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Social Isolation Increases the Stimulatory Effect of Ethanol on Locomotor Activity

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PÄIVÄRINTA, P. *Social isolation increases the stimulatory effect of ethanol on locomotor activity.* PHARMACOL BIOCHEM BEHAV **36**(2) 401–403, 1990.—The stimulatory effects of low alcohol doses are of great interest because of their role in human drinking and their possible relation to reinforcement from alcohol. The preferred animal model for studying them is the mouse. The effects of various doses of ethanol on locomotor activity were now studied in both group-housed mice and in mice socially isolated for 36–44 weeks. The housing situation was found to have a strong influence: a large stimulatory effect was observed in isolated mice but little effect was seen in group-housed animals. The results suggest that socially isolated mice are more sensitive to the stimulatory effect of ethanol on locomotor activity.

Locomotor activity Social isolation Ethanol Mice

SOCIALLY isolated laboratory rodents are known to respond differently from their group-housed partners to a variety of psychoactive drugs. For example, the central nervous system (CNS) stimulant, amphetamine, induces a greater rise in locomotor activity in isolated than in group-housed mice (11,26), and is more toxic in socially isolated mice (6). On the other hand, CNS depressants show reduced effects in isolated rodents (7). The altered behavioral responses to drugs may stem from alterations in brain function due to social isolation. It has been shown that social isolation enhances the sensitivity and function of brain dopaminergic transmission (14, 19, 21, 24–26), but decreases serotonergic activity by reducing serotonin (5-HT) binding and turnover (10, 17, 24). Thus, the behavioral effects of drugs acting mainly through dopaminergic and/or serotonergic mechanisms might be expected to be different in socially isolated and group-housed animals.

The stimulatory effect of a nonsedative dose of ethanol on locomotor activity in mice (9,12) resembles that of a small dose of amphetamine. Both drugs are thought to increase locomotor activity by enhancing brain catecholaminergic transmission (5,23), perhaps particularly in the mesolimbic dopamine (DA) system (8). Furthermore a reverse tolerance or sensitization of the locomotor activating effect of both drugs has been described in mice (4,20).

The present study was designed to determine what influence, if any, single versus group housing has on the locomotor activity effect of lower doses of ethanol. If the locomotor stimulatory effect of ethanol is indeed dependent upon the same mechanism as the effect with amphetamine, ethanol also would be expected to increase the activity more in isolated mice.

METHOD

Apparatus

The locomotor activity was measured with a 10-channel static charge sensitive bed (SCSB) system, as described in detail elsewhere (22). In short, the method uses movement sensitive electrical mattresses to detect vertical body movement, and appropriate hardware and software for data acquisition and analysis. A Macrolon size III cage was placed on a SCSB, a mouse put in, and a styrofoam lid was placed on top of the cage. The system measured cumulative 3-min activity scores and indicated them as seconds of locomotor activity in 3 min. The "minimum locomotor activity signal interval" on the software was set to 250 msec (rather than 10 msec) since it now appears to give a better quantification of changes in locomotor activity.

Subjects

Male Swiss-Webster mice (Charles River, Kingston, NY) were used. The mice arrived at 6 weeks of age and were group-housed in Macrolon size III cages, 8–10 mice per cage. They were allowed to adapt for at least 3 weeks to the reversed 12-hr light-dark cycle with lights on at 11:30 p.m. Thereafter, half of the mice, randomly selected, were individually housed for 36–44 weeks in Macrolon size II cages. Behavioral trials were conducted during the dark period in the same room where the animals were kept. The animal room had a temperature of 22–26°C and a relative humidity of 40–60%. Food (Ewos, R3, Södertälje, Sweden) and water were available ad lib except during trials.

Behavioral Trials

Seventeen mice isolated for 36–44 weeks [age 46–54 weeks, weight 49.5 ± 6.2 g (mean ± SD)] and 17 group-housed mice of the same age (weight 44.6 ± 2.4 g) were habituated to the recording cages 4 hours before injections at 2 p.m. Each animal was treated and tested 4 times, after injection with saline, 0.5 g/kg ethanol, 1 g/kg ethanol and 2 g/kg ethanol, with the order of treatment being randomized. Ten mice were tested at a time. Solutions were administered IP in a volume of 0.1 ml/10 g of body weight. Only one trial per mouse was conducted each week. A baseline recording started one hour before the injections; the test recording started immediately after the injections and lasted one hour.

Statistics

For statistical analysis the mean baseline activity (15 min before injection) of each mouse was subtracted from its activity counts during each test. These activity changes caused by each ethanol dose were compared at each time point (cumulative 3 min scores) using a one-way repeated measures ANOVA followed by Fisher's LSD test to find out whether there existed statistically significant differences in ethanol-induced activities between isolated and group-housed mice. Since the distributions of the activity scores were somewhat skewed, the scores were also analyzed using the Wilcoxon Signed-Rank test. The same statistics were also used to see if different doses of ethanol caused a significant change when compared to saline treatment. Regression analysis was used to see if the last baseline values correlated with first postinjection values. Since the isolated mice were significantly heavier than group-housed mice ($p<0.013$), regression analysis was used to find out if animal weight correlated with first postinjection values within the 8 treatment groups.

RESULTS

The statistical results from Wilcoxon Signed-Rank tests were essentially the same as those from ANOVAs. The isolated mice showed much more stimulatory effect from ethanol than the group-housed mice did (Fig. 1). With 1 g/kg ethanol, the difference was significant at each time point during the first 27 min after injection. The difference was also significant at the first time point after 0.5 g/kg. No significant differences were found with 2 g/kg ethanol between isolated and group-housed mice. Generally, whenever the isolated mice showed significantly more ethanol-induced activity than group-housed ones, they also showed significantly higher activity after ethanol than after saline. However, no dose of ethanol caused a significant rise in locomotor activity in group-housed mice above that after saline, although there was a tendency for increased activity after 2 g/kg (Fig. 1B). Before injections (during the 15 min before the injections, as shown in Fig. 1) isolated mice were significantly more active than group-housed mice ($p<0.001$). Because the mean baseline activity of the isolates was higher than that of the group-housed mice, a separate analysis was conducted on the 8 isolates with the lowest baselines compared to the 8 group-housed animals with highest baselines. The mean baseline activities of these subgroups were essentially the same; nevertheless, the 8 isolates showed significantly more increase in activity than the 8 group-housed mice at each time point during the first 24 min after 1 g/kg ethanol. The independence of the stimulatory effect from the baseline activity was also illustrated by the low correlation between these values in the entire isolate group ($r=.2$, $p>0.4$). No significant correlations were found between body weight and the first postinjection activity scores in any of the 8 treatment groups; they ranged from $r=.007$, $p>0.98$ to $r=.44$, $p>0.07$.

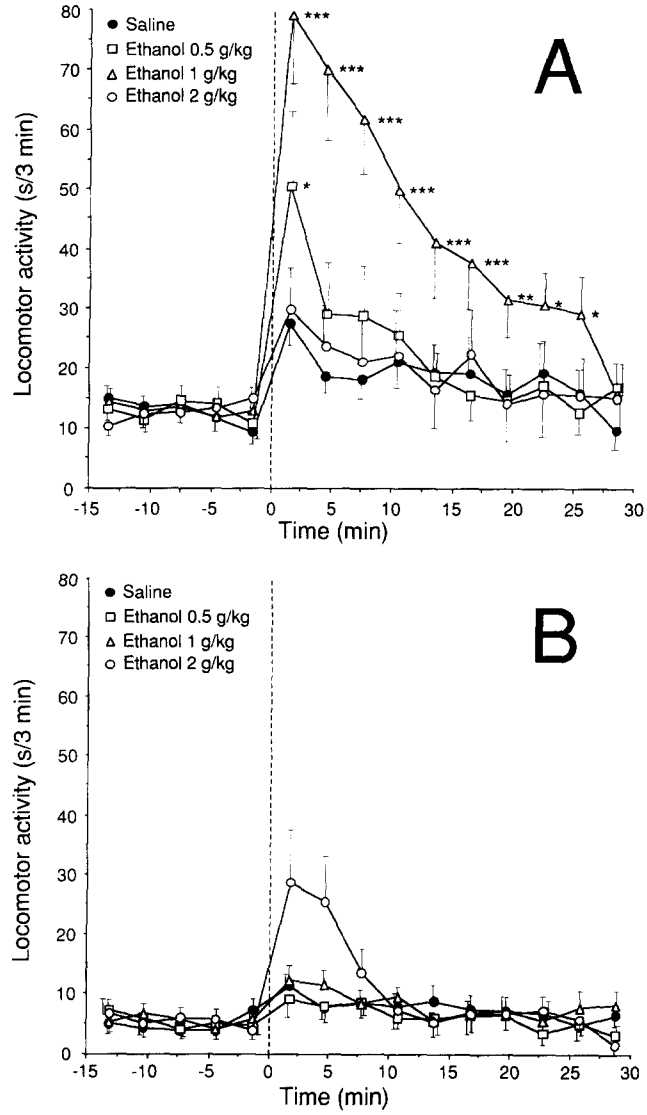

FIG. 1. Effects of ethanol on locomotor activity in socially isolated mice (A) and in group-housed mice (B). Shown are the mean activities 15 min before the injections and 30 min after the injections. At time = 0 is a nonrecorded interlude of 2 min during which the injections were given. N = 17. Significance of the difference in ethanol-induced activity changes between isolated and group-housed mice at equal doses: $*p<0.05$, $**p<0.01$, $***p<0.001$ (Fisher LSD).

DISCUSSION

The prior housing situation for mice was found to have a strong influence on the stimulatory effect from moderate doses of ethanol. A large stimulatory effect on locomotor activity was shown by individually housed mice after 1 g/kg ethanol and a smaller but still significant stimulation after 0.5 g/kg. In contrast, these doses had practically no effect on the activity of group-housed mice.

The ability of ethanol to produce locomotor stimulation is known to be age-dependent with old mice showing no stimulation (9). Although this cannot account for the difference between isolates and group-housed mice since both were the same age (about one year), it could be related to the failure to find a stimulatory effect in the group-housed animals. It should be noted

that the duration of isolation was very long: the mice had spent about 80% of their lives in individual cages. Although the animals all were healthy, this long period of differential housing could have produced profound changes. The observed differences in baseline activity and body weight, however, do not appear to account for the difference in the stimulatory effect.

Based on studies done with group-housed mice, there is evidence that the locomotor stimulatory effect of ethanol is linked to the activation of the catecholamine (CA) system of the brain (9,23), and perhaps particularly to the mesolimbic DA system (8). A widely accepted view today is that acute ethanol treatment first (within the first hour) induces an increase in the levels, synthesis, and release of CAs in the brain and then induces alternating cycles of decreased and increased CA activity, gradually dampening and returning to baseline activity after several hours (1). Social isolation is known to enhance the dopaminergic transmission of the brain. The turnover of DA increases (19,24) as does DA receptor binding (14,25). Single neurons become more sensitive to DA (21). It has been suggested that social isolation induces a state of DA autoreceptor subsensitivity (26). Thus, one explanation for the greater stimulatory effect after ethanol observed now in isolated mice could be that they have an enhanced functioning of dopaminergic system which mediates the stimulatory effect of ethanol.

Isolation, however, also affects the serotonergic system but causes a decrease in 5-HT turnover [see (17,24)]. The 5-HT system is implicated in the effects of amphetamine (13,15), for which similar differences in locomotor stimulation between isolates and group-housed animals are found (11, 18, 26). Consequently, a role for 5-HT (2) or for the well-established interaction between DA and 5-HT (3,16) cannot be excluded in the ethanol effects.

In conclusion, long-term isolated mice were found to be very sensitive to the locomotor activating effect of small doses of ethanol. An additional study is needed of the mechanism of action, but presently it is at least possible to hypothesize that the strong stimulatory effect in isolates was caused by combined additive effects of ethanol and isolation increasing activity in the brain DA system and perhaps decreasing activity in the 5-HT system.

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