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Context-Independent Sensitization to the Locomotor-Activating Effects of Cocaine

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PARTRIDGE, B. AND S. SCHENK. *Context-independent sensitization to the locomotor activating effects of cocaine.* PHARMACOL BIOCHEM BEHAV **63**(4) 543–548, 1999.—After repeated intermittent exposure to psychostimulants, an increase in the behavioral response to the drug is observed. The development of this sensitized response is greatly influenced by environmental cues. For example, when the pretreatments are administered in an environment distinct from the test, a sensitized response is often not observed. This finding has led some investigators to suggest that sensitization is completely context dependent. The present experiment established context-independent sensitization by administering pretreatments in an environment distinct from the test and measured the effects of pretreatment on potency and/or efficacy of subsequent cocaine administrations. Separate groups of rats received single or multiple daily injections of cocaine (10.0 mg/kg) or the saline vehicle in the home cage during a 5-day pretreatment phase. Ninety-six hours following the last of the pretreatment injections the locomotor-activating effects of cocaine (0.0, 5.0, 10.0, or 20.0 mg/kg) were measured. For control rats, a significant increase in motor activity was obtained following administration of the 20.0 mg/kg dose. Rats that received the cocaine pretreatment became sensitized to cocaine's motor activating effects. For these rats, cocaine pretreatment produced a leftward shift in the dose–effect curve, consistent with an increased potency. The maximum locomotor response was not altered by pretreatment, suggesting that drug efficacy was not effected by preexposure. Thus, context-independent sensitization to cocaine reflects an increased potency, but not efficacy, of the drug. © 1999 Elsevier Science Inc.

Cocaine Locomotor activation sensitization

A characteristic response to an acute injection of cocaine is an increase in forward locomotion. With repeated intermittent exposure, cocaine-induced hyperactivity increases, suggesting behavioral sensitization. Sensitization has been implicated as an important factor in the development of compulsive drug taking and in relapse to drug taking (4,10,11,28,33,35). As a result, it has been of great interest to determine the conditions under which the sensitized behavioral response occurs.

The amount of prior drug exposure required for the development of behavioral sensitization and the magnitude of the sensitized response is markedly influenced by environmental factors. A robust form of sensitization is produced when the drug is repeatedly experienced in the test environment (1,3,5,6,9,12,13,18,19,21,22,25,29,32,36,37). However, minimal exposures that produce this context-dependent form of sensitization are often ineffective in producing sensitization when administered in an environment distinct from the test.

In many studies, regardless of whether context-dependent or independent procedures have been used, the pretreatment phase is generally comprised of repeated, intermittent injections of a single dose of cocaine. A test phase that determines the behavioral response to a single dose of cocaine follows. The dose of cocaine administered during pretreatment and test and the number of pretreatment administrations and duration of the withdrawal period are some of the procedural variables that are most frequently varied across studies.

Although cocaine-induced activation may be increased by preexposure, the use of a single dose of cocaine during the test precludes an unambiguous interpretation of whether preexposure increased the potency or efficacy of the drug. A demonstration of increased potency, defined as a horizontal shift in the dose–effect curve, requires a test phase that assesses the response to multiple doses at the lower end of the dose–effect curve. A demonstration of increased efficacy, defined as a ver-

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tical shift in the maximum response to the drug, requires an assessment of the response to a high dose of the drug. When the response to a single dose of drug is measured on the test day, an increase in behavioral output could reflect one or both of these changes, depending on the dose of drug tested.

In a direct comparison of potency and efficacy changes following preexposure, a recent study examined behavioral sensitization produced by repeated administration of the dopaminergic D_2/D_3 agonist, quinpirole (36). Of particular interest was whether context-dependent and -independent sensitization were reflections of comparable changes in efficacy and/or potency. During the pretreatment phase, quinpirole was administered in either the home cage, an alternate cage, or the test environment. On the test day, the locomotor activating effect of a range of quinpirole doses was measured. Pretreatments in all three environments resulted in a increase in maximum responding, characteristic of a change in efficacy. The magnitude of the change in efficacy was dependent on the environment in which the drug was experienced. However, a change in potency was only obtained for rats that had received the pretreatments in the test environment. These data suggest that sensitization may reflect different neuroadaptations, depending on the environment in which the drug was experienced.

To our knowledge, context-independent sensitization to cocaine has not been examined in a manner that is amenable to the demonstration of changes in either efficacy or potency. In one study (14), rats were pretreated for 5 days with one of several doses of cocaine, administered in the home cage. They were subsequently tested with the same dose of cocaine that was administered during the pretreatment phase. Regardless of the dose of cocaine that was administered, an increase in cocaine-produced hyperlocomotion was obtained, suggesting increased efficacy of cocaine.

To more accurately determine changes in cocaine efficacy and potency as a result of preexposure, the present study obtained dose–effect functions for cocaine-induced locomotor activity following several different cocaine pretreatment regimens. The pretreatments were administered in the home cage to minimize the contribution of context to the development of sensitization.

METHOD

Subjects

Male Sprague–Dawley rats (Harlan, TX), weighing 350–400 g, were used. They were housed individually in clear plastic hanging cages in a climate- and humidity-controlled environment. The animal colony is fully accredited by AALAC, and all procedures were approved by the University Lab Animal Care Committee. Food and water were freely available except during testing. Upon arrival at the laboratory, there was a 4-day habituation period prior to the start of test procedures.

Four Digiscan Open field chambers (Omnitech), equipped with two banks of eight photocells on each wall, were used to measure horizontal and vertical locomotion. The open-field boxes were interfaced with a digital multiplexor (Coulbourn E61-58) located in an adjacent laboratory. Testing was conducted in the dark between 1000 and 1600 h. White noise was continually present to mask extraneous disturbances.

Pretreatment

Separate groups of rats received five daily pretreatments consisting of saline, single or multiple injections of cocaine (10.0 mg/kg/injection, IP). The multiple cocaine injections (two or three) were delivered at 1-h intervals. Immediately following each injection, the rats were returned to the home cage.

Test

Three days after the last of the pretreatment injections, a 2-day test of cocaine-induced hyperlocomotion was conducted. On both of these days, the test consisted of an initial 15-min period of habituation to the activity chambers. After this habituation period, the rats received a drug injection and were returned to the activity chambers for an additional 45 min. On day 1, saline (1.0 ml/kg) was administered following the habituation period and on day 2 cocaine (0.0, 5.0, 10.0, or 20.0 mg/kg, IP) was administered (n = 6–11). Total activity, a composite of horizontal and vertical activity measures, was obtained every 5 min during the habituation and postinjection periods.

Data Analysis

Data from the first test day, when all rats received an injection of saline following the habituation period, were analyzed by a two-way repeated-measures ANOVA (pretreatment condition × time). These data provided an indication as to whether baseline levels of activity were altered by cocaine pretreatment.

Data from the second test day, when all rats received an injection of cocaine following the habituation period, were analyzed by separate sets of ANOVAs. In the first set, the influence of cocaine dose on the total activity measure was determined for each of the pretreatment groups. The data were subjected to individual two-way repeated-measures ANOVAs (cocaine dose × time) for each of the four pretreatment conditions. In the second set, a three-way repeated-measures ANOVA (cocaine dose × pretreatment condition × time) compared dose–effect functions for cocaine-induced hyperlocomotion for rats from each of the pretreatment groups. Tukey post hoc tests were conducted where appropriate.

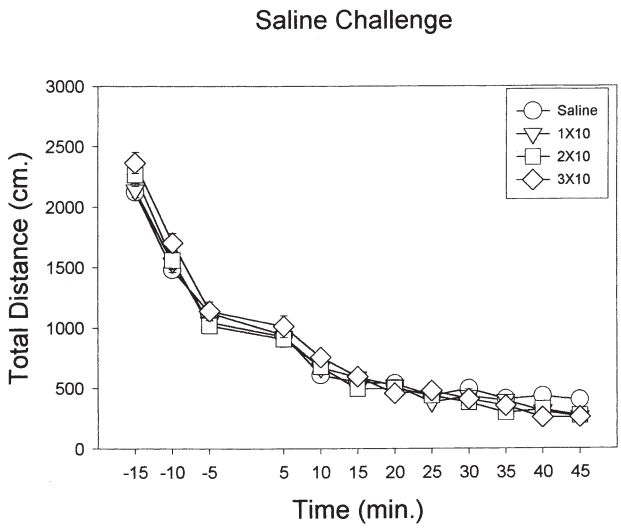

FIG. 1. Locomotor activity during a 15-min period prior to, and a 45-min period following, an injection of saline. This test occurred 72 h following the last pretreatment injection for rats that received daily exposure to either saline or single or multiple injections of cocaine (10.0 mg/kg). Symbols represent the average total distance (±SEM).

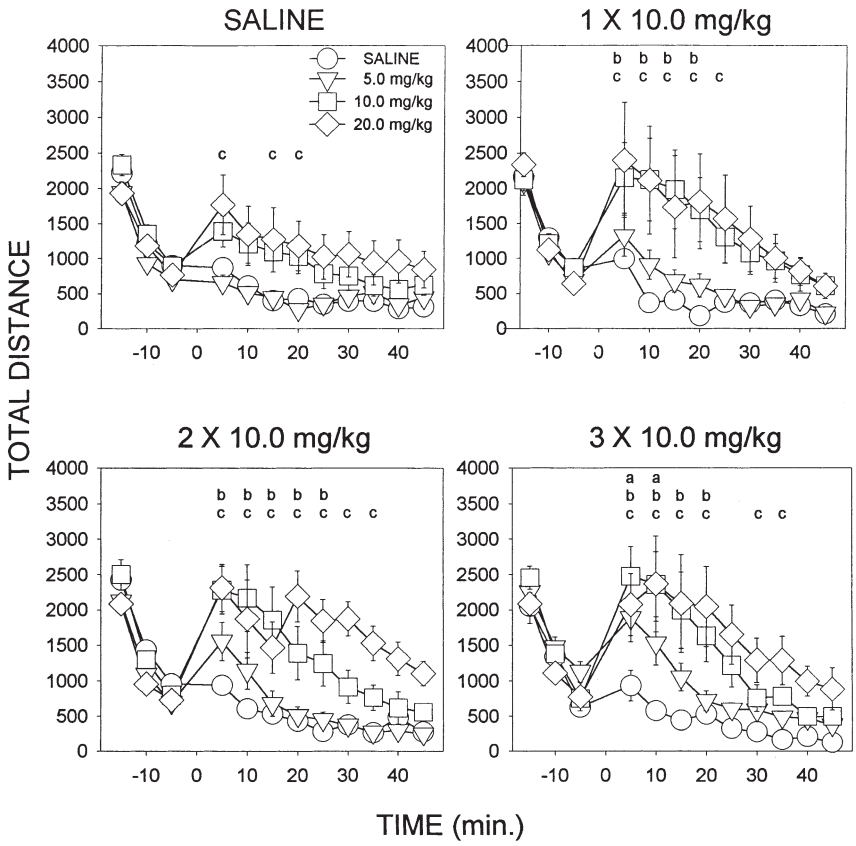

FIG. 2. Locomotor activity during a 15-min period prior to, and a 45-min period following, an injection of cocaine (0.0, 5.0, 10.0, or 20.0 mg/kg) for the various pretreatment groups. This test occurred 96 h following the last pretreatment injection for rats that received daily exposure to saline and single or multiple injections of cocaine (10.00 mg/kg). Symbols represent the average total distance (±SEM). Significant increases ($p < 0.05$) in response to each of the cocaine challenge doses relative to the response to the saline challenge dose are indicated by the lower-case letters in each panel. The letter indicates that the dose of drug produced a significant increase in activity at that time period. a = 5.0 mg/kg; b = 10.0 mg/kg; c = 20.0 mg/kg.

Drugs

Cocaine HCL (NIDA, Research Triangle Park) was dissolved in 0.9% saline and was administered IP in a volume of 1.0 ml/kg. Drug weights refer to the salt.

RESULTS

Response to Saline

Figure 1 shows the average total distance as a function of pretreatment condition for each 5-min interval during the habituation period and following the injection of saline. These data were derived on the first test day, 72 h following the last of the pretreatment injections. The profile and the amount of locomotor activity were similar for all pretreatment injections. The profile and the amount of locomotor activity were similar for all pretreatment groups. During the 15-min habituation period, activity was initially high and progressively decreased. Following the saline injection, activity increased slightly during the initial 5-min period, and decreased progressively during the remaining 40 min.

An ANOVA (pretreatment condition × time) failed to reveal a significant effect of pretreatment condition, $F(3, 122) = 0.6534$, NS), although the pretreatment × time interaction was significant, $F(33, 1342) = 1.92077$, $p = 0.0014$. Comparisons of activity during each 5-min time period after the saline injection failed to reveal any significant differences between groups (Tukey tests, NS).

Response to Cocaine

Figure 2 shows the average total distance as a function of pretreatment condition, cocaine dose, and time. The data, collected 24 h following the saline tests, are presented for each 5-min interval that comprised the habituation period and the 45-min period following the injection of cocaine. Individual panels show the response to cocaine for the rats from each of the four pretreatment conditions.

Cocaine produced a dose-dependent increase in activity for all groups. However, the rats that received cocaine pretreatment appeared to show a greater locomotor response to the 5.0 and 10.0 mg/kg doses. Separate ANOVAs (cocaine dose × time) were conducted to determine the minimum doses for cocaine-produced hyperlocomotion for rats in each pretreatment condition. Table 1 shows the resulting *F*-values and probability levels for the main effects and interaction

TABLE 1
RESULTS FROM ANOVAS (COCAINE DOSE × TIME) CONDUCTED ON THE DATA FROM EACH PRETREATMENT GROUP

		df	*F*	*p*
Saline				
	Cocaine dose	3	3.68	0.0200
	Time	11	37.18	< 0.0001
	Cocaine dose × time	33	1.89	0.0028
	Total *df*	431		
1 × 10 mg/kg				
	Cocaine dose	3	2.55	0.0700
	Time	11	24.39	< 0.0001
	Cocaine dose × time	33	2.72	< 0.0001
	Total *df*	359		
2 × 10 mg/kg				
	Cocaine dose	3	8.59	0.0004
	Time	11	36.02	< 0.0001
	Cocaine dose × time	33	5.45	< 0.0001
	Total *df*	359		
3 × 10 mg/kg				
	Cocaine dose	3	4.55	0.0100
	Time	11	35.10	< 0.0001
	Cocaine dose × time	33	3.53	< 0.0001
	Total *df*	359		

from each of the four analyses. A significant effect of cocaine dose was found for all groups, with the exception of the group that received pretreatment with the single daily injection of cocaine. Significant effects of time and a significant cocaine dose × time interaction were obtained for all groups.

Locomotor activity following 5.0 or 10.0 mg/kg cocaine was not significantly increased at any of the time periods for the saline pretreatment group (Tukey post hoc tests, NS). However, 20.0 mg/kg cocaine caused a significant increase in locomotor activity for this group. This significant increase in activity was obtained during three of the four 5-min intervals of the first 20-min period following the injection ($p < 0.05$).

Both the 10.0 and 20.0 mg/kg doses of cocaine produced significant increases in locomotor activity during each 5-min interval for the first 20–35 min postinjection for all cocaine pretreatment groups ($p < 0.05$). Additionally, significant hyperlocomotion was produced during each 5-min interval for the first 10 min following 5.0 mg/kg for the group that received the pretreatment consisting of three daily injections of cocaine ($p < 0.05$). Also apparent, particularly in the 3 × 10 mg/kg group, is that as the cocaine dose increased, the duration of cocaine-induced hyperlocomotion increased.

An additional analysis sought to determine the influence of pretreatment on activity produced by each dose of cocaine. Because the peak effect of the drug was obtained within the first 15 min following injection, this analysis was restricted to locomotor activity during this time period. The data are shown in Fig. 3. A repeated-measure ANOVA (pretreatment × cocaine dose × time) revealed a significant effect of pretreatment, $F(3, 125) = 3.86$, $p = 0.0114$, cocaine dose, $F(3, 125) = 19.2$, $p < 0.0001$, and time, $F(2, 252) = 68.46$, $p < 0.0001$. An interaction between all three variables approached significance, $F(18, 252) = 1.49$, $p = 0.09$. Pretreatment with cocaine increased the effect of 5.0 mg/kg cocaine during the initial 5-min period and increased the effect of 10.0 mg/kg cocaine during each of the first three 5-min periods relative to saline pretreated rats ($p < 0.05$). The effect of 20.0 mg/kg cocaine was nominally increased by cocaine exposure. Although the effects of cocaine pretreatment on cocaine-produced locomotor activity appeared to be graded, particularly for the groups that received the 5.0 mg/kg challenge dose, there were no differences in the effects of cocaine for the various cocaine pretreatment groups ($p > 0.05$).

DISCUSSION

Several investigators have suggested that sensitization to the behavioral effects of cocaine is determined by the ability of environmental cues to become paired with cocaine during preexposure. Although a sensitized response has been reported when cocaine is paired repeatedly with the same environment in which the animal is subsequently tested (1,3,5,9, 13,17,18,19,22,25,29,36,37), context-independent exposures to cocaine are less effective or ineffective (5,8,9,15,27,30,31,37) in producing a sensitized response.

In the present study, cocaine pretreatments were administered in a distinct environment to minimize the influence of context to the development of sensitization. Other cues associated with cocaine (injections, etc.) did not appear to become significant conditioned stimuli because there was no indication of conditioned hyperlocomotion in response to saline on day 1 for any of the groups that received cocaine preexposure.

To determine whether cocaine pretreatment produced sensitization to the locomotor activating effects, dose–effect curves were obtained for each of the three cocaine pretreatment groups and for the saline control group. Although slight increases in activity were produced by administration of 5.0 or 10.0 mg/kg cocaine to saline-pretreated control rats, only the 20.0 mg/kg dose produced significant increases in locomotor activity for these rats. Rats that were pretreated with cocaine demonstrated significant increases in locomotor activity in response to both the 10.0 and 20.0 mg/kg doses and, additionally, the group that received three daily injections of cocaine during pretreatment demonstrated significant hyperlocomotion in response to the 5.0 mg/kg challenge dose of cocaine. Further, the duration of cocaine-produced hyperactivity increased with higher dose administrations. This effect appeared to be related to the amount of cocaine preexposure.

These findings suggest that pretreatment increased the potency of cocaine. Further, the potency shift appeared to be the greatest for the rats that received the most stringent preexposure parameters. The differences in duration of action and in the minimum dose required to produce significant increases in activity suggest that sensitization may be a graded effect.

When the data were analyzed by comparing the response of each cocaine pretreatment group to the response of the saline-pretreatment group, all cocaine pretreatment groups appeared to demonstrate equivalent shifts in potency. Cocaine-produced activation was increased to a comparable degree for all pretreatment groups when compared to the response of the saline-pretreated rats. Thus, although the 5.0 mg/kg dose of cocaine failed to produce significant hyperlocomotion for the groups that received one or two daily injections of cocaine during pretreatment, this dose of cocaine produced activity that was greater than the saline pretreated group.

Under these testing conditions, 20.0 mg/kg cocaine produces maximal forward locomotion in control rats (unpublished). With higher doses, stereotypy competes with forward locomotion, and the activity scores decrease. Because the locomotor-activating effects of the 20.0 mg/kg dose of cocaine were comparable for rats that received cocaine or saline pre-

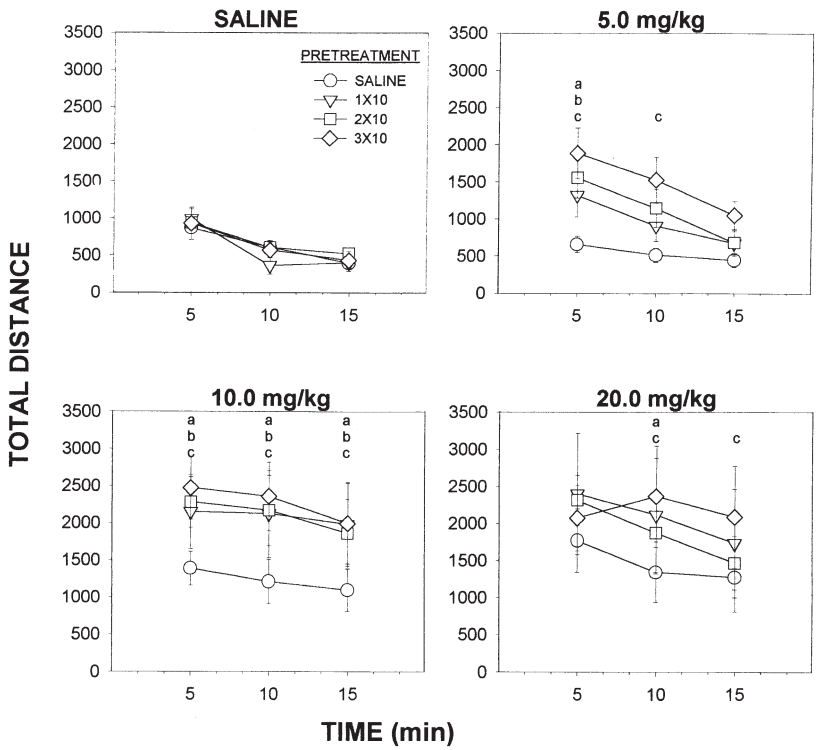

FIG. 3. Locomotor activity for each of the pretreatment groups during a 15-min period following the injection of each challenge dose of cocaine. Symbols represent the average total distance (±SEM). Significant increases ($p < 0.05$) for each cocaine pretreatment group relative to the saline pretreatment group are indicated by the lower-case letters in each panel. The letter indicates that the dose of drug produced a significant increase in activity at that time period. a = 1 × 10.0 mg/kg group; b = 2 × 10.0 mg/kg group; c = 3 × 10.0 mg/kg group.

treatment, the data suggest that preexposure produced minimal changes in efficacy.

To our knowledge, this is the first demonstration of changes in the dose–effect curve for a behavioral effect of cocaine following context-independent pretreatment. The increased potency rather than increased efficacy found in the current study may explain the increase in the response to single doses of various DA agonists such as GBR 12909 (2,20), mazindol (38), and apomorphine (23,24,26,34), that has previously been observed following repeated exposure. These data may also explain why sensitization is generally only demonstrated when low doses of cocaine are tested. The failure to observe increases in response to high-dose administrations following pretreatment would be expected, because efficacy appears to be unaltered.

The present data suggest that a minimum exposure to cocaine doses between 10.0 and 20.0 mg/kg/day during a 5-day pretreatment period is required to produce context-independent sensitization. However, other variables associated with the pretreatment may also be important. For example, when male rats were pretreated with two daily injections of 10.0 mg/kg cocaine separated by 9 h, rather than 1 h as in the present study, no behavioral sensitization was produced (7). These findings suggest that the interdose interval may be an important variable in the development of behavioral sensitization to cocaine when multiple daily injections of low doses are administered.

The changes in potency following cocaine preexposure do not compare favorably to sensitization following repeated administration of other direct and indirect dopamine agonists. For example, sensitization produced when pretreatments of the D_2/D_3 agonist, quinperole, were administered in a context-independent manner reflected changes only in efficacy without corresponding changes in potency (36). In contrast, pretreatment with low doses of quinpirole, which produced only a context-dependent form of sensitization to the locomotor activating effects of the drug, resulted in potency as well as efficacy changes. Similarly, context-dependent sensitization to the D_2 agonist bromocriptine, reflected a change in both efficacy and potency (16). These findings suggest that different neuroadaptations may accompany sensitization to different psychostimulants. Further, they point out the importance of examining these changes in studies of cross-sensitization between psychostimulants.

These findings highlight the importance of assessing changes in the dose–effect function following pretreatment with psychostimulants. The determination of changes in potency and/or efficacy will help to guide more molecular investigations aimed at determining the relevant neuroadaptations following context-dependent and -independent administration of drugs, and following administrations of drugs from different pharmacological classes.

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