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Effects of "Binge" Pattern Cocaine on Stereotypy and Locomotor Activity in C57BL/6J and 129/J Mice

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SCHLUSSMAN, S. D., A. HO, Y. ZHOU, A. E. CURTIS AND M. J. KREEK. *Effects of "binge" pattern cocaine on stereotypy and locomotor activity in C57BL/6J and 129/J mice.* PHARMACOL BIOCHEM BEHAV **60**(2) 593–599, 1998.—This study characterized the behavioral response to cocaine in two strains of mice, the C57BL/6J and 129/J strains, commonly utilized as host strains for transgenic and "knockout" mice. The psychomotor stimulating effects of four doses of cocaine (2.5, 5.0, 10.0, and 15.0 mg/kg/injection) with a saline control, administered in a "binge" pattern (three equal injections at hourly intervals) for 3 days were examined in adult male C57BL/6J and 129/J mice. Behavioral stereotypy in the home cage, was rated 15, 30, and 45 min following each injection. Spontaneous locomotor activity in the home cage was also monitored. Cocaine, at doses of 10.0 or 15.0 mg/kg, produced behavioral stereotypy in both C57BL/6J mice ($p < 0.0001$) and 129/J mice ($p < 0.0001$), whereas lower doses did not. The magnitude of stereotypy was significantly lower in 129/J mice than in C57BL/6J mice receiving identical doses of cocaine. C57BL/6J mice also demonstrated a dose-dependent cocaine-induced stimulation of locomotor activity following administration of 10.0 or 15.0 mg/kg of cocaine ($p < 0.0005$). In contrast, 129/J mice did not exhibit increased locomotion in response to any dose of cocaine tested. These results demonstrate that strain differences in drug-induced behavior may be more pronounced in one measure (i.e., locomotor activity) than in another (i.e., stereotypy) and indicate the importance of multiple behavioral measures. © 1998 Elsevier Science Inc.

C57BL/6J 129/J Mouse "Binge" pattern cocaine Stereotypy Locomotor activity Strain differences Dose response

COCAINE produces profound psychomotor effects in rodents, consisting of increased spontaneous locomotor behavior and the expression of behavioral stereotypy. Distinct neuroanatomical pathways are believed to mediate these behaviors with stereotypy being mediated by striatal dopaminergic mechanisms, while the nucleus accumbens has been implicated in locomotor activity [i.e., see (14–17,21)].

We have previously described a "binge" pattern cocaine administration paradigm in rats that models the human pattern of cocaine abuse in terms of multiple daily doses and in the temporal pattern of administration relative to the daily circadian cycle of rest and activity (2). In our "binge" pattern paradigm, animals receive multiple daily injections of cocaine (as in the human "binge") beginning shortly after the start of the daily light cycle (in a nocturnal animal equivalent to early evening for humans) (2). We have demonstrated that, in the rat, "binge" pattern cocaine administration, at a dose of 15.0 mg/kg/injection, results in a significant increase in spontaneous locomotor activity (30) and the expression of behavioral stereotypy (24). These behavioral manifestations of cocaine administration are evident following each "binge" injection.

With the expanding use of transgenic animals, it has become increasingly important to extend our earlier studies to the mouse model. It has previously been shown that mice respond to the psychostimulating effects of cocaine with increased locomotor activity, but with different degrees of responsiveness between strains (10,22,23,26,29,31,33). Cocaine induction of behavioral stereotypy in mice has not been consistently reported, with some studies finding no stereotypy in response to cocaine doses as high as 32 mg/kg and others re-

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porting that cocaine doses as low as 3.0 mg/kg significantly increased both grooming and rearing behavior (27,29).

Most transgenic or knockout animals are generated from targeting specific mutations in an embryonic stem cell, usually derived from the 129 strain of mouse (4,5,11,32). The ES cell containing the mutation is then microinjected into a blastocyst stage embryo, usually of C57BL origin (4,5,11,32). The adult transgenic chimera is then mated to a "wild-type" animal, frequently of the C57BL/6 strain. Therefore, the offspring of the F1 crossing, and subsequent crossings between siblings, would posses genetic characteristics of both the donor [129] strain and the host (C57BL/6) strain (4,5,11). The C57BL/6 strain is utilized as the host blastocyst or for the F1 mating because differences in coat color between the 129 and the C7BL/6 strains can facilitate the initial screening of offspring and, perhaps more importantly, because the C57BL/6 strain is known as a good breeder while the 129 strain, from which ES cells are most easily derived, has breeding difficulties (4,11). Behavioral characteristic of both parental strains may complicate the interpretation of behavioral responses in transgenic or knockout animals (4) and, thus, should be carefully investigated in prelude to analysis of the behavioral response in genetically engineered animals. Therefore, in the present report we examine the effects of various doses of cocaine, administered in a "binge" pattern, on locomotor activity and on the expression of behavioral stereotypy in male C57BL/6J and 129/J mice, common host strains for many transgenic lines.

METHOD

Animals

Male C57BL/6J and 129/J mice (8 weeks old, Jackson Lab) were individually housed in a sequestered room dedicated to this behavioral study with a 12 L:12 D cycle and free access to Purina Lab Chow and water. Animals were allowed to acclimate for 1 week prior to the start of experiments. The study was conducted in several sessions (three with C57BL/6J and three with 129/J mice), with experimental and control animals in each session. The final *n i*n each groups was 6 (the C57BL/6J animals were not run as a single contiguous unit; therefore, additional saline controls were utilized for a total *n* of 12). Animals received either 2.5, 5.0, 10.0 or 15.0 mg/kg/injection of cocaine administered in a "binge" pattern (three equal injections at 1-h intervals commencing one-half hour following the onset of the daily light cycle), or saline (1.0 ml/kg) in the same pattern. Cocaine concentration was adjusted such that all animals received an equal volume per injection. These doses of cocaine were chosen based on previous studies. All animals received a total of 3 days of "binge" pattern injections, with electronic monitoring of spontaneous locomotor activity on a 24-h basis and rating of behavioral stereotypy following every injection by a trained observer blind as to drug condition.

All animals were sacrificed by decapitation following brief CO_2 anesthesia 30 or 60 min following the last "binge" injection on the third day (the 30-min time point was chosen to allow comparisons of neurochemical analysis to previous studies in rats, to be reported separately).

Behavioral Monitoring

Rating of cocaine-induced stereotypic behavior. Stereotypy of each animal was scored, in its home cage, at 15, 30, and 45 min after each injection by a trained observer blind as to the animal's treatment group. The rating was based upon a modification of the scale described by Daunais and McGinty (7), originally used in the rat by Creese and Iverson (6), and used previously in our lab (24). The rating system consists of a graded scale of drug induced behaviors. The behaviors scored consists of 1) asleep, inactive; 2) alert, actively grooming; 3) increased sniffing; 4) intermittent rearing and sniffing; 5) increased locomotion; 6) intense sniffing in one location; 7) continuous pivoting and sniffing; 8) continuous rearing and sniffing; 9) maintained rearing and sniffing; 10) splayed hindlimbs (7). A score of 10 was never observed in this study.

Spontaneous locomotor activity. Individual animals were housed within standard plastic cages placed within a behavioral monitoring frame. The monitoring system provides three channels of digital information: interruptions of red light beams shone through the cage as the animal moves around. The three light beams cross the cage at the front, middle, and back. Data is collected in 6-min bins and hourly on a 24-h basis. With this technique, there is no change in the environment of the animal during activity measurement, and both stereotypy ratings and quantification of locomotion are available for each mouse following each injection.

Data Analysis

Stereotypy. Area under the curve (AUC) of stereotypy scores was calculated for each animal after each injection. Due to the timing of sacrifice, for some of the animals, the 45-min time point was not available for the third scoring on the last day of the study. Therefore, an unbiased estimate of the third rating following the third "binge" injection on the day of sacrifice was determined from the mean of the third rating of the last injection on days 1 and 2, and the second rating of the last injection on the day of sacrifice. The AUC stereotypy scores were analyzed by three-way analysis of variance (ANOVA), dose by day by injection, with repeated measures on the last two factors. When a significant dose main effect was found, Newman–Keuls post hoc tests were performed.

Spontaneous locomotor activity. Locomotor data, in 6-min bins, were analyzed by analysis of variance (ANOVA) with repeated measures for the 3-h period beginning immediately after the first daily "binge" injection. Missing data due to artifacts was estimated from the nearest day at the same time bin(s); such estimates were required for less than 4% of the 6-min bin data. When a significant main effect of dose was found, Newman–Keuls post hoc tests were performed. Values are expressed as mean ± SE of total activity counts/hour.

RESULTS

Stereotypy

In the C57BL/6J mouse (Fig. 1A), cocaine administration resulted in a dose dependent expression of behavioral stereotypy, $F(4, 31) = 34.6$, $p < 0.0001$. Newman–Keuls post hoc tests demonstrated that behavioral stereotypy in response to cocaine doses of 10.0 or 15.0 mg/kg/injection were significantly elevated on day 1 ($p < 0.0005$), day 2 ($p < 0.0005$) and day 3 ($p < 0.005$). Additionally, the stereotypy response to 15.0 mg/kg/injection of cocaine was significantly greater than the response to 10.0 mg/kg/injection ($p < 0.0005$) on all 3 days of the study. Lower doses of cocaine (2.5 and 5.0 mg/kg) did not result in the expression of behavioral stereotypy.

In the 129/J mouse (Fig. 1B), cocaine administration also resulted in a dose-dependent expression of behavioral stereotypy, $F(4, 25) = 28.9$, $p < 0.0001$. Newman–Keuls post hoc

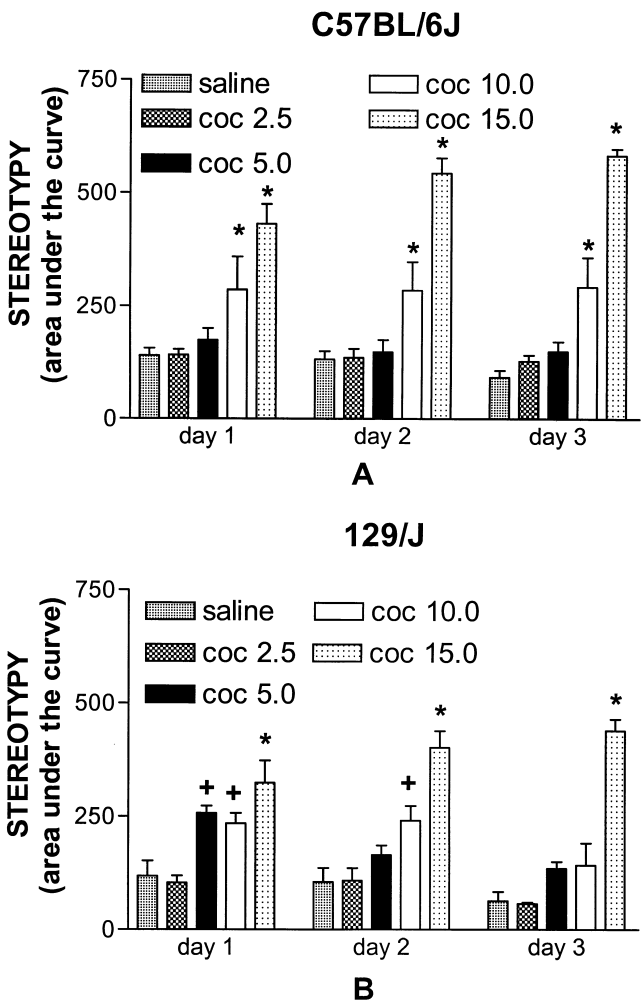

FIG. 1. Expression of cocaine-induced behavioral stereotypy in C57BL/6J (A) and 129/J (B) mice. Area under the curve was calculated for each animal following each injection. Data is expressed as mean ± SE, $n = 6$ except for C57BL/6J saline, where $n = 12$. $^{*}p < 0.0005$; $^{+}p < 0.005$.

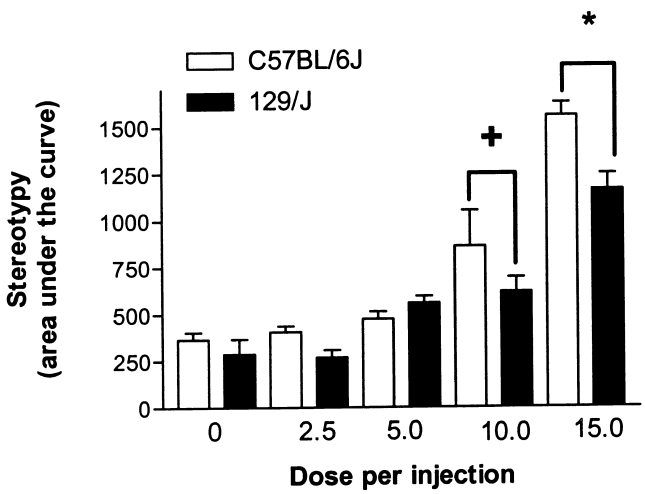

FIG. 2. Comparison of cocaine-induced expression of behavioral stereotypy in C57BL/6J and 129/J mice. The area under the curve derived from stereotypy scores for all 27 observations across the 3 days of the study were summed. Data is expressed as mean ± SE, $n = 6$ except for C57BL/6J saline, where $n = 12$. $^{*}p < 0.005$; $^{+}p < 0.05$.

tests demonstrated that behavioral stereotypy in 129/J mice was significantly increased by doses of 5.0, 10.0, or 15.0 mg/kg/injection ($p < 0.05$) on day 1 and by 10.0 or 15.0 mg/kg/injection on days 2 and 3 of the study ($p < 0.0005$). Across days, the expression of behavioral stereotypy was greater in response to 15.0 mg/kg than the response to 10.0 mg/kg ($p < 0.05$).

A comparison of cocaine-induced behavioral stereotypy in the two strains of inbred mice (Fig. 2) demonstrated that the expression of stereotypy was significantly greater in the C57BL/6J mouse compared to the 129/J mouse, in response to 10.0 or 15.0 mg/kg/injection of cocaine ($p < 0.05$ and $p < 0.005$, respectively). No differences were observed between the strains at lower doses of cocaine or following saline.

Locomotor Activity

Strain differences in baseline locomotor activity were not observed. C57BL/6J mice demonstrated a dose-dependent increase in spontaneous locomotor activity (Fig. 3A and B) following treatment with cocaine, $F(4, 31) = 15.1$, $p < 0.0005$. Locomotor activity was significantly elevated by each individual "binge" injection of cocaine at doses of 10.0 and 15.0 mg/kg ($p < 0.0005$). At lower doses of cocaine, locomotor activity was not elevated compared to saline controls. Interestingly, significant expression of cocaine-induced locomotor activity was not observed in 129/J mice at any dose of cocaine tested in this study (Fig. 4) even at those doses which produced a robust effect on stereotypy (Fig. 5).

DISCUSSION

These results demonstrate significant strain-specific, dose-dependent, expression of cocaine-induced behaviors. Behavioral effects were only observed at the higher doses of cocaine tested (10.0 mg/kg/injection and 15.0 mg/kg/injection). "Binge" pattern cocaine administration results in a significant expression of behavioral stereotypy in male C57BL/6J and 129/J mice. The expression of behavioral stereotypy was significantly different in these two important strains of mice, with the C57BL/6J mouse expressing a higher level of stereotypy than the 129/J mouse at both 10.0 mg/kg/injection and 15.0 mg/kg/injection. Significant expression of cocaine-induced locomotor behavior was observed in the C57BL/6J strain. Of importance, the 129/J mice did not demonstrate a cocaine-induced elevation of locomotor activity at any dose tested in this study.

The doses of cocaine utilized in the present study were determined based upon the doses previously reported in the literature. Ruth et al. utilized single injections of 2.5, 5.0, 10.0, or 15.0 mg/kg in their study of cocaine-induced locomotor activity in four inbred strains of mice (23). Cabib et al. used a single injection of 15.0 mg/kg of cocaine in the C57BL/6 mouse (3). Womer et al. administered single injections of cocaine at doses of 2.5, 5.0, 10.0, 15.0, 20.0, and 30.0 mg/kg in their comparative study of cocaine effects in C57BL/6 and DBA/2 mice (33). Filibeck et al. administered two daily injections of 20.0 mg/kg each to C57BL/6 mice for a total of 40 mg/kg/day (8). Xu et al. used 5.0 to 40.0 mg/kg of cocaine in their study of cocaine-induced locomotion in dopamine D_1 receptor knockout

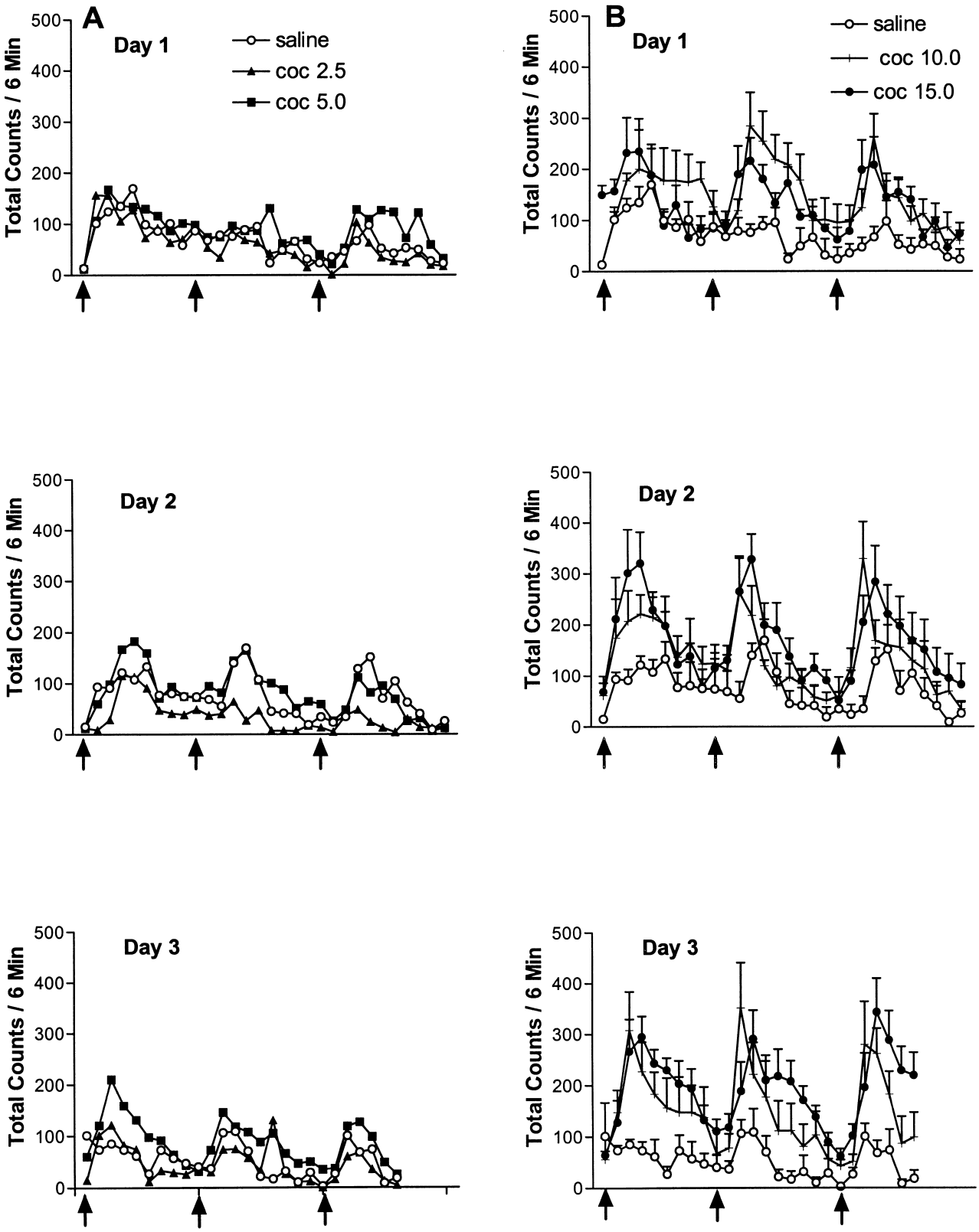

FIG. 3. Spontaneous locomotor activity following "binge" pattern cocaine administration in C57BL/6J mice. Locomotor activity is shown in 6-min bins. Arrows indicate each injection in the daily "binge." Data is expressed as mean ± SE, $n = 6$ except for C57BL/6J saline, where $n = 12$. (A) Data for saline control, 2.5 mg/kg/injection and 5.0 mg/kg/injection treatment groups is shown on the left. (B) Data for saline and the two higher doses of cocaine, which were significantly different than saline (no significant difference in locomotor activity was observed at lower doses of cocaine).

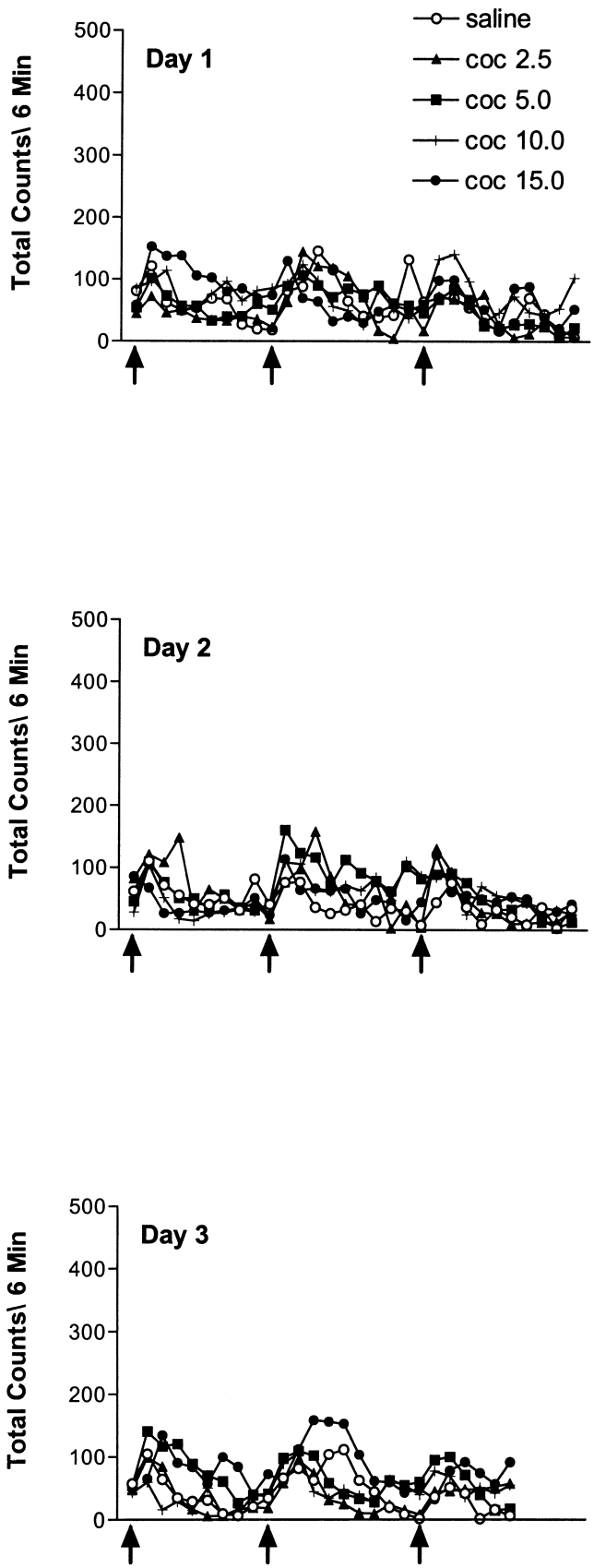

FIG. 4. Spontaneous locomotor activity following "binge" pattern cocaine administration in 129/J mice. Arrows indicate time of each "binge" injection. Data is expressed as mean ± SE, $n = 6$. No significant elevation in spontaneous locomotor activity was observed in 129/J mice following "binge" pattern cocaine administration at any dose tested.

mice (34) and Giros et al. utilized 40.0 mg/kg in their study of cocaine effects in DAT knockout mice (12). Therefore, the doses chosen for the present study correspond well with those used previously in the mouse in terms of individual injection doses and cumulative daily doses. Additionally, higher doses of cocaine, such as 40 mg/kg/injection, administered in a "binge" pattern, would result in a total dose of 120 mg/kg within a 2-h period. Such a high dose, in a relatively short period of time, could result in toxic and possibly lethal effects. Henricks et al. reported that, in the C57BL/6J mouse, a single IP injection of 50.0 mg/kg of cocaine was sufficient to induce seizures in 60% of their animals (13). Additionally, in other strains of mice, such as the LS/Ibg and SS/Ibg strains, cocaine-induced seizures occur with an ED_{50} of 41.7 and 80.9 mg/kg, respectively, and the LD_{50} values were reported to be 100.7 and 107.2 mg/kg (9). In the HS strain of mouse, the LD_{50} for cocaine, in males, was 101.55 mg/kg (19).

In an earlier study of the locomotor stimulating effect of cocaine on male BALB/cBy mice, cocaine at doses of 12.5, 25, or 40 mg/kg, administered in a single injection, was found to produce significant increases in locomotor activity, while a dose of 6 mg/kg did not (22). Interestingly, following 3 days of treatment, it was reported that the 25 mg/kg dose resulted in the expression of behavioral sensitization, while the 40 mg/kg dose of cocaine lead to tolerance to the locomotor stimulating effect of cocaine. In the present study, neither tolerance nor sensitization to the locomotor activating effects of cocaine were observed. The difference between the study of Reith (22) and the one reported herein may be related to strain differences and/or administration paradigm.

Previous studies conducted in the C57BL mouse have demonstrated that cocaine, administered in a single IP injection with different behavioral measurement or experimental paradigms, produced significant behavioral effects at a dose of 10.0 mg/kg (10,23). Ruth et al. (23) reported that the total number of crosses on a "Y" maze 15 min after a single 10.0 mg/kg IP injection of cocaine was significantly increased compared to controls. However, "Y" maze locomotor activity was not increased by 2.5 or 5.0 mg/kg of cocaine. Insofar as "Y" maze crosses may be interpreted to reflect overall activity level, these results are supported and extended by those reported in the present study. Cabib et al. demonstrated that 15.0 mg/kg of cocaine produced a significant increase in horizontal locomotor activity in male C57BL/6 mice (3). George (10) monitored spontaneous locomotor activity for 1 h following a single IP injection of cocaine. He reported that 10.0 mg/kg of cocaine significantly increased spontaneous locomotor behavior, whereas doses of 1.0 , 2.4, or 3.0 mg/kg did not. Our findings are in agreement with this report. In another report, Tolliver and Carney (27) reported a significant increase in locomotor activity in C57BL/6J mice in response to single injections of cocaine of 32 or 56 mg/kg. It should be noted, however, that in male ddY mice Ukai et al. (29) reported that a single IP injection of only 3.0 mg/kg of cocaine produced a significant increase in horizontal locomotor activity, while a dose of 1.0 mg/kg was ineffective. The locomotor stimulatory response of the ddY mouse to a much lower dose of cocaine, compared to the C57 mouse, may be due to strain differences.

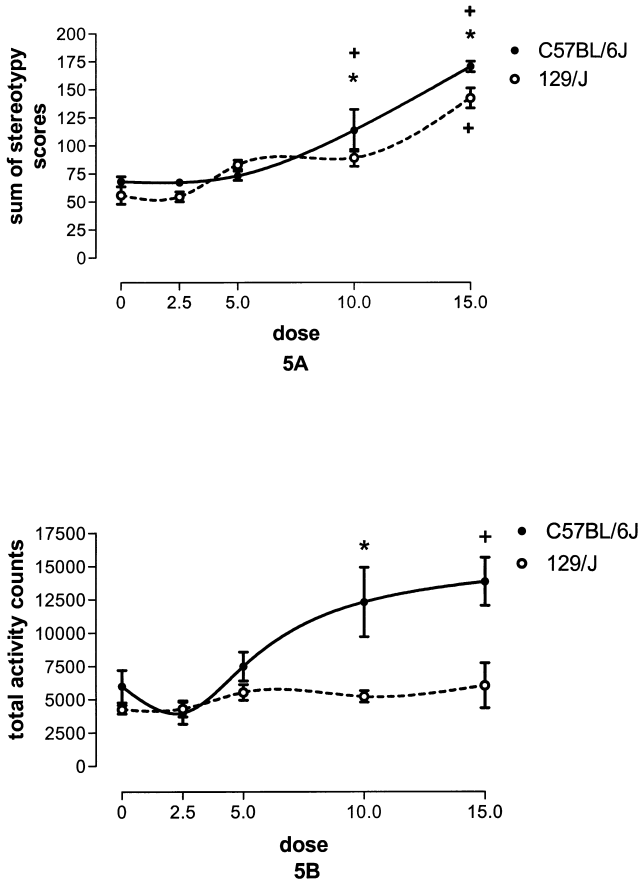

FIG. 5. (A) The sum of the raw stereotypy scores for all 3 days of the study plotted as a function of the dose of cocaine per injection. Two-way ANOVA (strain by dose) revealed a significant strain main effect, $F(1, 56) = 7.51$, $p < 0.001$, and a significant dose main effect, $F(4, 56) = 51.41$, $p < 0.00005$. Newman–Keuls post hoc tests demonstrated that cocaine doses of 10.0 and 15.0 mg/kg/injection produced significant expression of stereotypy in C57BL/6J mice ($p < 0.0005$). Significant expression of behavioral stereotypy in 129/J mice was only observed at 15.0 mg/kg of cocaine per injection ($p < 0.0005$). Additionally, at doses of 10.0 and 15.0 mg/kg/injection of cocaine the expression of behavioral stereotypy was significantly greater in C57BL/6J mice than in 129/J mice ($p < 0.05$). $^{*}p < 0.05$ compared to 129/J; $^{+}p < 0.0005$, compared to saline controls. (B) The sum of the total locomotor activity counts for the 3 days of the study plotted as a function of the dose of cocaine per injection. Two-way ANOVA (strain by dose) revealed a significant strain main effect, $F(1, 49) = 20.47$, $p < 0.00005$, a significant dose main effect, $F(4, 49) = 6.80$, $p < 0.0005$, and a significant strain by dose interaction, $F(4, 49) = 4.00$, $p < 0.01$. Newman–Keuls post hoc tests demonstrated a significant increase in spontaneous locomotor activity in C57BL/6L mice in response to cocaine at doses of 10.0 or 15.0 mg/kg/injection ($p < 0.01$ and 0.001, respectively). At these doses, locomotor activity in C57BL/6J mice was significantly greater than that observed in 129/J mice ($p < 0.05$ and 0.001, respectively). Locomotor behavior in 129/J mice was not affected by any dose of cocaine examined in the present study. $^{*}p < 0.01$ compared to saline, $p < 0.005$ compared to 129/J; $^{+}p < 0.001$ compared to saline, $p < 0.001$ compared to 129/J.

Differences in the stereotypic behavioral effects of cocaine in the mouse have been reported, e.g. (10,20,23,25,27) (Fig. 5). Ruth et al. reported that one expression of stereotypy, rearing activity, was not affected by cocaine up to 15.0 mg/kg in the C57BL mouse (23). Tolliver and Carney (27,28) reported that the C57BL/6J mouse did not develop behavioral stereotypy following 7 days of a single daily IP injection of cocaine (32 mg/kg). In the present study, when "binge" pattern administration was used, each of three daily 10.0 or 15 mg/kg IP injections of cocaine resulted in significant expression of behavioral stereotypy in both C57BL/6J and 129/J mice. There are several important differences between the current study and that of Tolliver and Carney. Tolliver and Carney utilized group housed animals (three/cage) and the animals were individually tested for expression of stereotypy in a novel environment (27,28). Additionally, the rating scale utilized by Tolliver and Carney was quite different from the one used in the present report, and it is likely that differences between the two studies may be related to these different rating scales. In contrast to previous studies in the C57 mouse, which failed to demonstrate cocaine-induced stereotypy, Ukai et al. reported increased circling behavior in ddY mice in response to 3.0 mg/kg cocaine and increased rearing and grooming in response to doses of cocaine as low as 1.0 mg/kg (29). Although the stereotypic nature of these behaviors was not discussed (i.e., the frequency of the individual behaviors), they are components of behavioral stereotypy. The differences between the study reported here and previous studies are probably related to strain differences, administration paradigm, and the use of different behavioral measures or rating scales. It is noteworthy that while 129/J mice demonstrated a significant expression of cocaine-induced behavioral stereotypy, although less than observed in C57BL/6J mice, they did not express a locomotor response to any dose of cocaine tested in the present study. Dissociation of the stereotypic and locomotor response may be related to differential regulation of these behaviors.

Thus, the findings of our study are in part similar to those of two earlier studies that show increased locomotor activity or "Y" maze crosses following single injections of cocaine at doses of 10.0 or 15.0 mg/kg. However, there are more divergent findings with respect to the expression of behavioral stereotypy and its components. The present study extends previous dose response studies in the mouse by use of the "binge" pattern paradigm of cocaine administration, originally developed for studies in the rat and designed to model a common human pattern of cocaine use (2). Findings using this "binge" pattern of cocaine administration are in agreement with previous reports that, in the C57 mouse, 10.0 mg/kg of cocaine generates a significant behavioral effect while lower doses (5.0 mg/kg and lower) do not. Additionally, these studies indicate that, for behavioral studies, there does not appear to be "carryover" from one "binge" injection to the next or, if there is a cumulative effect on locomotor or stereotypic behaviors, it is minimal. If the "binge" had a significant cumulative effect, one would have expected to observe an enhanced behavioral response following the second or third "binge" injection of 5.0 mg/kg cocaine. Statistical analysis failed to identify a cumulative dose effect on any day studied. A previous study from our laboratory has demonstrated that the half-life of cocaine in the dorsolateral striatum of male Fischer rats was 28.8 min (18); another laboratory found that the half-life of cocaine in plasma and brain of female BALB/c mice following a single IP injection of 10.0 or 25.0 mg/kg cocaine was 16 min (1). Therefore, each daily "binge" injection, in the mouse, was separated from the previous one by approximately four half-lives compared to two in the rat.

The present report represents the first analysis of cocaine-induced locomotor behavior and stereotypy in 129/J mice and demonstrates significant strain differences in cocaine-induced

behavioral responses in C57BL/6J and 129/J mice, two strains frequently utilized as host strains for genetically engineered mice. The results of the study reported here shows that strain differences may be more pronounced in one measure (i.e., locomotor activity) than in another (i.e., stereotypy), and shows that host strain is an important variable in determining the behavioral response to drugs of abuse in transgenic animals.

ACKNOWLEDGEMENTS

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