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Acute Sensitivity vs. Context-Specific Sensitization to Cocaine as a Function of Genotype

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ELMER, G. I., D. A. GORELICK, S. R. GOLDBERG AND R. B. ROTHMAN. *Acute sensitivity vs. context-specific sensitization to cocaine as a function of genotype.* PHARMACOL BIOCHEM BEHAV 53(3) 623-628, 1996. – Individual variability in the acute and chronic effects of psychomotor stimulants is due, in part, to genetic factors. The purpose of this series of studies was to utilize a behavioral model of sensitization, namely increased locomotor activity, to assess individual variability in sensitization to the chronic effects of cocaine and its relationship to the acute stimulant effects of cocaine. Because the degree of sensitization is proportional to the training dose, genetic differences in acute sensitivity to cocaine were assessed and incorporated into the sensitization paradigm. Acute sensitivity and context-dependent sensitization were determined in six inbred mouse strains. Large quantitative and qualitative differences were found in the acute potency and efficacy of cocaine to stimulate locomotor activity. The ED_{50} was higher in the strains in which cocaine was most efficacious. Context-specific sensitization was determined via chronic administration of equiactive doses of cocaine (ED_{50}) specifically paired with the test apparatus or with the home colony. Sensitization was time, environment, and genotype dependent. The differences in the number of trials required to show sensitization were unrelated to the acute locomotor stimulant effects of cocaine. These findings suggest that acute cocaine-induced locomotor activity and context-specific sensitization reflect different pharmacological properties of cocaine.

Sensitization Cocaine Behavior genetics Locomotor activity

REPEATED administration of psychostimulants and opioids can lead to an increased behavioral response (sensitization) to the drug. The degree of sensitization produced is determined by the drug, dose, schedule of administration, and environmental context. Sensitization to the locomotor stimulant effects of psychomotor stimulants or opioids, for example, increases with training dose (42), is greater with moderate vs. continuous interdose intervals (22,41), and is significantly enhanced when stimuli associated with chronic treatment are also present during expression of sensitization (32,43). In addition, a variety of data reviewed elsewhere suggest that cocaine-induced context-dependent sensitization may detect the incentive/motivational effects of cocaine (28,35,36).

Significant individual differences in the behavioral effects of repeated psychomotor stimulant administration exists in human and nonhuman subjects (24,29,30,34,38,40,42). The factors underlying these individual differences are due, in part, to the genotype of the subject. Genotype significantly affects both the potency and efficacy of the acute locomotor response to cocaine (19,37) as well as the response to chronic administration (42). For example, acute administration of 0.3-56.0 mg/kg cocaine produces no locomotor stimulation in LS/Ibg mice but results in >250% increase in SS/Ibg mice (20). Repeated administration of cocaine (20 mg/kg) to seven lines of the recombinant C57BL/ByJ × BALB/cByJ inbred strains results in 0 to >200% increases in the locomotor

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response to cocaine depending upon the genotype (42). As mentioned previously, numerous variables can influence the degree of sensitization, including dose and environmental context. Because previous studies have demonstrated that the degree of sensitization is proportional to the training dose and that there are large individual differences in sensitivity to the acute effects of cocaine, genetic differences in sensitization may be a result of a single dose of cocaine having different locomotor stimulant effects in each strain. In addition, the context-specific nature of the sensitization process may differ in a genotype-dependent manner similar to that seen in tolerance to opioid-induced analgesia (12). The degree of variance in sensitization to cocaine due to genotype would be more adequately characterized if underlying differences in sensitivity (1) and the context-specific nature of the sensitization phenomenon were taken into consideration (6).

The purpose of the current set of experiments was to investigate the relationship between the acute locomotor stimulant effects of cocaine and the degree of sensitization following its chronic administration. The experiments were conducted in two phases. First, sensitivity to the acute locomotor stimulant effects of cocaine was determined. Second, the degree of context-dependent sensitization following one, two, or three administrations of equiactive doses of cocaine (ED_{50} as determined in phase were determined. We conducted these experiments in six inbred mouse strains: C57BL/6J, BALB/cByJ, CBA/J, DBA/J, C3H/HeJ, and AKR/J mice. These strains were chosen because they provide a readily available means to manipulate genotype, demonstrate neurochemical differences in dopaminergic binding and monoaminergic uptake (4,5, 21,39), and have demonstrated differences in the acute effects of cocaine (16,37). The degree of genetic covariance across drug-naive and cocaine-related phenotypes will help determine innate behaviors important in an individual's initial drug response and the importance of the acute drug response to the sensitization process (9,11,15).

METHOD

Animals

Adult male C57BL/6J (C57), BALB/ByJ (BBy), CBA/J (CBA), DBA/J (DBA), C3H/HeJ (C3H), and AKR/J (AKR) mice (Jackson Laboratories), 60–100 days old and weighing approximately 21–26 g at the start of the experiment, were used. All animals were experimentally naive, housed in groups of five in a temperature-controlled room (21°C) with a 12 L : 12 D cycle (0700–1900 h lights on), and given free access to Purina Laboratory Chow and tap water during the entire experimental procedure. The animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC) and the studies were conducted in accordance with the Guide for Care and Use of Laboratory Animals provided by the NIH and adopted by NIDA.

Characterization of Acute Dose-Response Curves

Full dose-response curves for each inbred strain were determined under conditions identical to control groups run in the conditioned sensitization experiments (see Table 1). All subjects received two saline injections on day 1. The first saline injection was given immediately prior to being placed in the locomotor activity monitor for 60 min. The second saline injection was given 3 h later in the home colony. On day 2, saline, 0.1, 0.3, 1.0, 3.0, 10.0, 30.0, 56.0, or 71.0 mg/kg cocaine was given immediately prior to the mouse being placed in the locomotor activity monitor for 90 min. The dose-effect curve was generated with an $n = 6$–9 mice per strain per dose; no mouse was ever used more than once. Saline control values assessed under these conditions were used as baseline values for percent changes in locomotor activity produced by cocaine. Cocaine (expressed as base) and saline were administered IP in a volume of 0.01 ml/g body weight.

Locomotor activity was monitored in an Omnitech Activity Monitor (Omnitech Electronics Inc., Columbus, OH). Activity in the monitor was recorded by the interruption of photocells placed at 2.4-cm intervals across either side of the monitor. Animals were placed in a rectangular Plexiglas retainer (42 cm L × 24 cm W × 19 cm H) in the center of the 45-cm square monitor. Distance traveled (cm) was recorded as the dependent measure. Distance traveled was determined by photocell breaks in the 17 × 10 array of photocells covering the rectangular Plexiglas retainer. Data were collected in 10-min intervals. All activity measurements were conducted in a soundproof isolation chamber under red light.

Characterization of Context-Specific Sensitization

To compensate for significant genetic differences in sensitivity to the acute locomotor stimulant effect of cocaine, the dose of cocaine required to produce an equal locomotor stimulant effect (ED_{50} as defined by 50% of the maximal increase) in each strain was used as the training dose. Because cocaine did not produce a statistically significant stimulant effect in DBA and BBy mice under these conditions, the dose used for chronic administration in these strains was that which produced half-maximal effect. The training dose of cocaine for each strain was: 5.8, 8.1, 17.3, 10.0, 12.8, and 11.9 mg/kg for the C57, BBy, CBA, DBA, C3H, and AKR mice, respectively.

The experimental design to assess sensitization is similar to that used in numerous other studies of context-specific sensitization or tolerance (28,43,44). Subjects were randomly divided into three groups: Paired, Unpaired, and Controls. These designations were balanced within home cages. All subjects received two injections per day for the conditioning sessions. Subjects in the Paired group received cocaine (ED_{50}) in the locomotor activity monitor and saline (3 h later) in the colony room. Subjects in the Unpaired group received saline in the locomotor activity monitor and cocaine (ED_{50}, 3 h later) in the colony room. Thus, subjects in the Paired and Unpaired groups received the same total amount of drug per day; only the location of the drug injection differed between groups. Subjects in the control group received saline injection in the locomotor activity monitor and saline (3 h later) in the colony room. Animals received one, two, or three conditioning session. Animals were then tested the following day. On the test day (aproximately 1000 h), all animals were administered a lower dose of cocaine (ED_{25}) and immediately placed in the locomotor activity monitor. Sensitization was measured as the magnitude of the difference in the response to the chronic drug-treated vs. chronic saline-treated animals. The context-specific nature of the sensitization process was measured as the difference between the Paired and Unpaired groups. Each context group (Paired, Unpaired, Control) and each training group (1, 2, or 3 days) consisted of six to nine naive mice per strain.

Statistical Analysis

Acute dose-response curves. A three-way analysis of variance (ANOVA) was performed for dose-response curves

across genotype with a repeated-measures factor of session time. The potency (ED_{25} and ED_{50}) of cocaine-induced locomotor activity was derived from the regression analysis of the linear portion of each dose-response curve for values summed across 60 min. The ED_{25} and ED_{50} values were calculated as 25% and 50%, respectively, of the maximal percentage increase from their own saline baseline and not as equivalent locomotor activity increases in absolute terms.

Context-specific sensitization. A three-way ANOVA was performed for the analysis of context (Paired, Unpaired, Control), training (1, 2, 3 training sessions), and genotype. A one-way ANOVA for context with a LSD post hoc test was performed to determine presence or absence of context-specific sensitization in each genotype at each training time point.

Genetic correlations. The genetic correlations among phenotypes generated in this series of studies is an important step in building a genetic data base necessary for future determination of genetic covariance among these cocaine-related phenotypes and in implicating mechanisms responsible for observed variations in behavior (10,11,15).

A correlation between four dependent measures was performed: baseline locomotor activity (saline controls), locomotor stimulant potency, locomotor stimulant efficacy, and sensitization. A generalized linear model was used to incorporate discrete values derived from the chronic treatment portion of the study (8,47). Transformation of two sensitization measures taken on day 3 was used: the likelihood of the Paired value greater than Control mean (sensitization) and the likelihood of the Paired value greater than the Unpaired mean (context-specific sensitization). The maximum percent of locomotor stimulation was defined as the largest increase in locomotor activity compared to saline values obtained at any of the cocaine doses.

RESULTS

Baseline Differences in Locomotor Activity

Figure 1 shows baseline locomotor activity in all six inbred strains. There was a significant overall genotype × time effect for distance traveled [distance traveled: genotype × time, $F(35, 1213) = 9.2, p < 0.0001$; genotype, $F(5, 1213) = 16.9$, $p < 0.0001$; time, $F(8, 1213) = 180.3$, $p < 0.0001$]. The rank order for the rate of locomotor activity habituation was C57 < C3H < CBA < BBy < AKR < DBA.

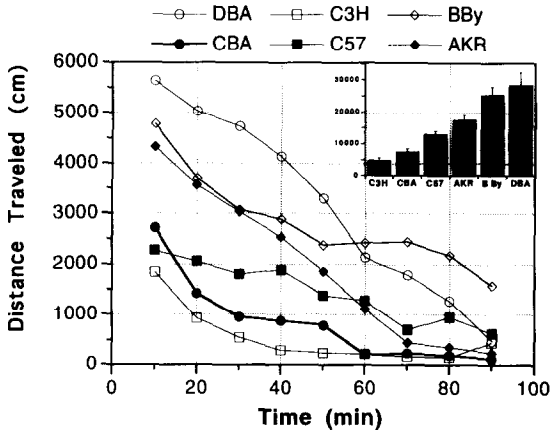

FIG. 1. Baseline locomotor activity (saline control values) in six inbred strains as a function of time. Each point represents the mean from six to nine mice. Inset: total cumulative locomotor activity during the 90-min session as a function of genotype.

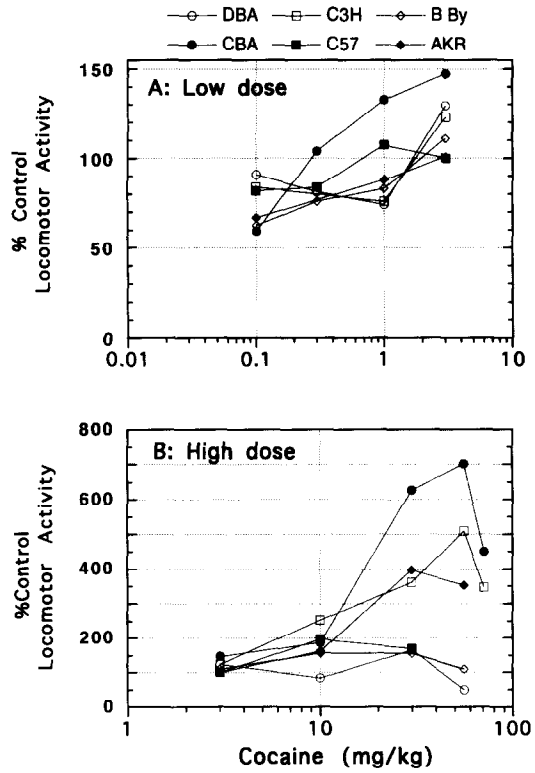

FIG. 2. (A) Low-dose cocaine-induced locomotor depression in six inbred mouse strains as a function of increasing cocaine dose. (B) High-dose cocaine-induced locomotor stimulation in six inbred mouse strains as a function of increasing cocaine dose. Each point in (A) and (B) is presented as a percent of saline control values (Fig. 1) and represents the mean from six to nine mice during a 60-min session.

Acute Sensitivity to Cocaine

There was a significant overall genotype × dose × time effect for distance traveled [distance traveled: genotype × dose × time, $F(240, 1560) = 1.95$, $p < .0001$; genotype, $F(5, 1560) = 10.6$, $p < 0.0001$; dose, $F(7, 1560) = 23.1$, $p < 0.0001$; time, $F(8, 1560) = 162.1$, $p < 0.0001$]. Figure 2A shows low-dose depressant effect of cocaine (0.1-3 mg/kg) as a function of genotype. CBA mice showed the greatest degree of locomotor depression (−41%) and C57 mice the least (−18%). Figure 2B shows dose-effect curves (3-71 mg/kg) for cocaine-induced stimulation of locomotor activity as a function of genotype. Relative sensitivity to and efficacy of cocaine-induced stimulation of locomotor activity differed significantly across genotype. Sensitivity to cocaine-induced locomotor activity (ED_{50}) differed by almost 3.5-fold from the most to least sensitive strain for which cocaine produced a significant locomotor stimulant effect. Cocaine did not produce a significant locomotor stimulant effect in DBA or BBy mice. In the other inbred mouse strains, cocaine was the least potent in the CBA mice and most potent in the C57 mice. The efficacy of cocaine-induced locomotor activity ranged from a nonsignificant increase of 156% in the BBy mice to a maximal increase of a 701% in the CBA mice. The locomotor stimulant

ED_{50} and maximal percentage increase for each strain are given in Table 1.

Context-Specific Sensitization

There was a significant interaction between the genotype of the subject, the number of trials run, and context in the development of sensitization [genotype × context × trials, $F(170, 867) = 3.91, p < 0.0001$; see Table 1]. Figure 3 shows the context-specific nature of sensitization to cocaine's locomotor stimulant effect as a function of genotype following one, two, or three training sessions. The values in Fig. 3 are presented as a percent of each strain's Control group value, that is, animals chronically treated with saline then tested with their ED_{25} dose of cocaine. A single pretreatment of cocaine produced sensitization in the C57 and BBy mice. However, sensitization was context specific only in the C57 mice; the Paired group was the only condition to demonstrate sensitization to the stimulant effect of cocaine. Sensitization was evident in the C57, BBy, C3H, and AKR mice following two training sessions but was not context specific in the BBy until three training sessions were performed. DBA and CBA mice did not demonstrate sensitization following three training sessions. The context-specific sensitization of all six inbred strains are presented in Table 1.

Genetic Correlations

The potency of cocaine as a locomotor stimulant was significantly correlated with the efficacy of cocaine as a locomotor stimulant ($r = -0.87, p < 0.05$). Baseline activity was marginally correlated with the efficacy of cocaine to induced locomotor stimulation ($r = -0.74, p = 0.09$). The potency of cocaine to induce locomotor stimulation, however, was not related to baseline activity. Neither of the sensitization phenotypes were significantly related to baseline locomotor activity or the acute effects of cocaine. None of the other measures taken under these conditions (habituation rate, stereotopy as defined by Omnitech Instruments, low-dose depression effects, etc.) were significantly correlated with the acute or chronic effects of cocaine.

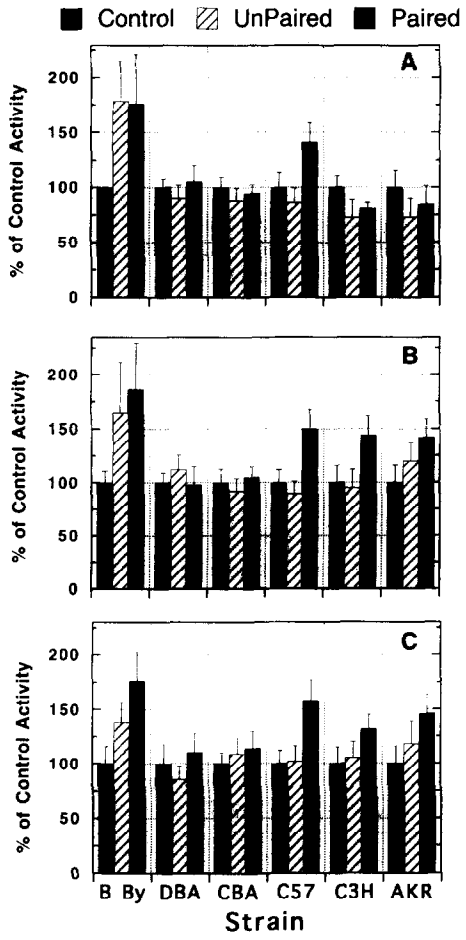

FIG. 3. Locomotor activity produced by cocaine (ED_{25} dose for each respective strain) in mice naive to cocaine (Control) or in mice specifically pretreated with cocaine (ED_{50} dose for each respective strain) in the colony room (Unpaired) or test chamber (Paired). (A, B, C) Results following one, two, or three training sessions, respectively. Each panel represents separate groups of mice. Each bar represents the mean ± SEM of six to nine mice during a 60-min session.

DISCUSSION

Genotype significantly influences the qualitative and quantitative response to the acute locomotor stimulant effects of cocaine. As previously reported (16), low doses of cocaine (0.1-3.0 mg/kg) can produce a significant degree of locomotor depression. Four of the inbred strains showed significant

TABLE 1

LOCOMOTOR STIMULANT EFFECTS OF COCAINE IN INBRED MICE

			Sensitization					
	Acute Response		1 Trial		2 Trials		3 Trials	
Strain	Potency (ED_{50})	Efficacy (max%)	S	CS	S	CS	S	CS
C57	5.8	198%	+	+	+	+	+	+
BBy	NS	156%	+	–	+	–	+	+
C3H	12.8	509%	–	–	+	+	+	+
AKR	11.9	397%	–	–	+	–	+	–
CBA	17.3	701%	–	–	–	–	–	–
DBA	NS	166%	–	–	–	–	–	–

NS nonsignificant increases; + present, – absent. S, sensitization; CS, context-specific sensitization.

locomotor depression; the degree of locomotor depression was unrelated to the potency or efficacy of cocaine's locomotor stimulant activity. Doses greater than 3 mg/kg produced significant locomotor stimulation in all but two of the six inbred strains (BBy, DBA). In the strains that were significantly stimulated by cocaine, the relative potency and efficacy of cocaine differed by 281% and 444%, respectively. Neither the potency or efficacy of cocaine's locomotor stimulant effects were significantly correlated with baseline locomotor activity. These data are dissimilar to previously reported investigations (29,30) this may be due to differences in the length or timing of preexposure to the test environment, the drug, or species differences. The potency and efficacy of cocaine's locomotor stimulant effects were inversely correlated. The more potent cocaine was as a stimulant the less efficacious it was as a locomotor stimulant. This may be due to an increased potency of cocaine in producing efficacy-limiting side effects in the low efficacy strains.

Despite demonstration of the importance of the dopamine transporter, dopamine D_1 or D_2 receptor sites in the expression of cocaine-induced locomotor activity (7,26), genetic differences in the affinity or number of dopamine transporter, D_1 or D_2 receptor sites have failed to explain observed genetic variance in cocaine's or amphetamine's stimulant actions (19,33). In agreement with these data, differences in the potency and efficacy of the stimulant effects of cocaine in these inbred mice appear unrelated to whole brain [^{3}H]spiroperidol or [^{3}H]ADTN B_{max} or K_d [three strains in common: (39,21); four strains in common: (4)] or to functional assays describing the ability of cocaine to inhibit norepinephrine, dopamine, or serotonin uptake [four strains in common: (4)]. Thus, the mechanisms essential for expression of cocaine's acute locomotor stimulant effects may not be similar to those responsible for variance seen across the genotypes.

Sensitization to cocaine-induced locomotor activity following chronic administration differed both quantitatively and qualitatively in the number of injections required to show sensitization and in its context specificity. The results of the data in the C57 and DBA mice are in agreement with those obtained using amphetamine (6). The utility of a behavior genetics design is the ability to compare several behavioral effects of a drug across genotype to determine if there are common inherited factors that influence each behavior. The results of the current study demonstrate that the differences in the number of trials required to show sensitization (or context-specific sensitization) were unrelated to the acute potency or efficacy of cocaine as a locomotor stimulant. A factor not immediately addressed in the current study is the possibility that tolerance to the low-dose depressant or high-dose rate depressant effects of cocaine are responsible for the eventual increases seen in the locomotor stimulant effects of cocaine. Full dose-response curves would be required to determine if tolerance had developed to the low-dose depressant effects of cocaine or if this effect of cocaine was merely shifted to the left. Overall, these results suggest that the pharmacological properties underlying the sensitization process are unrelated to the pharmacological properties underlying cocaine's acute stimulant effects. Several behavior genetic (27,40,42), behavior pharmacological (3,36,47), and neuroanatomical (23,25, 45,46) studies support independent processes involved in the acute vs. chronic locomotor stimulant effects of amphetamine, cocaine, and opioids. Thus, the primary acute and chronic stimulant effects of cocaine may be expressed through similar mechanisms, but the development of sensitization may occur through alternate neurochemical systems or neuroanatomical regions.

One advantage of using defined genotypes is the ability to determine the genetic/mechanistic relationship between several phenotypes. A recent theory has proposed a relationship between the sensitization process and drug addiction (35). This theory posits distinct primary reinforcement, classical conditioning, and incentive motivation factors in the addiction process, with sensitization of the latter component driving chronic addiction. Presumably, individuals vulnerable to addiction would be more sensitive to sensitization. In the present data set, the strain most readily showing context-specific sensitization is also the strain (C57) most sensitive to context-specific opioid tolerance and most readily trained to self-administer cocaine, ethanol, and opioids (13,14,18). At least one of the strains that did not demonstrate sensitization under these training procedures, DBA mice, consistently demonstrates aversion to abused drugs (17,31). However, several studies have demonstrated sensitization in DBA mice following chronic stress (2) or amphetamine (34) treatment. Although further studies are required to explore the proposed relationship between sensitization and addictive processes, a variety of data reviewed elsewhere suggest that cocaine-induced context-dependent sensitization may detect the incentive/motivational effects of cocaine (28,36).

In conclusion, the current series of studies investigated the influence of genotype on sensitization following chronic administration of equiactive doses of cocaine. There were large quantitative and qualitative differences in the acute and chronic effects of cocaine as a function of genotype. The occurrence of sensitization, whether context dependent or not, was unrelated to the potency or efficacy of cocaine's acute locomotor stimulant effects in these six inbred strains. These observations support the notion that acute cocaine-induced locomotor activity and cocaine-induced sensitization (context-dependent or indepenent) reflect different properties of cocaine.

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