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Behavioural Processes 65 (2004) 15–23

BEHAVIOURAL PROCESSES

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Novelty-seeking behavior and stress-induced locomotion in rats of juvenile period differentially related to morphine place conditioning in their adulthood

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Received 21 August 2002; received in revised form 14 January 2003; accepted 28 February 2003

Abstract

The relationship between motor responses in a novel environment and susceptibility to place conditioning effect of psychostimulants has been reported in adult rats. However, it is in question whether this correlation could be generalized to motor activity in rats of juvenile period and place conditioning effect in their adulthood for narcotic morphine. In the present study, we tested locomotor activity in an arena open-field and the subsequent novelty-seeking behavior after adaptation process in juvenile rats (P42) and morphine (2 mg/kg) place conditioning effect 56 days later in the same rats' adulthood (P98). Our results showed that rats with high response to novelty (HRN) spent more prolonged duration in the drug-paired compartment in the place conditioning test compared with their low response counterparts (LRN), with the latter group no salient change on this measure. Moreover, rats with high response to the open-field test (HRS) expressed equally elevated duration in drug-paired side relative to their low response counterparts (LRS). The present research demonstrated that novelty-seeking behavior and locomotor activity in the open-field in rats of juvenile period differentially related to morphine place conditioning in their adulthood, with slow acquisition of morphine place conditioning effect in LRN animals.

Keywords: Development; Morphine; Novelty seeking; Place conditioning; Stress

1. Introduction

Previous studies demonstrated that rats expressing higher motor response (HRs) in a novel environment, compared with their low response counterparts (LRs), showed stronger behavioral reactions to abusive drugs, either in psychostimulant effect (Exner and Clark, 1993; Gong et al., 1996; Kosten and Miserendino, 1998), behavioral sensitization (Hooks et al., 1991, 1992; Jodogne et al., 1994), conditioned place preference (CPP) (Klebaur and Bardo, 1999; Robinet et al., 1998), or self-administration (SA) (Nadal et al., 2002; Piazza et al., 1989; Suto et al., 2001). As with susceptibility to the rewarding effect like CPP, typical categorization of animals into HRs and LRs were conducted either under a forced choice in an inescapable environment (chamber or circular corridor) or a free-choice procedure in which animals could choose freely to approach the novelty or escape from it once they found it attractive or aversive. For example, by using a place preference procedure, Robinet et al. (1998) demonstrated a positive relationship between duration in the novel chamber and strength of the subsequent CPP effect (amphetamine).

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doi:10.1016/S0376-6357(03)00151-7

Similarly, Klebaur and Bardo (1999) also established a correlation between novelty-seeking behavior and the magnitude of CPP (cocaine) via a so-called playground maze procedure. In contrast, locomotor activity in an inescapable environment could not predict the CPP effect (Erb and Parker, 1994; Kosten and Miserendino, 1998; Gong et al., 1996). In fact, Exner and Clark (1993) found that the motor responses in a novel environment could be subtracted into two independent main components, the "escape" factor and the "explorative" factor. It is proposed that the former expressed stress-induced locomotion and the latter measured novelty-seeking behavior for the reward of novelty (Bardo et al., 1996; Exner and Clark, 1993) and that motor response characterized via distinct procedures differentially related to different behavioral effects of abusive drugs (Klebaur et al., 2001).

Until now, these kinds of studies focused more on adult rats and very few has been dedicated to juvenile ones, particularly to the relatedness between motor activity in rats of juvenile period and place conditioning effect in their adulthood. It has been well documented that juvenile rodents, compared with adult ones, manifested prominent differences in both neuroanatomical, neurophysiological and neurochemical aspects (for review, see Spear, 2000). Rats and mice of this ontogenetic period, chiefly featured by a hyporesponsive dopamine (DA) system (Laviola et al., 2001) expressed a unique and integrated behavioral and hormonal profile, such as elevated novelty-seeking behavior (Adriani et al., 1998; Spear and Brake, 1983), higher level of basal corticosterone secretion (CORT) and hyporesponsiveness of CORT to both forced novelty (Adriani and Laviola, 2000) and psychostimulant effect of drugs of abuse (Bolanos et al., 1998; for review, see Laviola et al., 1999).

Considering eminent differences existing between juvenile and adult rats, the first aim of the present study was to explore whether motor response in a novel environment in rats of juvenile period could also be divided into stressful and explorative components as seen in adult rats (Besheer and Bevins, 2000; Robinet et al., 1998). Secondly, to clarify whether these potentially distinct juvenile variables differentially related to place conditioning effect of morphine in the same rats' adulthood, given the hypothesis that partially genetic preexisting biobehavioral characteristics in early age might contribute to the use of abusive drugs later in their adulthood (Adriani et al., 1998; Ebstein and Belmaker, 1997; Gelernter et al., 1997). Finally, the present study focused on morphine given that morphine is most widely abused in Asia (Cai, 1998; Suwanwela and Poshyachinda, 1986) and molecularly different from psychostimulants, such as amphetamine and cocaine.

It has been demonstrated that rats confined in an inescapable environment expressed a higher CORT secretion compared with their baseline (File and Peet, 1980; Misslin et al., 1982; Piazza et al., 1990), suggesting that naive rats are involved in stress state in this paradigm. In the present study, we presumably tested stress-induced locomotion of naive juvenile rats in an arena open-field and novelty-seeking behavior in the same arena containing novel object (Renner and Rosenzweig, 1986; Wood-Gush and Vestergaard, 1991). The duration staying in the specified area (refer to procedure section) around the novelty and number of entries into this area were indexed as intensity of this novelty-seeking behavior.

2. Materials and methods

2.1. Animals and housing conditions

Male Sprague–Dawley rats (Grade I, Permission No. 199036, Institute of Genetics, Chinese Academy of Sciences, Beijing, China), weighing 180–220 g upon the start of experiment, were housed in hanging wire-mesh stainless steel cages sized 50 cm × 22.5 cm × 30 cm. Each cage contained eight rats with food and water ad libitum in home cages. Lighting schedule was on a 12-h-light/12-h-dark cycle (7:00–19:00 h) with all experiments conducted in the light portion (10:00–18:00 h) of this cycle. Subject rats were handled 3 days before formal start of the experiment. All experimental 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. Drugs

Morphine HCl (Qinghai Pharmaceutical Co. Ltd., China) was used in the present study. Morphine HCl

was dissolved in saline in a concentration of 2 mg/kg and injected i.p. immediately before place conditioning training session with an injection volume of 1 ml/kg.

2.3. Apparatus

2.3.1. Open-field activity and novelty-seeking behavior test

A circular blue iron-made bucket, 98 cm in diameter and 60 cm in height was used in the present study as arena open-field apparatus. A video camera was suspended from the ceiling to record the locomotor activity of each rat. When novelty-seeking behavior was tested, a small iron-made black cube cage (7 cm × 7 cm × 7 cm) was secured on the center of the arena floor before the test began.

2.3.2. Place conditioning test

The shuttle box consisted of 60 cm × 30 cm × 30 cm rectangular plastic chamber with two equally sized compartments separated by a removable guillotine door. The two compartments had distinct visual and tactile cues. One had white walls and smooth floor. The other had black walls and grid floor. A 8 cm × 6 cm opening centered at front lower part of the chamber allowing rats free access into it and with easy close during training and test.

2.4. Procedures

2.4.1. Open-field activity and novelty-seeking behavior test

On the first day (day 1) of the formal experiment, each rat was brought into lab room for 20-min adaptation. Then, it was initially placed on the arena floor for 15-min open-field test. The locomotor activity was videotaped by computerized tracking system at a 5-min interval. Seventy decibels of white noise was located in the test room. Rats were then characterized as high responders to stress (HRS) and low responders to stress (LRS) by median split characterization based on this locomotor activity measure (HRS-0–5 versus LRS-0–5, 0–5 min, day 1 or HRS-0–15 versus LRS-0–15, 0–15 min, day 1). The same procedure as day 1 was strictly repeated in days 2 and 3 allowing rats to get further familiarized with the environment.

On the novelty-seeking test of day 4, a small novel toy, a small black cube cage was secured on the center of the arena floor before the test began. After that, each rat was gently placed into the maze facing against the wall. Considering rats are biologically designed to avoid center of arena open field and seeking shelter near the edge of the maze in our behavior model, a 10-cm radius circular region around the novel toy was designated as novelty-seeking area, which makes sure that the animal should be within the monitoring scope when they snoop around the novel object. The overall locomotor activity, duration staying in the above novelty area and the number of entries into this area were simultaneously recorded for 15 min. Rats were then characterized as high responders to novelty (HRN) and low responders to novelty (LRN) by median split characterization on duration in this novelty area. A sample map of the rat's movement track in the open-field and analysis mode of novelty-seeking behavior is illustrated in Fig. 1.

2.4.2. Place conditioning test

Fifty-six days after novelty-seeking test, morphine place conditioning was conducted with a consecutive three-phased paradigm (preconditioning, conditioning, test). During baseline test session, the rat was

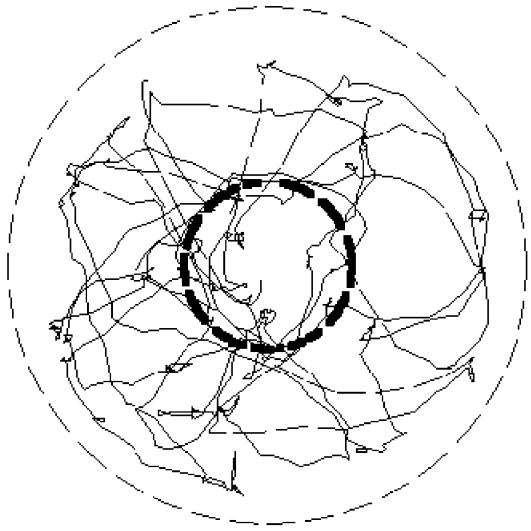

Fig. 1. A sample map of a rat's movement track. The outer circle depicts the open-field scope. A novel object is located on the center of the arena and the inner circle specifies the novelty-seeking area.

allowed to move freely in the shuttlebox for 15 min with the guillotine door removed. Time spent in each compartment and number of crossings between compartments were recorded by computerized system. The subsequent conditioning period lasted for four successive days with one morphine and one saline conditioning session each day. Morphine and saline training were employed in an alternative sequence and separated 4 h apart. Since all subject rats in the present experiment showed clear preference for black compartment, animals were confined to white side during morphine training session, and conversely, to the black one when saline training was conducted. Training sessions began immediately after morphine or saline injections (i.p.) and was 60 min in duration. On the day immediately following the last day of training period, place conditioning test was conducted. The guillotine door was removed and the animals were challenged with saline. Time spent in each compartment and number of crossings between compartments were recorded for 15 min. Preliminary data in our laboratory showed that, after the 4-day saline training, no salient change was obtained as with place conditioning effect (refer to Section 2.5 for details). Therefore, all rats were treated with morphine in place conditioning procedure and saline-treated group was omitted.

2.5. Design and data analysis

From approximately postnatal 42 days (P42), juvenile rats (Laviola et al., 1999; Spear and Brake, 1983) were tested for open-field activity and novelty-seeking behavior for four consecutive days. Fifty-six days later (P98), the same rats were tested for morphine place conditioning effect in their adulthood (Laviola et al., 1999).

The duration in novelty area and number of entries into this area (day 4) were indexed as dependent measures and analyzed via Student's t test based on HRS/LRS characterization (HRS-0–5, $n = 11$ versus LRS-0–5, $n = 10$; 0–5 min, day 1).

The duration in drug-paired compartment (white compartment) was indexed as dependent measure with "novelty" (HRN, $n = 11$, versus LRN, $n = 10$) or "stress" (HRS-0–5, $n = 11$, versus LRS-0–5, $n = 10$ or HRS-0–15, $n = 11$ versus LRS-0–15, $n = 10$) as between-subject factor and "session" (baseline versus test) as within-subject factor. A 2×2 ANOVA with repeated measure analysis was used to examine the duration shift in drug-paired compartment between base and test sessions. The number of crossings made between sides was also analyzed using 2×2 ANOVA (same factors). Similar place conditioning

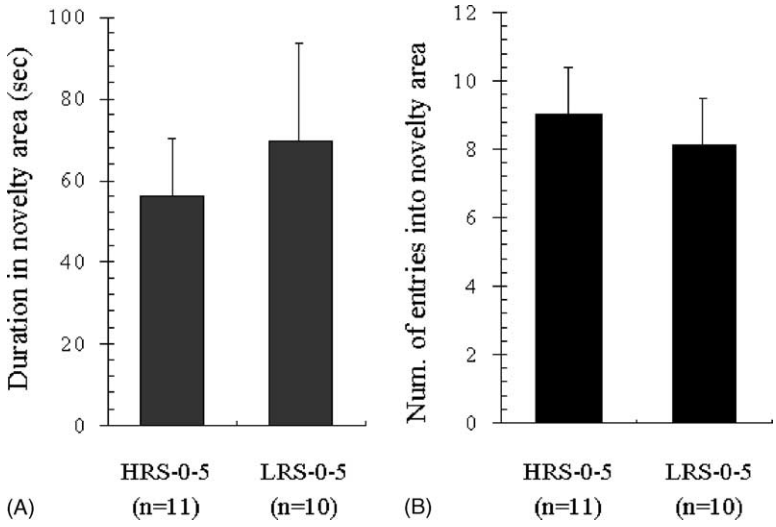

Fig. 2. (A) Mean duration in novelty area (second±S.E.M.) based on median split analysis of high- and low-locomotor activity characterization (HRS-0–5, $n = 11$ vs. LRS-0–5, $n = 10$; 0–5 min, day 1) in the open-field test. (B) Mean number of entries (number ± S.E.M.) into novelty area based on median split analysis of high- and low-locomotor activity characterization (HRS-0–5, $n = 11$ vs. LRS-0–5, $n = 10$; 0–5 min, day 1) in the open-field test.

analysis was taken based on "average locomotor activity" (locomotor activity in day 3, median split, HRS_day 3, $n = 11$ versus LRS_day 3, $n = 10$) which presumably reflected motor response in a more familiar environment after two-session exposure in the same apparatus. Because the place conditioning test was conducted drug-free, changes of the above two dependent measures would reflect conditioning effects.

Preliminary data in our laboratory showed that, after saline training, the duration in white compartment did not show appreciable shift compared with baseline session whether analyzed via HRN/LRN or HRS/LRS characterization (HRN versus LRN, session effect: $F(1, 14) = 0.721$, $P = 0.410$; HRS versus LRS, session effect: $F(1, 14) = 0.717$, $P = 0.411$); simultaneously, both HR and LR rats expressed comparable change between sessions (HRN versus LRN, $F(1, 14) = 0.288$, $P = 0.600$; HRS versus LRS, $F(1, 14) = 0.219$, $P = 0.647$). These preliminary results suggested that repeated exposure to CPP paradigm did not significantly influence place conditioning effect (figure not shown). Thus, significant effects obtained in the present study would reflect the conditioning effect of morphine.

3. Results

3.1. Dissociation of novelty-seeking behavior and locomotor activity in the open-field in rats of juvenile period

Upon HRS-0–5/LRS-0–5 categorization, no difference was found between these two groups for both duration in novelty area (Fig. 2A) and number of entries into this area, Ps > 0.05 (Fig. 2B). Simultaneously, no significant differences were found when examining the difference of locomotor activity in the open-field (0–5 min, day 1) based on HRN/LRN characterization. Very similar results could be obtained with respect to the relationship between novelty-seeking behavior and locomotor activity for 0–15 min of day 1 (figure not shown).

3.2. Relationship between novelty-seeking behavior in rats of juvenile period and morphine place conditioning in their adulthood

Based on HRN/LRN categorization, significant "session" effect, $F(1, 19) = 19.794$ $P < 0.001$, "novelty" × "session" interaction, $F(1, 19) = 6.584$,

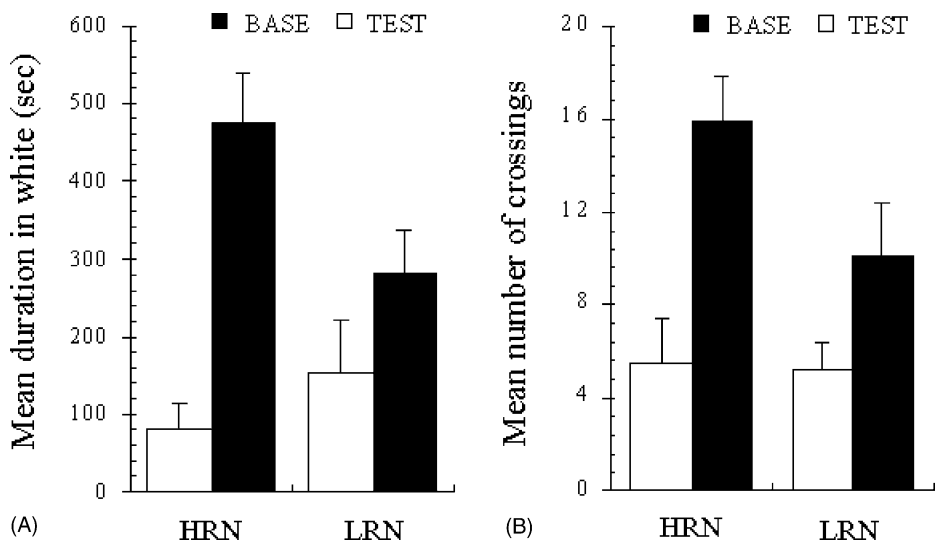

Fig. 3. (A) Mean duration (second ± S.E.M.) in morphine-paired white compartment in place conditioning test based on median split analysis of high- and low-response to novelty (HRN, $n = 11$ vs. LRN, $n = 10$; duration in novelty area, day 4). (B) Mean number of crossings (number ± S.E.M.) between compartments in place conditioning test based on median split analysis of high and low response to novelty (HRN, $n = 11$ vs. LRN, $n = 10$; duration in novelty area, day 4).

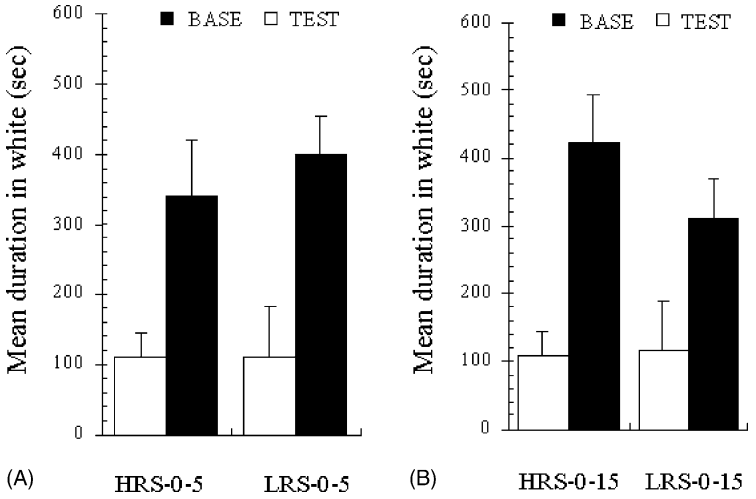

Fig. 4. (A) Mean duration (second ± S.E.M.) in morphine-paired white compartment in place conditioning test based on median split analysis of high- and low-locomotor activity characterization in the open-field test. (HRS-0–5, $n = 11$ vs. LRS-0–5, $n = 10$; 0–5 min, day 1). (B) Mean duration (second ± S.E.M.) in morphine-paired white compartment in place conditioning test based on median split analysis of high- and low-locomotor activity characterization in the open-field test. (HRS-0–15, $n = 11$ vs. LRS-0–15, $n = 10$; 0–15 min, day 1).

$P < 0.05$, were found for duration shift in drug-paired compartment. Simple effect examination illustrated that HRN rats expressed appreciably more time in drug-paired compartment from base session to test session, $F(1, 19) = 25.84$, $P < 0.001$; however, no significant change was obtained for LRN rats between sessions, $F(1, 19) = 1.69$, $P > 0.05$ (Fig. 3A).

Based on HRN/LRN characterization, main effect of "session," $F(1, 19) = 16.335$, $P < 0.01$, was found for number of crossings between compartments.

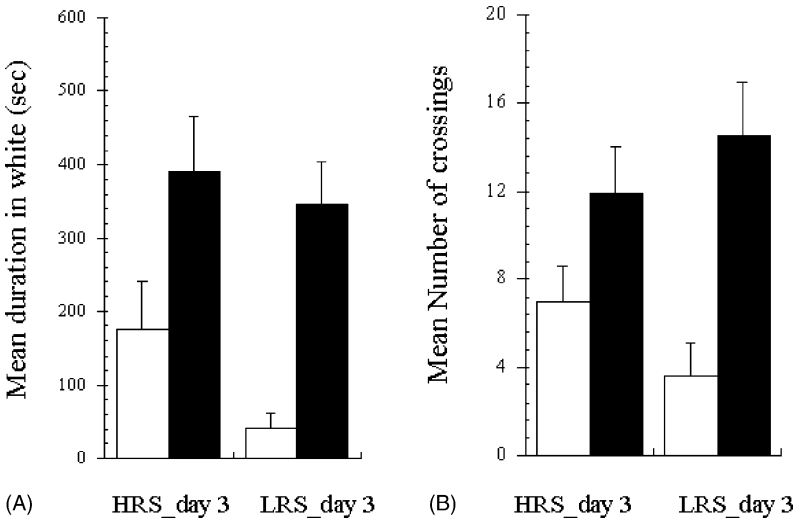

Fig. 5. (A) Mean duration (second ± S.E.M.) in morphine-paired white compartment in place conditioning test based on median split analysis of high- and low-locomotor activity characterization on day 3 (HRS_day 3, $n = 11$ vs. LRS_day 3, $n = 10$; 0–15 min). (B) Mean number of crossings (number ± S.E.M.) between compartments in place conditioning test based on median split analysis of high- and low-locomotor activity characterization on day 3 (HRS_day 3, $n = 11$ vs. LRS_day 3, $n = 10$; 0–15 min).

However, the interaction between "novelty" and "session" was not significant, $P > 0.05$ (Fig. 3B).

3.3. Relationship between locomotor activity in the open-field in rats of juvenile period and morphine place conditioning in their adulthood

Based on HRS-0–5/LRS-0–5 categorization, no "stress" × "session" interaction was found for duration shift in drug-paired compartment, $P > 0.05$. The only significant effect is "session" effect, $F(1, 19) = 15.848$, $P < 0.01$ (Fig. 4A). Similar results were found based on HRS-0–15/HRS-0–15 (day 1) characterization with only significant main effect of "session," $F(1, 19) = 15.858$, $P < 0.01$ (Fig. 4B).

3.4. Relationship between average locomotor activity in rats of juvenile period and morphine place conditioning in their adulthood

Based on HRS_day 3/LRS_day 3 characterization, no "average locomotor activity" × "session" interaction was found for either duration shift in drug-paired compartment or number of crossings between compartments, Ps > 0.05. Only significant "session" effects were found, $F(1, 19) = 16.180$, $P < 0.001$, for duration shift in drug-paired compartment (Fig. 5A), $F(1, 19) = 17.923$, $P < 0.001$, for crossing behavior between compartments (Fig. 5B).

4. Discussion

The susceptibility to drugs of abuse has been attributed to the interaction between responsiveness of HPA axis and basal and reactivity of mesolimbic dopamine system (MLDS). (Deroche et al., 1992a,b, 1993; Piazza and Le Moal, 1996, 1998). Locomotor activity in the open-field and novelty-seeking behavior were considered capable to reflect the activation of HPA axis and MLDS, thus could predict this vulnerability (Bardo et al., 1996).

In the present study, we found that there existed a dissociation between locomotor activity (0–5 and 0–15 min, day 1) in the open-field and the novelty-seeking behavior (day 4) in our juvenile rats. This result demonstrated that these behaviors in juvenile period are also different phenomena and might be activated by different neural and hormonal substrates as seen in adult rats (Besheer and Bevins, 2000; Robinet et al., 1998). In the above studies, the authors showed that locomotor activity in an inescapable chamber dissociated from the subsequent duration staying in the novel chamber with a place preference procedure. Our results was consistent with an early study achieved from adolescent rats by Spear and associates showing that novelty-motivated "holepoke" behavior was largely independent from the animal's gross locomotor activity (Spear and Brake, 1983) but contradictory to the study of Dellu et al. (1993). Dellu et al. (1993) demonstrated a relationship between activity in an inescapable environment and subsequent approaches to a novel environment. This discrepancy may be due to the age of rats tested and some methodological issues. Dellu et al. used adult rats and applied different apparatus to test these behaviors. This might bring the possibility of bringing "residues" of stressful component in its "novelty-seeking" behavior (Exner and Clark, 1993; Renner, 1990). In the present study, though introducing a small novel object into a previously familiarized environment (arena open-field) could also possibly induce stress and avoidance reactions of rats which could also express individual differences, however, the duration of HRN rats staying in the novelty area on the novelty-seeking test day is appreciably longer than the average duration from day 1 to day 3 in the same area (without novel object). Meanwhile, LRN rats showed no significant alteration before and after the novel object is placed in (data not shown), suggesting the expression of individual difference of neophilia rather than neophobia with our behavioral model. This is also consistent with the notion that novelty per se is not stressful, particularly when the novelty is escapable (Bardo et al., 1996). Indeed, when animals were initially placed in an inescapable environment, the plasma CORT increased, even to a level comparable to mild electric shocks (Dantzer and Mormede, 1983), while the CORT level did not increase in free-choice paradigm (Misslin et al., 1982).

Though previous studies have revealed the relationship between novelty-seeking behavior and place conditioning effect in adult rats (Klebaur and Bardo, 1999; Robinet et al., 1998), to our knowledge, no systematic data was available on this relationship between open-field activity, novelty-seeking behavior in rats of juvenile period and place conditioning effect in

their early adulthood. Our result demonstrated the predictive value of novelty-seeking behavior in juvenile period for the place conditioning effect expressed thereafter in adulthood, suggesting a common pathway existed between them. Moreover, this result also proposed a useful model for potential applications of preventive strategies employed for potentially vulnerable human adolescents to abusive drugs, specifically the high sensation seekers (Dellu et al., 1996).

In the present study, locomotor activity of day 3 did not predict morphine place conditioning effect, though the rats were in a seemingly more familiarized environment and seemed to explore more freely for the reward of novelty (Bardo et al., 1996). This result reminded us that commonly used paradigm to categorize rats into HRs and LRs in a forced choice procedure, to a greater extent, expressed the individual differences of stress-induced locomotion rather than explorative activities, and thus, could not predict place conditioning effect of abusive drugs (Kosten and Miserendino, 1998; Gong et al., 1996). In fact, previous evidence showed that both HR and LR rats in an inescapable novel environment expressed elevated CORT level with HRs stayed in a higher level until 120 min (Piazza et al., 1990).

Interestingly, in the present study, though morphine-treated animals expressed salient duration increase in drug-paired compartment as a whole, the LRN rats showed no appreciable change, suggesting slow acquisition of this effect in these rats. This result from narcotic morphine contrasted to the work of Erb and Parker (1994), Gong et al. (1996), and Kosten and Miserendino (1998) which, with amphetamine and cocaine, respectively, showed that both HRs and LRs demonstrated significant place conditioning effect. The result of differentiated acquisition capability between HRN and LRN rats in the present study would be of potential significance considering the preclinical finding that vulnerability to abusive drugs, especially the transition from occasional drug use to dependence could be predicted by the degree of positive reward derived from the initial drug experience (Haertzen et al., 1983; Laviola et al., 1999).

One of the main deficits in the present study is that this research could not ascertain the formation of CPP of morphine since we used biased procedure in place conditioning test and the time spent in drug-paired compartment, at the best circumstance, did not statistically exceed 50% of the total test duration. This uncertainty of whether morphine place conditioning enhanced the preference for the initial non-preferred compartment or just reduced the aversive properties of the non-preferred side, deserves further research under alternative CPP paradigm.

Acknowledgements

This project was supported by Innovation Grants (KSCX2-2-03, KSCX2-SW-204-02) from Chinese Academy of Sciences, and by National Natural Science Foundation of China (No. 30170324, No. 30230130). The authors also extend their great gratitude to Mr. Zheng Shaokang, father of the first author of this paper, for his great consideration and support to this work even in his last several months of his lifetime.

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