat (tail rattling). The behavior of each pair was recorded using a camera and video cassette recorder. At the end of each test period, the mice were returned to their home cages, and any boluses were removed and the box was wiped clean. Mice were tested in an order randomized for duration of isolation. In this and in all subsequent experiments testing took place between 08:30 and 13:00 hours.

Experiment 2. In the second experiment, the baseline social behavior under two different lighting conditions in mice was studied. Experiment 1 showed that when the mice were isolated for 5 days, they were not very aggressive but had a high level of social interaction. Therefore, 5-day-isolation was used in experiments 2, 3 and 4. Sixteen pairs of mice were tested in either a dim or bright light. The mice were tested on 3 consecutive days. On day 1, they were tested in pairs as in experiment 1. On day 2, they were individually familiarized with the apparatus for 7.5 min. On day 3, the social behavior of the pairs of mice was tested as on day 1.

Experiment 3. The third experiment investigated the effects of ethanol on the behavior of mice in the social interaction test. Only a low lighting condition was used. Pairs of mice were randomly allocated to each of the following groups: control (distilled water, $n=10$ pairs), and ethanol 0.8 g/kg ($n=10$ pairs), 1.6 g/kg ($n=10$ pairs) and 2.4 g/kg ($n=9$ pairs). Both water and ethanol were administered intraperitoneally in an injection volume of 10 ml/kg. It should be noted that concentration dependent effects of ethanol have been reported in a study using higher doses of ethanol (Gilliam and Collins 1983), and it is possible that differences in concentration may alter the behavior of mice in this experiment. However, in studies in which the dose of ethanol has been varied by varying the injection volume we have failed to find qualitative differences in behavioral responses to these lower doses of ethanol (unpublished observations). Thirty minutes after treatment the social behavior was tested as in experiment 1. The following day each mouse was familiarized with the apparatus in an undrugged state, and on day 3 the social behavior was again scored following drug treatment.

Experiment 4. Since Krsiak (1976) and Miczek and O'Donnell (1980) reported an increase in aggression by 0.4 g/kg ethanol, the effect of this dose on social interaction was tested in experiment 4 using the same paradigm used in experiment 3. Thus, ten pairs of mice received an IP injection of 0.4 g/kg ethanol (10 ml/kg) and eight pairs received distilled water.

Experiment 5. In experiment 1 the mice which were isolated for 10 days turned out to be the most aggressive. Since high doses of ethanol failed to decrease aggressive behavior in mice isolated for 5 days (which showed low basal levels of aggression), the effect of 0, 0.4, 0.8, 1.6 and 2.4 g/kg ethanol on mice being isolated for 10 days was studied. Ten pairs of mice in each treatment group were used, and they were tested only in an unfamiliar arena under a low lighting level. Ethanol was given as in experiment 3.

Statistical analysis. Data for the effect of isolation period, lighting conditions, and ethanol on social interaction (active social interaction + overt aggression) and motor activity were analysed using one-way analysis of variance or two-way analysis of variance with repeated measures. Between-group comparisons were made using Dunnett's multiple comparison statistic. All data concerning aggressive behavior (overt aggression and threat) – the time spent in it and the latency to first attack – were analysed using Kruskal-Wallis one-way analysis of variance. In experiments 2, 3 and 4 aggressive behavior on days 1 and 3 was analysed together. Between group comparisons were made using Dunn's procedure (Kirk 1968). The correlations between different observers and test-retest correlations were made using Spearman's test.

Results

The test-retest correlation of 21 pairs of mice scored by the same observer was 0.93. The correlation between two different observers scoring the same pairs of mice was also high (0.95).

Experiment 1

The results of experiment 1 are shown in Fig. 1. There was a significant main effect of isolation on the total time spent in social interaction [$F(5,91)=11.39$, $P<0.0001$], the longer the period of isolation, the greater the time spent interacting. In contrast, locomotor activity did not differ across the various groups (see Fig. 1).

The time spent in aggressive behavior was higher in mice isolated for 2–20 days than in mice isolated for a shorter time [$H(5)=34.2$, $P<0.0001$, see Table 1]. There was very little aggressive behavior in non-isolated mice or mice that were isolated for only 1 day. The latency to first attack failed to distinguish between the various periods of isolation (data not shown).

Experiment 2

There was a significant test day × lighting condition interaction in the analysis of the time spent in active social interaction [$F(1,14)=10.36$, $P<0.007$] (Fig. 2). When tested in an unfamiliar arena, the mice in the high light spent less time in social interaction than the mice in low light ($P<0.05$). After familiarization, however, both groups showed similar amounts of social interaction. That is, the mice tested in high light conditions increased the time spent in active social interaction from day 1 to day 3 ($P<0.01$), but the mice of low light conditions did not.

Motor activity was higher in mice tested in low light than in mice tested in high light [$F(1,14)=27.96$, $P<0.0001$]. There was also a main effect of familiarity [$F(1,14)=21.31$, $P<0.0004$], mice having lower activities on

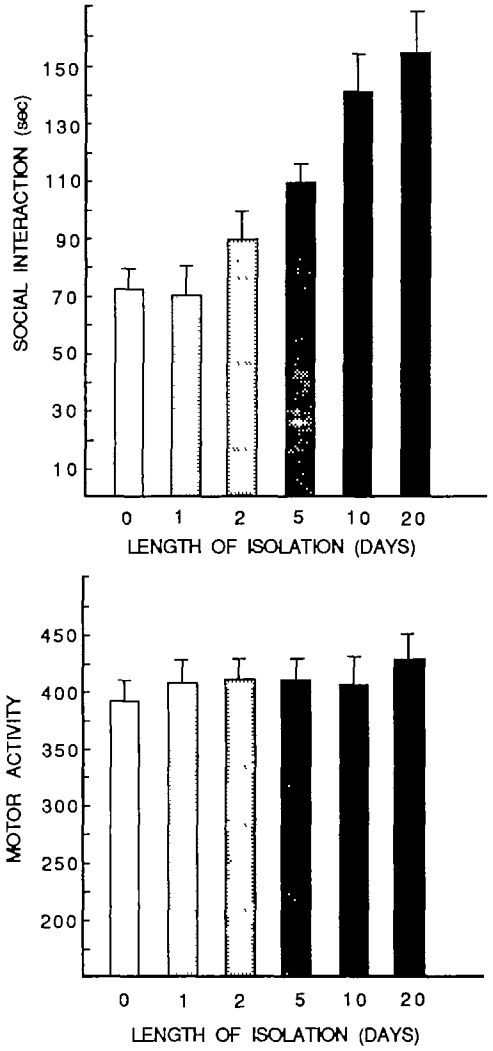

Fig. 1. The time spent in active social interaction (*top*) and the locomotor activity scores (*bottom*) of mice isolated for 0–20 days. Values are means ±SEM, $n = 12$–18 pairs per group

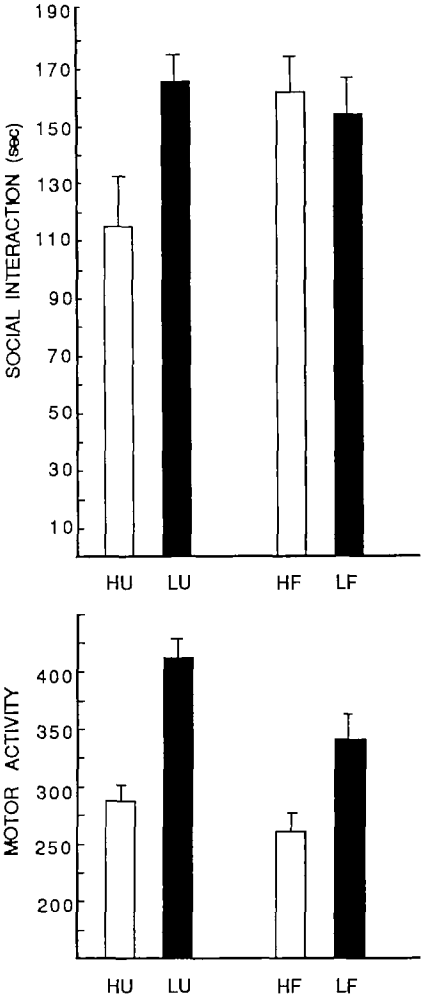

Fig. 2. The effect of high (*H*, *open columns*)) and low (*L*, *solid columns*) lighting conditions and unfamiliarity (*U*) and familiarity (*F*) with the testing arena on the time spent by pairs of mice in active social interaction (*top*) and locomotion (*bottom*). Values are means ±SEM, $n = 8$ pairs per group

Table 1. Aggressive behavior in mice isolated for 0, 1, 2, 5, 10 or 20 days. Medians (and range) of the time spent in aggressive behavior and the percentage of pairs showing aggressive behavior are shown

Length of isolation	*N*	Time aggression (s)	% of pairs showing aggression
0	18	0 (0–1.1)	5.6
1	16	0 (0–10.4)	12.5
2	19	0 (0–81.2)*	42.1
5	19	0 (0–66.1)**	47.4
10	13	29.3 (0–131.8)***	92.3
20	12	17.9 (0–106.3)***	66.7

Significantly different from non-isolated mice * $P < 0.02$, ** $P < 0.01$, *** $P < 0.001$

day 3 (when they were familiar with the apparatus) than on day 1 (when they were unfamilar, see Fig. 2).

The time spent in aggressive behavior (Table 2) and the latency to first attack did not differ between the groups (data not shown). Both in low and high light conditions mice tended to be more aggressive on day 3 than day 1, but the increase was not significant.

Experiment 3

In the third experiment, there was a significant departure from homogeneity of variance in the data for the time spent in social interaction ($P < 0.01$, Hartley's test). These scores were successfully transformed by a log transformation prior to the analysis of variance.

There was a significant interaction between ethanol and testing day [$F(3,35) = 7.09$, $P < 0.001$]. In Fig. 3 it can be seen that the mice which received vehicle increased the amount of social interaction from day 1 to day 3 ($P < 0.01$) but this effect decreased with increasing doses of ethanol, such that mice that received the highest ethanol dose spent less time interacting on day 3 than on day 1 ($P < 0.05$). After allowing for the interaction, there was still a significant main effect of ethanol [$F(3,35) = 43.7$, $P < 0.0001$]. In Fig. 3 it can be seen that ethanol caused a dose-related decrease in the total time spent in social interaction.

There was also a significant ethanol × familiarity interaction in the analysis of the locomotor activity scores

Table 2. Aggressive behavior under low and high lighting conditions of mice isolated for 5 days. Medians (and range) of the time spent in aggressive behavior and the percentage of pairs showing aggressive behavior are shown. Number of pairs per group = 8

Light condition	Time aggression (s)		% of pairs showing aggression	
	Unfamiliar	Familiar	Unfamiliar	Familiar
Low	0 (0–51.5)	0.3 (0–81.6)	37.5	50.0
High	0 (0–1.1)	0.2 (0–58.2)	25.0	50.0

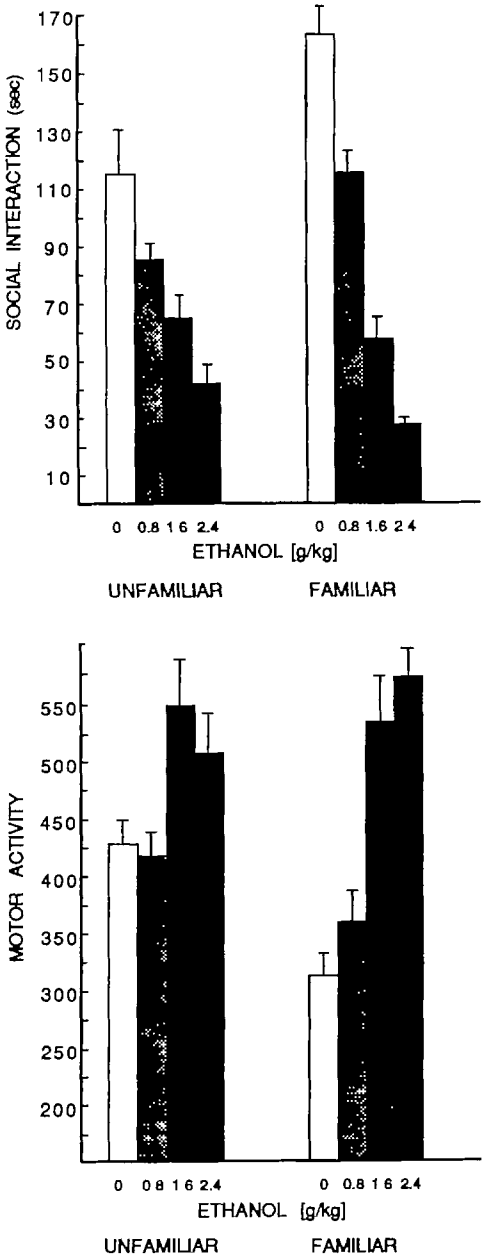

Fig. 3. The effect of ethanol (0–2.4 g/kg) on the time spent in active social interaction (top) and on locomotor activity (*bottom*) by pairs of mice previously isolated for 5 days and tested under unfamiliar (*left*) and familiar (*right*) testing conditions. Scores are means ±SEM, $n = 9$ or 10 pairs per group

Table 3. Aggressive behavior of mice isolated for 5 days and tested 30 min after treatment with ethanol (0–2.4 g/kg). The medians (and range) of the time spent in aggressive behavior and the percentage of pairs showing aggressive behavior are shown. Number of pairs per group = 9–10

Treatment	Time aggression (s)		% of pairs showing aggression	
	Unfamiliar	Familiar	Unfamiliar	Familiar
Vehicle	0 (0–1.1)	0.4 (0–40.0)	40.0	60.0
Ethanol				
0.8 g/kg	0.6 (0–22.9)	1.3 (0–23.6)	80.0	100.0
1.6 g/kg	0 (0–4.2)	0 (0–3.4)	70.0	70.0
2.4 g/kg	0 (0–5.7)	0 (0–0.9)	33.3	22.2

[$F(3,35) = 8.4$, $P < 0.0005$]. In Fig. 3 it can be seen that the animals that received the vehicle or the low dose of ethanol had lower motor activities on day 3 than on day 1, but mice that received the highest dose of ethanol tended to have higher motor activities on day 3 than on day 1. There was a significant main effect of ethanol on motor activity [$F(3,35) = 14.9$, $P < 0.0001$], and Fig. 3 shows that this was due to the motor stimulant action of the two highest doses.

Table 3 shows the effects of ethanol on aggressive behavior. There was a signficant effect of treatment on the time spent in aggressive behaviors [$H(3) = 17.37$, $P < 0.0006$]. Ethanol exerted a biphasic effect, the lowest dose increasing the duration of aggressive behavior ($P < 0.02$). Animals that received the higher two doses did not exhibit further increases in aggression, but spent less time in aggressive behavior (behaving like the controls). The latency to first attack showed a similar biphasic pattern of results (i.e., ethanol 0.8 g/kg decreased the latency to the first attack, $P < 0.001$) [$H(3) = 15.64$, $P < 0.002$] (data not shown).

Experiment 4

Ethanol (0.4 g/kg) did not affect either the time spent in social interaction or motor activity. Motor activity, however, decreased from day 1 to day 3 [$F(1,16) = 6.59$, $P < 0.03$], see Fig. 4.

The time spent in aggressive behavior [$H(1) = 5.5$, $P < 0.02$] was greater in the mice treated with 0.4 g/kg ethanol than in the vehicle-treated mice (see Table 4).

Experiment 5

In mice which were isolated for 10 days prior to the test there was a significant effect of ethanol on the time spent in social interaction [$F(4,45) = 5.64$, $P < 0.005$]. In Fig. 5 it can be seen that this was due almost entirely to the reduction in social interaction caused by the 2.4 g/kg dose. Due to a hardware fault motor activity scores were unavailable in this experiment.

There was also a significant effect of treatment on the time spent in aggressive behavior [$H(4) = 23.18$, $P < 0.0001$]. Table 5 shows that the two lower doses of ethanol increased, but the two higher doses decreased the duration of aggressive behavior.

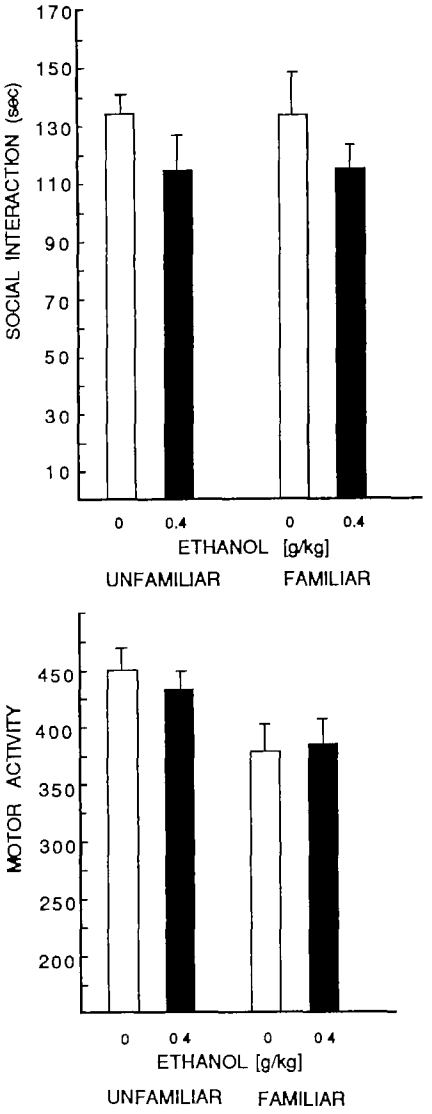

Fig. 4. The effect of ethanol (0.4 g/kg *solid columns*) or its vehicle (*open columns*) on the time spent by pairs of mice in active social interaction (*top*) and on locomotor activity (*bottom*) under unfamiliar (*left*) and familiar (*right*) testing conditions. Scores are means ±SEM, $n=8$ or 10 pairs per group

Table 4. Aggressive behavior of mice isolated for 5 days and tested 30 min after treatment with 0.4 g/kg ethanol. The medians (and range) of the time spent in aggressive behavior and the percentage of pairs showing aggressive behavior are shown

Treatment	N	Time aggression (s)		% of pairs showing aggression	
		Unfamiliar	Familiar	Unfamiliar	Familiar
Vehicle	8	13.1 (0–20.4)	6.6 (0–24.7)	75.0	100.0
Ethanol	10	29.1 (0.5–111.1)	25.3 (0–84.7)	100.0	90.0

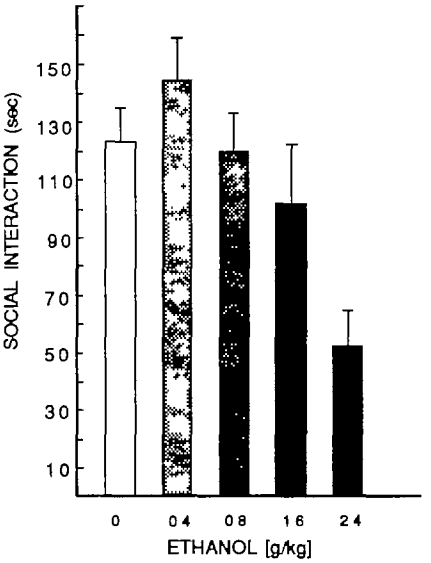

Fig. 5. The effect of ethanol (0–2.4 g/kg) on the time spent in active social interaction in an unfamiliar arena by pairs of mice isolated for 10 days. Values are means ±SEM, $n=10$ pairs per group

Table 5. Aggressive behavior of mice isolated for 10 days and tested in an unfamiliar environment 30 min after treatment with ethanol (0–2.4 g/kg). The medians (and range) of the time spent in aggressive behavior and the percentage of pairs showing aggressive behavior are shown. Number of pairs per group = 10

Treatment	Time aggression (s)	% pairs showing aggression
Vehicle	14.5 (0–51)	70.0
Ethanol 0.4 g/kg	45.0 (0–149)	80.0
0.8 g/kg	55.5 (0–103)	90.0
1.6 g/kg	0 (0–47)	20.0
2.4 g/kg	0 (0)	0

Discussion

The primary goal of the present study was to characterize a novel behavioral paradigm for assessing the social and aggressive behavior of mice, under testing conditions in which baseline levels of aggression are low. We used a paradigm similar to that used by File (1980) in rats, and found a number of similarities and several differences between the behavior of the NIH Swiss mice and those of rats in the social interaction test. In the studies of File (1980), the time spent in social interaction increased with increasing familiarity with the test arena, and was higher under low than under high lighting conditions. In the present experiments using mice the effect of familiarity was much less clear. In experiment 3 there was a significant increase in the time control mice spent interacting in the familiar arena. The size of the effect was not as great as has been observed in the rat version of the test (File 1980; File et al. 1984).

In experiments 2 and 4, under low lighting conditions there was no effect of familiarity. De Angelis and File (1979) noted in pilot experiments that the familiarity manipulation did not appear to work consistently in mice, and our more extensive investigations support this observation. In the present study the high lighting manipulation only decreased social interaction when mice were in the unfamiliar testing condition. De Angelis and File (1979) found that increasing

the light level decreased the social behavior of mice who were familiar with the test arena (but not with each other). Since our mice were also familiar with one another when tested in our "familiar condition", this might explain the discrepancy between the studies.

It may be noted that there is some variability in the behavior of the mice used in the current studies across the various experiments. Such variability is commonly observed in behavioral studies and emphasizes the importance of including a control group in each study.

Isolating mice has been shown to increase their aggressive behavior in other paradigms. In agreement with earlier studies (Brain 1976; Goldsmith et al. 1976; Cairns et al. 1985), experiment 1 showed that increasing the length of isolation increased the incidence of attacks. It should be noted that the incidence of aggressive behaviors was low in mice isolated for 5 days or shorter, with less than 50% of animals showing any aggression at all. This is most probably a result of the fact that animals were tested in a novel environment rather than in their home cage (cf Miczek and O'Donnell 1980). Furthermore, the total time spent in aggressive behavior was only a few per cent of the total time of social interaction.

In addition to altering the level of aggression, the length of isolation also affected the total time spent in social interaction. Social interaction increased with the duration of isolation. Interestingly, isolation failed to alter locomotor activity.

Ethanol exerted clear effects on both the total time in social interaction and on the time in aggressive behavior. The pattern was not the same on both these measures. All doses of alcohol tended to reduce the total social behavior in mice isolated for 5 days, whereas low doses of ethanol increased aggressive behavior. The aggression-reducing effects of ethanol were more clearly seen in mice isolated for 10 days, when baseline levels of aggression were higher. These results are consistent with those of Krsiak (1976), Miczek and O'Donnell (1980) and Berry and Smoothy (1985).

In earlier studies somewhat contradictory observations concerning the effect of ethanol on social behavior have been reported. According to Everill and Berry (1987) in a resident-intruder paradigm 2 g/kg ethanol reduced social investigative behavior in BALB/c mice but the same dose did not affect the social behavior of DBA/2 or C57BL/10 mice. Krsiak and Burgesova (1973) found that in rats tested in their home cage, 1.2–3 g/kg ethanol decreased all social behaviors they measured. In contrast, Smoothy and Berry (1986) found no change in total social behavior using a resident/intruder paradigm with Swiss-Webster or Tuck 'TO' mice. Krsiak (1976) found that only a 0.4 g/kg dose of ethanol reduced social behavior between pairs of outbred albino mice tested in a relatively novel environment. In this paradigm one mouse of each pair was housed differently to the other, and only one mouse received the drug treatment. The discrepancies between these different studies in the effect of ethanol on social behaviors is most probably due to the diversity of the procedures used.

In our study, the decreases in social interaction caused by the higher doses of ethanol occurred despite increases in motor activity. Thus, the decrease in social activities was not a consequence of a lowered motor capability but appears to be produced by the effect of ethanol on some more specific regulatory mechanisms.

Caution should be exercised in comparing the effects of the various manipulations on the locomotor activities of pairs of mice in the social arena with data obtained in other studies in which mice have been tested alone. Changes in social behavior may lead to changes in activity. For example, isolation has previously been shown to increase the locomotor activity of mice (e.g., Essman 1968) when tested individually in an activity box. However, in the present study no increase in motor activity was seen with isolation. Since we have found that isolated NIH Swiss mice do show increased locomotor activity when tested alone in a holeboard apparatus (in preparation), it would appear that locomotor activity changes observed in a social setting differ from those observed when animals are tested alone. In the present study, activity was lower under the high than in the low illumination level and was also lower when the test environment was familiar than when it was unfamiliar. These data parallel those of Nagy and Glaser (1970), of Middaugh et al. (1987) and of Crabbe et al. (1988).

In conclusion, the results of the present study show that environmental and pharmacological manipulations alter the social and aggressive behavior of NIH Swiss mice. It would appear that the social interaction test in its present form may not be suitable as a model of anxiety in the mouse, since the familiarity manipulation failed to reliably alter the total time animals spent in social interaction (cf. File 1980). Further, drugs which are known to increase anxiety (e.g., benzodiazepine receptor inverse agonists) failed to reduce the time mice spend interacting (Hilakivi and Lister, submitted for publication). Since basal levels of aggression are low, the paradigm is likely to prove useful in examining the effects of agents that increase aggressive behavior, and possibly for finding strains of mice with unusually high levels of aggressive behavior.

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