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The importance of housing conditions on behavioral sensitization and tolerance to ethanol

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Abstract

The differential outcomes of social isolation and crowding environment on the effects of single or repeated administration of ethanol on open-field behavior were examined in female mice. Whereas housing conditions did not alter the increase in locomotor activity induced by ethanol single administration, behavioral sensitization (a progressive increase of a drug effect following repeated drug administration) to the locomotor activating effect of ethanol was significantly greater in crowded mice as compared to isolated and control groups. Single administration of ethanol significantly decreased rearing frequency and increased immobility duration, there being tolerance to these ethanol behavior effects after repeated treatment. Social isolation attenuated the increase in immobility behavior induced by single administration of ethanol and potentiated the tolerance of ethanol-induced rearing decrease, verified after repeated treatment. These results point out that both sensitization and tolerance to the behavioral effects of ethanol can be critically influenced by housing conditions.

Keywords: Ethanol; Behavioral sensitization; Housing; Social isolation; Crowding; Mice

1. Introduction

While there is tolerance to many of the effects of ethanol and other drugs of abuse, drug addiction is characterized by uncontrollable drug craving and the addictive behavior has been linked to the phenomenon of behavioral sensitization (Wise and Bozarth, 1987; De Vries et al., 1988; Piazza et al., 1990). According to the theory of addiction proposed by Robinson and Berridge (1993) persistent neuroadaptations that occur as a consequence of drug exposure are manifested by the phenomenon of behavioral sensitization. This phenomenon is defined as a progressive increase of a drug effect following repeated drug administration.

There are several factors that may alter the effects of drugs of abuse. Studies of drug dependence and addiction cannot ignore the importance of the environmental conditions on the development of behavioral sensitization. Indeed, it has been demonstrated that environmental cues can be conditioned stimuli for drug-like conditioned responses, potentiating the development of behavioral sensitization (Hayashi et al., 1980; Costa et al., 2001; Frussa-Filho et al., 2004; Chinen et al., in press). Although sensitization to the locomotor-activating effect of ethanol and other drugs of abuse has been observed when drug injections are not paired with the observation environment

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(Bellot et al., 1996, 1997; Costa et al., 2001; Chinen et al., in press), this environmental modulation of sensitization is specially interesting because it is well known that environmental cues trigger craving and drug-seeking behavior in humans (Childress et al., 1986; Niaura et al., 1988; Carter and Tiffany, 1999). Within this context, another determining factor of behavioral sensitization induction may be "homogeneity of treatment". We have observed in our experiments that ethanol-, morphine- or amphetamine-treated mice sharing the cage with their pairs being treated with the same drug show a more marked behavioral sensitization than the same drug-treated mice sharing the cage with animals receiving saline (Araujo et al., submitted for publication).

An additional important factor that has to be considered in behavioral sensitization studies is the housing density. It has been demonstrated that social isolation alters the neuronal function of dopaminergic and serotonergic system of mice (Oehler et al., 1980; Matsuda et al., 2001), evokes changes in sympathetic neurotransmission in mice (D'Arbe et al., 2002), potentiates the postsensitization conditioned locomotion to cocaine in mice (Michel and Tirelli, 2002) and induces alterations in dopamine D_2 receptors density, which is modified by ethanol treatment (Rilke et al., 1995).

Whereas sensitization to the locomotor activating effect of ethanol has been extensively demonstrated (Phillips et al., 1995, 1997; Quadros et al., 2002), the single administration of ethanol can produce a decrease in other parameters of rodents' motor activity such as rearing behavior, which seems to undergo to tolerance rather than sensitization (Smoothy and Berry, 1985; Pohorecky et al., 1989). In this respect, the quantification of open-field behavior is a simple and effective experimental paradigm to evaluate simultaneously the effect of drugs on different aspects of the behavioral repertoire of both rats (Frussa-Filho and Palermo-Neto, 1988; Maiolini et al., 1994; Abílio et al., 1999, 2003) and mice (Conceição and Frussa-Filho, 1996; Queiroz et al., 2002; Araujo et al., 2004).

Studies with housing conditions and drinking have shown that crowded rats consume more ethanol than isolated animals (Hannon and Donlon-Bantz, 1975), which drink more than the control (4 animals per cage) group (Wolffgramm, 1990). Within this context, it would be expected that housing conditions could modify the stimulant effect of a single administration of ethanol and its sensitization after repeated treatment. However, the relationship between housing conditions and behavioral sensitization (or tolerance) to ethanol is still obscure. In the present study, we have examined the influence of different housing conditions (isolation, crowding) on the effects of single or repeated ethanol administration on these different parameters of mice's open-field behavior: locomotion and rearing frequencies and immobility duration.

2. Materials and methods

2.1. Subjects

Three month-old female EPM-M1 mice (30–40 g) from our own colony were used. Until the beginning of experimental procedure, the animals were housed in groups of 15 in polypropylene cages ($41 \times 34 \times 16.5$ cm^3) with free access to food (Purine standard powered rat chow) and water in a room with controlled temperature (22 ± 1 °C) and under a 12 h light/ dark cycle with lights on at 6:30 a.m. All experiments took place between 08:00 A.M. and 11:00 A.M. The animals were maintained and used in accordance with the guidelines of the Committee on Care and Use of Laboratory Animal Resources, National Research Council, USA.

2.2. Drugs

Ethanol absolute (Merck) was diluted in saline to a concentration of 0.18 g/ml and given i.p. in a volume of 10 ml/kg of body weight in order to obtain a dose of 1.8 g/kg. Saline was used as control solution.

2.3. Experimental design

2.3.1. Experiment I

Effects of different population densities on open-field behavior of mice repeatedly treated with ethanol.

Five days before the beginning of drug treatment, the animals were placed and maintained in $30 \times 20 \times 12.5$ cm^3 cages alone (isolated group, ISO), in groups of 5 (G5) or in groups of 15 (G15). All mice were treated with saline solution (S) or 1.8 g/kg ethanol (E) once a day for 21 days. Twenty-four hours after the last injection, the animals were challenged with saline or 1.8 g/kg ethanol. Thus, the groups ($n = 15$) were as follows: SS-ISO, SE-ISO, EE-ISO, SS-G5, SE-G5, EE-G5, SS-G15, SE-G15 and EE-G15. Mice were transported to the observation room where they were allowed to habituate for 1 h. Five minutes after the challenge injection, each animal was placed in the center of an open-field arena (40 cm in diameter), which was divided in 19 segments and surrounded by a 50 cm high wall. During the observation, hand-operated counters were used to quantify locomotion (number of inter-segments lines crossed) and rearing (number of times the animal stood on hind legs) frequencies, and stopwatches were used to quantify duration of immobility (total of seconds of lack of movement) and grooming (total seconds of mouth or paws on the body and on the head). The observation was conducted blind. The dose and schedule of ethanol treatment were chosen on the basis of previous studies of our research group which succeeded to demonstrate behavioral sensitization to ethanol in mice (Bellot et al., 1996; Camarini et al., 2000; Quadros et al., 2002).

2.3.2. Experiment II

Effects of different population densities on blood ethanol levels of mice repeatedly treated with ethanol.

Five days before the beginning of drug treatment, the animals were placed and maintained in $30 \times 20 \times 12.5$ cm^3 cages alone (ISO, $n=15$), in groups of 5 (G5, $n=15$) or in groups of 15 (G15, $n=15$). All mice were treated with 1.8 g/kg ethanol once a day for 22 days. Five minutes after the last injection, a 20-μl blood sample was collected from the caudal vessel of each mouse. Samples were prepared for analysis by diluting one part of blood with one part 0.02% aqueous *n*-propanol, as internal standard. The samples were analyzed for ethanol concentration by gas chromatography using the headspace technique. The analyses were performed using a 6 ft by 1.8 mm i.d. Porapak QS, 80–100 mesh; column at 200 °C with flame ionization detection. Nitrogen served as the carrier gas at a flow rate of 40 ml/min. Concentrations of ethanol were determined from a previously constructed aqueous calibration curve identically prepared.

2.4. Statistical analysis

Data were analyzed by one or two-way analysis of variance (ANOVA) followed by Duncan's test. A probability of $p<0.05$ was considered to show significant differences for all comparisons made.

3. Results

3.1. Experiment I

Effects of different population densities on open-field behavior of mice repeatedly treated with ethanol.

Concerning locomotion frequency, two-way ANOVA revealed significant effects of population density (ISO, G5 or G15) [$F(2,133)=3.32$, $p<0.05$] and of treatment (SS, SE or EE) [$F(2,133)=87.14$, $p<0.001$], but no population density × treatment interaction effect was found. As displayed in Fig. 1A, post-hoc analysis revealed that all SE-treated groups presented locomotion frequencies significantly higher than respective SS-treated control groups, demonstrating the acute effect of ethanol in all housing situations. In addition, all EE-treated groups presented locomotion frequencies significantly higher than respective SS and SE-treated groups, showing the development of ethanol-induced behavioral sensitization in all housing situations. Furthermore, EE-G15 group presented locomotion frequency significantly higher than EE-ISO and EE-G5 groups, revealing that crowding environment potentiates ethanol-induced behavioral sensitization, when evaluated by locomotion frequency.

Regarding rearing frequency, two-way ANOVA revealed significant effects of population density [$F(2,133)=8.23$; $p<0{,}001$] and of treatment [$F(2,133)=43.46$, $p<0.001$], but no population density × treatment interaction effect was found. As displayed in Fig. 1B, post-hoc analysis revealed that all SE-treated groups presented rearing frequencies significantly lower than respective SS-treated control groups. In addition, all EE-treated groups presented rearing frequencies significantly higher than respective SE-treated groups, showing that the inhibitory effect of single ethanol administration was tolerated in repeatedly treated animals. Furthermore, EE-ISO group presented rearing frequency significantly higher than EE-G5 and EE-G15 groups, revealing that this tolerance was more intense in the isolated group.

With respect to immobility duration, two-way ANOVA revealed only a significant effect of treatment [$F(2,133)=14.49$; $p<0{,}001$]. As displayed in Fig. 1C, all SE-treated groups presented duration of immobility higher than respective SS-treated control groups, reaching statistical

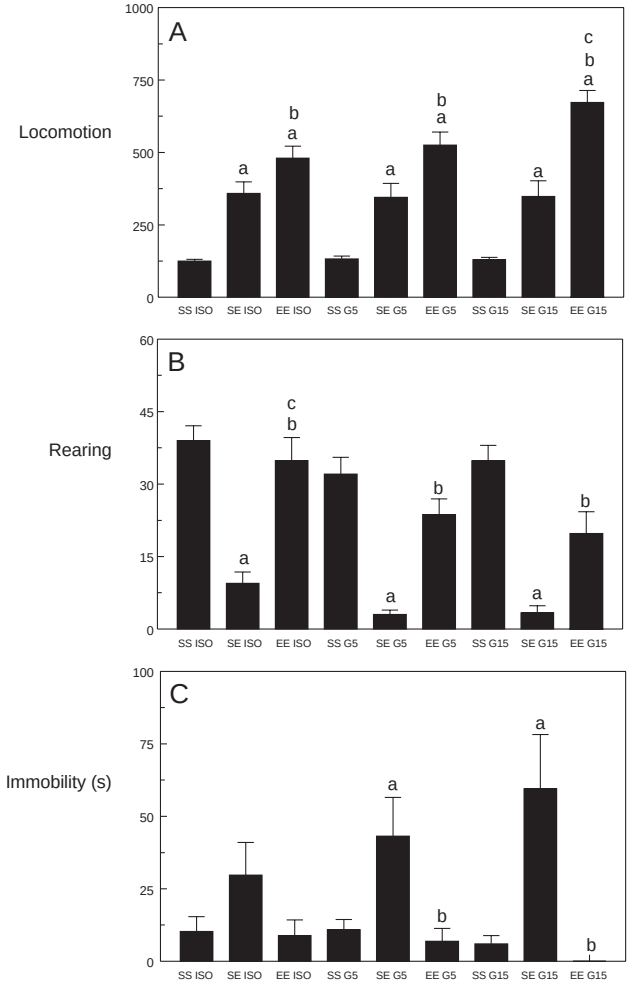

Fig. 1. Mean±SE of locomotion (A) and rearing (B) frequencies and immobility duration (C) of mice maintained isolated (ISO), in groups of 5 (G5) or in groups of 15 (G15) challenged with saline (S) or 1.8 g/kg ethanol (E) 24 h after a repeated treatment with saline or 1.8 g/kg ethanol (two-way ANOVA followed by Duncan's test). [a]$p<0.05$ compared to SS-treated group submitted to the same housing condition. [b]$p<0.05$ compared to SE-treated group submitted to the same housing condition. [c]$p<0.05$ compared to groups submitted to the same treatment and different housing conditions.

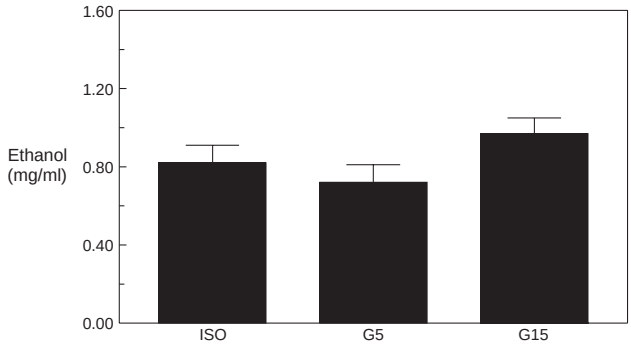

Fig. 2. Mean ± SE of blood ethanol levels of mice maintained isolated (ISO), in groups of 5 (G5) or in groups of 15 (G15) repeatedly treated with 1.8 g/kg ethanol (two-way ANOVA).

significant levels in G5 and G15 groups. In addition, all EE-treated groups presented duration of immobility lower than respective SE-treated groups (reaching statistical significant levels in G5 and G15 groups), showing that this effect of single ethanol administration was tolerated in repeatedly treated groups.

3.2. Experiment II

Effects of different population densities on blood ethanol levels of mice repeatedly treated with ethanol.

As shown in Fig. 2, no differences in blood ethanol levels were found among the experimental groups.

4. Discussion

The major findings of the present study were that while crowding housing condition potentiated the sensitization phenomenon to the locomotor activating effect of ethanol, social isolation potentiated the tolerance to the rearing inhibitory effect of the drug and attenuated the increase in immobility duration induced by single ethanol administration. This critical influence of housing conditions on the behavioral effects of single and repeated ethanol administrations was not correlated with blood ethanol concentration, since housing condition did not alter this measurement.

Regardless of the population density (control, crowding or isolation) the 1.8 g/kg dose of ethanol was effective in inducing locomotor activating effect and behavioral sensitization following repeated ethanol treatment. Stimulant effect of alcohol on motor activity of the SE group did not differ with housing density. Our findings differ from Päivärinta (1990) study, which showed that social isolated mice are more sensitive to the locomotor activating effect of single ethanol administration. The reasons for these inconsistencies are likely due to methodological differences, including the strain and sex of subjects used and ethanol doses. Also, in our study each animal was tested only once for the investigation of the effects of a single ethanol administration whereas in the other study cited each mouse was treated and tested 4 times after injection with saline or different ethanol doses, with the order of treatment being randomized.

The locomotor activity results showed that the magnitude of behavioral sensitization was greater in crowded animals compared to both control and isolated mice. Odd housing conditions such as crowding or social isolation are effective stressor factors (Gamallo et al., 1986) and several studies have shown the influence of stress on behavioral sensitization (Phillips et al., 1997; Prasad et al., 1998; Pacchioni et al., 2002; Barr et al., 2002).

Housing conditions have been used in several studies as a model of psychological stress (Mashaly et al., 1984; Gamallo et al., 1986; Brown and Grunberg, 1996). Stress may disturb the system's homeostasis and induce various disorders. Several types of stresses influence the hypothalamic-pituitary-adrenal axis, resulting in increases in the levels of glucocorticoids and catecholamines in the circulating blood (Carrasco and Van de Kar, 2003).

Psychostimulants that induce behavioral sensitization, such as amphetamine and cocaine, activate the hypothalamo-pituitary-adrenal (HPA) axis (Knych and Eisenberg, 1979; Budziszewska et al., 1996) and chronic amphetamine treatment induces an 'anxiogenic-like' response when animals are tested in the elevated plus-maze (Cancela et al., 2001). Alcohol administration also enhances the activity of the HPA axis of both male and female rats, with females secreting more adrenocorticotropin (ACTH) and corticosterone than males in response to alcohol (Ogilvie and Rivier, 1997). Both social isolation and crowding increases the adrenal function in rats (Gamallo et al., 1986).

Within this context, one could suggest that only crowding environment but not social isolation was a marked stressful factor capable to induce cross-sensitization with the stimulant effect of ethanol or to potentiate the behavioral sensitization to ethanol. However, contradicting this hypothesis, crowding condition did not alter the stimulant effect of a single ethanol administration. In addition, it must be remembered that female mice were used in the present experiments and it has been reported that male rats have higher corticosterone levels under crowded conditions whereas female rats have higher levels when individually housed (Brown and Grunberg, 1995). Furthermore, two-way analysis of variance revealed no significant housing condition effect for grooming behavior (data not shown), a behavioral parameter elicited by stressful conditions (Kalueff and Tuohimaa, 2004). Thus, it is possible to hypothesize that the dependence power of the drug may be potentiated in an environmental condition where a crowded population is experiencing the same addictive drug.

Several studies have demonstrated that social isolation alters dopaminergic transmission. It has been found increase in dopamine receptor binding (Guisado et al., 1980), in DA and 5-HT turnover (Lasley and Thurmond, 1985) and enhancement in cortical DA release and the brain DA

receptor function (Matsuda et al., 2001). Other few studies have reported the effects of crowding on dopaminergic transmission, with high-density cages increasing the dopamine release in diencephalon (Holladay and Edens, 1987) and increasing striatal elimination of dopamine in rats (Lokiec et al., 1981).

We have demonstrated that behavioral sensitization to ethanol increases D_2 receptor binding in the anterior caudate-putamen of mice (Souza-Formigoni et al., 1999) and the role of dopaminergic system on behavioral sensitization to drugs of abuse is very well established (Vanderschuren and Kalivas, 2000). The present study was not aimed to address the involvement of dopamine transmission on the influence of housing condition on the behavioral effects of single or repeated ethanol administration. This concern notwithstanding, this is an interesting working hypothesis to be systematically investigated.

With regard of rearing parameter, our results found that single administration of ethanol depressed rearing frequency independently of housing conditions, which was reverted with the chronic treatment. This result is in agreement with studies showing a depressor effect of acute ethanol on this parameter (Smoothy and Berry, 1985; Pohorecky et al., 1989) followed by a tolerant effect with chronic ethanol administration. Another likely explanation resides on the behavioral competition between locomotor activity and rearing. The decrease in rearing frequency might be due to the increase in locomotor activity found after single ethanol administration.

Here, rearing frequency also showed distinct behavioral features between the crowded and the isolated mice following chronic ethanol administration. While crowding potentiated the behavioral sensitization to the locomotor activating effect of ethanol, social isolation potentiated the tolerance to the rearing depressive effect of ethanol. Within this context, while locomotion and rearing have been related to the mesoaccumbens and nigrostriatal dopaminergic systems, respectively (Al-Khatib et al., 1995), rearing has also been associated with GABAergic transmission in the hippocampus (Sierra-Paredes and Sierra-Marcuno, 1996; Hannesson et al., 2001). Thus, the possibility is raised that crowding and social isolation differently influence the effects of repeated ethanol administration in these specific brain areas.

In relation to immobility parameter, Smoothy and Berry (1984) have demonstrated that single ethanol administration increases immobility duration and that this parameter is not influenced by housing conditions. However, when the duration of individual bouts of immobility was measured, ethanol did not change this specific factor in isolated mice. In our study, such detailed experimental protocol was not designed. Even though only the immobility duration was measured, here we also found that single administration of ethanol increased immobility duration of group-housed mice (control and crowding) but not of isolated mice, and the chronic ethanol administration promoted tolerance to this effect. The results from immobility duration may be a clue to the hypothesis that behavioral sensitization, rather than a progressive increase of locomotor activity, may be a reflex of the tolerance effect of immobility duration.

The results indicate that some of the aspects of behavioral sensitization and tolerance to ethanol, measured by different behavioral parameters, can be influenced by the different conditions of *housing*. Studies of housing conditions may also have a social interest in human drinking pattern, since lone drinkers may experience a different ethanol effect than group drinkers. In addition, social isolation facilitates alcohol consumption (Juarez and Vazquez-Cortes, 2003).

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