



Differences in cocaine- and morphine-induced cognitive impairments and serum corticosterone between C57BL/6J and BALB/cJ mice

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ABSTRACT

Addictive drug exposure is associated with impairments in various cognitive domains. Murine models of drug-induced cognitive impairment have helped to inform research on interventions to attenuate such cognitive diminishment; however, while differences between the drug-induced cognitive impairments exhibited by C57BL/6J and BALB/cJ mice have been observed, they remain unclear. This study measured differences in cognitive behavior performance on the object recognition test (ORT) and social recognition test (SRT) and serum levels of corticosterone (CORT) between C57BL/6J and BALB/cJ mice after 14-day chronic exposure to either cocaine (5 mg/kg) or morphine (3 mg/kg) at a dosage of 10 ml/kg/day. The ORT revealed that cocaine and morphine exposure significantly reduced the discrimination ratio in both C57BL/6J and BALB/cJ mice, exploration time was only reduced in C57BL/6J mice: the exploration times of C57BL/6J mice from the control ($p < 0.05$), cocaine ($p < 0.05$), and morphine ($p < 0.01$) administration groups were significantly less than those of BALB/cJ mice. The SRT demonstrated that drug exposure significantly reduced exploration time (cocaine, $p < 0.01$; morphine, $p < 0.01$) and impaired social recognition in C57BL/6J mice. No significant effect in BALB/cJ mice was observed. Serum CORT levels were lower in control C57BL/6J mice than in control BALB/cJ mice ($p < 0.05$), but no difference was observed after drug administration. In conclusion, changes in object and social learning recognition indicate that C57BL/6J mice are more sensitive than BALB/cJ mice to chronic drug exposure, especially to cocaine; concomitant changes in serum CORT may mediate these effects.

1. Introduction

Chronic drug exposure has been associated with impairments in various cognitive domains (Dougherty et al., 1996; Li et al., 2001; Miladi et al., 2008, 2011; Spronk et al., 2013) and social skills (Hulka et al., 2014; Preller et al., 2014a, 2014b). For example, chronic morphine exposure impairs spatial memory and hippocampal long-term potentiation – a form of synaptic plasticity and potential cellular substrate of learning and memory (Bao et al., 2007; Salmanzadeh et al., 2003) – possibly due to an accumulation of extracellular adenosine and the resulting increased activation of adenosine A1 receptors (Pu et al., 2002). Interspecies differences in drug-induced cognitive changes have rarely been observed, especially among species with different learning and memory capacities, such as C57BL/6J and BALB/cJ mice.

C57BL/6J mice perform better in learning and memory tasks and exhibit approach responses toward a novel environment, whereas BALB/cJ mice exhibit avoidance (Belzung and Berton, 1997; Belzung

and Barreau, 2000). BALB/cJ mice demonstrate less sociability (Sankoorikal et al., 2006; Wang et al., 2014) and higher levels of anxiety-like behaviors than do C57BL/6J mice (Priebe et al., 2005; Verleye et al., 2011). Moreover, C57BL/6J and BALB/cJ mice differ in several aspects of drug abuse: when the former are exposed allow to self-administer cocaine (Deroche et al., 1997; Thomsen and Caine, 2011), they exhibit cocaine-induced conditioned place preference (CPP); BALB/cJ mice fail to develop cocaine-induced CPP at the same doses (Belzung and Barreau, 2000; Kennedy et al., 2012). We therefore hypothesized that cognitive effects of drug exposure may differ between C57BL/6J and BALB/cJ mice.

Experimental and clinical data have reported hyper-secretion of glucocorticoids in recognition-related diseases, such as post-traumatic stress disorder (Brinks et al., 2007); such findings have prompted research on the effects of glucocorticoids on memory formation and its extinction (Brinks et al., 2007; De Quervain et al., 2007). The primary glucocorticoid in rodents, Corticosterone (CORT) plays a critical role in

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the regulation of the hypothalamic–pituitary–adrenal (HPA) axis and cognitive behaviors (Schwabe et al., 2012; Lupien et al., 2007). The administration of CORT triggers the inhibition of learning and memory retrieval (Roosendaal et al., 2004). Interestingly, cocaine exposure activates the HPA axis (Armario, 2010), implicating CORT in drug addiction and abuse (Goeders, 2002; Li and Sinha, 2008).

The present study explores the hypothesis that cocaine- and morphine-induced impairment of object and social recognition behaviors differ between C57BL/6J and BALB/cJ mice. Subsequent analyses were further performed to confirm a potential association between CORT and cognitive deficits following chronic drug exposure.

2. Materials and methods

2.1. Subjects

Adult male mice (90 days of age) from two inbred strains, C57BL/6 ($n = 30$) and BALB/cJ ($n = 30$), were obtained from Northwest Normal University breeding colony (Lanzhou, China). Five mice were housed per Plexiglass cage ($42 \times 26 \times 20$ cm); the sawdust bedding placed therein was changed weekly. The colony temperature was maintained at 24 °C. Mice subjected to for motor activity and operant studies were maintained under a regular light/dark cycle (lights on at 06:00, lights off at 18:00). Subjects were provided *ad libitum* access to food and water. The maintenance and treatment of animals were in accordance with the Guidelines for the Care and Use of Laboratory Animals. Our protocols were approved by the animal care and use committee at Northwest Normal University.

2.2. Procedure

The experimental procedures were divided into the following two phases: drug exposure and behavioral testing (two sessions). The former was conducted at 9 a.m. and 12 a.m., 5 days per week; a 2-day interval separated the first and second drug exposure sessions (Belzung and Barreau, 2000). Mice were intraperitoneally injected with either vehicle or drug (10 ml/kg). All drugs were dissolved in physiological saline (0.9%). Cocaine chlorhydrate (Northwest Pharmaceutical, Sinopharm, China) or Morphine sulfate pentahydrate (Northwest Pharmaceutical, Sinopharm, China) was administered to C57BL/6J mice (cocaine, 5 mg/kg, $n = 10$; morphine, 3 mg/kg, $n = 10$) and BALB/cJ mice (cocaine, 5 mg/kg, $n = 10$; morphine, 3 mg/kg, $n = 10$) to induce location preference (Belzung and Barreau, 2000). A vehicle of the same volume was administered to control C57BL/6J ($n = 10$) and BALB/cJ mice ($n = 10$). Behavioral testing was conducted between 9 am and 12 am, and animals were subjected to the aforementioned drug regimen between 2 and 6 pm (Chart 1).

2.2.1. Object recognition test (ORT)

ORT was performed as described by Ennaceur and Delacour (1988). The testing apparatus was an open-field box (50 cm³). The mice were habituated to the testing apparatus for 5 min/day for two consecutive days. Recognition behavior was examined on the second day. The ORT consisted of a familiarization phase followed by a test phase with a 15-min inter-trial interval. During the familiarization phase, the mouse

was allowed to explore two identical objects for 5 min and was then returned to its home cage. Both objects were removed during the 15-min interval and were replaced with one object identical to the two removed objects and one novel object. The mouse was then placed back in the box for a 5-min test phase. Both objects and object location were counterbalanced to remove any effect of object and/or location preference. The experimenter was blind to the group to which each mouse belonged, and video of each trial was obtained for later analysis. Exploration of an object was defined as the mouse directing its nose toward the object at a distance of 1 cm and/or touching the object with its nose or paws. To measure object discrimination, four parameters were recorded: (a) time (T) spent exploring objects A and B during the familiarization phase (T1A, T1B) and (b) time spent exploring the familiar (A) and novel objects (N) during the test phase (T2A, T2N). The discrimination ratio $(T2N - T2A)/(T2N + T2A)$ was analyzed with initial exploration time (T1A + T1B) as a covariate.

2.2.2. Social recognition test (SRT)

SRT was performed on the day after the ORT. This protocol consisted of an additional two consecutive days of testing: habituation–dishabituation (h–d) and discrimination tests were performed on the first and second days, respectively. On both days, test animals were initially habituated to the testing arena, a cubic (33 × 33 × 25 cm) white plastic container with fresh sawdust covering the bottom, for 10 min. Social recognition was tested using same-sex juvenile mice placed in the center of the testing arena where the experimental mouse was present. During the h–d component of the test, test mice were repeatedly exposed to a juvenile mouse for 2 min: four times with the same animal (habituation) and then with a novel mouse in a final 5th trial (dishabituation). There was a 10-min interval between each 2-min trial in which the test animal remained alone in the arena. After the five trials, all mice were returned to their home cages and remained there overnight. On day two, 24 h after the h–d test was completed, test mice were simultaneously exposed to two juvenile mice stimuli (fixed approximately 10 cm apart and at the same orientation) for 2 min: a familiar mouse (used in the habituation trials) and a novel, unfamiliar mouse. All animals were returned to their home cages after testing. Stimulus animals used for the h–d and discrimination tests came from different home cages and breeding pairs. No stimulus animal was used for more than five test animals. All trials were recorded using an overhead camera and the time spent investigating the stimulus animal was scored. Independent scoring was performed by tained personnel who were blind to the genotype of the tested animal. Social investigation was defined as any direct or nasal contact by the experimental animal with any body part of the stimulus mouse.

2.3. Serum corticosterone (CORT) test

Two hours after the SRT, all mice were deeply anesthetized with sodium pentobarbital and blood was collected directly from the heart *via* a terminal bleed (for details, refer to Yu et al., 2012).

The serum concentration of CORT was measured using a mouse-specific enzyme-linked immunosorbent assay kit (Shanghai Hushang Biotechnology, Shanghai, China) according to standard procedures. The optimal dilutions of plasma (1:5) were determined using dilution curves

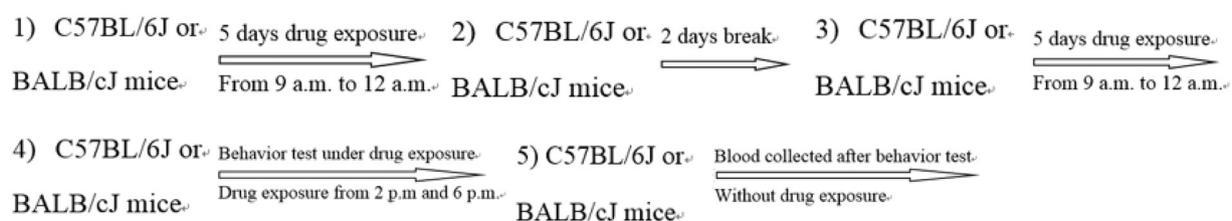


Chart 1. The procedure of addictive drug exposure.

(1:1, 1:5, and 1:10). The prepared sample and the standard were placed in separate well plates and incubated at 37 °C for 30 min. The plate was washed four times with wash solution. Horseradish peroxidase (HRP)-conjugate reagent was then added, and the solution was incubated at 37 °C for 30 min. After the plate was washed four more times, Chromogen solutions A and B were added. After 15 min of incubation at 37 °C, the reaction was terminated using a stop solution. The optical density (OD) of the sample was determined at 450 nm using a Metertech micro-plate reader (BioTek Instruments, Winooski, USA) after the reader was zeroed using the blank well. The inter- and intra-assay coefficients of variation were 17.3% and 4.3%, respectively.

2.4. Statistical analysis

Statistical analyses were conducted using SPSS 13.0 (SPSS Inc., Chicago, USA). Data were checked for normality using a one-sample Kolmogorov-Smirnov test. The exploration time, discrimination ratio, and serum CORT were analyzed using a two-way analysis of variance (ANOVA; mice strain \times drug). The daily social investigation times were analyzed using a one-way ANOVA with treatment as the dependent variable. Multiple post-hoc comparisons were conducted using Tukey's method. The differences between the time spent investigating familiar and novel stimuli were analyzed with an independent two-tailed *t*-test. The social investigation times were compared using ANOVA with repeated measures and Tukey's multiple post-hoc comparisons. All data are presented as mean \pm SEM and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Effects of cocaine and morphine exposure in ORT

The two-way ANOVA showed that exploration time in the ORT was significantly affected by drug administration ($F_{(5, 54)} = 6.438$, $p < 0.01$), but no significant interaction between mice strain and drug administration was found. However, the discrimination ratio was significantly reduced by the interaction between mice strain and drug administration ($F_{(2, 57)} = 3.68$, $p < 0.01$) (Figs. 1, 2).

The post-hoc comparisons showed that the exploration time of control C57BL/6J mice was less than that of control BALB/c mice ($p < 0.05$) (Fig. 1). While cocaine and morphine exposure reduced the

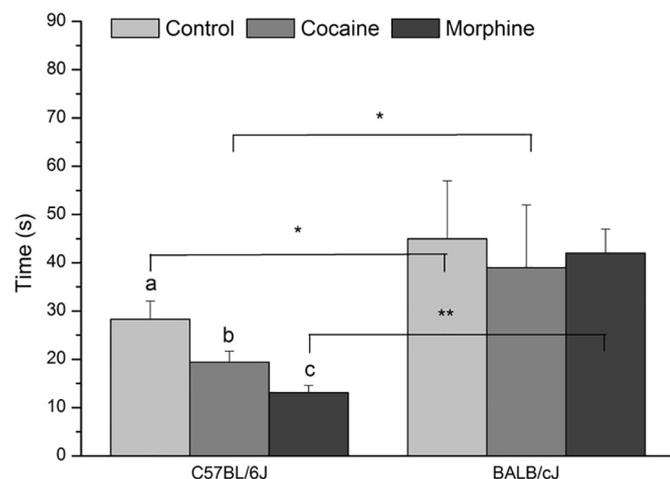


Fig. 1. The time spent exploring objects during the familiarization phase of the object recognition test. Control: control group; Cocaine: cocaine administration group; Morphine: morphine administration group. Data are shown as mean \pm S.E.M. Different letters indicate significant within-species differences. Asterisk (*) ($p < 0.05$) and asterisks (**) ($p < 0.01$) indicate significant difference between C57BL/6J and BALB/cJ mice.

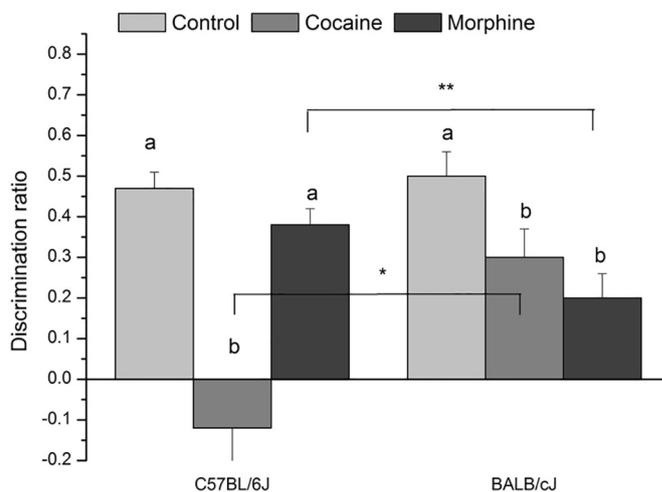


Fig. 2. The discrimination ratio during the test phase of the object recognition test. Control: control group; Cocaine: cocaine treatment group; Morphine: morphine treatment group. Data are shown as mean \pm S.E.M. Different letters indicate significant within-species differences. Asterisk (*) ($p < 0.05$) and asterisks (**) ($p < 0.01$) indicate significant difference between C57BL/6J and BALB/cJ mice.

exploration time in C57BL/6J mice (cocaine: $p < 0.05$; morphine: $p < 0.01$), drug administration did not significantly affect the exploration times of BALB/cJ mice (Fig. 1). In C57BL/6J mice, the discrimination ratio significantly decreased after cocaine administration ($p < 0.05$) but was unaffected by morphine administration. In BALB/cJ mice, the discrimination ratio decreased after both cocaine and morphine administration (cocaine: $p < 0.01$; morphine: $p < 0.01$) (Fig. 2).

3.2. Effects of cocaine and morphine in SRT

The repeated measures showed that the investigation time of C57BL/6J mice in the SRT significantly reduced after drug administration ($F_{(2, 27)} = 11.390$, $p < 0.01$; Fig. 3), while that of the BALB/cJ mice in the SRT was no significant variation ($F_{(2, 27)} = 8.29$, $p = 9.28$; Fig. 3). Post-hoc tests showed that control C57BL/6J mice spent more time investigating than did those that received cocaine ($p < 0.01$, Fig. 3) or morphine ($p < 0.01$, Fig. 3). The one-way ANOVA showed that drug administration significantly impacted investigation times in the first, second, and fifth trials ($F_{(2, 27)} = 7.774$, $p < 0.01$; $F_{(2, 27)} = 7.344$, $p < 0.01$; and $F_{(2, 27)} = 5.772$, $p < 0.05$; respectively). Post-hoc tests showed that C57BL/6J mice in the cocaine and morphine groups spent less time investigating (cocaine: $p < 0.01$ for the first, second, and fifth trials; morphine: $p < 0.01$ for first and second trials, $p < 0.05$ for the fifth trial; Fig. 3). There were no significant differences among the different BALB/cJ mice groups.

The independent *t*-test showed that C57BL/6J mice in the control and morphine groups spent more time investigating the novel subject than the familiar stimulus during the SRT discrimination test (control: $t_{(18)} = 3.581$, $p < 0.01$; morphine: $t_{(18)} = 10.983$, $p < 0.05$; Fig. 4). No significant effect was observed in the cocaine-treated C57BL/6J mice ($t_{(18)} = 0.233$, $p = 0.585$; Fig. 4). BALB/cJ mice in all three groups spent more time investigating the novel subject compared to the familiar one (control: $t_{(18)} = 1.352$, $p < 0.01$; cocaine: $t_{(18)} = 2.766$, $p < 0.01$; morphine: $t_{(18)} = 2.620$, $p < 0.05$; Fig. 4).

3.3. Effects of cocaine and morphine on serum CORT

The two-way ANOVA showed that levels of serum CORT were significantly increased by the interaction between mice strain and drug administration ($F_{(2, 57)} = 2.58$, $p < 0.01$). Post-hoc tests demonstrated

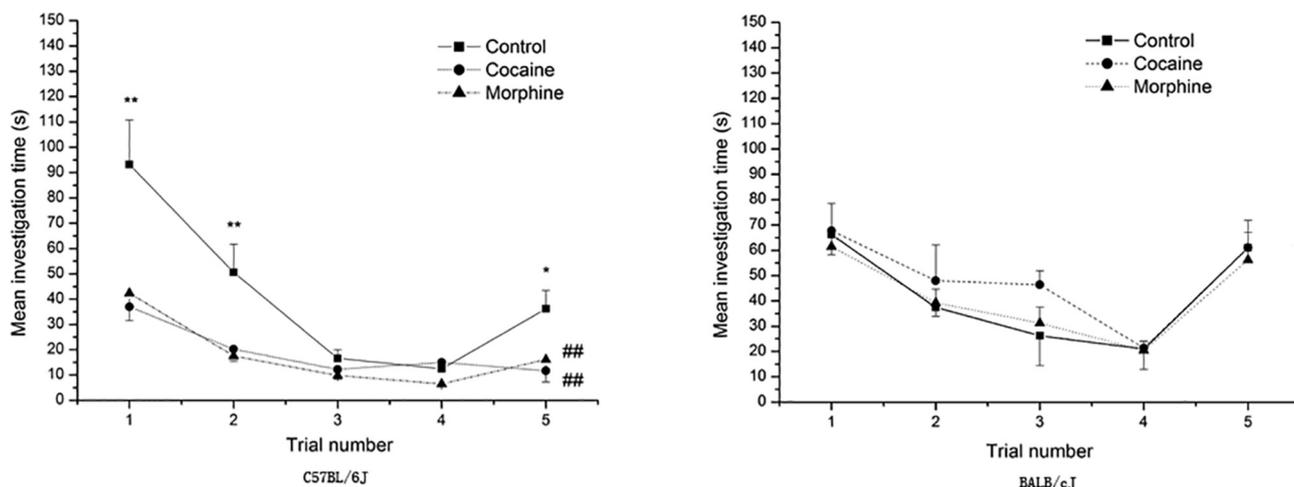


Fig. 3. The investigation times of C57BL/6J and BALB/cJ mice in the social recognition test on day one. Control: control group; Cocaine: cocaine treatment group; Morphine: morphine treatment group; Data are shown as mean + S.E.M. Hashes (##) ($p < 0.01$) indicate significant difference. Asterisk (*) ($p < 0.05$) and asterisks (**) ($p < 0.01$) indicate significant difference.

that serum CORT levels in control C57BL/6J mice were lower than in control BALB/cJ mice ($p < 0.05$), but there was no significant difference between the animals after drug administration (Fig. 5).

4. Discussion

4.1. Effects of cocaine or morphine exposure on object recognition

Our results indicate that cocaine and morphine administration reduced the discrimination ratio in both C57BL/6J and BALB/cJ mice, especially following cocaine exposure. This finding agrees with those of previous reports: chronic cocaine administration impairs multiple aspects of cognitive function in C57BL/6 mice (Krueger et al., 2009); and chronic exposure to morphine results in cognitive deficits and alterations of apoptotic proteins promoting cell death in the hippocampus, a brain region critically involved in learning and memory (Bao et al., 2007; Pu et al., 2002; Salmanzadeh et al., 2003).

Cocaine and morphine administration reduced exploration time only in C57BL/6J mice, a result that may be attributable to drug addiction. The behavior change of C57BL/6J mice after drug exposure was greater than that of BALB/cJ mice, which has also been proved in the following social cognition experiment in this study. These results

are consistent with previous research: C57BL/6J mice are more sensitive to cocaine or morphine, and more prone to addiction (Belzung and Barreau, 2000; Kennedy et al., 2012).

4.2. Effects of cocaine or morphine exposure on social recognition

In the SRT, C57BL/6J mice spent significantly less time investigating after cocaine and morphine administration, while no effect of drug administration on BALB/cJ mice was observed. This may be due to low sensitivities to cocaine and morphine exhibited by BALB/cJ mice. C57BL/63SJL mice reportedly acquire cocaine self-administration readily and maintain stable levels of daily drug intake. In contrast, BALB/cByJ mice fail to acquire cocaine self-administration under the same test conditions (Deroche et al., 1997). Moreover, only C57BL/6J mice developed CPP after binge cocaine administration; 129/J mice did not (Zhang et al., 2002).

The discrimination test performed on day two indicated that, unlike the BALB/cJ mice from the cocaine and morphine groups, the C57BL/6J mice from the cocaine group were unable to maintain stable memories. Social interaction can serve as a protective factor against drug-related behavior (Aragona et al., 2007; Adams et al., 2013). Conversely, the removal or absence of these rewards can increase behavioral

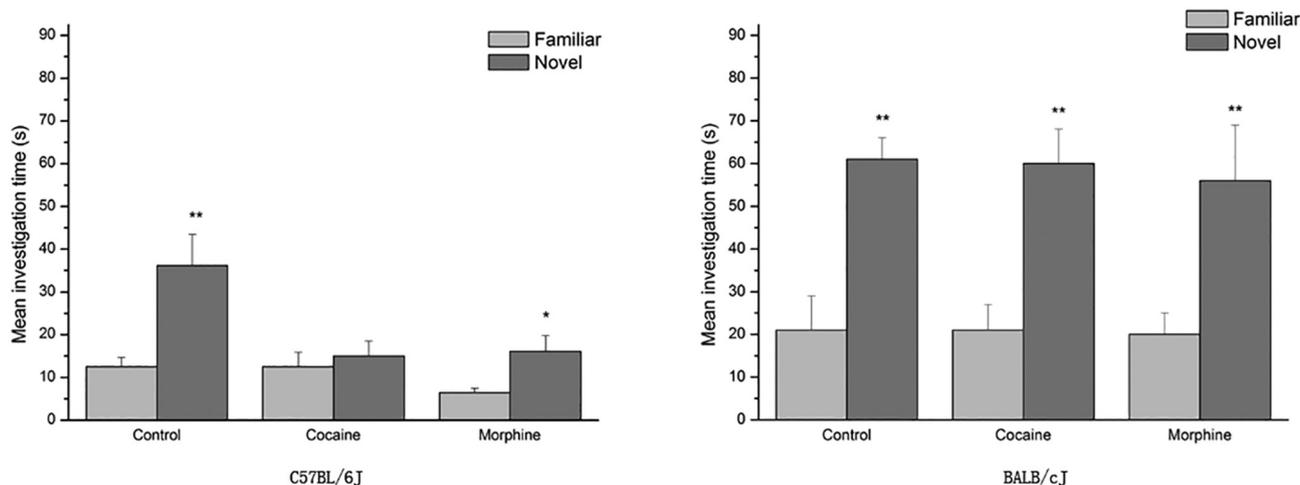


Fig. 4. Times spent investigating by C57BL/6J and BALB/cJ mice during the social recognition test on day two. Familiar: familiar stimulus mouse; Novel: novel stimulus mouse; Control: control group; Cocaine: cocaine treatment group; Morphine: morphine treatment group; Asterisk (*) ($p < 0.05$) and asterisks (**) ($p < 0.01$) indicate significant difference.

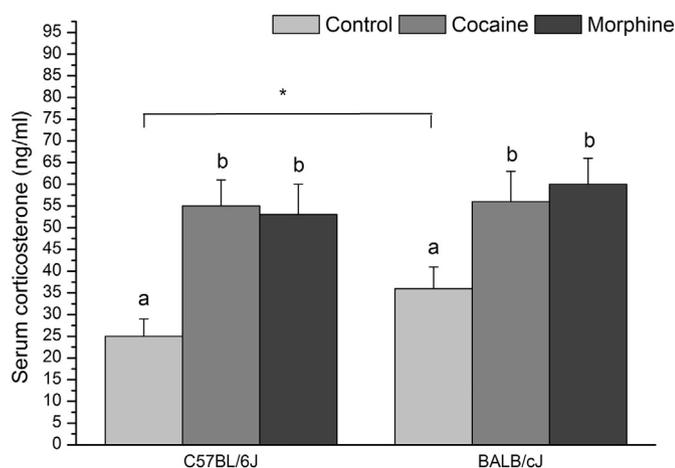


Fig. 5. The serum corticosterone levels in C57BL/6J and BALB/cJ mice. Control: control group; Cocaine: cocaine treatment group; Morphine: morphine treatment group; Data are shown as mean + S.E.M. Different letters indicate significant within-species differences. Asterisk (*) ($p < 0.05$) and asterisks (**) ($p < 0.01$) indicate significant difference between C57BL/6J and BALB/cJ mice.

responses to drugs of abuse (Alexander et al., 1981; Pitchers et al., 2013). In addition, exposure to drugs of abuse can in turn influence a rodent's expression of social behavior (Zernig and Pinheiro, 2015). The present study found that the discrimination rate and investigation time during the SRT were significantly lower in C57BL/6J than in BALB/cJ mice. These results may be related to the correlation between social behavior and drug exposure: high levels of social behavior are accompanied by low levels of drug exposure and cognitive impairment.

4.3. Effects of cocaine or morphine exposure on serum CORT

The serum levels of CORT in C57BL/6J and BALB/cJ mice significantly increased after cocaine and morphine administration. These results are consistent with those of previous reports: several classes of drugs have been shown to increase HPA axis activity in animal models, and inhibiting corticosterone synthesis can effectively decrease drug self-administration. Moreover, administration of benzodiazepine, an anti-anxiety drug, effectively decreases serum levels of CORT, associated anxiety behavior, as well as drug self-administration and seeking in animal models of drug abuse (Armario, 2010; Goeders and Guerin, 1996; Goeders et al., 2009).

Serum CORT levels in control C57BL/6J mice was less than that in control BALB/cJ mice. While there was no significant difference between two kinds of mice after drug administration. This indicates that the increase of serum CORT levels in C57BL/6J mice was greater than that in BALB/cJ mice, which may account for the differences in performances in the novel object recognition and social recognition tests.

Glucocorticoids play an important role in cognitive function, and fluctuations in glucocorticoid levels are associated with learning and memory deficits. A large number of glucocorticoid receptors are distributed in the hippocampus, making it particularly sensitive to changes in glucocorticoid levels (Sapolsky et al., 1985). Glucocorticoids exert an inverted-U shaped effect: very high and low levels of glucocorticoids impair learning, while moderate levels tend to facilitate learning and memory processes (Roosendaal, 2003; Salehi et al., 2010). Prolonged elevation of glucocorticoids can exert neurotoxic effects in the hippocampi of adult humans and other animals (Lupien and McEwen, 1997). However, the mechanism of drug-induced cognitive impairment mediated by CORT in C57BL/6J and BALB/c mice still requires investigation.

In summary, our findings suggest that the impairment of object and social recognition after chronic exposure to cocaine and morphine may

be genetic. As evinced by the results from object and social learning tests, C57BL/6J are more sensitive than BALB/cJ mice to chronic drug exposure, especially cocaine. Our results further indicate that a potential CORT-mediated mechanism underlying drug-induced impairment of cognitive competence warrants further study.

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