Differences in cocaine-induced place preference persistence, locomotion and social behaviors between C57BL/6J and BALB/cJ mice

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Abstract: C57BL/6J and BALB/cJ mice display significant differences in sociability and response to drugs, but the phenotypic variability of their susceptibility to cocaine is still not well known. In this study, the differences between these two mice strains in the persistence of cocaine-induced conditioned place preference (CPP), as well as the locomotion and social behaviors after the 24-hour withdrawal from a four-day cocaine (20 mg/kg/day) administration were investigated. The results showed that the cocaine-induced CPP persisted over two weeks in C57BL/6J mice, while it diminished within one week among BALB/cJ mice. After 24-hours of cocaine withdrawal, high levels of locomotion as well as low levels of social interaction and aggressive behavior were found in C57BL/6J mice, but no significant changes were found in BALB/cJ mice, indicating that cocaine-induced CPP persistence, locomotion and social behavior are not consistent between these two strains, and that overall C57BL/6J mice are more susceptible to cocaine than BALB/cJ mice at the tested doses.

Keywords: Cocaine; Conditioned place preference; Locomotion; Social behavior; Withdrawal

C57BL/6J and BALB/cJ mice are two widely used strains in biomedical research, especially in behavioral neurosciences. Because these two strains have different neurochemical and endocrinological substrates (Ågmo et al, 1999; Scislowska-Czarnecka et al, 2004; Bach et al, 2011; Kundakovic et al, 2013), they display different responding patterns on many behavioral tasks. For example, BALB/cJ mice are with less sociability (the tendency to seek social interaction) (Sankoorikal et al, 2006; Brodkin, 2007; Moy et al, 2007) but higher levels of anxiety-like behaviors (Bouwknecht & Paylor, 2002; Priebe et al, 2005; Verleye et al, 2011). C57BL/6J mice performs better in learning and memory tasks (Crawley et al, 1997; Van Dam et al, 2006; Shi et al, 2008). C57BL/6J mice exhibit approaching responses toward a novel environment, while BALB/cJ mice exhibit avoidance (Belzung & Berton, 1997; Belzung & Barreau, 2000). Bardo et al (1996) previously claimed that high levels of novelty seeking are associated with an increased risk of drug abusing. Studies also indicated that C57BL/6J and BALB/cJ mice differ in several aspects of drug abuse. For example, C57BL/6J mice are prone to cocaine self-administration (Deroche et al, 1997; Thomsen & Caine, 2011) and display a cocaine-induced conditioned place preference (CPP), however, BALB/cJ mice fail to demonstrate place preference to cocaine at the previously tested doses (Belzung & Barreau, 2000). Additionally, morphine preferences of C57BL/6J and BALB/cJ mice are differentially affected by social group and isolation during the CPP test (Kennedy et al, 2012).

Drug abuse is often associated with sociability, emotion and memory (Curtis & Wang, 2007; Perrine et al, 2008; Niigaki et al, 2010). Given the differences in these aspects between C57BL/6J and BALB/cJ mice, the comparisons of drug abuse between the two strains may provide more background information. CPP is a widely used paradigm in studying the rewarding effects of drugs and modeling some aspects of long term drug-seeking and relapse (Schechter & Calcagnetti, 1993; Sakoori &

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Murphy, 2005). The drug paired cues play a critical role in the reinstatement of drug-seeking behaviors after a period of abstinence (Crombag et al, 2008; Su et al, 2013). Although differences in the susceptibility to the reinforcing properties of cocaine, morphine, and ethanol have been described among inbred mice strains (Cunningham et al, 1992; Eisener-Dorman et al, 2011), the persistence of CPP during cocaine withdrawal in C57BL/6J and BALB/cJ mice remains unclear. Zhang et al previously (2002) proposed that the persistence of cocaine-induced CPP is strain dependent. Accordingly, the present study investigated: (1) the phenotypic variability between these two mice strains in cocaine-seeking behaviors reflected by the persistence of cocaine-induced CPP; (2) the differences in locomotion and social behaviors after the 24-hour cocaine withdrawal.

MATERIALS AND METHODS

Animals

Male C57BL/6J and BALB/cJ mice at 8-week of age were obtained from the Laboratory Animal Center of Xi'an Jiaotong University (Shaanxi, China). The animals were housed in groups of four in standard transparent Makrolon cages (42 cm×26 cm×20 cm, length×width×height). The colony room was illuminated on a 12:12 light-dark cycle (lights on 2000h) and the temperature was maintained at 23±2 ℃. Food and water were available *ad libitum*. Mice were allowed to adapt to housing conditions for one week and were handled daily by the same technician for three days prior to testing. All protocols and procedures were approved by the Animal Care and Use Committee of Shaanxi Normal University.

Chemicals and injection

Cocaine-hydrochloride (Northwest Pharmaceutical Co., Ltd. Sinopharm, Xi'an, China) was diluted in saline (0.9% NaCl) and was administrated subcutaneously (s.c. 20 mg/kg) (Zhang et al, 2002; Eisener-Dorman et al, 2011).

Conditioned place preference test

The place preference apparatus consisted of two large compartments (34 cm×25 cm× 32 cm, length×width×height) with different visual cues (one had gray walls and the other had white-black striped walls) separated by a small middle compartment (11 cm×25 cm×32 cm, length×width×height). The middle compartment was an acclimation chamber with a door (7 cm×9 cm, height×width) in the center of the base.

Pre-test: On the day prior to conditioning, all animals were tested to determine any individual innate preference to either of the large lateral chambers. The mice (C57BL/6J, *n*=12; BALB/cJ, *n*=12) were given free access to each cue-decorated chamber when received a subcutaneous injection of physiological saline. Following 10-minute acclimation, the time spent in two lateral chambers was recorded for 15 minutes by a camera (Sony, HDR-XR260E) mounted 70 cm above the arena. After each trial, the chamber was thoroughly cleaned with 70% ethanol solution.

Conditioning with cocaine: Each strain of mice (C57BL/6J, *n*=8; BALB/cJ, *n*=9) were conditioned with cocaine. Both cocaine and equivalent volume of physiological saline injections were given on the same day for four consecutive days. Specifically, in the morning, subjects were placed in one of the outer chambers with cocaine injections and were placed in the opposite chamber with saline injections at afternoon. Two injections per day in an alternating counter balanced sequence for four days, thus, providing four associative pairings for cocaine and saline. Mice were conditioned for 2 h after injections. The morning session and the afternoon session were at least 6 hr apart to allow time for cocaine clearance (Thiel et al, 2008).

Post-test: CPP testing was conducted 24 hour after the last conditioning trial. Mice in a drug-free and a saline-free state were allowed to free access to each compartment. The time spent in two lateral chambers was recorded for 15 minutes.

The persistence of CPP: Mice were housed in their home cages after the CPP testing. The day of post-test was taken as intermission day zero and then the place preference testing was conducted on intermission day 7, 15 in BALB/cJ and on day 7, 15, 25 in C57BL/6J mice, respectively.

Open-field test

Another group of C57BL/6J and BALB/cJ mice was used in open-field test and social interaction test. Mice were randomly assigned into cocaine-treated groups (*n*=8) and control groups (*n*=8). The cocaine-treated groups (CC: C57BL/6J mice treated with cocaine, BC: BALB/cJ mice treated with cocaine) were administrated with cocaine (20 mg/kg) at 0900h for four consecutive days. Control groups (CS: C57BL/6J mice treated with saline, BS: BALB/cJ mice treated with saline) were administrated with saline instead. Locomotion and anxiety-like behaviors were assessed in an open field chamber 24 hr after the last injection. The open field chamber (50 cm×50 cm×25 cm, length×

width×height) made of white glacial polyvinyl chloride was brightly and evenly illuminated by four 60 W lamps mounted 1.5 m above (400 lux in the center of arena). The square arena was divided into 16 quadrants (four central and 12 peripheral) (Fiore & Ratti, 2007). Mouse was placed in the center of the arena and allowed to explore for 5 minute. The time spent in the central and peripheral zones and numbers of crossings between quadrants were recorded. The anxiety-like behaviors were assessed by the time spent in the center of the arena and the locomotion was determined by the numbers of crossings.

Same-sex social interaction test

The social interaction test was conducted between 1500h and 1700h. To eliminate possible influences from sexually motivated behaviors, only male-male dyads were used. The stimulus mouse was an unfamiliar, sexually naive individual that was approximately of the same age and size as the tested mouse. Testing were conducted in a neutral plastic cage (44 cm×22 cm×16 cm, length×width×height) with wood shavings bedding (2 cm) and a removable opaque divider in the middle. The stimulus and tested mouse was confined in each side of the cage for 3 minute, then the divider was removed and the activities of the mice were recorded for 15 min by a video-recorder mounted 70 cm above.

Mice behaviors were classified as investigatory behavior (sniffing face, body or anogenital area), aggressive behavior (pouncing, i.e. jumps or lunges; fighting, i.e. tumbling or biting; chasing), body contact (staying together with another mouse or amicable grooming); self-grooming (cephalocaudal progression that begins with rhythmic movements of the paws around the mouth and face, ears, descending to the ventrum, flank, anogenital area and tail) and other behaviors (digging, jumping, climbing the cage and resting).

Statistical analysis

All behavioral variables were scored from video footage according to established definitions by a naïve observer using Observer 5.0 (Noldus, Netherlands). Statistical analyses were carried out via SPSS 10.0 (SPSS Inc., Chicago, Illinois, USA). Data were checked for normality using the one-sample Kolmogorov–Smirnov test. The expression of place conditioning was analyzed using repeated-measures, with the intermission day as a repeated measure. Paired-samples *t*-test was used to evaluate the differences in time spending during the pre-test and intermittent tests. Data from the open-field test and the social interaction test were compared using two-way ANOVA with strains and cocaine treatment as factors. Group differences were compared using *post-hoc* test except aggressive behavior which was abnormally distributed and was compared using Mann–Whitney *U*-test. All data were expressed as mean±*SE*. Statistical significance was taken at $P < 0.05$.

RESULTS

Conditioned place preference

The pre-test indicated that neither C57BL/6J ($t_{(11)}$=1.76, P=0.106) nor BALB/cJ mice ($t_{(11)}$=0.484, P=0.638) showed preferences to either of the chambers (Figure 1A). Post-testing and intermittent testing

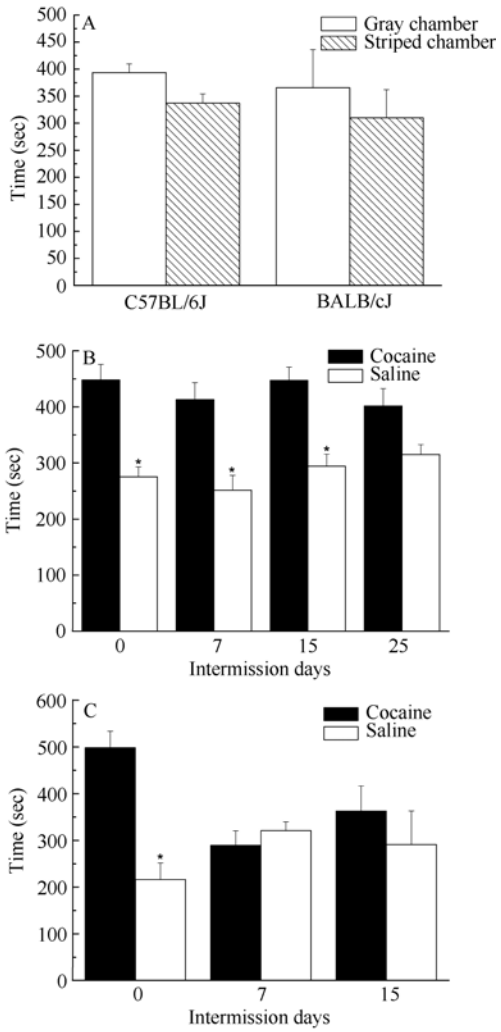

Figure 1 Time spent in saline- or cocaine-paired compartments by C57BL/6J and BALB/cJ mice

A: Pre-test; B and C: Post-test and intermittent test in C57BL/6J and BALB/cJ mice following cocaine conditioning, respectively; The day of post-test was taken as intermission day 0; *: $P \leqslant 0.05$; **: $P \leqslant 0.01$.

indicated that cocaine could induce place preference in both mice strains (C57BL/6J, $F_{(3,28)}$=217.381, P<0.001; BALB/cJ, $F_{(2,24)}$=7.101, P<0.001). However, a significant interaction between cocaine conditioning and intermission day was found only in BALB/cJ mice ($F_{(2,\ 24)}$= 7.239, P=0.003) but not in C57BL/6J mice ($F_{(3,28)}$=1.043, P=0.384).

A significant preference to the cocaine-paired compartment was shown in both mice strains on the day of post-testing (intermission day 0) (C57BL/6J: $t_{(7)}$= 3.849, P=0.006; BALB/cJ: $t_{(8)}$=4.092, P=0.03) (Figure 1B, C) and persisted to intermission day 7 ($t_{(7)}$=3.304, P=0.013) and 15 ($t_{(7)}$=3.862, P=0.006), but not on day 25 ($t_{(7)}$=1.985, P=0.094) in C57BL/6J mice (Figure 1B). However, this preference persistence was not found in BALB/cJ mice on either day (day 7: $t_{(8)}$=0.779, P=0.458; day 15: $t_{(8)}$=0.638, P=0.054) (Figure 1C).

Open field behavior

The main effect of strain was significant in the time spent in the central area ($F_{(3,\ 28)}$=4.736, P=0.038) and transitions ($F_{(3,\ 28)}$=28.776, P < 0.001). However, the interactions between strain and cocaine administration had no effects on either the total transitions ($F_{(3,\ 28)}$=2.028, P=0.165) or the time spent in the central area ($F_{(3,\ 28)}$=3.461, P=0.073).

Although no differences were found in the time spent in the central area between C57BL/6J and BALB/cJ control mice *(Mean difference*=1.158, P= 0.996), C57BL/6J control mice showed a higher level of locomotor activity (total transitions) (*Mean difference*=46.000, P=0.02). Cocaine-administrated C57BL/6J mice showed a greater number of total transitions than both the C57BL/6J control mice (*Mean difference*= 35.375, P=0.04) and the cocaine-administrated BALB/cJ mice (*Mean difference*=79.250, P<0.001), as well as spent more time in the central area (*Mean difference*=14.799, P=0.008) than the cocaine-administrated BALB/cJ mice. However, cocaine-administration did not affect either the total transition ($F_{(3,\ 28)}$=2.580, P=0.119) or the time spent in the central area ($F_{(3,\ 28)}$=0.178, P=0.677) in BALB/cJ mice (Figure 2).

Same-sex social interaction

The male-male interactions indicated that strain and cocaine both significantly affected the social investigations (strain [duration: $F_{(3,\ 28)}$=18.216, P<0.001, frequency: $F_{(3,\ 28)}$=107.113, P < 0.001]; cocaine [duration: $F_{(3,28)}$=8.817, P=0.006, frequency: $F_{(3,28)}$=20.502, P < 0.001]), the contact behaviors (strain [duration: $F_{(3,28)}$=30.856, P<0.001, frequency: $F_{(3,28)}$=$F_{(3,28)}$= 356.608, P < 0.001]; cocaine [duration: $F_{(3,28)}$=8.891, P=0.006, frequency: $F_{(3,28)}$= $F_{(3,\ 28)}$=0.888, P=0.354]) and the frequencies of self-grooming (strain: $F_{(3,28)}$=66.336, P< 0.001; cocaine: $F_{(3,28)}$=14.131, P<0.001). The frequencies of aggressive behaviors between two mice strains were significantly different ($F_{(3,\ 28)}$=33.618, P<0.001). Moreover, significant interactions between strain and cocaine were found in the social investigation (duration: $F_{(3,\ 28)}$=15.386, P=0.001; frequency: $F_{(3,\ 28)}$=16.084, P < 0.001), the self-grooming (Duration: $F_{(3,\ 28)}$=14.598, P=0.001; Frequency: $F_{(3,\ 28)}$=25.121, P<0.001), duration of contact behavior ($F_{(3,\ 28)}$=9.675, P=0.004) and aggressive behaviors ($F_{(3,28)}$=4.423, P=0.045).

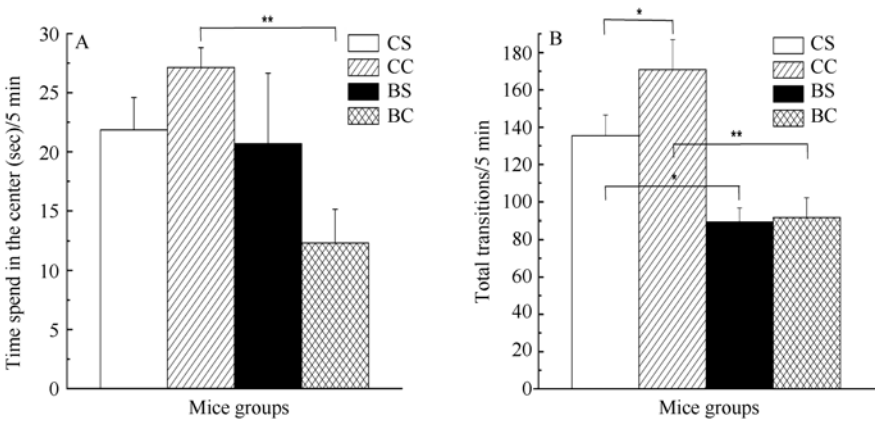

Figure 2 Open-field behavior of C57BL/6J and BALB/cJ mice after the 24 h cocaine withdrawal

A: The time spent in the central area; B: Total transitions; *: P≤0.05; **: P≤0.01; CS and CC: C57BL/6J mice administrated with saline and cocaine, respectively; BS and BC: BALB/cJ mice administrated with saline and cocaine, respectively.

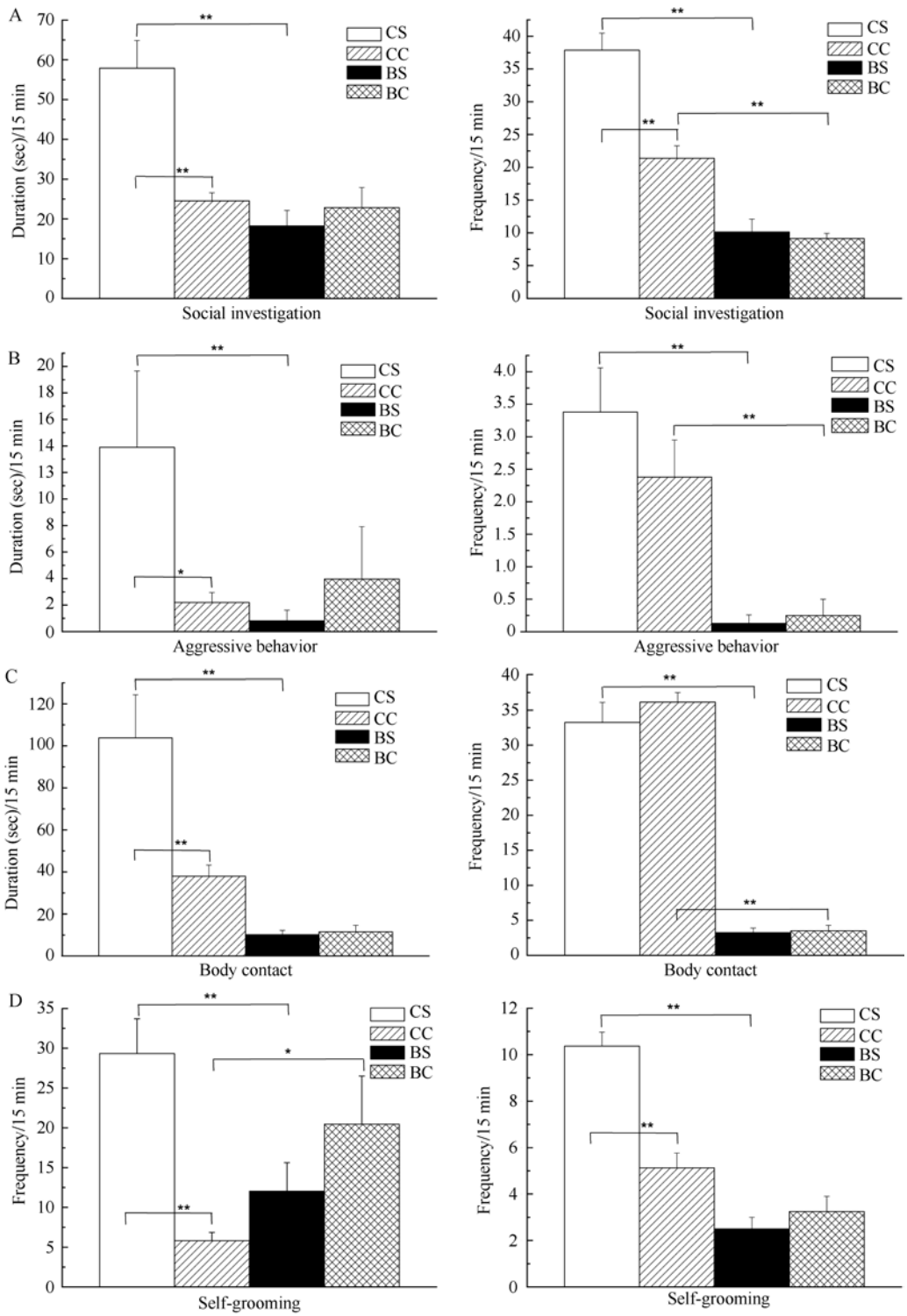

Figure 3 Duration and frequency of same-sex social interactions in C57BL/6J and BALB/cJ mice after the 24 h of cocaine withdrawal

A: Investigation; B: Aggression; C: Body contact; D: Self-grooming; *:$P \leqslant 0.05$, **:$P \leqslant 0.01$; CS and CC: C57BL/6J mice administrated with saline and cocaine, respectively; BS and BC: BALB/cJ mice administrated with saline and cocaine, respectively.

C57BL/6J control mice showed high levels of the social investigations (duration: *mean difference*=39.646, $P < 0.001$; frequency: *mean difference*=27.750, $P < 0.001$), the aggressive behaviors (duration: U=3;

P=0.001; frequency: *U*=1, *P*＜0.001) and the contact behavior (duration: *mean difference*=93.608, *P*=0.000; frequency: *mean difference*=30.005, *P* ＜ 0.001) compared with the BALB/cJ control mice. Moreover, the levels of the self-grooming behaviors between these two control mice groups were also significantly different (duration: *mean difference*=17.296, *P*=0.007; frequency: *mean difference*=7.875, *P*＜0.001) (Figure 3).

Cocaine-administrated C57BL/6J mice exhibited attenuations in the social investigations (duration: *mean difference*=−33.360, *P*＜0.001; frequency: *mean difference*=−16.500, *P* ＜ 0.001), the self-grooming behaviors (duration: *mean difference*=−23.524, *P*＜0.001; frequency: *mean difference*=−5.250, *P* ＜ 0.001), the contact behaviors (duration: *mean difference*=−65.813, *P*=0.001; frequency: *mean difference*=−2.875, *P*=0.230) and the aggressive behaviors (duration: *U*=9, *P*=0.015; frequency: *U*=22, *P*=0.328) than those of their control mice (Figure 3).

Cocaine withdrawal had no apparent effect on social investigations (duration: *mean difference*=4.6140, *P*=0.506; frequency: *mean difference*=–1.000, *P*=0.717), aggressive behaviors (duration: *U*=31.5, *P*=0.927; frequency: *U*=31.5, *P*=0.927), contact behaviors (duration: *mean difference*=1.390, *P*=0.928; frequency: *mean difference*=0.250, *P*=0.916) or self-grooming behaviors (duration: *mean difference*=8.401, *P*=0.166; frequency: *mean difference*=0.750, *P*=0.383) in BALB/cJ mice (Figure 3).

Compared with cocaine-administrated BALB/cJ mice, cocaine-administrated C57BL/6J mice were more engaged in social investigations (duration: *mean difference*=1.6725, *P*=0.809; frequency: *mean difference*=12.250, *P*＜0.001), aggressive behaviors (duration: *U*=15, *P*=0.083; frequency: *U*=6.5, *P*=0.005), contact behaviors (duration: *mean difference*=26.495; *P*=0.095; frequency: *mean difference*=32.625, *P*＜0.001), but less in self-grooming behaviors (duration: *mean difference*=–14.630; *P*=0.02; frequency: *Mean difference* =0.875; *P*=0.35) (Figure 3).

DISCUSSION

Persistence of cocaine-induced place preference

Although Belzung & Barreau (2000) claimed that cocaine may be not able to induce place preference in BALB/cJ mice, in this study, after cocaine conditioning, both C57BL/6J and BALB/cJ mice showed a significant preference to the cocaine-paired compartment, indicating that cocaine induces rewarding effects in both mice strains (Miner, 1997; Zhang et al, 2002; Eisener-Dorman et al, 2011). Since the rewarding effects of cocaine could be influenced by administration patterns (Zhang et al, 2002), this discrepancy may be due to the fact that Belzung & Barreau (2000) chose a dose of 10 mg/kg and a conditioning trial of half-hour, instead of 20 mg/kg and two-hour, respectively, as in this present study. These phenomena indicate that the CPP establishment could be affected by both the doses of cocaine and the duration of reinforcement.

In this study, the cocaine-associated preference diminished within one week after the withdrawal in BALB/cJ mice, but persisted at least two weeks after the withdrawal in C57BL/6J mice, which is consistent with previous studies indicating that the cocaine-induced CPP could be maintained by repeated testing two or four weeks after conditioning (Mueller & Stewart, 2000; Zhang et al, 2002). Tran-Nguyen et al (1998) found that the cocaine-seeking behaviors were getting more intense during the course of cocaine withdrawal in rats. Su et al (2013) reported that the cocaine-induced CPP could remain viable at three weeks of the withdrawal. Mueller & Stewart (2000) found that in animals tested only once, a spontaneous reduction in CPP was shown at six weeks after conditioning. These findings suggest that CPP may be variably maintained or extinguished dependent upon the timing and frequency of testing following conditioning (Sakoori & Murphy, 2005). Intermittent re-testing for CPP itself may act as a secondary reinforce that strengthens the association between drug experience and environment and may actually help maintain cocaine-induced CPP (Mueller & Stewart, 2000; Sakoori & Murphy, 2005). However, no such reinforcement was shown in BALB/cJ mice. The genetic variations in pharmacokinetic may not account for the differences in cocaine responsiveness observed because no difference in the incorporation of [^{3}H]-cocaine has been found between C57BL/6J and BALB/cJ mice (Seale, 1991). An alternative explanation of the differences in the persistence of CPP expression is the poor capacity of learning and memory of BALB/cJ mice (Crawley, 2000; Shi et al, 2008) because the CPP task involves learning processes (Fleming et al, 1994; Thiel et al, 2008). Similarly, Oler & Markus (1998) found that young rats showed a stronger retention for conditioning context after conditioning than aged rats. Thus, the persistence of

CPP expression indicates that the development of ordinary memory and addictive memory between C57BL/6J and BALB/cJ mice are quite different.

Studies suggested that place conditioning may be used to model some aspects of long term drug-seeking, drug relapse, and the hedonic properties of drugs (Sakoori & Murphy, 2005). Our results indicate that the persistence of cocaine-induced CPP during prolonged withdrawal may contribute to the sustained vulnerability to "relapse" of cocaine-seeking behavior. Moreover, compared with C57BL/6J mice, BALB/cJ mice are characterized by higher levels of anxiety-like behaviors, lower locomotor activities and are less sociability (Crawley et al, 1997; Sankoorikal et al, 2006; Brodkin, 2007; Moy et al, 2007). The different CPP persistence showed in this study between the two mice strains is in accordance with the previous study indicating that the highly social species have different susceptibility to the effects of drug compared with the less social species (Curtis & Wang, 2007).

Cocaine-induced locomotor activities

In this present study, the 24-hour cocaine withdrawal had no effect on the anxiety-like behaviors of the two mice strains, which is consistent with previous reports (Niigaki et al, 2010; Stoker & Markou, 2011). However, in rats, cocaine withdrawal is associated with increased anxiety-like behaviors in the elevated plus maze (Perrine et al, 2008; Hall et al, 2010). Moreover, the anxiogenic effects of abstinence from cocaine are also correlated with different protocols (e.g. the elevated plus maze, the open field or the light-dark box) (Stoker & Markou, 2011; de Oliveira Citó Mdo et al, 2012).

In this study, after a 24-hour cocaine withdrawal, the level of locomotor activities of C57BL/6J mice increased while that of BALB/cJ mice was maintained at the same level. These results are consistent with previous studies indicating that a marked increase or dose-dependent stimulant effects on locomotor activities in response to cocaine have been found in C57BL/6J mice (Zhang et al, 2002; Eisener-Dorman et al, 2011; Thomsen & Caine, 2011). BALB/cJ mice are less sensitive to the cocaine-associated stimulant effects on locomotor activities (Ito et al, 2007; Eisener-Dorman et al, 2011; Thomsen & Caine, 2011), though some reports claimed that BALB/cJ mice show hyperlocomotor activities in response to cocaine (Miner, 1997; Kuzmin et al, 2000). In the open field test, the increased locomotion activities were found in rats after 24-hour of abstinence from cocaine (de Oliveira Citó Mdo et al, 2012). However, some studies showed that cocaine withdrawal suppresses locomotor activities in rats (Baldo et al, 1999; Koeltzow & White, 2003). One potential explanation for these discrepancies is that the locomotor activity may be influenced by the measurement environment (e.g. the open field, the conditioning chamber or the light-dark box) or cocaine dosage, administration pattern and withdrawal time (Zhang et al, 2002; Niigaki et al, 2010; Eisener-Dorman et al, 2011; Stoker & Markou, 2011; de Oliveira Citó Mdo et al, 2012). For example, the context in which a drug is experienced can significantly influence both acute and sensitized responses to the drug (Badiani & Robinson, 2004; Eisener-Dorman et al, 2011). A specific interaction between the cocaine and the environment may result in context-dependent sensitization in BALB/c mice (Eisener-Dorman et al, 2011). The present results indicate that cocaine withdrawal induces locomotion changes in C57BL6/J mice.

Cocaine-induced social behaviors

In this present study, when interacting with same-sex individuals, C57BL/6J mice were more active in social investigation, body contact and aggression than those of BALB/cJ mice, which are consistent with previous reports (Sankoorikal et al, 2006; Brodkin, 2007; An et al, 2011). Fairless et al (2008) demonstrated that the size of the corpus callosum relative to brain weight is associated with sociability among these two mice strains. Moreover, compared with the saline control, cocaine withdrawal induced remarkable decreases in social investigation, contact behavior and aggressive behavior in C57BL/6J mice as described in previous reports (Rademacher et al, 2002; Estelles et al, 2007). Although cocaine induces complicated changes in social behaviors, no agreement has been reached on its specific effects on aggression (Moeller et al, 1997; Dhossche, 1999). Some studies also indicated that other than strains or species, the aggressive behaviors may also be affected by the patterns of drug administration (single or binge administration), the dosing regimens and the specific temporal window assessed (Estelles et al, 2004, 2007; Wang et al, 2012).

Interestingly, no significant effects of cocaine withdrawal on either the social behaviors or the locomotor activities were found in BALB/cJ mice, indicating that there may be a dissociation between cocaine-induced

CPP and locomotion or social behavior in BALB/cJ mice. Compared with C57BL/6J mice, different mechanisms may underlie such effects in BALB/cJ mice. Combined the persistence of CPP test, these results indicate that C57BL/6J mice are more susceptible to cocaine withdrawal than BALB/cJ mice. However, because BALB/cJ mice are characterized with low levels of social investigation and contact behavior, it is possible that what we have observed in this study is only a 'floor effect' of cocaine on the two behaviors.

Mesolimbic dopamine (DA) is responsible for cocaine-induced behavior and locomotor activation (Sarnyai, 1993; Tran-Nguyen et al, 1998). Hyperlocomotion induced by psychostimulants is mediated by the mesolimbic dopaminergic system, whereas stereotyped behaviors are mediated by the nigrostriatal dopaminergic system (Ito et al, 2007). The balances of the activation of dopaminergic neurons between mesolimbic and nigrostriatal systems may play an important role to engender corresponding behavioral outcomes (Ito et al, 2007). The differences between C57BL/6J and BALB/cJ mice in dopaminergic function within the prefrontal cortex and the striatum have been reported (Hervé et al, 1979; Helmeste & Seeman, 1982). Thus, the differences in dopaminergic neurotransmission between C57BL/6J and BALB/cJ mice may have induced their different behavioral response to cocaine. Moreover, these two mice strains have different hypothalamic–pituitary–adrenal (HPA) responses to stressors (Anisman et al, 1998). Therefore, the interactions between the HPA axis and the DA system may also affect their sensitized behavioral responses (Wang et al, 2010). Additionally, Deroche et al (1997) found that the genetically based differences in sociability between the two strains may play an important role in determining the sensitivity to cocaine. Taken together, the susceptibility to cocaine in the two mice strains may be mediated by the complex interaction between neurobehavioral and epigenetic outcomes and genetically based differences.

In conclusion, this study demonstrates that the cocaine-associated rewarding effects, drug seeking behaviors, locomotor activities and social behaviors are inconsistent in C57BL/6J and BALB/cJ mice stains; C57BL/6J mice are more susceptible to cocaine than BALB/cJ mice at the doses tested in the present study. Further studies are necessary to explore the specific neural mechanisms underlying these differences.

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