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Drug-induced home cage conspecifics' behavior can potentiate behavioral sensitization in mice

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Abstract

The effect of home cage conspecifics' behavior on locomotor sensitization to amphetamine (AMP) or ethanol (ETOH) were investigated. Female mice were repeatedly treated with saline or AMP (2.0 mg/kg for 13 days — Experiment 1) or saline or ETOH (1.8 g/kg for 21 days — Experiment 2) in home cages where all the animals had the same treatment (homogeneous home cages — HOM-HC) or in home cages where half of the animals were drug-treated and half of them were saline-treated (heterogeneous home cages — HET-HC). Behavioral sensitization was evaluated by the quantification of open-field locomotor activity after AMP or ETOH challenge injection, respectively. In both experiments, behavioral sensitization was potentiated in HOM-HC maintained animals. These results suggest that the behavioral sensitization phenomenon can be modified by home cage conspecifics' behavior.

Keywords: Addiction; Amphetamine; Ethanol; Open-field behavior; Social learning

1. Introduction

Most, if not all, drugs of abuse potential (including amphetamine and ethanol) stimulate locomotion in rodents. This locomotor stimulation has been extensively related to increased dopaminergic neurotransmission in the mesoaccumbens system (Kelly et al., 1975; Gessa et al., 1985), which has been extensively related to drug reward (Di Chiara and Imperato, 1988; Kalivas and Stewart, 1991; Koob, 1992; Hooks et al., 1993).

Chronic intermittent administration of these drugs of abuse produces a progressive and enduring increase in locomotor hyperactivity in rodents (Masur et al., 1986; Robinson and Becker, 1986; Wise et al., 1996). This phenomenon, called behavioral sensitization, has received increasing attention because sensitization-related neuroplasticity in brain reward mesotelencephalic dopamine systems might contribute to addiction (Robinson and Berridge, 1993).

As with human drug addiction (O'Brien et al., 1992), the development and expression of behavioral sensitization seem to be largely influenced by contextual cues surrounding drug administration. Indeed, sensitization is often absent or reduced if animals are tested in an environment where they have not experienced the drug before, even following treatments that produce very robust sensitization (Stewart and Vezina, 1991; Anagnostaras and Robinson, 1996; Wise et al., 1996; Carey and Gui, 1998; Quadros et al., 2003; Frussa-Filho et al., 2004). Accordingly, it has been suggested that environmental cues might be conditioned stimuli for drug-like conditioned responses, potentiating the development of behavioral sensitization (Pierce and Kalivas, 1997) — although sensitization to the locomotor-activating effects of cocaine and amphetamine and other drugs of abuse such as ethanol was observed when drug injections were not paired with the observation environment (Hooks et al., 1993; Bellot et al., 1996; 1997; Chinen et al., 2006).

Although the effects of the environmental context on the phenomenon of behavioral sensitization have been extensively

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studied and discussed (see above as well as Crombag et al., 2001; Anagnostaras et al., 2002), the influence of other potentially important contextual cues surrounding drug administration has not been investigated. That seems to be the case of home cage conspecifics' behavior. Within this context, the behavior of individual animals can be influenced in both dramatic and subtle ways by the presence and behavior of conspecifics (Nicol, 1995). This phenomenon, called social learning, has widespread, diverse and exciting examples (Nicol, 1995; Choleris and Kavaliers, 1999; Caldwell and Whiten, 2002).

The aim of the present study was to investigate the effects of social stimuli on the development of locomotor sensitization to amphetamine or ethanol in mice. To address this question, mice were repeatedly treated with one of these drugs of abuse in home cages where all the animals had the same treatment (homogeneous home cages) or in home cages where half of the animals were drug-treated and half of them were repeatedly treated with saline (heterogeneous home cages).

2. Material and methods

2.1. Subjects

Three-month-old female Swiss mice ranging in weight from 35 to 40 g were used. Female mice were used because it has been demonstrated that behavioral sensitization is higher in female animals (see Robinson and Becker, 1986). The animals arrived at the experimental laboratory at least 10 days before the beginning of the experiments. They were housed in plastic cages with ad libitum access to food and water. Light/dark cycle (lights on at 7:00 am, off 7:00 pm) and temperature (22 °C) were kept constant. Animals used in this study were maintained in accordance with the guidelines of the Committee on Care and Use of Laboratory Animal Resources, National Research Council, USA.

2.2. Drugs

Amphetamine (Sigma) and ethanol absolute (Merck) were freshly diluted in saline solution and were given intraperitoneally in a volume of 10 ml/kg body weight. Saline was used as control solution.

2.3. Experimental procedure

2.3.1. Experiment 1 — Effect of home cage conspecifics' behavior on amphetamine-induced behavioral sensitization

Fifty-six mice were allocated to 4 home cages (41 × 34 × 16.5 cm) with 14 animals each. All the animals of the first home cage were treated with 2.0 mg/kg amphetamine, i.p., once a day every other day for 13 days. Under our experimental conditions, this dose of amphetamine has been shown to produce a significant increase in open-field locomotion frequency after acute administration (Conceição et al., 1996), which is "sensitized" after this repeated treatment schedule (Costa et al., 2001). This first home cage was named amphetamine homogeneous home cage: (HOM-AMP). All the animals of the second home cage received saline in the same treatment schedule described above (saline-homogeneous home cage: HOM-SAL). Concerning the 3rd and 4th home cages, half of the animals in each cage were treated with saline and half of them were treated with amphetamine (in the same treatment schedule described above). These two home cages were operationally defined as heterogeneous home cages (HET). Thus, the four groups of animals are as follows: HOM-AMP, HOM-SAL, HET-AMP and HET-SAL. Forty-eight hours after the last injection of their respective treatments, all the animals received a challenge i.p. injection of 2.0 mg/kg amphetamine. Fifteen minutes later, the animals were individually placed in the center of the open-field arena for direct quantification of locomotion frequency during 5 min. The open-field apparatus used in the present study was a circular box (40 cm in diameter and 50 cm high) with an open-top and a floor divided into 19 squares. Hand-operated counters were used to score locomotion frequency (number of floor units entered during the 5 min session).

2.3.2. Experiment 2 — Effect of home cage conspecifics' behavior on ethanol-induced behavioral sensitization

Forty mice were allocated to 4 home cages (41 × 34 × 16.5 cm) with 10 animals each. The same experimental design described for Experiment 1 was used except that instead of amphetamine mice received 1.8 g/kg ethanol (ETOH), once a day, every day for 21 days. Under our experimental conditions, this dose of ethanol has been shown to produce a significant increase in open-field locomotion frequency after acute administration, which is sensitized after this repeated treatment schedule (Bellot et al., 1996; Camarini et al., 2000; Quadros et al., 2002). Thus, the four groups of animals are as follows: HOM-ETOH, HOM-SAL, HET-ETOH and HET-SAL. Twenty-four hours after the last injection of their respective treatments all the animals received a challenge i.p. injection of 1.8 g/kg ethanol. Five minutes later, open-field locomotor activity was quantified as described for Experiment 1.

Experiments 3 and 4 were designed to provide a non-drug reference point to assess the findings obtained in Experiments 1 and 2, respectively.

2.3.3. Experiment 3 — Effect of amphetamine treatment in home cage conspecifics on non-drug behavior of mice

Forty-eight mice were allocated to 4 home cages (41 × 34 × 16.5 cm) with 12 animals each. The same experimental design described for Experiment 1was used except that mice were challenged with saline instead of amphetamine.

2.3.4. Experiment 4 — Effect of ethanol treatment in home cage conspecifics on non-drug behavior of mice

Forty-eight mice were allocated to 4 home cages (41 × 34 × 16.5 cm) with 12 animals each. The same experimental design described for Experiment 2 was used except that mice were challenged with saline instead of ethanol.

It should be noted that the methodological procedures used in this work (such as amphetamine and ethanol doses, intervals

between drug administration and open-field session, duration of open-field session and the behavioral parameter quantified) have been shown to be optimum to evaluate the behavioral sensitization phenomenon to both amphetamine (Bellot et al., 1997; Costa et al., 2001; Chinen et al., 2006) and ethanol (Bellot et al., 1996; Araujo et al., 2005) under our specific laboratory conditions. For example, we have shown that these methodological procedures are specially effective in avoiding behavioral competition between locomotor and stereotyped behaviors in amphetamine-treated mice (Chinen et al., 2006, Fukushiro et al., unpublished data). Concerning ethanol, we have demonstrated that — opposite to locomotor activity — there is no sensitization to its effects on rearing and immobility of mice observed in an open-field (Araujo et al., 2005).

Five experimenters were involved in the quantification of open-field locomotor activity. The scorers were counterbalanced across groups and were blind to the treatment group assignment.

Each animal was used in only one experiment.

3. Results

3.1. Experiment 1 — Effect of home cage conspecifics' behavior on amphetamine-induced behavioral sensitization

Two-way ANOVA revealed a significant effect of amphetamine treatment [F (1,52)=56.8; $p<0.001$] as well as a significant amphetamine treatment × home cage condition interaction [F (1,52)=4.4; $p<0.05$]. Duncan´s post hoc test revealed that both HOM-AMP and HET-AMP groups presented higher locomotion frequencies than their respective treatment control groups (HOM-SAL and HET-SAL). Thus, behavioral sensitization was developed in both home cage conditions. However, the magnitude of behavioral sensitization was increased by the homogeneous home cage condition since animals of the HOM-AMP group presented higher locomotion frequency than that presented by the HET-AMP group (Fig. 1).

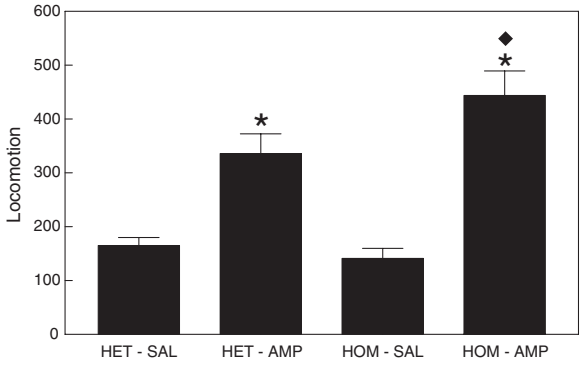

Fig. 1. Locomotor activity of mice treated with saline or amphetamine housed in three kinds of home cage situation: Homogeneous SAL (HOM-SAL) — all the mice in the home cage received saline; Homogeneous AMP (HOM-AMP) — all the mice in the home cage received 2.0 mg/kg amphetamine; and Heterogeneous (HET) — half of the animals in the home cage received saline (HET-SAL) and the other half received amphetamine (HET-AMP). The animals received their respective treatment for 13 days, every other day (7 injections). Forty-eight hours after last injection, all the animals were challenged with 2.0 mg/kg amphetamine and after 15 min locomotor frequency was quantified in the open-field for 5 min. Values are reported as means±SEM. * Differs from the respective saline treatment group; ◆Differs from the HET-AMP group. Two-way ANOVA and Duncan's Test.

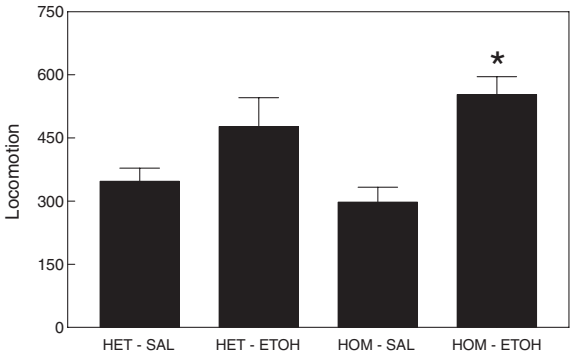

Fig. 2. Locomotor activity of mice treated with saline or ethanol (1.8 g/kg) housed in three kinds of home cage situation: Homogeneous SAL (HOM-SAL) — all the animals in the home cage received saline; Homogeneous ETOH (HOM-ETOH) — all the mice in the home cage received 1.8 g/kg ethanol; and Heterogeneous (HET) — half of the animals in the home cage received saline (HET-SAL) and the other half received ethanol (HET-ETOH). The animals received their respective treatment for 21 days. Twenty-four hours after last injection, all the animals were challenged with 1.8 g/kg ethanol and after 5 min, locomotor frequency was quantified in the open-field for 5 min. Values are reported as means±SEM, * Differs from the HOM-SAL group. Two-way ANOVA and Duncan's test.

3.2. Experiment 2 — Effect of home cage conspecifics' behavior on ethanol-induced behavioral sensitization

Two-way ANOVA revealed a significant effect of ethanol treatment [F (1,36)=17.1; $p<0.001$]. Duncan's post hoc test revealed that only HOM-ETOH group presented higher locomotion frequency than that presented by its respective control group HOM-SAL (Fig. 2). Thus, behavioral sensitization to ethanol was developed only in the homogeneous home cage condition.

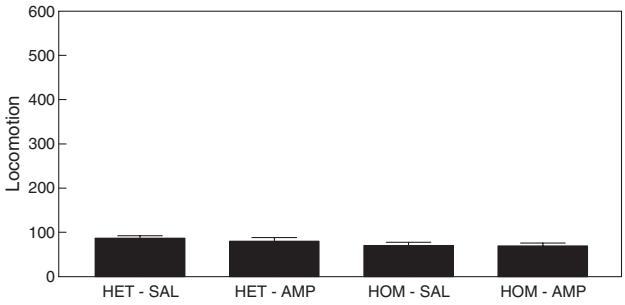

Fig. 3. Locomotor activity of mice treated with saline or amphetamine housed in three kinds of home cage situation: Homogeneous SAL (HOM-SAL) — all the mice in the home cage received saline; Homogeneous AMP (HOM-AMP) — all the mice in the home cage received 2.0 mg/kg amphetamine; and Heterogeneous (HET) — half of the animals in the home cage received saline (HET-SAL) and the other half received amphetamine (HET-AMP). The animals received their respective treatment for 13 days, every other day (7 injections). Forty-eight hours after last injection, all the animals were challenged with saline and after 15 min locomotor frequency was quantified in the open-field for 5 min. Values are reported as means±SEM.

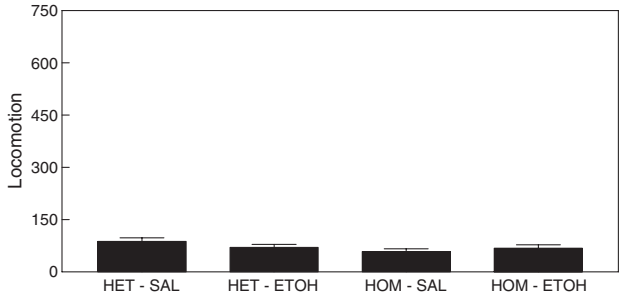

Fig. 4. Locomotor activity of mice treated with saline or ethanol (1.8 g/kg) housed in three kinds of home cage situation: Homogeneous SAL (HOM-SAL) — all the animals in the home cage received saline; Homogeneous ETOH (HOM-ETOH) — all the mice in the home cage received 1.8 g/kg ethanol; and Heterogeneous (HET) — half of the animals in the home cage received saline (HET-SAL) and the other half received ethanol (HET-ETOH). The animals received their respective treatment for 21 days. Twenty-four hours after last injection, all the animals were challenged with saline and after 5 min, locomotor frequency was quantified in the open-field for 5 min. Values are reported as means ± SEM.

3.3. Experiment 3 — Effect of amphetamine treatment in home cage conspecifics on non-drug behavior of mice

Two-way ANOVA did not reveal any significant difference among locomotor activity of HOM-SAL, HET-SAL, HOM-AMP and HET-AMP groups (Fig. 3).

3.4. Experiment 4 — Effect of ethanol treatment in home cage conspecifics on non-drug behavior of mice

Two-way ANOVA did not reveal any significant difference among locomotor activity of HOM-SAL, HET-SAL, HOM-ETOH and HET-ETOH groups (Fig. 4).

4. Discussion

The major findings of the present study were that: (1) locomotor sensitization to amphetamine was developed in both homogeneous and heterogeneous home cage-maintained mice, but the phenomenon had a clear-cut enhanced magnitude in the homogeneous home cage-maintained animals and (2) locomotor sensitization to ethanol was developed only in homogeneous home cage mice. Thus, under our specific experimental conditions, the behavioral sensitization phenomenon was more evident with amphetamine than with ethanol — a fact that is probably related to the considerable individual variability of ethanol sensitization in mice (Quadros et al., 2002, 2003). This concern notwithstanding, the present data demonstrate that behavioral sensitization to both amphetamine or ethanol can be critically affected by home cage conspecifics' behavior.

Regarding the effects of home cage conspecifics' behavior on ethanol-induced behavioral sensitization, we performed an additional experiment in which mice were treated and challenged exactly as described for Experiment 2 but its locomotor activity was quantified for 30 min in rectangular activity cages which detect locomotion by interruptions of horizontal photoelectric beams instead of the 5 min session in the circular open-field apparatus (data not shown). Results showed that during the first 5 min exposure, only the HOM-ETOH group presented higher locomotion frequency when compared to the HOM-SAL and HET-SAL groups. No significant difference among the four groups was verified after 15 and 30 min of continuous exposure. Thus, although the effect of home cage conspecifics' behavior on ethanol-induced behavioral sensitization was less evident than its effect on amphetamine-induced sensitization, it seems to occur under different experimental conditions, with a similar time course.

Several types of social learning have been proposed (Zentall, 1996). The term social facilitation has been commonly (but not always) used to label situations where the behavior of a companion releases the performance of the same behavior by the subject (see Nicol, 1995). Galef (1988) and Zentall (1996) suggest that "contagious behavior" would be a less ambiguous term for this phenomenon. Examples of contagious behavior include synchronised courtship, predator evasion (in flocking and herding animals) and coordinated consummatory behavior (see Nicol, 1995; Zentall, 1996). Thus, mice observing and interacting with hyperactive conspecifics may have produced a contagious hyperactivity which would potentiate the locomotor stimulant effect of amphetamine (or ethanol) thereby increasing the behavioral sensitization phenomenon.

Interestingly, saline-treated mice maintained in heterogeneous home cage presented the same locomotor activity after amphetamine or ethanol challenge injection as saline-treated animals maintained in homogeneous home cage. Thus, it seems that drug-state was necessary for the above alleged potentiating effect of social learning on locomotor activity. In other words, contrary to amphetamine or ethanol-treated mice locomotion, saline-treated animals' behavior was not influenced by the amphetamine- (or ethanol-) induced hyperactivity in conspecifics. The findings reported here seem to be in accordance with the incentive sensitization theory of addiction, hypothesized by Robinson and Berridge (1993). This theory postulates that addictive behavior is due to progressive and persistent neuroadaptations in the mesotelencephalic dopamine systems which mediate the incentive motivational properties of many different drugs of abuse. Sensitization of this neuronal system by drugs would result in an enhancement in the incentive salience to the act of drug taking. In addition, the co-activation of associative learning would direct the focus of this neurobehavioral system to specific targets that are associated with drugs, leading to an increasing focus of incentive salience on drug-related stimuli. Within this context, conspecifics hyperactivity would be more salient to amphetamine (or ethanol) "sensitized" mice, thereby enhancing social learning. Alternatively, conspecifics hyperactivity would be an additional environmental cue to be associated with amphetamine (or ethanol) locomotor stimulant effect (as would be injection procedure, for example). Thus, after repeated pairing of the amphetamine- (or ethanol-) induced behavioral effect, i.e., locomotor hyperactivity (unconditioned stimulus) with conspecifics' hyperactivity (conditioned stimulus), the conditioned stimulus alone would acquire the ability to elicit the drug-like

response (conditioned response) thereby potentiating the conditioned component of the behavioral sensitization phenomenon.

In line with the suggestion that drug-state is necessary for the alleged potentiating effect of social learning on locomotor activity, no effect of home cage drug (amphetamine or ethanol) homogeneous treatment condition was verified when mice were challenged with a saline injection instead of amphetamine or ethanol (Experiments 3 and 4, respectively). This finding also suggests that the home cage drug treatment regimen effect is a drug treatment sensitization effect rather than a behavioral baseline effect.

The aim of the present study was not to define mechanisms by which home cage conspecifics' behavior can modify behavioral sensitization to amphetamine or ethanol. Thus, the considerations discussed above are speculative and further experiments are required. This concern notwithstanding, the present findings have far reaching methodological implications concerning behavioral sensitization studies. Indeed, our data demonstrate that the phenomenon can be strongly modified by the specific pharmacological treatment designed to each animal in the same home cage.

From another standpoint, our data seem to support the usefulness of the rodent behavioral sensitization model for studying mechanisms underlying drug craving in humans. Indeed, the demonstration that behavioral sensitization can be potentiated by drug-induced behavioral effects in home cage conspecifics agrees well with the notion that social learning is one of the basis of development of craving in humans (Monti et al., 1988).

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