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Conditioned place preference after single doses or "binge" cocaine in C57BL/6J and 129/J mice

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Abstract

The rewarding effect of cocaine as reflected by the development of conditioned place preference was examined in C57BL/6J and 129/J mice. Cocaine was administered in a single daily dose (2.5, 5, 10 and 20 mg/kg ip) or in a "binge" pattern (15 mg/kg ip ×3, hourly). Mice remained in the conditioning compartment for 30 min immediately after each injection. Single injections of cocaine from 5 to 20 mg/kg induced conditioned place preference in each strain of mice. Only C57BL/6J mice developed conditioned place preference after "binge" cocaine administration. Both strains showed significantly greater locomotion in the conditioning compartment across the range of single doses of cocaine and after "binge" cocaine administration, but only 129/J mice showed sensitization. When mice that had received the single 10 mg/kg dose were retested 4 weeks later, the amount of time spent in the preferred side was significantly reduced compared to the initial test in the 129/J, but not in C57BL/6J mice. Thus, the persistence of conditioned place preference is strain dependent. The fact that 129/J mice did not develop conditioned place preference after "binge" cocaine administration, but did after single doses, suggests that the rewarding effects of cocaine are influenced by pattern of administration, a factor that may be relevant to the development of human cocaine addiction.

Keywords: Conditioned place preference; Locomotor activity; "Binge" cocaine; C57BL/6J mice; 129/J mice

1. Introduction

Cocaine is a commonly abused stimulant drug that produces conditioned place preference and locomotor activity in rodents. The mesolimbic dopamine systems are postulated to be involved in rewarding and locomotor stimulating effects of cocaine, since both effects have been shown to be blocked either by lesions of the nucleus accumbens or by systemic administrations of D1 dopamine receptor antagonists (Kelley et al., 1980; Kalivas et al., 1983; Shippenberg and Herz, 1987; Cervo and Samanin, 1995; Pruitt et al., 1995).

Substrains of C57BL and 129 mice are among the most commonly used background strains in the production of transgenic mice. Several studies report that substrains of C57BL and 129 mice differ significantly in their behavioral response to cocaine (Miner, 1997; Schlussman et al., 1998). C57BL/6J mice were found to develop conditioned place preference to environments associated with cocaine (Seale and Carney, 1991; Miner, 1997; Cunningham et al., 1999), whereas129/SvJ mice did not (Miner, 1997). Kuzmin and Johansson (2000) found that C57BL/6J mice self-administered cocaine, but 129/OlaHsd mice did not. Both strains have been found to show hyperlocomotor activity in response to a single injection of cocaine (Womer et al., 1994; Miner, 1997; Kuzmin et al., 2000). However, we found that C57BL/6J mice show significant increases in both locomotor activity and stereotypic behavior in response to acute "binge" pattern cocaine administration, while 129/J mice show only increases in stereotypic behavior following acute "binge" pattern cocaine administration, and the amount of stereotypy was significantly lower than that of the C57BL/6J mice (Schlussman et al., 1998).

The behavioral and neurochemical responses to "binge" pattern cocaine administration, a paradigm used to mimic the abuse pattern of cocaine in humans, have been studied extensively in rodents (e.g. Branch et al., 1992; Daunais and McGinty, 1995, 1996; Maisonneuve

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and Kreek, 1994; Unterwald et al., 1994; Maisonneuve et al., 1995; Schlussman et al.,1998). However, conditioned place preference in response to "binge" pattern cocaine administration has not yet been studied.

It has been shown that different cocaine administration regimens can lead to different neurochemical outcomes. For example, single daily cocaine injections resulted in a significant increase of mu opioid receptors in the nucleus accumbens only, whereas two and three daily cocaine injections increased mu opioid receptors in the nucleus accumbens, caudate–putamen and Layer I of the rostral cingulate cortex (Unterwald et al., 2001). Thus, both the dose and pattern of administration may be crucial determinants of the effects of cocaine.

Studies using the technique of in vivo microdialysis have shown that significant increases in dopamine levels in the nucleus accumbens and caudate–putamen are induced by cocaine in both the C57BL/6J and 129 mice (He and Shipenberg, 2000; Zhang et al., 2001). The reported failure of 129 mice to develop conditioned place preference with cocaine (Miner, 1997) and to show locomotor stimulating effects after cocaine (Schlussman et al., 1998) led to the systematic studies of both single doses of cocaine and "binge" cocaine-induced place preference in both strains reported below. First, we conducted a dose–response study of single daily injections of cocaine (0, 2.5, 5, 10 and 20 mg/kg) in each strain. Then, in the second study, we examined whether daily "binge" pattern cocaine (15 mg/kg ip ×3 at hourly intervals) would induce conditioned place preference in each strain.

2. Method and materials

2.1. Animals

Male C57BL/6J and 129/J inbred mice (Jackson Laboratory) weighing 22–25 g were individually housed with free access to food and water in a light (12:12 h light/dark cycle, lights on at 7:00 AM)- and temperature (25 °C)-controlled room. All animal care and experimental procedures were conducted according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The experimental protocols were approved by the Institutional Animal Care and Use Committee of The Rockefeller University.

2.2. Mouse place preference chambers

The mouse place preference chambers (model ENV-3013) were purchased from Med Associates (Med Associates, VT). Each chamber has three distinct compartments that can be separated by removable doors. Automated data collection is accomplished by individual infrared photobeams on a photobeam strip, with six beams in the white and black compartments and two beams in the smaller central gray compartment. The center compartment has a neutral gray floor. The black compartment is 16.8×12.7×12.7 cm with a stainless-steel grid rod floor. The white compartment (also 16.8×12.7×12.7 cm) has a stainless-steel mesh floor.

2.3. Locomotor activity and conditioned place preference determinations

2.3.1. Dose–response study

Five groups of eight mice in each strain were studied, one group at each dose: 0, 2.5, 5, 10 and 20 mg/kg of cocaine. Experiments were performed in a dimly lit, sound-attenuated chamber described above. The study used an unbiased, counterbalanced design in which eight mice were randomly assigned to either the cocaine or saline compartment on the first day. Half the animals had white and half had black as the cocaine-paired side. During the preconditioning session, each animal was placed in the center compartment with free access to the black and white compartments, and the amount of time spent in each compartment was recorded for 30 min. During the conditioning sessions, mice were placed into and restricted to the appropriate compartment for 30 min after cocaine or saline injection. Locomotor activity was assessed as the number of "crossovers" defined as breaking the beams at either end of the conditioning compartment. The animals were injected with cocaine and saline on alternate days, for a total of eight conditioning sessions with four cocaine and four saline trials for each animal. Conditioning sessions were conducted daily. The postconditioning test session was performed on the day after the last conditioning session, and was identical to the preconditioning session: Each mouse had free access to both white and black compartments. The schedule of sessions is shown in Table 1. The difference between the pre- and postconditioning sessions in the amount of time spent on the drug-paired compartment was used to determine whether the mice had developed a conditioned place preference to cocaine (compared to saline or 0-dose controls).

2.3.2. Test of retention of conditioned place preference after 4 weeks

Mice of both strains that had received the 10 mg/kg dose of cocaine were tested again for place preference 4 weeks after the initial postconditioning session. During this retest, each mouse (without cocaine administration) was placed into the center compartment and had free access to the black and white compartments, as in the initial postconditioning test session.

Table 1
CS: conditioning session

	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Week 1	Pre-CS	CS	CS	CS	CS	–	–
Week 2	CS	CS	CS	CS	Post-CS		

2.3.3. "Binge" cocaine administration study

Two groups of eight mice of each strain were studied. One group received "binge" pattern cocaine administration on the drug side and "binge" pattern saline administration on the other side, whereas the saline control group received "binge" pattern saline on both sides of the conditioning chamber. This study also used an unbiased, counterbalanced design with eight mice randomly assigned to either the cocaine or saline compartment on the first day, and half the animals had white and half had black as the cocaine-paired side. During the conditioning sessions, mice were restricted to one compartment for 30 min following the first cocaine (15 mg/kg) injection and were then returned to their home cage. Thirty minutes later, the mice were injected with the second dose of cocaine (15 mg/kg) and again restricted to the same compartment for 30 min before returning to their home cage for 30 min. Thirty minutes later, the mice were given the third injection of cocaine and once again restricted to the same compartment for 30 min. The exposure time to the conditioning compartments of 30 min has often been used in such studies and is reasonable since the half-life of cocaine in C57BL/6J mice has been reported to be 22.3 min (Azar et al., 1998). Thus, three injections of cocaine (45 mg/kg, total) were given over a 2-h period, in a "binge" pattern of administration. On alternate days, mice were injected with saline in the same pattern and restricted in the other compartment for 30 min after each saline injection. The daily schedule of conditioning sessions was the same as in the single-dose study described above. The postconditioning test session was performed on the day after the last conditioning session and was identical to the preconditioning test session.

2.3.4. Statistical analysis

Analyses of variance (ANOVAs), with repeated measures when needed, followed by Newman–Keuls post hoc tests were used to examine the significance of differences in behavior between drug doses, strains and sessions. Since between- and within-groups interactions cannot be tested by Newman–Keuls post hoc tests, the results of each strain were then separately examined by ANOVA. We used Newman–Keuls post hoc tests when significance of interaction F's were <0.10, and planned comparisons when appropriate.

3. Results

A preliminary analysis was made for each study of the amount of time spent during the preconditioning session in the compartment that was later paired with cocaine versus the side that would be paired with saline. ANOVAs (Strain×Side) showed that in neither study was there a significant main effect of strain or side, nor was there a significant interaction effect (means±S.E.M. are shown in Table 2).

Table 2

	Single-dose study		"Binge" study	
	Cocaine side	Saline side	Cocaine side	Saline side
C57BL/6J	709±105	704±129	665±123	733±144
129/J	715±132	711±126	718±93	690±98

3.1. Conditioned place preference in C57BL/6J and 129/J mice

3.1.1. Dose–response study

The increase in the amount of time spent on the drug-associated side, indicating a conditioned place preference produced in each strain of mouse by single daily injections of cocaine at each of five doses, is shown in Fig. 1. Two-way ANOVA (Dose×Strain) showed a significant main effect of Dose [$F(4,68)=7.60$, $P<.00005$], with no significant difference between strains [$F(1,68)=1.05$] and no significant Dose×Strain interaction. Newman–Keuls post hoc tests showed that a significant conditioned place preference was induced at each cocaine dose from 2.5 to 20 mg/kg compared to the 0 dose.

When the strains were examined separately by one-way ANOVA, C57BL/6J mice showed a significant main effect of Dose [$F(4,34)=4.13$, $P<.01$]. A significant preference for the drug-paired side was not produced by the lowest dose, 2.5 mg/kg, but there was a significant preference induced by each dose from 5 to 20 mg/kg compared to the 0 dose. Similarly, in 129/J mice, there was a significant main effect of Dose on increased time on the drug-paired side [$F(4,34)=3.92$, $P<.02$], with doses from 5 to 20 mg/kg inducing significant preference compared to the 0 dose.

3.2. Retest of conditioned place preference after 4 weeks: strain difference in retention

To examine the retention of the conditioned place preference, animals of each strain that had received the 10 mg/kg dose of cocaine during the conditioning sessions were retested 4 weeks after the original postconditioning test. The results of the original test and the retest 4 weeks later are shown in Fig. 2. Two-way ANOVA with repeated measures (Strain×Test–Retest) showed a significant overall reduction in the amount of time spent in the drug-paired compartment 4 weeks after the initial post conditioning test [$F(1,14)=7.61$, $P<.05$], with no significant main effect of Strain [$F(1,14)<1.00$]. However, a planned comparison of the 129 strain test–retest change in time (suggested by the reportedly poorer performance of 129 s in memory-related tasks, e.g. Crawley et al., 1997; Balogh et al., 1999) showed a significant reduction [$F(1,14)=9.26$, $P<.01$]. As can be seen in Fig. 2, the C57BL/6J mice did not show a significant reduction in the conditioned place preference over 4 weeks.

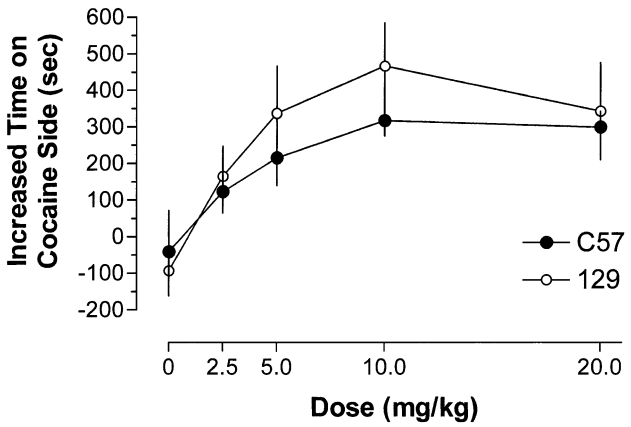

Fig. 1. Conditioned place preference as reflected by the mean (±S.E.M.) increased number of seconds spent in the drug-paired compartment in the postconditioning session (postconditioning time minus preconditioning time) in groups given one of five single doses of cocaine. Cocaine induced a dose-dependent increase in time spent in the drug-paired compartment [$F(4, 68)=7.60$, $P<.00005$], with no significant strain difference.

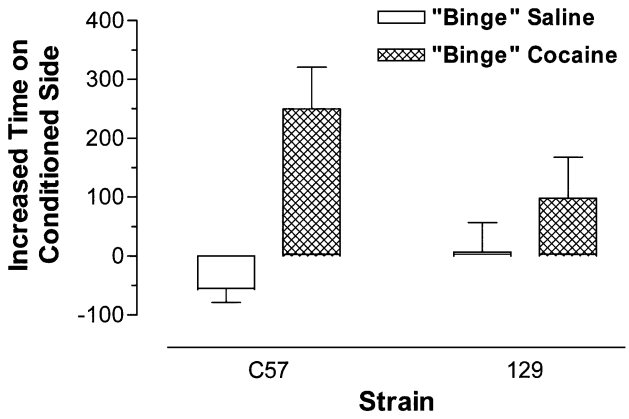

Fig. 3. Conditioned place preference as reflected by the increased number of seconds spent in the drug-paired compartment in the postconditioning sessions (postconditioning time minus preconditioning time) in groups given "binge" cocaine or saline (mean and S.E.M., $n=8$ per group). C57BL/6J mice formed a conditioned place preference as shown by significantly increased time in the cocaine-paired side in the postconditioning session ($P<.05$), but the 129/J mice did not.

3.2.1. "Binge" cocaine administration study

The increased amount of time spent on the cocaine side after the conditioning sessions using three injections of 15 mg/kg (or saline in control groups) is shown for each strain in Fig. 3. Two-way ANOVA (Cocaine–Saline Group×Strain) showed that cocaine administered in the "binge" pattern resulted in conditioned place preference for the cocaine-paired compartment [$F(1,27)=12.12$, $P<.002$], with no main effect of Strain [$F(1,27)<1.00$] and with an interaction that missed statistical significance [$F(1,27)=3.57$, $P=.0695$]. Newman–Keuls post hoc tests showed that C57BL/6J mice formed significant preferences for the drug-paired compartment compared to controls ($P<.05$). In contrast, 129/J mice failed to show a significant increase in the amount of time spent in the cocaine-paired compartment compared to the saline control group ($P=.27$).

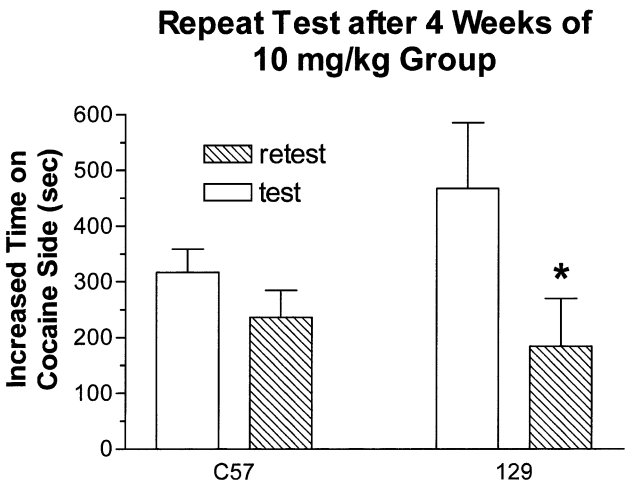

Fig. 2. Conditioned place preference as reflected by the increased number of seconds spent in the drug-paired compartment in the postconditioning test session (postconditioning time minus preconditioning time) and 4 weeks later in the groups that had received 10 mg/kg cocaine during conditioning sessions (mean+S.E.M., $n=8$ per group). ANOVA followed by a planned comparison showed that in 129/J mice, there was a significant reduction in time spent in the drug-paired compartment 4 weeks later ($P<.01$).

3.3. Cocaine-induced locomotor activity during conditioning sessions

3.3.1. Dose–response study

Locomotor activity in the cocaine conditioning sessions as measured by the number of crossovers from one end of the compartment to the other for each dose from 0 to 20 mg/kg in each strain is shown in Fig. 4. ANOVA (Dose×Strain×Conditioning Session) revealed a dose-dependent increase in activity [$F(4,68)=29.62$, $P<.000001$]. Overall, there was no significant difference between strains [$F(1,68)<1.00$] in the number of crossovers in the 30 min period after cocaine administration. Newman–Keuls post hoc tests of Dose showed that each dose of cocaine from 2.5 to 20 mg/kg induced significant increases in locomotor activity compared to saline or 0-dose controls.

When the locomotor activity in the cocaine-paired compartment on the 4th day of each strain was analyzed separately, another strain difference was found. In the C57BL/6J mice, each dose of cocaine from 2.5 to 20 mg/kg induced significant increases in locomotor activity compared with the saline or 0-dose control. In the 129/J mice, however, there was significantly greater locomotor activities induced only by the 5–20 mg/kg doses of cocaine, but not by 2.5 mg/kg.

3.3.2. "Binge" cocaine administration study

The locomotor activity across the conditioning sessions in response to "binge" cocaine expressed as mean number of

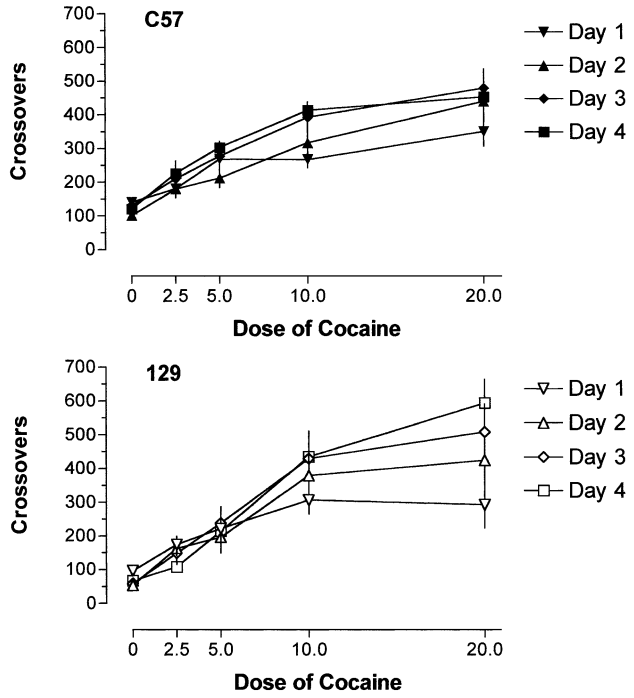

Fig. 4. Locomotor activity in the cocaine-paired compartment expressed as mean (±S.E.M.) number of crossovers in 30 min in each of the four cocaine conditioning sessions (n=7–8 per group). Cocaine produced a dose-dependent increase in crossovers [$F(4,68)=29.62$, $P<.000001$], with no significant difference between strains.

crossovers after the three injections on each day in each strain is shown in Fig. 5 (with the respective control saline "binge" groups). Four-way ANOVA (Cocaine–Saline×Strain×Cocaine Conditioning Session×Injection Order) showed that "binge" pattern cocaine administration significantly increased the number of crossovers compared to that of the saline control groups [$F(1,29)=28.12$, $P<.00002$].

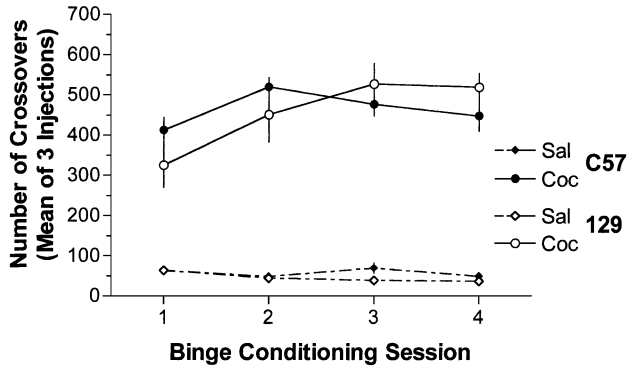

Fig. 5. Locomotor activity in the conditioned compartment expressed as mean (±S.E.M.) number of crossovers across the three 30 min postinjection period from the first through the fourth conditioning sessions (n=8 per group). There was a significant increase in crossovers in the "binge" cocaine groups compared to the "binge" saline controls [$F(1,29)=28.12$, $P<.00002$], with no significant difference between strains.

There was no significant difference between strains in locomotor response to "binge" pattern cocaine administration [$F(1,29)<1.00$]. There was a significant main effect of Conditioning Day [$F(3,87)=2.77$, $P<.05$], with no significant effect of Injection Order [$F(2,58)=1.88$].

3.4. Sensitization in locomotor response to cocaine: difference between strains

In each of the conditioned place preference studies, the dose–response and "binge" cocaine administration studies, we examined the magnitude of the locomotor response to cocaine to see if there was sensitization to the repeated dose between the 1st and 4th day of cocaine conditioning sessions. The results are shown in Fig. 6.

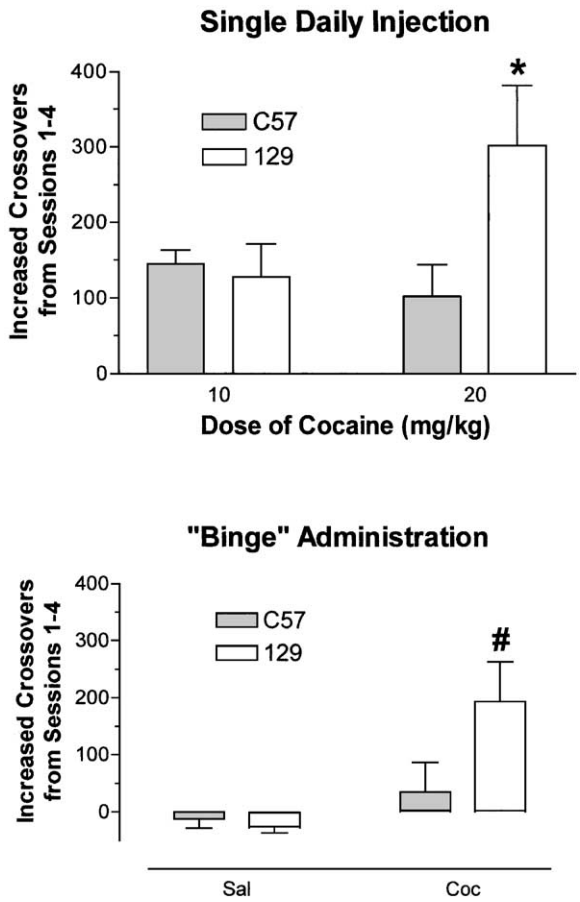

Fig. 6. Sensitization to the locomotor stimulatory effects of cocaine as reflected by mean (+S.E.M.) increased number of crossovers from the first to fourth conditioning session of each group given the two highest doses, 10 or 20 mg/kg, is shown in the top panel (n=7–8 per group). While there was no difference between strains at the 10 mg/kg dose of cocaine, 129/J mice showed a significantly greater increase than C57BL/6J mice in number of crossovers at the 20 mg/kg dose ($P<.05$). Mean and S.E.M. of increased crossovers from the first to the fourth conditioning sessions during "binge" cocaine administration are shown in the lower panel (n=8 per group). In this study, while there was no evidence of locomotor sensitization in the C57BL/6J mice, the 129/J strain showed a significant increase in mean crossovers from the first to the fourth sessions ($P<.01$).

In the dose–response study of conditioned place preference, ANOVA of the increase in crossovers from the 1st to 4th conditioning session at the two highest doses tested, 10 and 20 mg/kg, showed no significant main effect of dose or strain, but there was a significant interaction [$F(1,27)=4.50$, $P<.05$]. Newman–Keuls post hoc test showed a strain difference only at the highest dose, 20 mg/kg ($P<.05$; Fig. 6, upper panel). These data are part of those shown in Fig. 4.

Then, in the study of conditioned place preference after "binge" cocaine, examination of crossovers from the 1st to the 4th conditioning session showed a significant effect of Cocaine [$F(1,27)=8.92$, $P<.01$], no main effect of Strain [$F(1,27)=2.57$, $P=.12$], with an interaction effect that missed statistical significance [$F(1,27)=3.58$, $P=.0694$]. Whether examined by Newman–Keuls post hoc test ($P<.01$) or by planned comparison based on the results of the single-dose study above [$F(1,27)=11.50$, $P<.005$], there was evidence of sensitization only in the 129/J strain (Fig. 6, lower panel).

4. Discussion

These studies demonstrate that both C57BL/6J and 129/J mice develop conditioned place preference to cocaine. Each strain developed conditioned place preference to single injections of 5, 10 and 20 mg/kg of cocaine. In contrast, "binge" pattern cocaine administration (three injections for a total of 45 mg/kg over 2 h) produced conditioned place preference only in C57BL/6J mice, and not in 129/J mice.

The single-dose cocaine-induced conditioned place preference found in the C57 BL/6J mice in this study is consistent with earlier reports (Seale and Carney, 1991; Miner, 1997; Cunningham et al., 1999). The fact that the129/J mice also developed conditioned place preference is in contrast to the earlier report showing that 129/SvJ mice failed to do so (Miner, 1997). This discrepancy may be due to the fact that Miner used four conditioning trials (two cocaine and two saline), whereas eight trials were given in the present study. It is also possible that the difference in substrains used in the two experiments may contribute to the discrepancy.

The finding that the 129/J mice, but not C57BL/6J mice, showed significant reduction in the amount of time spent in the drug-paired compartment 4 weeks after the last conditioning session may be due to the fact that 129/J mice are poor performers in memory-related tests (e.g. Crawley et al., 1997; Balogh et al., 1999). That 129/J mice are slower to learn than C57BL/6J is indicated by the fact that in the Miner (1997) study, two cocaine trials were sufficient to induce conditioned place preference in C57BL/6J, but not in 129/SvJ mice. With four cocaine conditioning trials in our study, in the original test, there were no differences between strains in the increased amount of time spent in the cocaine side at any dose from 5 to 20 mg/kg, an effectively identical expression of preference. However, 4 weeks later, the 129 mice showed a significantly lower increase in the amount of time spent on the conditioned side, while the C57 mice did not.

It is surprising that 129/J mice failed to show conditioned place preference to "binge" pattern cocaine injections since they did develop conditioned place preference to single doses of 5, 10 or 20 mg/kg of cocaine. The "binge" study involved three injections of cocaine, 15 mg/kg per injection, 15 mg/kg falling within the range of single doses of cocaine that had induced conditioned place preference in the single-dose study. Also, the total number of cocaine-compartment pairings (12, three injection times, four sessions) was greater than the four pairings that had produced conditioned place preference in the single-dose study. Finally, extracellular concentrations of dopamine in the nucleus accumbens and caudate–putamen have been found to increase following each cocaine injection in each strain (Zhang et al., 2001). In vivo microdialysis showed that cumulative or "binge" pattern cocaine-induced increases in dopamine level in the caudate–putamen in response to a given dose of cocaine are significantly higher in 129 mice than in C57BL/6J mice (He and Shippenberg, 2000; Zhang et al., 2001). The fact that 129/J mice developed conditioned place preference to cocaine in the single-dose study, but did not after "binge" pattern cocaine administration, and have been shown not to self-administer cocaine (Kuzmin et al., 2000) suggests that dose and timing of cocaine administration are crucial in producing a rewarding effect in this strain.

It is important to note that 129/J mice did not show conditioned place aversion after the "binge" pattern of cocaine administration. In fact, the 129 mice showed a directional but nonsignificant increase in the amount of time spent on the cocaine-paired side. In C57BL/6J mice, the increase in the amount of time spent on the cocaine side at the 20 mg/kg single dose was comparable to that of the same strain after "binge" cocaine administration, while in the 129/J mice, there were several differences in this measure. The increased amount of time spent on the cocaine side by 129/J mice that received 20 mg/kg cocaine is directionally but not significantly less than that of the group that received 10 mg, and much less after "binge" cocaine. These differences are consistent with a less rewarding effect in the 129/J mice of higher doses of cocaine, 20 mg/kg in the single-dose study and 45 mg/kg over 2 h in the "binge" administration study. Thus, it is possible that a lower dose "binge" cocaine administration may induce conditioned place preference in the 129/J strain of mice.

In contrast, in both strains of mice, locomotor activity within the conditioning compartment was significantly increased by both single doses of cocaine and by "binge" pattern cocaine administration. These findings confirm earlier reports that single-dose cocaine (Womer et al., 1994; Miner, 1997) and "binge" pattern cocaine administration (Schlussman et al., 1998) dose-dependently increased loco-

motor activities in C57 BL/6J mice. The cocaine-induced increase in locomotor activity in the 129/J strain found here differs from the result of our earlier studies in which "binge" cocaine administration failed to stimulate locomotion in this strain (Schlussman et al., 1998). This discrepancy is likely to be due to differences in the measurement environment, since our earlier study was carried out in home cages, while in the present study, locomotor activity was recorded when the mouse was placed in the conditioning chamber. This interpretation is supported by Miner's (1997) finding that cocaine induced locomotor activity in the conditioning chamber, even when conditioned place preference did not develop.

Moreover, in the present study, "binge" cocaine administration in one compartment was followed by "binge" saline administration in the other compartment on alternate days, a paradigm of intermittent administration likely to induce behavioral sensitization. Indeed, we found sensitization in locomotor activity in the 129/J mice after both single-dose and "binge" cocaine administration. The fact that this behavioral sensitization was not found in the C57BL/6J mice is another difference between these strains. It is noteworthy that "binge" cocaine administration failed to induce place preference in the 129/J mice but did produce behavioral sensitization in these mice, suggesting a dissociation between sensitization and reward.

In conclusion, we demonstrate for the first time that 129/J mice do develop conditioned place preference when given a range of single doses of cocaine. Further, our studies have extended earlier reports by showing conditioned place preference for the first time in C57BL/6J mice following "binge" pattern cocaine administration. That 129/J mice did not develop conditioned place preference with "binge" cocaine administration suggests a difference between strains in the rewarding effects of different patterns of cocaine administration.

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