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Cocaine Cross-Sensitization to Dopamine Uptake Inhibitors: Unique Effects of GBR12909

G. I. ELMER,* A. BROCKINGTON,† D. A. GORELICK,‡ F. I. CARROL,§ K. C. RICE,§ D. MATECKA,§ S. R. GOLDBERG* AND R. B. ROTHMAN†[1]

*Behavioral Pharmacology and Genetics, †Clinical Psychopharmacology and ‡Pharmacotherapy Sections, Division of Intramural Research, National Institute on Drug Abuse, National Institutes of Health, P.O. Box 5180, 4940 Eastern Ave., Baltimore, MD 21224 and §Laboratory of Medicinal Chemistry, Bldg. 8-B132, NIDDK, National Institutes of Health, Bethesda, MD 20892

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ELMER, G. I., A. BROCKINGTON, D. A. GORELICK, F. I. CARROL, K. C. RICE, D. MATECKA, S. R. GOLDBERG AND R. B. ROTHMAN. *Cocaine cross-sensitization to dopamine uptake inhibitors: Unique effects of GBR12909.* PHARMACOL BIOCHEM BEHAV **53**(4) 911-918, 1996.—Repeated administration of cocaine will cross-sensitize the locomotor response to a variety of psychomotor stimulants. The ability of cocaine to cross-sensitize the locomotor effects of other psychomotor stimulants provides information relevant to the pharmacological mechanisms underlying the sensitization process. The purpose of the current experiment was to investigate the ability of cocaine to cross-sensitize the locomotor effects of several dopamine uptake blockers with unique pharmacological profiles. Cocaine (40 mg/kg, IP) or saline was administered prior to a locomotor session on day one. On day 2, a full dose-effect curve was established for the locomotor effects of cocaine, RTI-55, mazindol, and GBR12909. Previous exposure to cocaine significantly affected locomotor activity and stereotopy-like behavior produced by cocaine, mazindol, RTI-55, and GBR12909. However, GBR12909 was unique in that the maximal stimulant effect and slope of the dose-effect curve was significantly depressed and the stereotopy-like behavior was unchanged. Thus, despite the similarity of these compounds in their ability to inhibit dopamine uptake, cocaine-induced sensitization did not generalize to GBR12909. This study further demonstrates the unique pharmacology of GBR12909 and supports the further study of this compound as a potential treatment medication for cocaine abuse.

Sensitization Cocaine Mazindol RTI-55 GBR12909

THE ABILITY OF A DRUG to substitute for cocaine in the drug discrimination paradigm has frequently been used to evaluate the psychopharmacological effects of abused drugs and to explore pharmacological mechanisms underlying cocaine's discriminative cues (36,37). The results of such studies indicate that several drugs will substitute for the cocaine cue, including amphetamine and methylphenidate (10). In particular, the relative selectivity (4,22) and potency (9,37) of a drug at the dopamine (DA) vs. norepinephrine (NE) and serotonergic (5-HT) uptake sites correlates well with the efficacy and potency of the drug to produce a cocaine-like discriminative stimulus cue. Furthermore, substitution studies with selective DA agonists suggest that stimulation of either the D_1 or D_2 receptor subtype alone is a significant component but not a sufficient explanation for the production of a cocaine-like discriminative cue (6,22,37). In general, the substitution of a test compound in animals trained to discriminate the interoceptive cues produced by repeated training with cocaine has been a useful paradigm for exploring the pharmacology of what is thought to be an important component of cocaine's addictive properties.

The ability of a drug to substitute for or cross-sensitize to the training drug in a sensitization paradigm has been used in a manner similar to the drug discrimination paradigm to

[1] To whom requests for reprints should be addressed.

investigate the pharmacology and neurobiology of sensitization (19,32). To this end, the ability of repeated administration of a psychomotor stimulant or an opioid to produce cross-sensitization to a test drug in the same or distinct pharmacological class has been used to suggest a specific behavioral pharmacology associated with the sensitization process (25,33,34). For instance, repeated administration of amphetamine produces sensitization to the locomotor response to stress (2), apomorphine (3), and morphine (32). Observations such as these have led to the proposal that changes in mesoaccumbens and mesostriatal DA transmission are associated with the sensitization process and are influenced in a complex manner by other neurotransmitter systems (19). The concordance between substitution in the drug discrimination paradigm and cross-sensitization as measured in the sensitization paradigm has not been fully characterized. Determination of the pharmacology of sensitization and its relationship to drug discrimination merit further investigation due to the utility and importance of the drug discrimination paradigm and to the renewed interest in the sensitization process as an important component in the development of drug addiction (28).

The purpose of the present investigation was to investigate the ability of cocaine to produce sensitization to the locomotor and stereotopy-like behaviors of several DA uptake blockers with distinct pharmacological profiles to 1) further explore the pharmacological mechanisms underlying sensitization, and 2) to determine if the occurrence of cross-sensitization is predictive of cocaine-like subjective effects. Towards this end we chose to study the prototypical addictive DA uptake inhibitor cocaine; the nonaddictive, moderate potency, DA uptake inhibitor mazindol; the high affinity, long-acting DA uptake inhibitor GBR12909, and the high affinity, long-acting cocaine analog RTI-55. As reported in Table 2, mazindol and GBR12909 are selective DA uptake blockers (relative to the 5-HT transporter) with intermediate and long in vivo durations of action, respectively (18,29,31). Cocaine and RTI-55 are actually more potent at the 5-HT transporter than at the DA transporter and have the least and most potent in vitro DA uptake K_i values, and short and long in vivo duration's of action, respectively, compared to mazindol and GBR12909 (29,31). All four drugs fully substitute for cocaine in rats trained to discriminate 10 mg/kg cocaine from saline (4,9, 22,35). Determining the ability of cocaine to produce sensitization to the locomotor effects of other psychomotor stimulants provides information relevant to the pharmacological mechanisms underlying the sensitization process and potential information on the ability of this model to predict the effects of these agents in humans.

METHODS

Animals

Subjects used in this experiment were male Sprague-Dawley rats (Charles River Laboratories) weighing 180–200 g. The animals were housed in trios in clear plastic cages with wire grid lids. Access to food and water was unrestricted. The animals were kept in the animal facility maintained on a 12 L : 12 D cycle (lights on at 0700 h). 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.

Cross-Sensitization

Full dose-response curves were obtained for each drug (cocaine, mazindol, RTI-55, and GBR12909) with either cocaine or saline given on the previous pretreatment day. All subjects received two injections on the pretreatment day. The first injection (saline or 40 mg/kg cocaine) was given immediately prior to being placed in the locomotor activity monitor for 60 min. A second saline injection was given 2 h later in the home colony. On day 2, dose-response curves for cocaine, mazindol, RTI-55, and GBR12909 were determined. Again, the test drug was given immediately prior to the subject being placed in the locomotor activity monitor for 60 min. Within-session data was collected in 10-min intervals. This sensitization paradigm is similar to previously described procedures (26,27) with the exception that full dose-response curves were determined on day 2.

Each animal was used only once for each drug, dose, and condition (cocaine/saline pretreated). All injections were given IP in an injection volume of 1 ml/kg body weight. All drug doses are based upon the salt solution. Cocaine, mazindol, and RTI-55 were dissolved in saline. GBR12909 was dissolved in DMSO.

Locomotor activity was monitored in an Opto-Varimex Auto Track System. Animals were placed in a rectangular (45 cm L × 45 cm W × 25 cm H) Plexiglas retainer. Activity in the monitor was recorded by photobeam interruptions. Distance traveled was determined by photocell breaks, while time spent in stereotopy was determined by the type of movement that occurred within a 0.1-s interval. If movement during the 0.1-s interval did not exceed 4.8 cm yet broke the photocell beam repeatedly, the interval was counted as stereotypic time. Resting time was determined by the duration of time during which no photobeam interruptions were recorded. Fifteen photocells were equally distributed along each axis of the monitor. Photocell interruption criterion was set at two photocell beams. All activity measurements were conducted in a soundproof isolation chamber under red light.

Observational Confirmation of Automated Measures

To better characterize the behavior measured by the automated activity monitor, behavior induced by cocaine administration was monitored simultaneously by video camera and the Omnitech Digiscan monitor. The video camera (Panasonic CD1 System) was placed directly above the activity monitor. The lighting conditions were maintained exactly as those maintained during the cross-sensitization experiments. The experimental procedure was conducted as described above. Animals were rated according to a modified version of a previously established observational method developed for dopaminergic agonists (15). Observational data for a full cocaine dose-response curve was collected (0, 10, 20, and 40 mg/kg; n = 5/dose) and compared to computer-collected data. The following behaviors were observed and scored for their presence or absence during each 5-min interval: Still, asleep or not moving; Sniffing, sniffing for more than 3 s; Licking, licking for more than 3 s; Gnaw, gnawing for more than 3 s; Grooming, grooming for more than 3 s; Locomotion, all four legs moving; Rearing, both front feet off the cage floor; Head down, animal standing, walking or running with its nose below horizontal for more than 5 s; Swaying, rhythmic swaying movements of the animal's head or body for more than 3 s; Circling, animal walking or running in a continuous circle for more than 5 s.

TABLE 1

DIRECT OBSERVATION VS. COMPUTER DERIVED VALUES

	Still	Sniff	Lick	Gnaw	Groom	Loco	Rear	H. Down	Sway	Circle
DT	−.75	+.99*	−.70	−.82	−.89	−.79	+.97*	+.96*	−.89	+.97*
RT	+.89	−.99*	+.50	+.67	+.96*	+.92	−.87	−.96*	+.80	−.86
ST	−.96*	+.63	+.29	+.25	−.81	−.94*	+.32	+.65	−.31	+.32

DT: distance traveled; RT: resting time; ST: stereotopy time. Each value represents the correlation between computer derived values (DT, RT or ST) and direct observational scores (Still, Sniff etc.) across four cocaine doses (0, 10, 20 and 40 mg/kg). *: a significant correlation ($p < 0.05$).

Statistical Analysis

The presence or absence of sensitization was determined for each drug by a three-factor repeated measures ANOVA (pretreatment, dose, time). The potency (ED_{50}) of cocaine-induced locomotor activity and cocaine-induced stereotopy-like behavior was derived from the regression analysis of the linear portion of each dose–response curve for values summed across the 60-min session. The ED_{50} values were calculated as 50% of the maximal percentage increase from the vehicle baseline. Because the dose–response curve did not turn over for stereotopy scores, the dose that produced a 50% increase in stereotopy was calculated. The locomotor stimulant efficacy (maximal percentage increase) of each drug as defined by distance traveled was determined by second-order polynomial curve fitting of the entire dose–response curve. Curve fitting and statistical analysis was conducted using statistical formulas found in Kenakin (20) integrated into the curve-fitting software package KaleidaGraph (1).

Dose–response correlations for each of three computer-derived dependent variables (distance traveled and time spent in stereotopy) and each of the nine ethogram variables were determined. The correlations were used to provide a description of the response topography measured by the computer generated values.

RESULTS

Observational Confirmation of Computer-Generated Values

The results of the correlational analysis indicate that distance traveled and time spent in stereotopy as defined by computer analysis measure distinct but overlapping response topographies. Table 1 presents the correlation between computer-derived values (DT, RT, or ST) and direct observational scores (still, sniff, etc.) across the four cocaine doses (0, 10, 20, and 40 mg/kg). As the cocaine dose was increased, increases in computer-derived distance traveled was significantly related to increased sniffing, rearing, head down, and circling behavior. Conversely, as the cocaine dose was increased, increases in computer-derived stereotopy was significantly related to a decrease in stillness and locomotion, and unlike distance traveled, there was an increase in gnawing and licking. Resting time was inversely related to distance traveled and stereotopy in 10 and 8 of the measures, respectively. In general, the time spent in stereotypic behavior as measured by computer analysis was not classically defined as stereotypic (13). The direct observational data suggest that this computer-derived measurement describes a compilation of behaviors distinct from those given by distance traveled, yet clearly reflects dopamine agonist-induced behaviors (15). As a result of the direct observational analysis, computer-derived time spent in stereotopy is referred to in the text as stereotopy-like behavior to distinguish it from classically defined stereotopy.

Locomotor Activity

Figures 1, 2, 3, and 4 (panels A), show dose–response curves for cocaine-, mazindol-, RTI-55-, and GBR12909-induced locomotor activity, respectively, in the presence and absence of previous cocaine pretreatment. There was a significant effect of cocaine pretreatment on locomotor stimulant dose–effect curves for each drug [cocaine: F(pretreatment × dose; 5, 456) = 6.3, $p < 0.0001$; mazindol: F(pretreatment; 4, 390) = 8.1, $p < 0.0001$; RTI-55: F(pretreatment; 3, 312) = 7.8, $p < 0.0001$]. Unlike cocaine, mazindol, and RTI-55, cocaine pretreatment depressed the entire GBR12909 dose–effect function [GBR12909: F(pretreatment × dose; 3, 402) = 18.1, $p < 0.0001$]. Discrete analysis of the ascending limb of the dose–

TABLE 2

PHARMACOLOGICAL PROFILE OF DOPAMINE UPTAKE INHIBITORS

Uptake Blocker	Drug Discrim. Assay (ED_{50})*	DA Transporter K_i (nM)†	5-HT Transporter K_i (nM)†	5-HT Transporter/ DA Transporter	In Vivo Duration of Action‡
Cocaine	2.0§	341.0	129.0	0.4	short
Mazindol	1.0§	38.0	631.0	16.6	intermediate
RTI-55	0.5¶	0.8	0.2	0.3	long
GBR12909	13.0§	3.7	126.0	34.1	long

*ED_{50} mg/kg in rats trained to 10.0 mg/kg cocaine. §Derived from Witkin et al., 1991; ¶Derived from Cline et al., 1992. †Values from Rothman et al., 1995. ‡Scheffel et al., 1992; Izenwasser et al., 1994; unpublished observations.

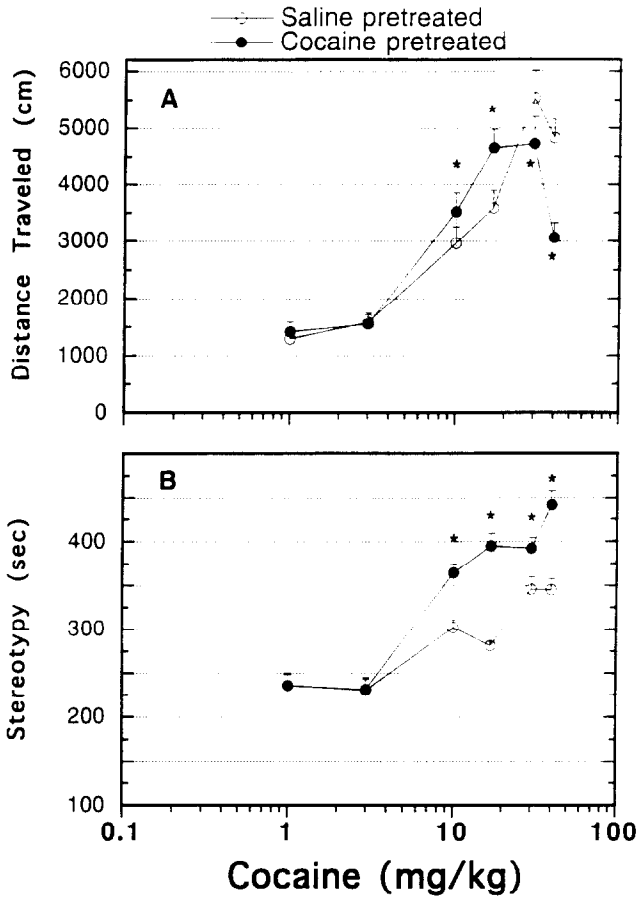

FIG. 1. The average 10-min interval locomotor stimulant (A) and stereotopy-like (B) behavioral effects of cocaine in rats pretreated once with cocaine (40 mg/kg) or saline the previous day and placed in the locomotor activity monitor for 60 min. Note the distinction between computer-derived stereotypy and classically defined stereotypy made in the text. Asterisk indicates a significant difference from saline-pretreated subjects at the same dose. Each point represents the mean (±SEM) of six to nine rats.

effect curve did not yield statistically significant shifts in ED_{50} values (see Table 3). The significant pretreatment effect produced by cocaine is a function of combined shifts in the ascending and descending limbs of the dose-effect curve. Cocaine pretreatment did not alter the time course of cocaine-, mazindol-, or RTI-55-induced locomotor activity. The locomotor activity time course for cocaine (17 mg/kg), mazindol (3 mg/kg), RTI-55 (3 mg/kg), and GBR12909 (30 mg/kg) are shown in Fig. 5, panels A, B, C, and D, respectively.

Stereotypy-Like Behavior

Figures 1, 2, 3, and 4 (panels B), show dose-response curves for cocaine-, mazindol-, RTI-55-, and GBR12909-induced stereotopy-like behavior, respectively, in the presence and absence of previous cocaine pretreatment. Cocaine pretreatment altered drug-induced time spent in stereotopy to a greater extent than distance traveled. There was a significant effect of cocaine pretreatment on cocaine-, mazindol-, and RTI-55-induced stereotopy-like behavior but not for GBR12909. Cocaine pretreatment shifted the cocaine, mazindol, and RTI-55 dose-effect curves to the left [cocaine: F(pretreatment × dose; 5, 456) = 6.7, $p < 0.0001$; mazindol: F(pretreatment; 4, 390) = 6.3, $p < 0.0001$; RTI-55: F(pretreatment; 3, 312) = 12.0, $p < 0.0001$]. ED_{50} values for stereotopy-like behavior are presented in Table 3. Cocaine pretreatment shifted the cocaine, mazindol, and RTI-55 dose-effect curves 3.7-, 5.0-, and 1.8-fold to the left, respectively. Cocaine pretreatment did not affect the GBR12909 dose-effect curve. In general, the ED_{50} dose for induction of stereotopy-like behavior was less than that for the induction of increased distance traveled as measured by computer analysis. These data support direct observation correlates suggesting that computer-generated stereotopy scores do not represent the classic high-dose stereotopy behavior produced by dopamine agonists. Cocaine pretreatment did not alter the time course of cocaine-, mazindol-, RTI-55-, or GBR12909-induced locomotor activity. The time course for cocaine (17 mg/kg), mazindol (3 mg/kg), RTI-55 (3 mg/kg), and GBR12909 (30 mg/kg) are shown in Fig. 6, panels A, B, C and D, respectively.

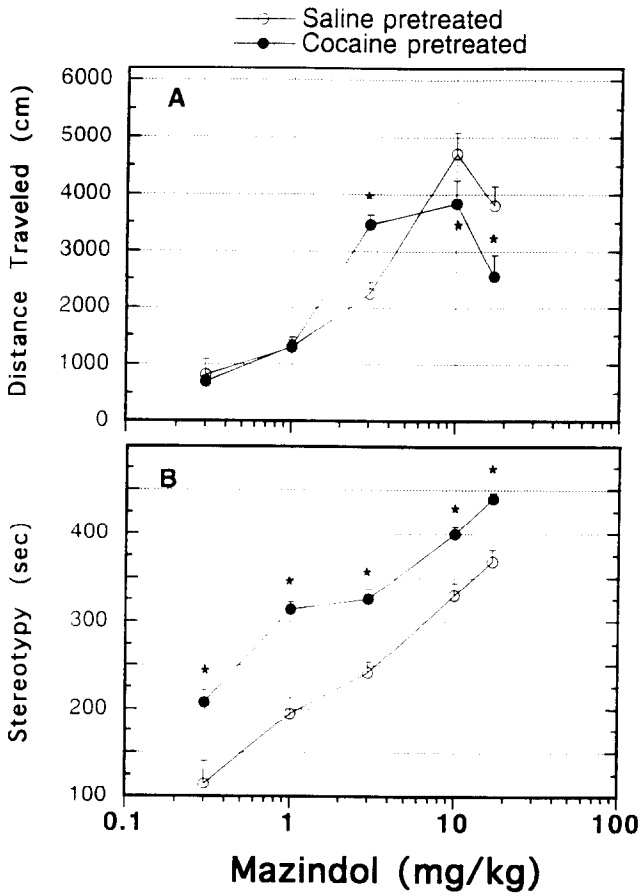

FIG. 2. The average 10-min interval locomotor stimulant (A) and stereotopy (B) effects of mazindol in rats pretreated once with cocaine (40 mg/kg) or saline the previous day and placed in the locomotor activity monitor for 60 min. Note the distinction between computer-derived stereotopy and classically defined stereotypy made in the text. Asterisk indicates a significant difference from saline-pretreated subjects at the same dose. Each point represents the mean (±SEM) of six to nine rats.

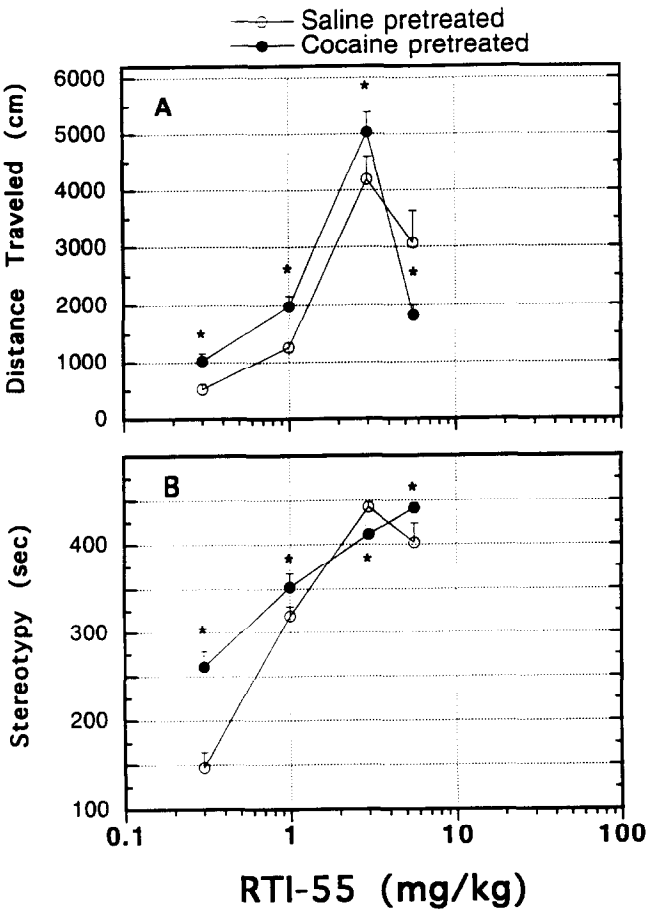

FIG. 3. The average 10-min interval locomotor stimulant (A) and stereotopy (B) effects of RTI-55 in rats pretreated once with cocaine (40 mg/kg) or saline the previous day and placed in the locomotor activity monitor for 60 min. Note the distinction between computer-derived stereotypy and classically defined stereotypy made in the text. Asterisk indicates a significant difference from saline-pretreated subjects at the same dose. Each point represents the mean (± SEM) of six to nine rats.

DISCUSSION

The ability of cocaine pretreatment to produce cross-sensitization to the locomotor stimulant effects of mazindol, RTI-55, and GBR12909 was investigated to explore the pharmacological mechanisms underlying sensitization and to determine the ability of this assay to distinguish between cocaine-like (cocaine and RTI-55) and noncocaine-like (mazindol and GBR12909) DA uptake blockers. As summarized in Table 2, generalization to the cocaine discriminative stimulus occurs with all four drugs, despite significant differences in pharmacodynamic properties. Cocaine and mazindol are low potency, shorter-acting DA uptake blockers compared to GBR12909 and RTI-55. Whereas mazindol and GBR12909 are selective for the DA transporter relative to the 5-HT transporter, cocaine and RTI-55 are more potent at 5-HT transporters than at DA transporters.

Previous exposure to cocaine significantly affected cocaine, mazindol, and RTI-55 locomotor activity and stereotypy-like behavior. These results suggest that potency and selectivity at the DA transporter and duration of action of a test drug do not influence the occurrence of cross-sensitization. Conversely, previous cocaine treatment significantly reduced the efficacy of GBR12909's locomotor effects while the stereotypy-like behaviors remained unchanged. Thus, despite the similarity of these compounds in their ability to inhibit DA uptake, GBR12909 was unique in its resistance to cross-sensitization to cocaine administration.

The results of this study further demonstrate the unique pharmacology of GBR12909 compared to other DA uptake inhibitors. For example, while GBR12909 fully substitutes for cocaine in the drug discrimination paradigm (4,9,22,35), and maintains drug-reinforced behavior in animals trained to self-administer cocaine (8), GBR12909 is uniquely unable to substitute for the imipramine discriminative cue (38) and antagonizes several effects of cocaine (7,30) including cocaine-maintained behavior when given chronically (16). In addition, the pharmacology of GBR12909 substitution for cocaine in the discrimination paradigm may differ from other uptake inhibitors (e.g., GBR12909 is more sensitive to haloperidol antagonism) and its ability to fully substitute wanes upon repeated testing (4).

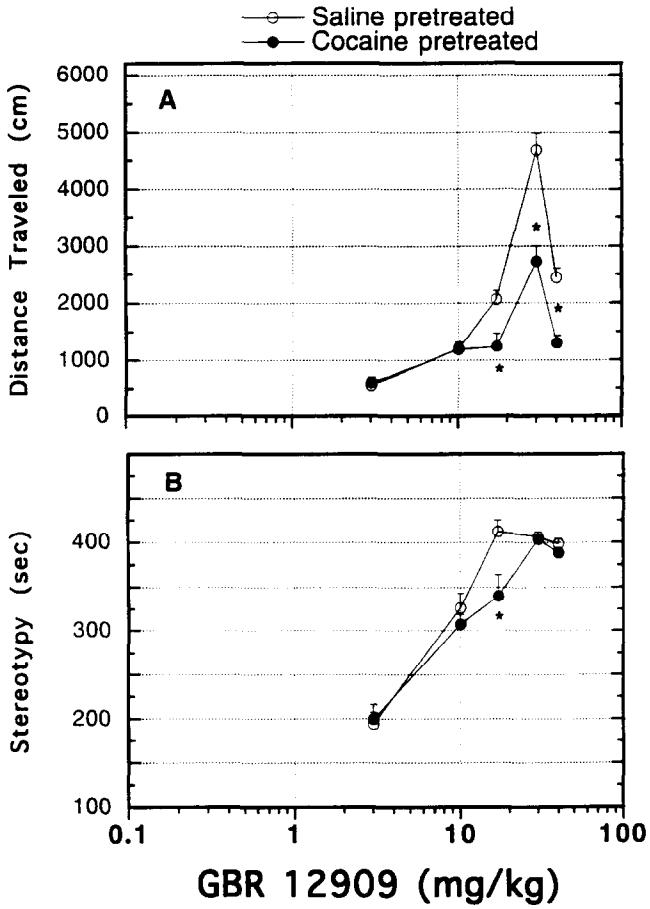

FIG. 4. The average 10-min interval locomotor stimulant (A) and stereotopy (B) effects of GBR12909 in rats pretreated once with cocaine (40 mg/kg) or saline the previous day and placed in the locomotor activity monitor for 60 min. Note the distinction between computer-derived stereotypy and classically defined stereotypy made in the text. Asterisk indicates a significant difference from saline-pretreated subjects at the same dose. Each point represents the mean (± SEM) of six to nine rats.

TABLE 3

POTENCY AND EFFICACY OF AGONIST-INDUCED INCREASES IN DISTANCE TRAVELED (DT) AND STEREOTYPY-LIKE BEHAVIOR (ST)

	Cocaine				Mazindol				RTI-55				GBR12909			
	ED_{50}		Efficacy		ED_{50}		Efficacy		ED_{50}		Efficacy		ED_{50}		Efficacy	
Treatment	Sal	Coc.	Sal	Coc.	Sal	Coc.	Sal	Coc.	Sal	Coc.	Sal	Coc.	Sal	Coc.	Sal	Coc.
DT	8.9	8.1	4824	5115	2.1	2.0	4235	4708	1.4	0.9	4196	4818	11.4	9.8*	3505	2089
ST	31.1	8.5			1.5	0.3			0.9	0.5			5.6	5.4		

*Estimated change in ED_{50}; cocaine pretreatment significant depressed the slope of the GBR12909 dose-effect curve.

ED_{50} values based upon linear fit of ascending limb of dose-response curve. Efficacy estimates based upon second-order polynomial fit of each dose-response curve.

There are relatively few systematic reports investigating the pharmacology of compounds that show cross-sensitization after cocaine administration. Cross-sensitization after repeated cocaine administration has been observed with coceth-ylene (14), apomorphine (21), morphine (Shippenberg, personal communication), and the opioid peptides DAMGO and DADLE (12). Conversely, repeated administration of GBR12909 will produce cross-sensitization to low (5 mg/kg)

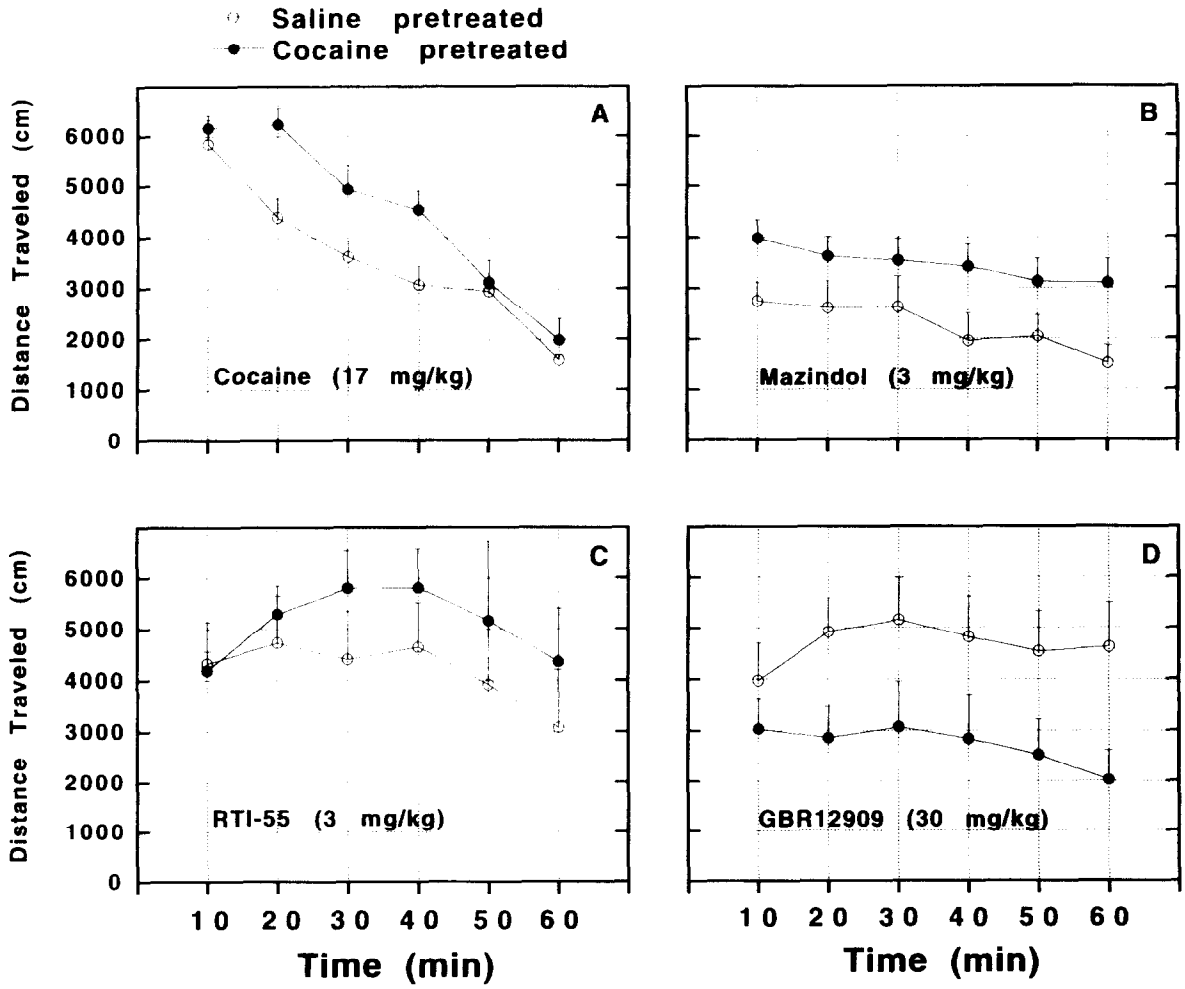

FIG. 5. The locomotor stimulant time course for a single dose of cocaine, mazindol, RTI-55, and GBR12909 when rats were pretreated once with cocaine (40 mg/kg) or saline the previous day and placed in the locomotor activity monitor for 60 min. Each point represents the mean (±SEM) of six to nine rats.

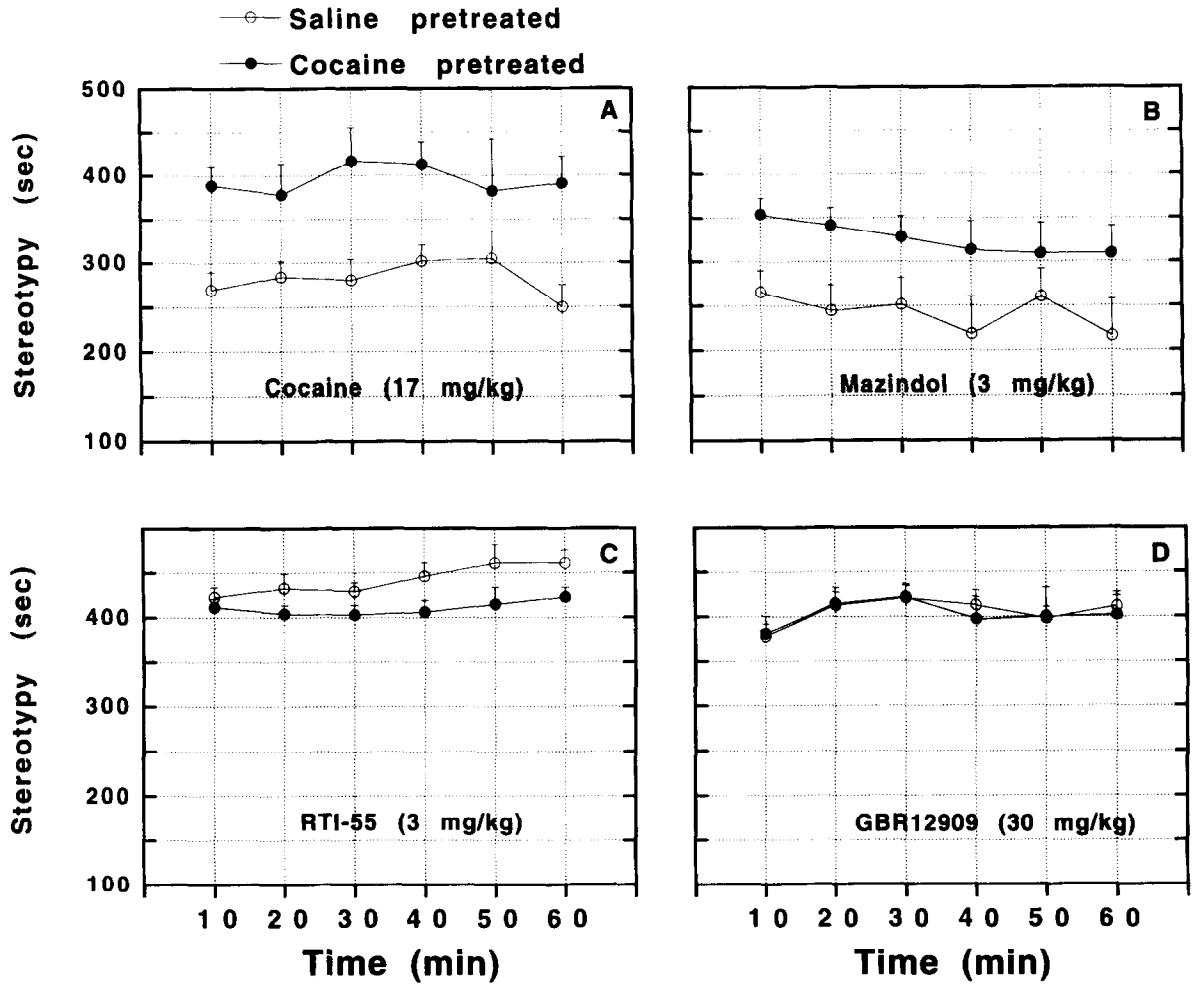

FIG. 6. The stereotypy-like behavioral time course for a single dose of cocaine, mazindol, RTI-55, and GBR12909 when rats were pretreated once with cocaine (40 mg/kg) or saline the previous day and placed in the locomotor activity monitor for 60 min. Note the distinction between computer-derived stereotypy and classically defined stereotypy made in the text. Each point represents the mean (± SEM) of six to nine rats.

but not high doses of cocaine (10 mg/kg) (5). The results of this study, viewed in the context of previous reports using a variety of dependent measures, suggest that GBR12909 may act as a low efficacy agonist, i.e., one that produces submaximal responses when given alone and competitively blocks the effects of higher intrinsic efficacy agonists when given in combination (20). Consistent with this model, GBR12909 does not produce equivalent maximal locomotor stimulant effects and blocks the DA increasing effects of cocaine (7,18,30). If GBR12909 acts as a low efficacy agonist it may not substitute in a paradigm using a relatively high dose of cocaine (40 mg/kg). In the drug discrimination paradigm, low efficacy agonists produce only partial generalization in animals trained to high morphine doses while producing full generalization at lower morphine training doses (11,23). Therefore, cross-sensitization may occur at lower cocaine training doses. Further insight into the properties of indirect acting partial agonists is required for this hypothesis because shifting the dose-effect curve to the left (as occurs in sensitization) may also be expected to increase the observed efficacy of partial agonists. Another potential explanation for the observed data is that GBR12909 and cocaine act differentially at receptor sites other than those typically described, i.e., sigma or PCP sites. Thus, the dissimilarities in the receptor systems activated outside those typically described may be responsible for the lack of cross-sensitization and may provide an important clue to the sensitization process. Either one of these proposed mechanisms provides further support for the study of this compound as a treatment medication for cocaine abuse. A low efficacy agonist with a long duration of action may be used in a manner similar to that of methadone in the treatment of heroin addiction (17,24). Recent interest in the sensitization process in drug addiction also supports further investigation of a compound that does not show cross-sensitization after cocaine treatment (28). A low efficacy agonist that is not cross-sensitized by cocaine may prove valuable in the pharmacotherapeutic intervention of cocaine dependence.

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