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Social crowding sensitizes high-responding rats to psychomotor-stimulant effects of morphine☆

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Abstract

Large individual differences have been identified toward varied addictive effects as evidenced in self-administration, place conditioning, and psychomotor stimulation paradigms, which have been primarily attributed to the role of congenital factors. However, it remains unknown whether environmental factors, like extraneous social stress events, could distinctively modulate animals with differentiated biobehavioral traits, such as rats with higher motor activity (high responder, HR) developed in a novel environment and their counterparts, LR (low responder) rats. In the present study, the influence of social crowding procedure upon morphine psychomotor effect was investigated. Moreover, the roles social stress played, respectively, on HRs and LRs were explored based on previous observation that HRs not only responded more to drugs but also to stress. Our results revealed that social crowding procedure could sensitize morphine psychomotor effect as a whole, and this effect was only evident for HR but not LR rats. The individual differences toward morphine psychomotor effects was indiscernible in rats housed in normal social conditions and only turned out to be significant under stress conditions. Given the fact that the occurrence of human addictive behavior usually happens within social environment permeated with various stress factors, the genetic and environmental elements may collaboratively contribute to the ultimate susceptibility of drug-prone individuals.
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1. Introduction

Stress experiences, such as tail pinch (Piazza et al., 1990), restraint (Shaham et al., 1992), food restriction (Carr, 2002; Macenski and Meisch, 1999), etc., could sensitize animals to the reinforcing effect of additive drugs as evidenced in oral and intravenous self-administration paradigms. Besides, stress events could also enhance the psychomotor effect (Deroche et al., 1992, 1993a, 1994, 1995; Marinelli et al., 1996). These stress-induced sensitization has been considered as a kind of cross-sensitization and closely related to drug-seeking behavior (Kalivas and Stewart, 1991; Robinson and Becker, 1986).

In fact, in socially organized mammals, the predominant stressors are not physical but varied social ones, such as social crowding, which evokes prominent psychosocial reactions in humans and could be mimicked in laboratory animals (Armario et al., 1984; Bugajski, 1999). This procedure has been reported to activate the hypothalamic–pituitary–adrenal axis (HPA axis) and enhance basal level or reactivity of plasma corticosterone secretion to stress events (Brown and Grunberg, 1995; Gamallo et al., 1986; Ishida et al., 2003; Viveros et al., 1988).

In drug abuse research field, a predominant phenomenon is the differentiated susceptibility to abusive drugs

☆ The experimental protocol and procedures are in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

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upon identical drug exposure. With the same drug treatment, large individual differences have been identified in different behavioral paradigms, such as self-administration (Klebaur et al., 2001; Piazza et al., 1989), conditioned place preference (Klebaur and Bardo, 1999; Zheng Xigeng et al., 2003), and psychostimulant effect (Deroche et al., 1993b; Exner and Clark, 1993; Piazza et al., 1989). For example, Deroche et al. (1993b) found that rats expressing higher motor activity in a novel environment (high responders, HRs) showed stronger morphine-induced psychomotor activity compared with their low responder counterparts (LRs), which indicated that congenital factors played important roles in it. However, it remains elusive whether environmental factors, such as extraneous stress events, could modulate HRs and LRs toward drug's effect in a distinct way.

In the present study, the effect of social crowding procedure upon morphine psychomotor effect was investigated to examine whether this particular social stressor could sensitize drug's effect as evidenced with physical stressors. Moreover, the roles social stress played, respectively, on HRs and LRs were explored given the fact that HRs not only responded more to drugs but also to stress (Piazza et al., 1991; Rouge-Pont et al., 1993). Finally, the comparison of individual differences for morphine psychostimulant effect under normal and stressful situations was examined. The former was applied to identify the influence of inherent biobehavioral features upon potentially differentiated drug's effect and the latter, to some extent, to mimic the occurrence of human addictive behavior that usually happens within social environment permeated with various stress factors (Kalivas and Stewart, 1991; Robinson and Becker, 1986; Robinson and Berridge, 2003).

2. Materials and methods

2.1. Animals and housing

Thirty male Sprague–Dawley rats (Grade I, Permission No. 199036, Institute of Genetics, Chinese Academy of Sciences, Beijing, China) weighing 350–420 g were used in the present study. Animals were housed in hanging wire-mesh steel cages in a colony of 4 (normal housing condition, namely "normal cage") (Wongwitdecha and Marsden, 1996) in each 50 cm (length)×22.5 cm (width)×30 cm (height) cage for 7-day accommodation period. Food and water were ad libitum. The lighting schedule was on a 12-h light–dark cycle (7:00–19:00) and all experiments were conducted in the light phase (8:00–18:00). Rats were gently handled 3 days before formal experiment began. The experimental protocol and procedures were in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

2.2. Apparatus

2.2.1. HR and LR screening test for motor activity developed in a novel environment

Eight identical rectangular black plastic chambers each sized 40 cm (length)×40 cm (width)×35 cm (height) were used to characterize rats into high and low responding ones (HR vs. LR) according to the motor activity developed in this inescapable novel environment. These chambers were placed in a dimly illuminated room lit by one 60-W light bulb. A video camera was suspended from the ceiling to record the horizontal movement of each rat.

2.2.2. Social crowding treatment

The apparatus for social crowding treatment was the same as the normal housing cages used in adaptation period with only exception that their sizes were exactly half sized [25 (length)×22.5 (width)×30 (height)] compared with normal housing cages. These cages were accordingly named as "crowding cage".

2.2.3. Morphine psychostimulant test

The apparatus used for morphine psychostimulant test was the same as those used for the above locomotor screening test.

2.3. Design of the experiment

The formal experiment was conducted in a succession of three stages: (1) locomotor screening test (day 1); (2) social-crowding treatment (day 2–5); (3) morphine psychostimulant test (day 6).

2.4. Procedures

2.4.1. HR and LR screening test for motor activity developed in a novel environment

On day 1, each rat was initially placed into the test chamber to measure the novelty-induced locomotor activity in 60 min. Eight rats were tested simultaneously. A 70-dB white noise was located in the test room. Half rats with longer distance traveled above the median were categorized as HRs (n=15), and the remains as LRs (n=15). After the test, rats were sent back to their home cages with housing conditions as adaptation period.

2.4.2. Social crowding protocol and constitution of experimental groups

From day 2 to day 5, one half of HR rats and one half of LR rats were subjected to social crowding treatment for the following examination of social crowding-induced morphine psychostimulant effect. Social crowding procedure was based upon previous research (Bugajski, 1999) with slight local alterations. After the procedure began, rats subjected to crowding treatment were barely transferred from "normal cage" to "crowding cage" with no other

Table 1
Constitution of experimental groups and the initial locomotor activity developed in the novel chamber (cm±SEM)

Screening test	Experimental group	Locomotor activity
HR (n=15)	HRN (n=7)	4182±263
	HRS (n=8)	3768±225
LR (n=15)	LRN (n=8)	2466±177
	LRS (n=7)	2303±180

Mean±SEM novelty-induced locomotor activity (cm) for respective experimental groups. HR and LR referred to high and low responding rats in the screening test (day 1). HRS/LRS and HRN/LRN referred to high and low responding rats subjected to social-crowding treatment or housed in normal conditions (days 2–5).

alterations of experimental conditions, such as feeding situation and constitution of animals in each colony. To avoid possible adaptations (Garcia et al., 2000), 48 h later, one non-subject rat was added into each "crowding cage" and 36 h later, another two non-subject rats were added into the "crowding cage" to make each crowding cage containing seven rats in the end. The remaining one half of HR and LR rats were kept undisturbed in normal housing conditions as controls. Therefore, before morphine psychostimulant test, altogether four experimental groups were specified, respectively, as HRN (HR animals in normal housing conditions, n=7); HRS (HR animals with social crowding treatment, n=8); LRN (LR animals in normal housing conditions, n=8); LRS (LR animals with social crowding treatment, n=7) (see Table 1 for details).

2.4.3. Morphine psychomotor stimulation test

On day 6, the morphine psychostimulant test was conducted. Each subject rat (precluding the interruptive rats put into the crowding cage) was placed into the test chamber for 120-min accommodation. Then, a saline injection was given and locomotor activity was examined for 60 min. After that, each rat was injected with morphine and locomotor activity was examined for 120 min. In this test, eight animals with approximately equal number of HRN, HRS, LRN, LRS rats were tested simultaneously to counterbalance the possible day effect.

2.5. Drug treatment

Morphine HCl (Qinghai Pharmaceutical, China) was dissolved in physiological saline with concentration of 2 mg/kg. The injection volume of both saline and morphine was kept 1 ml/kg. All injections were given intraperitoneally (i.p.).

2.6. Data analysis

A 2×2 ANOVA with repeated measure analysis was used to examine the change of locomotor activity from toward saline to morphine injections (data were expressed as mean±SEM), with "treatment" (saline vs. morphine) as within-subject factor and "stress" (non-crowded vs. crowded) or "novelty" (HR vs. LR) as between-subject factor. Since the duration for saline and morphine treatment is different in length, all post hoc analyses were conducted within either saline or morphine treatment period.

3. Results

3.1. Locomotor activity developed in the novel chamber

According to locomotor activity screening test of day 1, significant difference of motor activity toward novelty between HR (HRS plus HRN, n=15) and LR (LRS plus LRN, n=15) rats existed (p<0.05). No significant difference of motor activity was found, respectively, within two HR (HRN and HRS) and two LR (LRN and LRS) groups (p>0.05) (Table 1).

3.2. Psychostimulant effect of morphine between non-stressed and stressed rats

The psychomotor effect of morphine for non-stressed and stressed rats was illustrated in Fig. 1. After 120-min accommodation period, non-stressed and stressed rats responded identically to saline injection. However, stressed rats responded more vigorously to morphine than non-stressed rats. Stress treatment did not modulate locomotor activity under drug-free state (p>0.05) but enhanced morphine-induced psychomotor effect. These results were supported by significant "stress"×"treatment" interaction [F(1,28)=12.839, p<0.001] and appreciable difference between stressed and non-stressed rats after morphine injection [F(1,28)=11.72, p<0.01] (Fig. 1).

3.3. Differential effects social crowding played on HR and LR rats, respectively, toward morphine administration

In HR group, HRS and HRN rats responded equally to saline (p>0.05) but differently to morphine injection

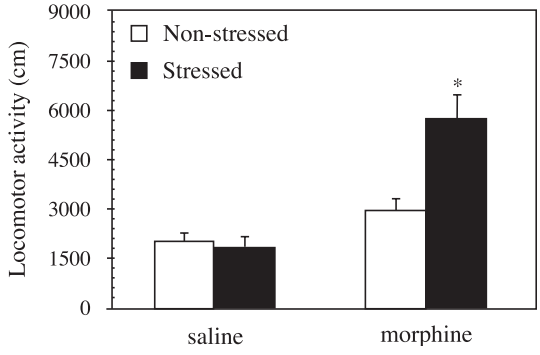

Fig. 1. Mean±SEM locomotor activity (cm) for stressed (n=15) and non-stressed (n=15) rats toward saline and morphine administration. Stressed and non-stressed rats responded equally to saline injection. In contrast, stressed rats responded more vigorously than non-stressed rats to morphine administration. An asterisk (*) represents significant difference between them.

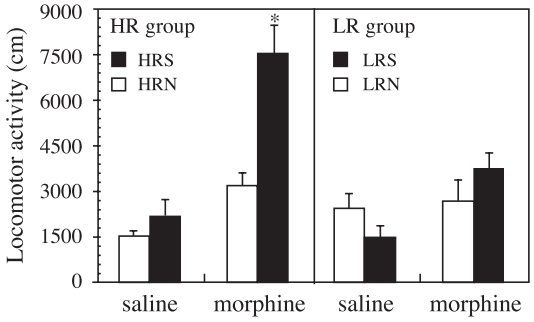

Fig. 2. Left panel: mean±SEM locomotor activity (cm) for stressed and non-stressed rats in HR group (HRS, n=8 vs. HRN, n=7) toward saline and morphine treatment. Social crowding treatment significantly enhanced the responsivity of HRS rats to morphine administration compared with HRN rats. An asterisk (*) represents significant difference between them. Right panel: mean±SEM locomotor activity (cm) for stressed and non-stressed rats in LR group (LRS, n=7 vs. LRN, n=8) toward saline and morphine treatment. Social crowding treatment played null role in the modulation of locomotor activity to morphine in LRS rats compared with LRN rats.

["stress"×"treatment" interaction, $F(1,13)=9.179$, $p<0.01$, significant difference to morphine injection, $F(1,13)=17.51$, $p<0.001$] (Fig. 2, left panel). While in LR group, though a significant "stress"×"treatment" interaction was found [$F(1,13)=6.258$, $p<0.05$], no differences were found between LRS and LRN rats to either saline or morphine injections, $p_s>0.05$ (Fig. 2, right panel). The above results indicated that crowding treatment significantly enhanced the responsivity of HR rats to morphine administration and the same treatment took null effect in LR animals.

3.4. Individual differences of morphine psychostimulant effect in non-stressed and stressed rats

Within non-stressed group, no significant differences were found between HRN and LRN rats for morphine psychostimulant effect ("novelty"×"treatment" interaction, $p>0.05$) (Fig. 3, left panel). In contrast, within stressed group, significant "novelty"×"treatment" interaction [$F(1,13)=6.638$, $p<0.05$], insignificant difference between HRS and LRS rats to saline injection ($p>0.05$) and significant difference to morphine injection [$F(1,13)=12.44$, $p<0.01$] were found (Fig. 3, right panel). The above results indicated that under normal housing conditions, the individual difference toward morphine administration was indiscernible and it only turned out to be appreciable under stressed conditions.

4. Discussion

The present study presented the following results: first, social crowding treatment sensitized rats to morphine psychostimulant effect as a whole (Fig. 1), which showed consistency to previous studies conducted with physical stress protocols (Carr, 2002; Macenski and Meisch, 1999; Piazza et al., 1990; Shaham et al., 1992). In fact, Deroche et al. (1994) has found that short-term social isolation enhanced the psychostimulant effect of morphine. Second, social stress significantly enhanced the sensitivity to morphine in HRS but not in LRS rats (Fig. 2). These results clearly demonstrated that HRS animals were the major contributors to the above overall stress-induced sensitization of morphine psychostimulant effect (Fig. 1) and showed consistency with drug-prone behaviors of HR animals in self-administration paradigm (Klebaur et al., 2001; Piazza et al., 1989).

We fully know that the crowding procedure used in the present study may involve other heterogeneous factors, such as altered food and water intake and reconstruction of social hierarchy after strange rats were added in, all of which have been reported to modulate the neural and hormonal substrates (Armario et al., 1984; Bartolomucci et al., 2001; Chaouloff and Zamfir, 1993) such that would potentially contribute to the present results. Thus, the nature and interpretation of this procedure will be further refined. Anyway and interestingly, in the present study, we found that HRN and LRN animals showed no individual differences to morphine psychostimulant effect (Fig. 3, left panel) and the individual differences only turned out to be significant under stressed conditions between HRS and LRS animals (Fig. 3, right panel). Stress experience amplified the merged individual differences under normal housing conditions, per se. This result extended previous findings of stress-sensitized drug's psychostimulant effect to stress-sensitized individual differences to this effect. Some previous reports did manifest that individual differences toward psychostimulant effect of abusive drugs were more appreciably significant under challenged situations, like social isolation (Deroche et al., 1994) other than non-challenged conditions (standard social housing conditions) (Hooks et al., 1991). This hypothesis is supported by the fact that blockade of corticosterone secretion by adrenalectomy plus pellet substitution sup-

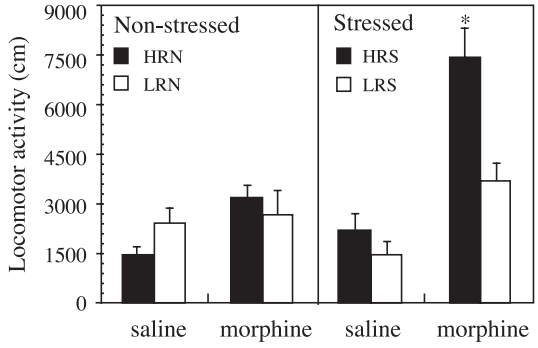

Fig. 3. Left panel: mean±SEM individual differences of locomotor activity (cm) toward saline and morphine in non-stressed rats (HRN, n=7 vs. LRN, n=8). No individual difference was identified between HRN and LRN rats toward morphine administration. Right panel: mean±SEM individual differences of locomotor activity (cm) toward saline and morphine in stressed rats (HRS, n=8 vs. LRS, n=7). Robust individual difference was found between HRS and LRS animals. An asterisk (*) represents significant difference between them toward morphine administration.

pressed the above individual differences (Deroche et al., 1993b).

The individual difference between HRS and LRS rats could not be attributed to their inherently different motor activity since they responded equally to saline injection. It also may not derive from potentially differentiated reactivity to morphine alone since non-crowded rats did not express this individual difference toward morphine. Worthy to be paid attention here is that the present characterization of HRs and LRs was conducted in an inescapable environment that has been suggested to be a mild stressor to rodents (File and Peet, 1980; Piazza et al., 1989). The above results further implied that differentiated neural and hormonal activation between HRs and LRs might play greater role in the ultimate individual differences toward morphine psychostimulant effect at least under the present social crowding situation. The above finding invited us to hypothesize that suppression of the intense reactions of HRs toward stress would be a constructive way to prevent higher propensity of these animals to develop drug-prone behavior and should be of potential clinical significance. Firstly, adrenalectomy abolished the individual difference to morphine psychostimulant effect between HRs and LRs (Deroche et al., 1993b). Secondly, administration of corticosterone to LR rats commonly insensitive to self-administration could promote the acquisition behavior in these animals (Piazza et al., 1991). Thirdly, blockade of corticosterone secretion to stress selectively decreased HRs' extracellular dopamine level (Rouge-Pont et al., 1998) with this neurotransmitter hypothesized to closely relate to drug-taking behavior.

Previous studies strongly suggested that higher propensity of HR animals toward drug use, compared with their LR counterparts, is somewhat inherent and may be partially determined genetically (Castanon and Mormede, 1994; Mormede et al., 2002). Our results further revealed that HR animals are also susceptible to environmental stress-modulated drug effects. Given the fact that the occurrence of human addictive behavior usually happens within social environment permeated with various stress factors, the genetic and environmental elements could collaboratively contribute to the ultimate susceptibility of drug-prone individuals.

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