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Locomotion, stereotypy, and dopamine D_1 receptors after chronic "binge" cocaine in C57BL/6J and 129/J mice

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Abstract

We have shown that C57BL/6J and 129/J mice differ in their behavioral response to "binge" pattern cocaine (three daily injections of 15 mg/kg separated by 1 h). To determine if these differences persist during chronic binge cocaine administration, we examined the effects of 14-day binge pattern cocaine on home cage behavior. Since the dopamine D_1 receptor may be an important mediator of cocaine-induced locomotor activity, we examined binding to the dopamine D_1 receptor. Locomotor activity was increased by chronic binge cocaine in C57BL/6J ($P<.0001$) but not in 129/J mice. C57BL/6J mice developed tolerance to the locomotor-activating effects of cocaine. Stereotypic responses were greater in C57BL/6J than in 129/J mice ($P=.03$), with neither tolerance nor sensitization in either strain. Dopamine D_1 receptor binding in the nucleus accumbens and olfactory tubercle did not differ between strains and was not affected by chronic binge cocaine. In the caudate putamen, subregion specific strain differences in dopamine D_1 receptor binding were observed; chronic binge cocaine increased dopamine D_1 receptor binding in the caudal ($P<.05$), but not rostral caudate putamen. There was no correlation between locomotor activity or stereotypy and dopamine D_1 receptor density. Thus, with chronic binge cocaine administration, behavioral differences persist between the C57BL/6J and 129/J mice, and cocaine-induced locomotor activity is not correlated with changes in dopamine D_1 receptor binding.

Keywords: Cocaine; Mouse strain differences; Dopamine D_1 receptor binding; Behavior; Nucleus accumbens; Caudate putamen; Olfactory tubercle

1. Introduction

Cocaine is one of the most widely abused illicit drugs. A psychostimulant, cocaine produces characteristic behavioral effects in rodents, including increased horizontal activity (locomotion) and the expression of behavioral stereotypy. It has been suggested that separate dopaminergic pathways mediate these distinct behaviors and that the extent of psychomotor activation may be related to the reinforcing properties of drugs of abuse (Wise and Bozarth, 1987).

The rewarding effects of cocaine are believed to be mediated predominantly by increased levels of extracellular dopamine in the nucleus accumbens, and dopamine in the nucleus accumbens has been shown to induce locomotor behavior (e.g., Jackson et al., 1975; Pijnenburg and Van Rossum, 1973). Therefore, it is likely that the locomotor response to drugs of abuse is mediated, at least in part, by the mesolimbic dopaminergic system projecting from the ventral tegmental area to the nucleus accumbens. Stereotypy, on the other hand, has been suggested to be more closely linked to the nigrostriatal dopaminergic projection (e.g., Creese and Iversen, 1974).

In the Fischer (F344) rat, chronic (14-day) binge pattern cocaine administration resulted in a significant increase in locomotor behavior on all days of the study; however, over the course of the study, the rats developed sensitization to the locomotor-stimulating effects of cocaine. On the last day of the study, the locomotor response to cocaine was significantly increased compared to the first day. Chronic binge cocaine resulted in a significant increase in binding to the dopamine D_1 receptor in several brain regions in these F344 rats. The density of dopamine D_1 receptor binding in the nucleus accumbens and the olfactory tubercle were each

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found to be correlated with the level of locomotor activity on the last day of the study, and it was suggested that upregulation of dopamine D_1 receptors in these regions may be involved in behavioral sensitization (Unterwald et al., 1994).

In an earlier study, we found that the C57BL/6J and 129/J mice, common host strains for many knockout or transgenic animals, show dramatically different behavioral responses to a short-term (3-day) exposure to binge pattern cocaine administration (Schlussman et al., 1998). We found that C57BL/6J mice showed both a significant elevation of spontaneous locomotor activity and expression of behavioral stereotypy in response to cocaine. The 129/J mice also showed a significant level of stereotypy in response to cocaine, but this response was significantly lower than that of the C57BL/6J mice. The 129/J mice, however, did not respond to cocaine injections with increased levels of locomotor activity. We have also reported strain differences in cocaine-induced extracellular levels of dopamine in the striata of these mouse strains (Zhang et al., 2001).

Therefore, in the present report, we extend our studies, using both C57BL/6J and 129/J mice, to an examination of chronic (14-day) binge cocaine administration on locomotor activity and stereotypy and also on dopamine D_1 receptor binding in the nucleus accumbens, caudate putamen, and olfactory tubercle.

2. Materials and methods

All animal procedures were approved by The Rockefeller University Animal Care and Utilization Committee (ACUC) and comply with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

2.1. Animals

Male C57BL/6J and 129/J (now known as 129P3/J; A^w/A^w p Tyr^c/p Tyr^c) mice (8 weeks old, Jackson Laboratories, Bar Harbor, ME) were individually housed in a sequestered room dedicated to this behavioral study, with a 12:12-h light/dark cycle and free access to food and water. Animals were allowed to acclimate for 2 weeks prior to the start of experiments. The study was conducted in two cohorts, with experimental and control animals in each session. A total of 55 mice (30 C57BL/6J, 25 129/J) were utilized in both cohorts of this study. Animals received 45.0 mg/kg/day of cocaine administered in a binge pattern (three equal injections at 1 h intervals commencing 0.5 h following the onset of the daily light cycle), or the same volume of saline in the same injection pattern. Cocaine concentration was adjusted such that all animals received an equal volume per injection. All animals received a total of 14 days of binge pattern injections at the home cage, with electronic monitoring of spontaneous locomotor activity on a 24-h basis and videotaping of behavioral stereotypy following every injection. Animals in the drug-naive group were housed identically to experimental and control groups; however, they were only handled during this study in the course of routine cage changes. Animals were sacrificed by decapitation following brief CO_2 anesthesia 45 min after the last binge injection on the 14th day.

3. Behavioral monitoring

3.1. Rating of cocaine-induced stereotypic behavior

Twenty minutes following each injection, each mouse was individually videotaped in its home cage. Videotapes were later rated for stereotypy by a trained observer blind as to the animal's treatment group. The rating was based upon the scale of Creese and Iversen (1974) as modified by Daunais and McGinty (1994) and used successfully in mice in our studies (Schlussman et al., 1998). The rating system consists of a graded scale of drug-induced behaviors: (1) asleep, inactive; (2) alert, actively grooming; (3) increased sniffing (occasional light sniffing, often while exploring the cage); (4) intermittent rearing and sniffing (two to three rears in a 20-s period, with sniffing frequently at the apex of the rear); (5) increased locomotion; (6) intense sniffing in one location (rapid sniffing, often with head down, is the predominant behavior displayed); (7) continuous pivoting and sniffing; (8) continuous rearing and sniffing (constant up and down rearing behavior); (9) maintained rearing and sniffing (animal remains up on hind legs throughout the observation period); (10) splayed hind limbs (Daunais and McGinty, 1994). A score of 10 was never observed in this study. Each animal received a single score following each injection, which corresponded to the specific stereotypic behavior predominantly observed. The median stereotypy score of each mouse on each day was used for later analysis. Drug-naive animals were not videotaped for behavioral analysis.

3.2. Cocaine-induced locomotor activity

Individual animals were housed in 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. Drug-naive animals were individually housed in identical cages, but since they were not placed in monitoring frames, no behavioral data from these mice is available.

3.2.1. Dopamine D_1 receptor autoradiography

Animals were sacrificed 45 min following the last injection of saline or cocaine (see above) on the 14th day of the study, and the brains were immediately removed, quick frozen, and stored at −80 °C until sectioning. Serial sections of mouse brains were thaw-mounted on gelatin-coated slides, desiccated, and stored at −80 °C until use. Dopamine D_1 receptor autoradiography was carried out as previously described (Unterwald et al., 1994, 2001). Briefly, slides containing 10-μm frozen sections were preincubated for 30 min at room temperature in Tris–salt buffer (50 mM Tris HCl/120 mM NaCl/5 mM KCl/2 mM $CaCl_2$/1 mM $MgCl_2$). For specific binding, sections were then incubated in Tris–salt buffer containing 0.005 μM [^{3}H] SCH-23390 (a dopamine D_1 receptor-selective ligand; NEN, Boston, MA) and 0.001 mM mianserin (to block binding to 5-HT receptors) at room temperature for 45 min. Slides were then washed twice at 4 °C for 5 min each in ice-cold Tris–salt buffer, dipped in ice-cold dH_2O and allowed to air-dry overnight. For non-specific binding, conditions remained the same, except that slides were incubated in a solution of Tris–salt buffer containing 0.005 μM [^{3}H] SCH-23390, 0.001 mM mianserin and 0.01 mM fluphenazine (to block binding to dopamine D_1 receptors). Slides were then air-dried overnight.

The following morning, slides and [^{3}H] standards (Amersham, Piscataway, NJ) were loaded into cassettes containing [^{3}H] sensitive film (Hyperfilm, Amersham; sequestered for the purposes of this study) and exposed for 2 weeks in the dark and developed with conventional techniques. The optical density of each region or subregion was determined with a video-based imaging system (Imaging Research, Ontario, Canada). Multiple sections from each brain were imaged so that the entire nucleus was analyzed and a single mean value of optical density was determined. The number of sections imaged in each region (mean ± S.E.M.) was anterior CPu 5.0 ± 0.2; posterior CPu 3.3 ± 0.1; NAc 1.8 ± 0.1; olfactory tubercle 1.5 ± 0.1.

Optical density was converted to femtomoles of bound ligand per milligram of tissue relative to the calibration reference for each film determined from the [^{3}H] standards. Binding from background regions was subtracted from the total and nonspecific binding and the corrected nonspecific values subtracted from total binding to yield total specific binding in femtomoles per milligram.

4. Data analysis

4.1. Stereotypy

The median stereotypy score of each animal after each injection on each day was used as the raw data for subsequent analysis. Two statistical approaches were used, ANOVA and nonparametric Mann–Whitney *U* tests.

4.2. Cocaine-induced 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 followed by planned comparisons. 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. Values are expressed as mean ± S.E.M. of total activity counts per hour.

4.3. Autoradiography

The nucleus accumbens was divided into the following subregions based upon acetylcholine esterase activity; rostral pole, core, medial shell, and ventral shell. In the caudate putamen, data was analyzed in the rostral and caudal regions, which were defined with the aid of a mouse brain atlas (Franklin and Paxinos, 1997). The rostral caudate putamen corresponds to Franklin and Paxinos Plates 18 (Interaural 5.34 mm, Bregma 1.54 mm) to 30 (Interaural 3.94 mm, Bregma 0.14 mm), while the caudal portions correspond to Plates 33 (Interaural 3.58 mm, Bregma −0.22 mm) to 38 (Interaural 2.98 mm, Bregma −0.82 mm). Autoradiographic data in these regions were analyzed by three-way ANOVA; Strain (C57BL/6J or 129/J) × Condition (Drug Naive, Saline, or Cocaine) × Subregion (see above) with repeated measures on the last factor. Data on dopamine receptor binding in the olfactory tubercle were analyzed by two-way ANOVA; Strain (C57BL/6J or 129/J) × Condition (Drug Naive, Saline or Cocaine). ANOVA was followed by Newman–Keuls post hoc tests when appropriate.

5. Results

5.1. Stereotypy

Binge pattern cocaine administration resulted in significant expression of behavioral stereotypy in both C57BL/6J and 129/J mice (Fig. 1). Three-way ANOVA, Strain (C57BL/6J, 129/J) × Condition (Saline, Cocaine) × Order (day 1–14), with repeated measures on the last variable, showed significant main effects of Strain [$F(1,29) = 5.49$ $P < .05$], of Condition [$F(1,29) = 45.87$ $P < .0001$], of Order [$F(13,377) = 2.82$ $P < .001$], and a significant Strain × Condition interaction [$F(1,29) = 5.37$ $P < .05$]. Newman–Keuls post hoc tests demonstrated that in the C57BL/6J and 129/J mice, the expression of behavioral stereotypy was significantly greater in cocaine-treated animals than in their saline controls ($P < .0005$ and $P < .05$, respectively). During the course of the study, C57BL/6J mice administered cocaine had a mean median stereotypy score of 6.2, which corresponds to behavior characterized by increased sniffing. Neither tolerance nor sensitization of this effect was observed across the 14 days. 129/J mice also showed

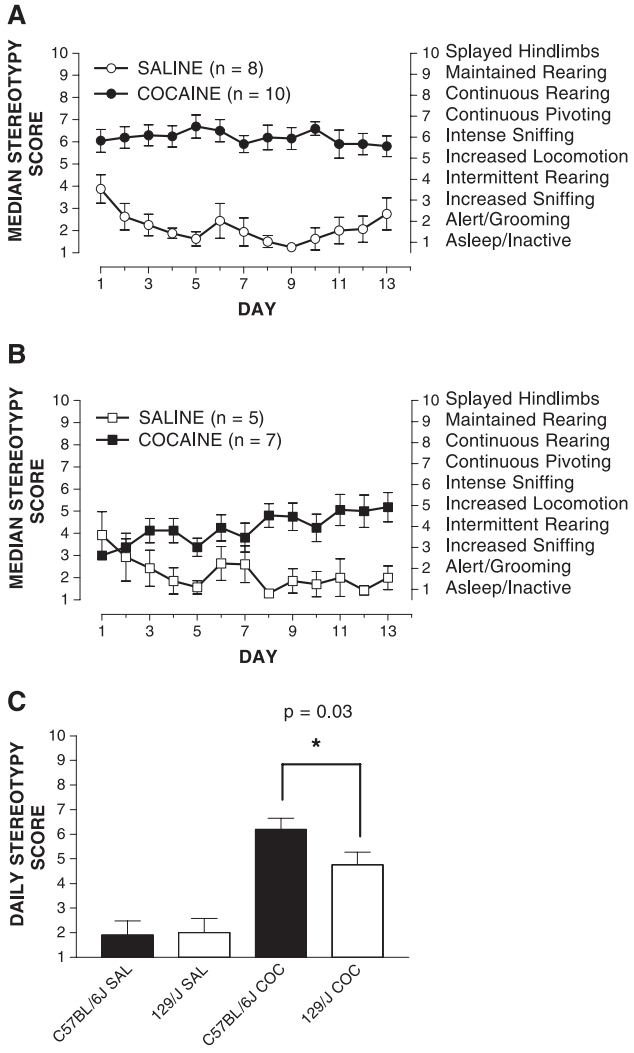

Fig. 1. The mean of the median daily stereotypy scores in C57BL/6J (A) and 129/J (B) mice (+S.E.M.). "Binge" pattern cocaine administration significantly increased levels of behavioral stereotypy [$F(1,29)=45.87$, $P<.0001$]. Across all days of the study (C), the median daily score of behavioral stereotypy (mean ± S.E.M.) was significantly higher in C57BL/6J mice than in 129/J mice ($P=.03$, Mann–Whitney U test). Strain differences in behavioral stereotypy in saline-injected animals were not observed.

increased behavioral stereotypy in response to cocaine administration (Fig. 1B). The mean of the median stereotypy scores in 129/J mice administered cocaine was 4.8, which corresponds to a behavior of increased locomotion with some intermittent rearing. Unlike the C57BL/6J mice, in the 129/J strain, significant differences in the level of behavioral stereotypy between cocaine and saline groups did not emerge until the third or fourth day of the study. The level of behavioral stereotypy was significantly greater in the C57BL/6J mice than in the 129/J animals ($P<.005$; Fig. 1C). This was not due to a lower level of basal activity in the 129/J animals, since there was no significant difference in the level of stereotypy between the saline-treated groups ($P=.99$, Fig. 2). Since the expression of behavioral stereotypy was measured with a behavioral rating scale, we confirmed this important finding with the nonparametric Mann–Whitney U test, which confirmed that the level of cocaine-induced behavioral stereotypy was significantly higher in C57BL/6J mice than in 129/J animals ($U=7.0$, $P=.03$).

5.2. Locomotor activity

Binge pattern cocaine administration significantly increased locomotor activity in C57BL/6J, but not 129/J mice (Fig. 2A and B). Three-way ANOVA, Strain (C57BL/6J, 129/J), × Condition (Saline, Cocaine) × Day (day 1 and day 13), with repeated measures on the last variable, showed significant main effects of Strain [$F(1,25)=16.86$, $P<.0005$], Condition [$F(1,25)=40.58$, $P<.0001$], Day [$F(1,25)=8.23$, $P<.01$] and a significant Strain × Condition interaction [$F(1,25)=29.61$, $P<.0001$]. Planned comparisons showed that cocaine did not increase locomotor activity in 129/J mice ($P=.55$).

In the C57BL/6J mice, binge pattern cocaine administration resulted in a significant increase in horizontal locomotor activity ($P<.0001$; Fig. 2A and B). Locomotor activity was significantly increased following each binge cocaine injection, compared to saline controls. This persisted throughout the entire study. In C57BL/6J mice, cocaine-induced locomotor activity was significantly lower on day 13 than on day 1 ($P<.05$) demonstrating the development of tolerance (Fig. 3A). Interestingly, the 129/J mice did not show a locomotor response to binge cocaine on either the 1st or 13th day of the study (Fig. 2C and D). However, 129/J mice did display a characteristic clockwise rotation within the nest area, which we interpret as an expression of behavioral stereotypy rather than increased locomotion. It is likely that a monitoring frame with more photocells would have detected this circling behavior, perhaps erroneously, as locomotor activity, but not as ambulations.

5.2.1. Dopamine D_1 receptor binding density in the nucleus accumbens

In the nucleus accumbens, the density of dopamine D_1 receptors did not differ between the C57BL/6J and 129/J strains of mice. Fourteen days of binge pattern cocaine administration had no effect on the density of dopamine D_1 receptors in the nucleus accumbens of either strain of mice. Within the nucleus accumbens, the binding density of dopamine D_1 receptor was significantly greater in the rostral pole than in either the core or the medial or ventral shell [$F(3,66)=22.95$, $P<.0001$; Table 1].

5.2.2. Dopamine D_1 receptor binding density in the caudate putamen

Overall, in the caudate putamen, the density of dopamine D_1 receptors did not differ between strains. However, there was a significant Strain × Region interaction [$F(1,33)=$

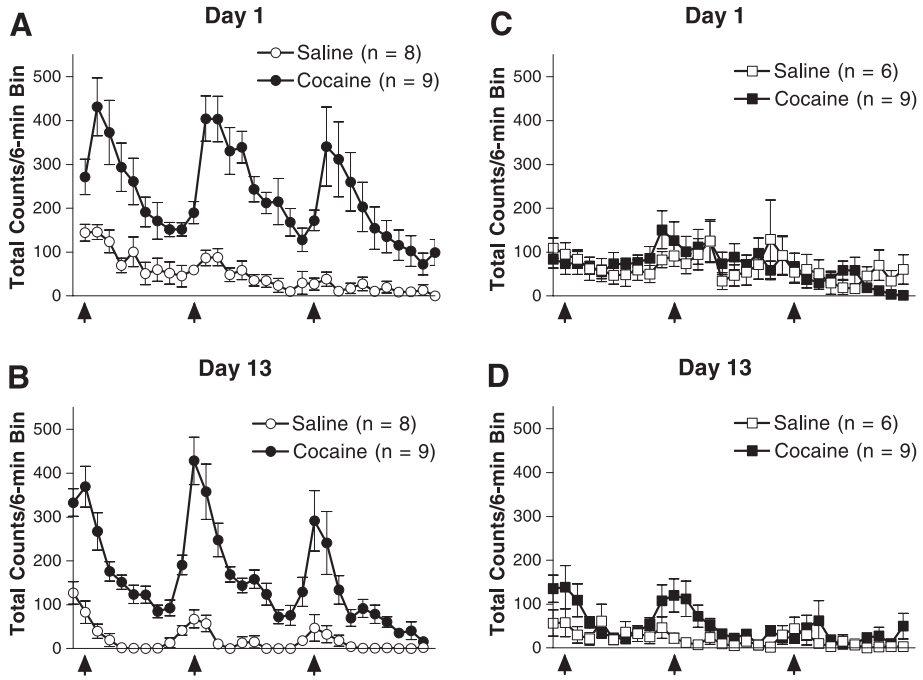

Fig. 2. Locomotor activity in C57BL/6J (A, B) and 129/J (C, D) mice, collected in 6-min bins following "binge" pattern cocaine administration on days 1 and 13 of the study. Locomotor activity was increased following each "binge" injection of cocaine (represented by arrows on *x*-axis).

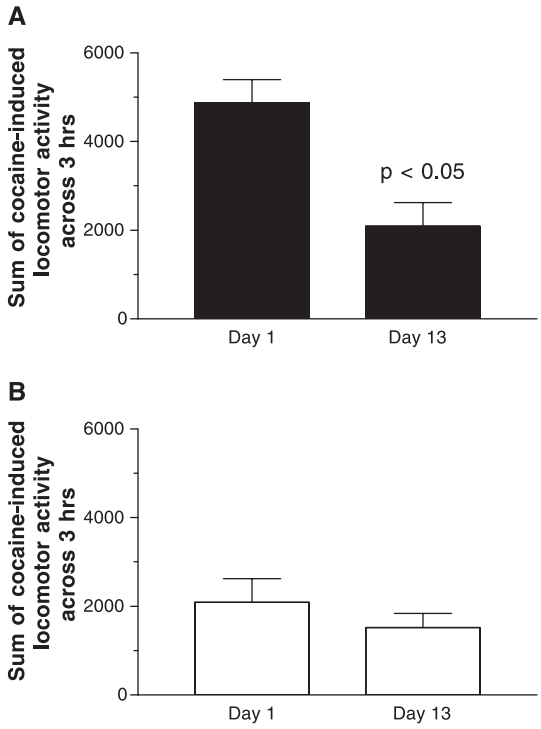

Fig. 3. C57BL/6J mice develop tolerance to the locomotor stimulating effects of cocaine (A). The sum of the cocaine-induced locomotor activity on day 13 was significantly lower than cocaine-induced locomotor activity on the first day of the study in C57BL/6J mice ($P < .05$). 129/J mice did not demonstrate significant levels of cocaine-induced locomotor behavior on either the 1st or the 13th day of the study (B).

11.47, $P < .05$], such that, in the rostral portion of the caudate putamen, the dopamine D_1 receptor density was significantly greater in 129/J mice than in C57BL/6J animals (Table 2). No strain differences were observed in the caudal portion of the caudate putamen. Interestingly, within the caudate putamen, there was a significant rostrocaudal gradient in the density of dopamine D_1 receptors [$F(1,33) = 111.17$, $P < .0001$] with the highest density in the rostral portions and lower density in the caudal (Table 2). While there was no significant main effect of Condition [$F(2,33) < 1.0$, $P = .71$], a significant Condition × Subregion interaction was observed in the caudate putamen, which indicated that 14 days of binge pattern cocaine administration significantly elevated dopamine D_1 receptor density in

Table 1
Dopamine receptor density in the nucleus accumbens (mean ± S.E.M.)

Group	Dopamine D_1 receptor density (fmol/mg)
C57BL/6J ($n = 18$)	230.56 ± 14.59
129/J ($n = 15$)	196.33 ± 12.89
Naive ($n = 14$)	194.25 ± 8.29
Saline ($n = 9$)	228.87 ± 21.49
Cocaine ($n = 10$)	231.55 ± 24.36
Rostral pole ($n = 30$)	291.88 ± 16.91[a]
Medial shell ($n = 32$)	156.59 ± 11.07
Ventral shell ($n = 31$)	208.61 ± 13.67
Core ($n = 31$)	211.92 ± 13.41

[a] $P < .0001$ relative to the medial shell, ventral shell, and core (ANOVA followed by Newman–Keuls post hoc tests).

the caudal, but not rostral, portion of the caudate putamen [$F(2,33) = 11.47$, $P < .005$; Table 2].

In primates, the striatum has been divided into functional domains, based on afferent connections from the cortex, thalamus, and midbrain (e.g., Selemon and Goldman-Rakic, 1985; McFarland and Haber, 2000; for review, see Haber and McFarland, 1999) or dopaminergic activity (e.g., Cragg et al., 2000; Cragg et al., 2002). While these functional distinctions are not as clearly established in rodents (Cragg et al., 2000), we divided the rostral portion of the caudate putamen into medial, lateral, and internal regions and examined dopamine D_1 receptor density by a three-way ANOVA, Strain × Condition × Subregion. Although the main effect of Strain just missed significance in this analysis [$F(1,24) = 3.79$, P=.06] and there was no effect of cocaine [$F(2,24) = 0.15$, P=.86], we did observe a significant main effect of Subregion [$F(2,48) = 32.47$, $P < .0001$; Table 2], in which the medial subregion had significantly lower dopamine D_1 receptor binding density than did either the lateral ($P < .0005$) or internal ($P < .0005$) subregions. We also observed significant Condition × Subregion and Strain × Condition × Subregion interactions [$F(4,48) = 3.00$, $P < .05$; $F(4,48) = 3.11$, $P < .05$, respectively], although clear patterns were difficult to discern.

5.2.3. Dopamine D_1 receptor binding density in the olfactory tubercle

In the olfactory tubercle, chronic administration of cocaine had no effect on dopamine D_1 receptor density [$F(2,29) < 1.0$, P=.622; Table 3], and a strain difference was not observed in this region [$F(1,29) < 1.0$, P=.88; Table 3].

Table 2
Dopamine receptor density in the caudate putamen (mean ± S.E.M.)

Group	Dopamine D_1 receptor density (fmol/mg)
C57BL/6J ($n = 22$)	285.50 ± 13.23
129/J ($n = 18$)	300.59 ± 13.14
Rostral ($n = 39$)	340.19 ± 12.0[a]
Caudal ($n = 40$)	246.46 ± 7.93
Rostral C57BL/6J ($n = 22$)	318.73 ± 17.60
Rostral 129/J ($n = 18$)	367.95 ± 13.14[b]
Rostral naive ($n = 12$)	338.69 ± 11.29
Rostral saline ($n = 12$)	347.02 ± 25.45
Rostral cocaine ($n = 14$)	335.72 ± 24.20
Rostrolateral ($n = 30$)	353.57 ± 15.43
Rostrointermediate ($n = 32$)	352.97 ± 16.21
Rostromedial ($n = 32$)	311.56 ± 13.93[c]
Caudal naive ($n = 12$)	240.67 ± 7.04
Caudal saline ($n = 12$)	222.23 ± 16.85
Caudal cocaine ($n = 15$)	270.92 ± 14.16[d]

[a] Within strains, dopamine D_1 receptor density is greater in the rostral than caudal CPu ($P < .0001$).

[b] Within the rostral CPu, dopamine D_1 receptor density is greater in 129/J mice than in C57BL/6J mice ($P < .005$).

[c] Within the rostral CPu, dopamine D_1 receptor binding was significantly lower in the rostromedial subregion.

[d] In the caudal CPu, chronic "binge" cocaine significantly increased dopamine D_1 receptor density.

Table 3
Dopamine receptor density in the olfactory tubercle (mean ± S.E.M.)

Group	Dopamine D_1 receptor density (fmol/mg)
C57BL/6J ($n = 19$)	184.04 ± 15.18
129/J ($n = 16$)	187.10 ± 13.40
Naive ($n = 13$)	196.60 ± 13.72
Saline ($n = 10$)	170.45 ± 19.80
Cocaine ($n = 12$)	185.85 ± 20.13

5.2.4. Lack of relationship between specific behaviors and dopamine D_1 receptors density

There was no significant correlation between dopamine D_1 receptor binding density in the nucleus accumbens (r=.25) or the olfactory tubercle ($r = -.16$) with locomotor activity on the 13th day of the study. No correlation was observed between dopamine D_1 receptor binding in either the rostral (r=.01) or caudal ($r = -.005$) caudate putamen with median stereotypy scores on the 13th day of the study.

6. Discussion

In the present report, we demonstrate behavioral differences between the C57BL/6J and 129/J strains of mice in response to chronic binge pattern cocaine administration. This finding extends our earlier report, in these strains of mice, demonstrating significant differences in the behavioral response to subacute (3-day) binge pattern cocaine (Schlussman et al., 1998). By extending our studies to longer time points, we have been able to demonstrate that, over time, the 129/J strain of mice do not develop a locomotor response to cocaine; their hyporesponsivity to this effect persists throughout the duration of the study. These findings are consistent with the study of Kuzman et al., which demonstrated that C57BL/6J mice developed locomotor activation in response to acute cocaine administration, while 129/Ola mice did not (Kuzmin et al., 1999). Our findings are, however, in contrast to those of Miner (2000), who showed that 129/Sv mice did have increased locomotor behavior in response to cocaine. However, in addition to differences in the 129 substrains studied, our behavioral analysis was carried out in the home cage as opposed to in a second, novel, environment, a conditioned place chamber, in the Miner study. Another difference between these two studies was the finding that 129/Sv mice were hypoactive compared to the C57BL/6J mice (Miner, 2000). In our study, we did not observe any difference in baseline activity between the 129/J and C57BL/6J mice. This again may reflect the importance of environment (home cage versus habituated novel) or substrain in influencing behavioral outcomes. In the C57BL/6J mouse, we observed significant elevation of locomotor activity on all days of the study. Additionally, as observed following 3-day binge cocaine administration, both strains expressed significant levels of behavioral stereotypy in response to cocaine, although the levels of stereo-

typy, as measured by the rating scale described above, was significantly greater in C57BL/6J mice compared to 129/J mice.

Tolerance to the locomotor-stimulating effects of cocaine was observed to develop in the C57BL/6J mouse, confirming and extending our previous finding (Ho et al., 1997). On the 13th day of the study, a time point chosen to correspond to our earlier rat study (Unterwald et al., 1994), the behavioral response to binge pattern cocaine administration was significantly lower than on the first day of the study. This is in contrast to an earlier study on the locomotor-stimulating effects of binge pattern cocaine in Fischer (F344) rats, which demonstrated that an identical binge pattern cocaine administration paradigm resulted in the development of locomotor sensitization (Unterwald et al., 1994). In the earlier rat study, it was suggested that the sensitization of cocaine-induced locomotor effects observed in F344 rats might be related to observed increases in binding to the dopamine D_1 receptor in the nucleus accumbens and the olfactory tubercle (Unterwald et al., 1994). To test the hypothesis that sensitization of the locomotor-stimulating effects of cocaine is related to dopamine D_1 receptor upregulation in these regions, we examined the dopamine D_1 receptor density in C57BL/6J mice, which show locomotor tolerance, and 129/J mice, which do not show increased locomotor activity in response to binge cocaine at any time point tested. If sensitization is associated with increased dopamine D_1 receptor density in the nucleus accumbens or olfactory tubercle, we would not expect to observe a cocaine-induced increase in binding in either strain of mice. If, on the other hand, the upregulation of dopamine D_1 receptors reported in the F344 rat was related to cocaine-induced activity rather than the increase in activity over time, then we would expect to observe this phenomenon in the C57BL/6J strain but not the 129/J mice. In contrast to our earlier study in the F344 rat, we did not find an upregulation of the dopamine D_1 receptor in the nucleus accumbens or olfactory tubercle in either strain of mouse. Nor did we observe a correlation between locomotor activity and dopamine D_1 receptor density in either region. These findings taken together are consistent with the idea that cocaine-induced increases in receptor density may be functionally related to the development of behavioral sensitization, rather than with cocaine-induced activity per se; however, our data provides no direct support for this hypothesis.

In the present study, we did not observe an effect of chronic binge pattern cocaine administration on dopamine D_1 receptor binding density in the nucleus accumbens of either strain of mouse. In the caudate putamen, we did observe an increase in the density of dopamine D_1 receptors in the caudal portions of the nucleus following chronic cocaine administration. Both of these findings are in apparent contrast to our earlier rat study in which significant increases in binding to dopamine D_1 receptors were observed in the nucleus accumbens and the olfactory tubercle but not in the caudate putamen (Unterwald et al., 1994). These findings also differ with earlier studies in the rat, which showed that following cocaine administration binding to striatal dopamine D_1 receptors was increased (Alburges et al., 1993) or decreased (e.g., Tsukada et al., 1996).

Our finding of no cocaine-induced changes in the binding density of dopamine D_1 receptors in the nucleus accumbens and in the rostral portion of the caudate putamen are in agreement with the findings of Peris et al. (1990), who found no changes in dopamine D_1 receptor binding in either the striatum or nucleus accumbens following 7 days of cocaine administration in the rat. However, other studies in rats have reported that, in response to cocaine, dopamine receptor levels increased (Alburges et al., 1993; Unterwald et al., 1994) or decreased (Kleven et al., 1985; Maggos et al., 1998; Tsukuda et al., 1996). These differences are probably related to length of cocaine administration, whether the animals underwent withdrawal from cocaine and the method of analysis (e.g., see Unterwald et al., 1994; Tsukada et al., 1996).

The significance of our report of regional differences in dopamine D_1 receptor binding in the nucleus accumbens and rostral portion of the caudate putamen remains to be determined. In primates, the striatum has been subdivided into functional domains based on afferent projections from the cortex, the thalamus, and the midbrain (e.g., Cragg et al., 2002; Haber and McFarland, 1999; Selemon and Goldman-Rakic, 1985). Briefly, the ventral striatum has been defined as that portion of the striatum which receives afferents from the orbital and pre-frontal cortices as well as thalamic and midbrain regions which mediate reward processes (e.g., Haber and McFarland, 1999), while the caudate and putamen nuclei in primates have been divided into associative (central), sensorimotor (dorsolateral), and limbic (ventral medial) domains (e.g., Cragg et al., 2002; McFarland and Haber, 2000; Selemon and Goldman-Rakic, 1985). However, such a clear delineation of projections and function has not been observed in rodents. In the absence of a clearer understanding of the neuroanatomy of afferent projections to the striatum in the mouse, it is difficult to speculate on a possible functional significance of our findings of regional differences in dopamine D_1 receptor binding density.

Individual vulnerability to drugs of abuse has been demonstrated in both laboratory animals (e.g., Piazza et al., 1989; Cador et al., 1993; Guitart et al., 1993; Hooks et al., 1994; Kosten et al., 1997) and humans (e.g., Siegel, 1984; Piazza et al., 1989), and an individual's vulnerability to develop addictions may be a critical factor in determining clinical prognosis. The question of individual predisposition to self-administer drugs of abuse is frequently studied in laboratory animals by using behavioral or neurochemical measures to identify predictors of vulnerability in outbred strains (e.g., Hooks et al., 1994; Piazza et al., 1989, 1991) or by utilizing inbred strains known to differ in their propensity to self-administer drugs of abuse (e.g., Suzuki et al., 1988,

1992; Grahame and Cunningham, 1995; Kosten et al., 1997). Comparison of divergent strains provides an opportunity to examine inherent factors which may contribute to the development of addictive diseases. We have demonstrated that the C57BL/6J and 129/J mice differ in their locomotor response to binge pattern cocaine administration. The expression of locomotor behavior is believed to be at least partially mediated by the mesolimbic dopaminergic projection from cell bodies in the A 10 area to the shell of the nucleus accumbens (e.g., Jackson et al., 1975; Pijnenburg and Van Rossum, 1973). Since this projection is also known to be important in the ''reward pathway,'' the expression of this behavior may be reflective of the rewarding effects of drugs of abuse (e.g., Wise and Bozarth, 1987). Therefore, the C57BL/6J and 129/J mice may be a useful model for examining individual differences in the rewarding effects of drugs of abuse. Indeed, we have demonstrated that C57BL/6J mice develop conditioned place preference to binge pattern cocaine administration while 129/J mice do not (Zhang et al., 2002). This idea is supported by the finding of Miner (2000), who showed that C57BL/6J mice developed conditioned place preference to cocaine while 129/SvJ mice, which are closely related to the 129/J strain, did not. However, it has been suggested that vulnerability to self-administer drugs of abuse in rats is associated with increased binding to dopamine D_1 receptors in the nucleus accumbens of rats (Hooks et al., 1994). We did not observe strain differences in dopamine D_1 receptor binding in this region.

The present report extends earlier studies on cocaine-induced behavioral effects in C57 and 129 strains of mice (Kuzmin et al., 1999; Schlussman et al., 1998). This report documents regional differences in dopamine D_1 receptor density in the nucleus accumbens and the caudate putamen and shows regional strain and cocaine-induced effects on dopamine D_1 receptor density in the caudate putamen.

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