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Susceptibility to morphine place conditioning: relationship with stress-induced locomotion and novelty-seeking behavior in juvenile and adult rats

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Abstract

Previous studies demonstrated that the rewarding effect of psychostimulants, such as amphetamine and cocaine, can be predicted by locomotor activity toward novelty in a free-choice situation but not motor response developed in inescapable environment. However, whether this relationship also exists with narcotic morphine remains unclear. In the present study, the relationship between morphine place conditioning and open field as well as novelty-seeking behavior was examined in both juvenile and adult rats. By using arena open field and the same arena containing novel object, we investigated the initial open-field activity and novelty-seeking behavior after familiarization process, respectively, in juvenile and adult rats. Subsequently, the relationship between morphine (2 mg/kg) place conditioning and the above two behaviors was examined. Our results demonstrated that morphine place conditioning effect was readily acquired in both groups. The magnitude of this effect positively correlated with novelty-seeking intensity but not with open-field activity. This is the case whether juvenile or adult group was examined separately or across ages. However, only rats with high response to novelty (NHR) from their respective group expressed significant duration increase in drug-paired compartment. Rats with low response to novelty (NLR) showed no sign of this effect after the same drug training, suggesting slow acquisition of this effect in NLRs. These results also indicated that novelty-seeking actions and the rewarding effect of morphine possessed a common pathway and that neural and hormonal substrates activated in a mild stress environment like in the open field may not be critically involved in this process. The ontogenetic specificity and nonspecificity between different-aged rats as with the above relationship were discussed in this paper.

Keywords: Open field; Novelty seeking; Place conditioning; Morphine; Ontogenesis

1. Introduction

"Novelty response" has received more attention recently for the establishment of the correlation between behavioral effects of drugs of abuse and novelty-induced motor activities in rodents. In general, researches in this field mainly provided two kinds of correlation. One was the relationship between motor activity in an inescapable environment (inescapable novelty) and the reinforcing effect of drugs of abuse as expressed by self-administration (Klebaur et al., 2001; Nadal et al., 2002; Piazza et al., 1989; Suto et al., 2001). Researchers found that this correlation could not be generalized to the rewarding effect of abusive drugs, such as conditioned place preference (CPP) (Erb and Parker, 1994; Gong et al., 1996; Kosten and Miserendino, 1998). The other was the relationship between explorative activities or so-called novelty-seeking behavior (free-choice novelty) and the rewarding effect of drugs of abuse like CPP (Klebaur and Bardo, 1999; Robinet et al., 1998). Likewise, this correlation could not be generalized to self-administration (Klebaur et al., 2001). In fact, the literature suggested that locomotor activity developed in novel inescapable environment and locomotor behavior toward novelty can be related to different behavioral effects of drugs of abuse, i.e., reinforcing and rewarding effect, respectively. It has been proposed that locomotor activity expressed in an inescapable environment reflected the stressful component of motor activation (Exner and Clark, 1993), while novelty-seeking behavior expressed the motivation for and driven by the seeking of novelty reward (Bardo et al., 1996).

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Although previous studies demonstrated the above relationship with psychostimulants, such as amphetamine and cocaine, whether it is the case with narcotic morphine remains unclear. Moreover, most of these kinds of studies focused on adult rodents, and very few have been dedicated to juvenile ones, particularly the comparison between them. It has been well documented that rats or mice of distinct ontogenetic period manifested prominent differences in neuroanatomical, neurophysiological and neurochemical aspects, especially from juvenile period to early adulthood (Gelbard et al., 1989; Kalsbeek et al., 1988; Laviola et al., 2001; Teicher et al., 1995; for review, see Spear, 2000). Behaviorally, these different-aged rats or mice responded distinctively in stress responsiveness (Adriani and Laviola, 2000), novelty-seeking behavior (Adriani et al., 1998), psychostimulants (Adriani and Laviola, 2000; Bolanos et al., 1998; Spear et al., 1982) and rewarding effect (Bolanos et al., 1996) to abusive drugs, such that may influence the relationship between inherent motor response and their rewarding effect.

The aim of the present study was twofold. The first aim is to explore the relationship among stress-induced locomotion, novelty-seeking behavior and rewarding effect of morphine in juvenile and adult rats with CPP paradigm. Second is to further clarify the specificity or nonspecificity as with the acquirement of CPP and the above relationship in different-aged rats. Morphine was used in the present study because it is molecularly different from psychostimulants and is most abused in Asia (Cai, 1998; Suwanwela and Poshyachinda, 1986).

In the present study, the stress-induced locomotion was presumably measured on initial locomotor activity in the arena open-field test (0–5 and 0–15 min, day 1) based on previous evidence that both high and low responders (HR vs. LR) confined in a novel chamber expressed elevated level of plasma corticosterone (Hennessy et al., 1979) until 30 min after initial exposure (Piazza et al., 1991). Novelty-seeking intensity was measured via approaching behavior toward the novel toy placed in the arena based on previous study (Renner et al., 1992) with slight alterations.

2. General method

2.1. Animals and housing

Seventeen male Sprague–Dawley juvenile rats (~ 42 days old, P42) and fifteen adults (~ 92 days old, P92) were used in the present study (Grade I, Permission no. 199036, Institute of Genetics, Chinese Academy of Sciences, Beijing, China). Animals were housed in hanging wire-mesh stainless steel cages in a colony of eight in each 50 × 22.5 × 30-cm cage. Food and water were available ad libitum in home cages. Lighting schedule was on a 12-h light/dark cycle (7:00–19:00 h), and all experiments were conducted in the light phase (10:00–18:00 h) of this cycle. Rats were handled 3 days before the formal start of the experiment. The experimental protocol and procedures complied 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. Open-field and novelty-seeking behavior test

A circular barrel (98 cm in diameter, 60 cm in height) was used as the open-field arena to test both open-field activity and novelty-seeking behavior. This apparatus was painted dark blue and placed in the dimly illuminated laboratory room lit by one 60-W yellow light bulb. A video camera was suspended from the ceiling to record the locomotor activity of each rat. When novelty-seeking behavior was tested (days 3 and 4), a gray rubber cylinder (7 × 7 × 5 cm, day 3) and a black iron-made cube cage (7 × 7 × 7 cm, day 4), respectively, were secured on the center of the barrel floor as novel objects before the test began.

2.2.2. Place conditioning test

Place conditioning test was conducted in eight identical rectangular plastic chambers [60 (length) × 30 (width) × 30 (height) cm] with two equally sized compartments separated by a removable guillotine door. The two compartments had distinct visual and tactile cues, one with white walls and smooth floor and the other with black walls and grid floor. An 8 × 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.

2.3. Procedures

2.3.1. Open-field and novelty-seeking behavior test

On the first day (day 1) of the formal experiment, each rat was brought into laboratory for 20-min habituation to the laboratory environment. Then, it was initially placed on the center of the arena floor for 15-min open-field test. The distance traveled by each rat was recorded by computerized tracking system at a 3-min interval. A 70-dB white noise was located in the test room. Rats were then characterized as high and low responders to this open-field test (SHR vs. SLR) by median split analysis on this measure.

The same procedure as open-field test was strictly repeated in day 2 for rats to be further familiarized with the arena environment. On days 3 and 4, an alternative novel toy, a gray rubber cylinder (day 3) and a black iron-made cube cage (day 4) were secured on the center of the arena floor beforehand to test the novelty-seeking behavior. After the test began, each rat was placed near the edge of the arena facing against the wall. Considering rats are biologically designed to avoid the center area of arena open field and seek 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 tested animals should be within the monitoring scope when they snoop around the novel object. Duration for each rat staying in this area was recorded for 15 min at a 3-min interval. Rats were then characterized as high and low responders to novelty (NHR vs. NLR) by median split characterization based on this duration measure. A sample map of the rat's movement track in the open-field and novelty-seeking test is presented in Fig. 1.

2.3.2. Place conditioning test

The place conditioning test was based on previous study (Kosten and Miserendino, 1998) using a successive three-phased paradigm (preconditioning, conditioning and test). Because the main purpose of the present study was to compare potentially differentiated susceptibility with morphine place conditioning among individuals under the same drug exposure, all rats were administered with morphine; the saline group was omitted.

A biased procedure was used here to determine morphine-induced place conditioning effect. During preconditioning (baseline) session, each rat was allowed to move freely in the chamber with the guillotine door removed. Time spent in each compartment and number of crossings between compartments were recorded for 30 min. The subsequent conditioning period lasted for 4 successive days, with one morphine and one saline training session each day. Morphine and saline training were employed in an alternative sequence and separated 4 h apart. Animals were confined to the compartment with less preference in the baseline test during morphine training session and conversely to the other side when saline training was conducted. Training sessions began immediately after respective morphine or saline injection (intraperitoneal) and lasted 60 min. On the day immediately following the last conditioning session, the CPP test was conducted. Rats were challenged with saline, placed into the middle part of the chamber from the opening of the box (refer to place conditioning apparatus) and allowed to move freely in the chamber with the guillotine door removed. Time spent in each compartment and number of crossings between compartments were recorded for 30 min by computerized system. The CPP score was calculated by duration shift in drug-paired compartment or change of number of crossings from base to test session.

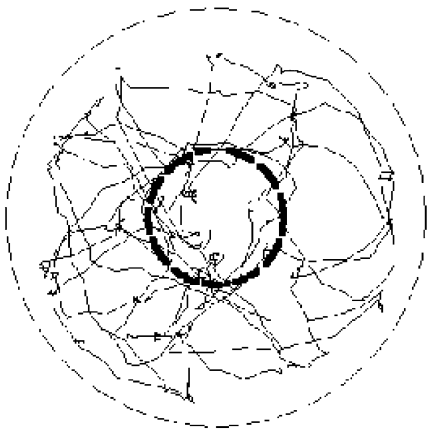

Fig. 1. A sample map of a rat's movement track. The outer circle illustrates the open-field scope and the inner circle portraits the novelty-seeking area.

2.4. Drug treatment

Morphine HCl (Qinghai Pharmaceutical, China) was dissolved in physiological saline with concentration of 2 mg/kg and injection volume of 1 ml/kg.

2.5. Design and protocol

To avoid possible influence of the initially somewhat stressful open-filed exposure on following novelty-seeking and CPP test, which derived from within-subjects design in the present study, novelty-seeking and CPP tests were set 2 and 4 days apart, respectively, from the open-field test. Specifically, from P42 and P92, juvenile and adult rats (Laviola et al., 1999; Spear and Brake, 1983) were tested for their open-field activity and novelty-seeking behavior, respectively, in 4 successive days (days 1–4). Two days after these tests, the rats were examined for morphine-induced place conditioning effect.

2.6. Data analysis

The locomotor activities in the open field (0–5 and 0–15 min, day 1) were analyzed using Student's t test based on NHR/NLR characterization on duration in novelty area for either day 3 or 4 (median split: juveniles, $n=10$ for each group; adults, $n=8$ for NHR group and $n=7$ for NLR group). Reciprocally, the duration in novelty area (days 3 and 4) was analyzed via Student's t test based on SHR/SLR characterization on open-field activity of either 0–5 or 0–15 min of day 1 (median split: juveniles, $n=10$ for each group; adults, $n=8$ for SHR group and $n=7$ for SLR group).

A 2×2 repeated-measures ANOVA was used to examine the duration shift in drug-paired compartment between base and test session, with Novelty (NHR vs. NLR; median split, duration in novelty area of day 3: juveniles, $n=9$ for NHR group and $n=8$ for NLR group; adults, $n=8$ for NHR group and $n=7$ for NLR group) or Stress (SHR_0_5 vs. SLR_0_5; median split, 0–5-min open-field activity of day 1: juveniles, $n=9$ for SHR_0_5 group and $n=8$ for SLR_0_5 group; adults, $n=8$ for SHR_0_5 group and $n=7$ for SLR_0_5 group) as between-subjects factor and Session (Base vs. Test) as within-subjects factor. The number of crossings made between compartments in the CPP test was also analyzed using a 2×2 repeated-measures ANOVA (same factors).

3. Results

3.1. Dissociation of locomotor activity in open-field and novelty-seeking behavior

In either juvenile or adult group, the Pearson coefficient for duration in novelty area between days 3 and 4 was significant (juveniles, r=.563, $P<.01$; adults, r=.540, $P<.05$), which to some extent validated the reliability of our novelty-seeking behavioral model.

As seen in Fig. 2, a dissociation effect existed between open-field activity and novelty-seeking behavior in juvenile rats. High and low novelty seekers, screened either day 3 or 4, possessed statistically undifferentiated open-field activity for the first 0–5 min (Fig. 2A, left panel) and 0–15 min of day 1 (Fig. 2A, right panel) (P's>.05). Reciprocally, high and low responders in the open-field test expressed statistically equal novelty-seeking intensity, as expressed on either day 3 (Fig. 2B, left panel) or day 4 (Fig. 2B, right panel) (P's>.05). Very similar results were obtained with adult rats demonstrating the dissociation of the above two behaviors (figure not shown).

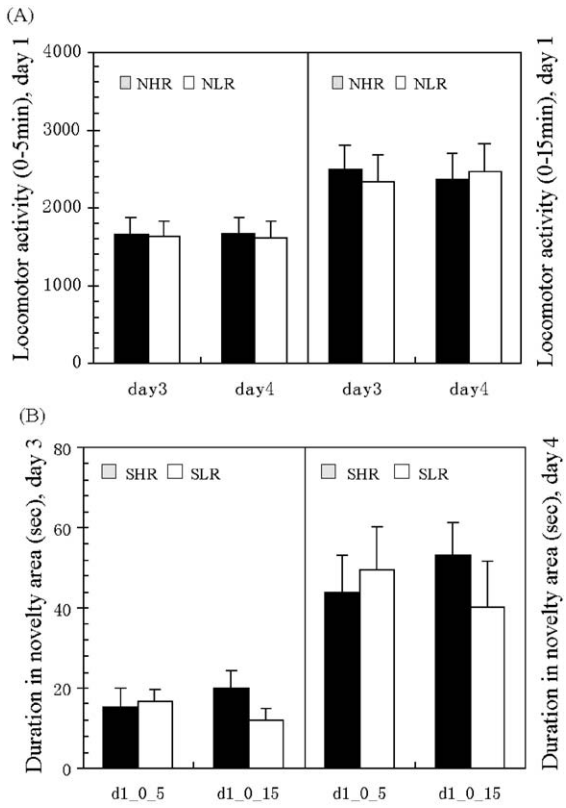

Fig. 2. (A) Left panel: Mean ± S.E.M. locomotor activity (cm) in the open-field test (0–5 min, day 1) based on median split characterization of high and low novelty seekers screened on either day 3 or 4 (NHR vs. NLR, n=10 for each group) in juvenile rats. Right panel: Mean ± S.E.M. locomotor activity (cm) in the open-field test (0–15 min, day 1) based on median split characterization of high and low novelty seekers screened on either day 3 or 4 in juvenile rats (NHR vs. NLR, n=10 for each group). (B) Left panel: Mean ± S.E.M. duration (s) in novelty area in the novelty-seeking test (day 3) based on median split characterization of high and low responders in the open-field test screened via locomotor activity of either 0–5 or 0–15 min of day 1 in juvenile rats (SHR vs. SLR, n=10 for each group). Right panel: Mean ± S.E.M. duration (s) in novelty area in the novelty-seeking test (day 4) based on median split characterization of high and low responders in the open-field test screened via locomotor activity of either 0–5 or 0–15 min of day 1 in juvenile rats (SHR vs. SLR, n=10 for each group).

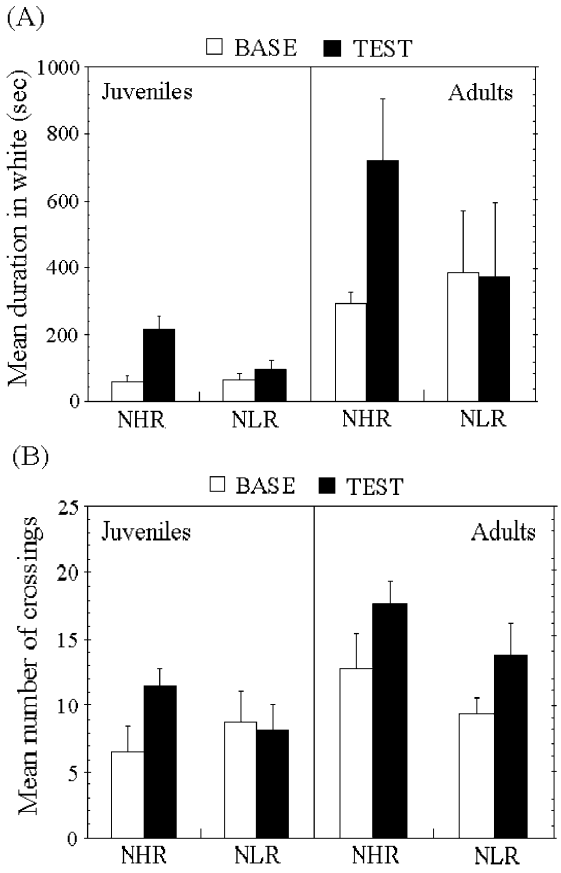

Fig. 3. (A) Left panel: Mean ± S.E.M. duration shift in drug-paired compartment (s) after morphine conditioning for juvenile rats based on median split characterization of high and low response to novelty (NHR, n=9 vs. NLR, n=8; duration in novelty area, day 3). Right panel: Mean ± S.E.M. duration shift in drug-paired compartment (s) after morphine conditioning for adult rats based on median split characterization of high and low response to novelty (NHR, n=8 vs. NLR, n=7; duration in novelty area, day 3). (B) Left panel: Mean ± S.E.M. shift for number of crossings between compartments (n) after morphine conditioning for juvenile rats based on median split characterization of high and low response to novelty (NHR, n=9 vs. NLR, n=8; duration in novelty area, day 3). Right panel: Mean ± S.E.M. shift for number of crossings between compartments (n) after morphine conditioning for adult rats based on median split characterization of high and low response to novelty (NHR, n=8 vs. NLR, n=7; duration in novelty area, day 3).

3.2. Relationship between novelty-seeking behavior and morphine place conditioning in juvenile and adult rats

Fig. 3 depicted duration shift in drug-paired compartment and the change of number of crossings after morphine conditioning based on NHR/NLR characterization. As with

duration shift in drug-paired compartment, either juvenile or adult rats expressed significant duration increase after conditioning, which was supported by significant session effect in both groups [juveniles, $F(1,15)=6.472$, $P<.05$; adults, $F(1,13)=5.209$, $P<.05$]. Furthermore, NHR animals from either group demonstrated more prolonged duration increase compared with their relative NLR counterparts as expressed by significant Novelty × Session interaction [juveniles, $F(1,15)=5.738$, $P<.05$; adults, $F(1,13)=5.276$, $P<.05$] and appreciable duration increase from base session to test session [juveniles, $F(1,15)=12.96$, $P<.01$; adults, $F(1,13)=11.23$, $P<.01$]. Meanwhile, no significant duration change was obtained for either juvenile or adult NLR rats between sessions (P's>.05). Regardless of age factor, a more robust overall effect of Session [$F(1,29)=9.752$, P=.004] and Session × Novelty interaction [$F(1,29)=7.892$, P=.009] emerged, which strongly supported that novelty response determined the propensity of rewarding effect of morphine across ages (Fig. 3A).

For number of crossings in the CPP test, the response of juvenile and adult rats somewhat differed. Juvenile NHRs crossed more frequently than juvenile NLRs after morphine conditioning. This was supported by significant Session × Novelty interaction [$F(1,15)=7.610$, $P<.05$] and the number increase in NHRs from base to test session [$F(1,15)=6.90$, $P<.05$] (Fig. 3B). For adult group, however, the above individual difference disappeared, although this behavior was intensified as a whole after morphine conditioning, which was supported by significant Session effect [$F(1,13)=7.317$, $P<.05$] and insignificant Novelty × Session interaction in this group.

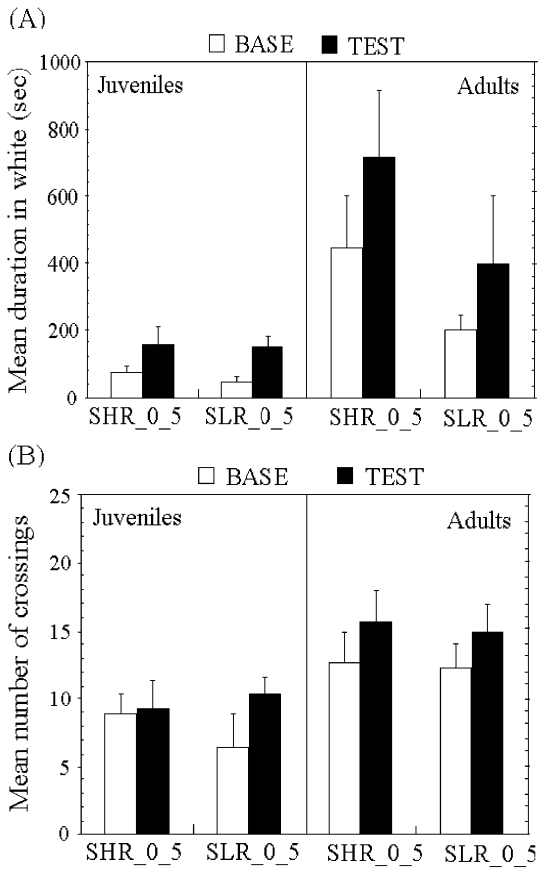

Fig. 4. (A) Left panel: Mean ± S.E.M. duration shift in drug-paired compartment (s) after morphine conditioning for juvenile rats based on median split characterization of high and low response in the open-field test (SHR_0_5, $n=9$ vs. SLR_0_5, $n=8$; 0–5 min locomotor activity, day 1). Right panel: Mean ± S.E.M. duration shift in drug-paired compartment (s) after morphine conditioning for adult rats based on median split characterization of high and low response in the open-field test (SHR_0_5, $n=8$ vs. SLR_0_5, $n=7$; 0–5 min locomotor activity, day 1). (B) Left panel: Mean ± S.E.M. shift for number of crossings between compartments (n) after morphine conditioning for juvenile rats based on median split characterization of high and low response in the open-field test (SHR_0_5, $n=9$ vs. SLR_0_5, $n=8$; 0–5 min locomotor activity, day 1). Right panel: Mean ± S.E.M. shift for number of crossings between compartments (n) after morphine conditioning for adult rats based on median split characterization of high and low response in the open-field test (SHR_0_5, $n=8$ vs. SLR_0_5, $n=7$; 0–5 min locomotor activity, day 1).

3.3. Relationship between locomotor activity in the open field and morphine place conditioning in juvenile and adult rats

Fig. 4 depicted the CPP effect of high and low responders in the open-field test. In both juvenile and adult groups, SHR_0_5 and SLR_0_5 animals expressed undifferentiated change after conditioning for either duration shift in drug-paired compartment or conditioned crossing behavior (P's>.05). It was the case whether juvenile and adult group was examined separately or across ages. Similar results could be found based on SHR_0_15/SLR_0_15 characterization on open-field activity of the first day (0–15 min, figure not shown).

4. Discussion

The present study presented the following results. Firstly, dissociation existed between open-field activity and duration for novel object interactions in both juvenile and adult rats, suggesting that stress-induced locomotion and novelty-seeking behavior are different biobehavioral phenomena and might be activated by different neural and hormonal substrates. Secondly, novelty-seeking behavior, rather than locomotor activity developed in the open field, predicted the duration shift in drug-paired side in the CPP test. This was the case whether examined in juvenile and adult groups separately or across ages. These results were consistent with previous studies (Klebaur and Bardo, 1999; Robinet et al., 1998) achieved with psychostimulants done on adult rats. They also accorded with the notion that novelty-seeking actions and the rewarding effect of abusive drugs possessed a common pathway (Bardo et al., 1996) and that neural and hormonal substrates activated in a mild stress environment like in the open field may not be critically involved in this process. Our study extended previous findings to narcotic

morphine and demonstrated consistency with the results from psychostimulants.

From the present study, no ontogenesis specificity as with the relationship between morphine place conditioning and open field as well as novelty-seeking behavior was found, except conditioned crossing behavior in the CPP test. As illustrated in Section 3, juvenile NHRs responded more vigorously than NLRs after morphine conditioning (Fig. 3B, left panel), while this individual difference disappeared in adult rats (Fig. 3B, right panel). Specifically, NHRs and NLRs in adult group expressed undifferentiated increase on this measure. This result may indicate larger variations of juvenile rats for morphine-conditioned motor response compared with their adult counterparts; however, this needs to be further confirmed, considering the grossness of this measure.

Worthy to be paid attention is that, in the present study, only NHRs among respective groups showed an appreciable duration increase in drug-paired compartment. In contrast, NLR rats expressed no significant change. This result indicated slow acquisition of place conditioning for outbreed NLR rats relative to NHRs in different-aged rats and would be of potential significance, given the preclinical finding that differentiated initial rewarding effects between individuals will play some role in the ultimate vulnerability to drugs of abuse (Haertzen et al., 1983). Further identification of underlying neural processes and cellular events by which NHR rats developed a ready propensity to the rewarding effect of morphine and NLR rats delayed to react within given conditioning trials might shed light on the specific mechanisms of the rewarding effect of morphine. Moreover, a question of whether novelty-seeking behavior stayed as a stable biobehavioral trait, making juvenile invulnerable NLR rats in the present study develop to invulnerable adult rats, will be proved valuable and should be answered via a within-subjects design other than between-subjects design in the present study.

As one possibility, animals showing difficulties in some learning processes, such as attention deficit, will compromise the conditioning effect, which is independent of rewarding properties. However, detailed time course analysis of the novelty-seeking test illustrated that both NHR and NLR animals did not show any difference in their interactions with the novel object in the first 3 min (data not shown), which warranted that the NHR/NLR categorization in the overall 15-min novelty-seeking test did reflect the differentiation of the interest toward novelty other than that of attention process. Similarly, the association between novelty-seeking behavior and place conditioning could also be independent of drug's rewarding effect if NHR and NLR animals possessed differentiated mnemonic ability to associate the environment with drug treatment. However, to our knowledge, no reliable data were available demonstrating the deficient ability in NLR animals in associative memory process. In fact, LR rats were even more sensitive in amphetamine discrimination task (Exner and Clark, 1993), which necessitated associative learning capability.

From above, the differentiated susceptibility to morphine place conditioning between NHR and NLR rats may be attributed to and predicted by the inherent difference of novelty-seeking drive for both juvenile and adult rats in the present study. Meanwhile, further study is needed to explore the causal relationship that manipulation of the neural substrates underlying novelty-seeking behavior will interfere with the acquirement of morphine CPP effect, especially from individual difference stand.

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