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Lack of Cocaine-Like Discriminative-Stimulus Effects of σ Receptor Agonists in Rats

Takato Hiranita^{1,2}, Paul L. Soto³, Gianluigi Tanda¹, and Jonathan L. Katz¹

¹Psychobiology Section, Medications Discovery Research Branch, Intramural Research Program, Department of Health and Human Services, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD 21224

²JSPS Research Fellowship for Japanese Biomedical and Behavioral Researchers at NIH

³Department of Psychiatry and Behavioral Sciences, Johns Hopkins University

Abstract

Previous studies demonstrated effectiveness of selective sigma-receptor (σ R) agonists (DTG, PRE-084) as reinforcers in rats trained to self-administer cocaine. Like cocaine, these drugs increased nucleus accumbens shell dopamine levels, and effects of DTG, but not PRE-084, on dopamine appeared to be mediated by σ Rs. Additionally, σ R antagonists blocked self-administration of σ R agonists, but were inactive against reinforcing and neurochemical effects of cocaine. Thus pharmacologically distinct mechanisms likely underlie the reinforcing and neurochemical effects of σ R agonists and cocaine. The present study further examined the cocaine-like effects of σ R agonists in rats trained to discriminate injections of cocaine from saline to assess the similarity of their subjective effects. Standard dopamine-uptake inhibitors (WIN 35,428, methylphenidate), but neither σ R agonist (PRE-084, DTG) produced full cocaine-like discriminative-stimulus effects. The lack of effects of σ R agonists was obtained regardless of route of administration (i.p., s.c. or i.v.) or pretreatment time (5- or 30-min before sessions). The present results demonstrate differences in the discriminative-stimulus effects of cocaine and selective σ R agonists, indicating that an overlap of subjective effects is not necessary for σ R agonist self-administration. The previously found differences in neurochemical effects of cocaine and σ R agonists may contribute to their different subjective effects.

Keywords

cocaine; discriminative-stimulus effects; σ receptor; dopamine uptake inhibitor; DTG; PRE-084; WIN 35,428; methylphenidate

Introduction

Previous studies have suggested a role for the σ receptor (σ R) in several of the behavioral effects of cocaine. For example, an early study showed that the σ R antagonists, BMY 14802 and rimcazole, blocked the locomotor stimulant effects of cocaine at doses that were

Correspondence: Jonathan L. Katz, Psychobiology Section, National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health, 251 Bayview Blvd, Suite 200, Baltimore, MD 21224, USA, jkatz@intra.nida.nih.gov, Phone: 443-740-2582, FAX: 443-740-2829.

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inactive when administered alone (Menkel et al., 1991). This antagonist action was more selective than that obtained with dopamine receptor antagonists, which only blocked the locomotor-stimulant effects of cocaine at doses that also decreased activity when administered alone (see also Chausmer and Katz, 2001). Other studies showed that more selective σ R antagonists, such as 1-[2-(3,4-dichlorophenyl)-ethyl]-4-methylpiperazine (BD 1063), also blocked cocaine-induced locomotor stimulant effects, as well as convulsions and lethality in mice (Matsumoto et al., 2001). In further studies, several σ R antagonists attenuated the development of cocaine-induced locomotor sensitization (Ujike et al., 1992; Witkin et al., 1993). These studies prompted others described below on the role of σ R in various behavioral effects related to the abuse liability of stimulant drugs.

Several studies have indicated that, despite the above cited antagonism of cocaine by several σ R antagonists, σ R agonists were devoid of cocaine-like behavioral effects. For example, the σ R agonist (+)-pentazocine did not affect locomotor activity in naïve mice (Okuyama et al., 1996). Other σ R agonists, 1,3-di-o-tolylguanidine (DTG) and 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride (SA 4503), only decreased locomotor activity in rats across the range of behaviorally active doses (Maj et al., 1996; Rodvelt et al., 2011a; Rodvelt et al., 2011b). On the other hand, the σ R agonist DTG potentiated cocaine induced locomotor stimulant effects in rats (Skuza, 1999). In rats trained to discriminate injections of 10 mg/kg cocaine from saline in a shock avoidance procedure, DTG (1 and 10 mg/kg, 30 minutes before sessions) failed to produce effects different from vehicle (Ukai et al., 1997). Further, a recent study on substitution of the σ R agonist, SA 4503, for cocaine (5 mg/kg) demonstrated that SA 4503 produced at most partial, but not full, substitution in rats trained with food to discriminate injections of cocaine from saline under a fixed-ratio ten-response schedule of reinforcement (Rodvelt et al., 2011a).

Consistent with the lack of stimulant-like effects of σ R agonists, (+)-N-cyclopropylmethyl-N-methyl-1,4-diphenyl-1-ethylbut-3-en-1-ylamine hydrochloride (igmesine) and 2-(4-morpholinethyl) 1-phenylcyclohexanecarboxylate hydrochloride (PRE-084), both selective σ R agonists, failed to produce place conditioning under conditions in which cocaine was effective (Romieu et al., 2002). In contrast, σ R antagonists given in combination with cocaine can block the development of a place preference (Romieu et al., 2000). The place conditioning studies together with those focused on locomotor activity with σ R agonists and antagonists suggest that stimulation of σ R is necessary but insufficient for these two effects of cocaine.

In other studies, the σ R agonist, igmesine, reinstated a previously extinguished cocaine place-conditioned response in mice (Romieu et al., 2004). In addition, a recent study from our laboratory indicated the σ R agonists, DTG and PRE-084, were reinforcing in rats with a history of cocaine self administration. Further, both σ R agonists increased dopamine concentrations in the shell of the nucleus accumbens and those effects of DTG, but not PRE-084 were antagonized by the σ R antagonist, BD 1008 (Garcés-Ramírez et al., 2011). In contrast, σ R antagonists had no effect on cocaine self-administration (Hiranita et al., 2010; see also Martin-Fardon et al., 2007) nor on cocaine-induced increases in nucleus accumbens dopamine (Garcés-Ramírez et al., 2011). In addition, pretreatment with i.p. injections of PRE-084 or DTG before sessions produced leftward shifts in the cocaine self-administration dose-effect curve, suggesting an additive effect or possibly a potentiation of the reinforcing effects of cocaine (Hiranita et al., 2010).

The present studies were prompted by the findings by Romieu et al., 2004, and Hiranita et al., 2010, and re-examined the potential of σ R agonists to produce cocaine-like discriminative-stimulus effects. A substantial overlap with cocaine in the discriminative (subjective) effects of these drugs would hypothetically explain the σ R agonist-induced

reinstatement of place conditioning or the substitution of σ R agonists in subjects trained to self-administer cocaine. Thus, the present study examined the substitution of the σ R agonists, PRE-084 or DTG, for cocaine in rats trained with food to discriminate injections of cocaine from saline under a fixed-ratio twenty-response schedule of reinforcement. We compared cocaine-like discriminative-stimulus effects of the σ R agonists with those of standard dopamine uptake inhibitors, WIN 35,428 and methylphenidate. In the previous study, both σ R agonists potentiated the reinforcing effects of cocaine, when pretreated i.p. 30 minutes before sessions (Hiranita et al., 2010). In addition, i.v. injections of DTG maintained responding, when substituted for those of cocaine. On the other hand, s.c. injections of DTG 30 minutes before sessions have been reported to produce their own discriminative-stimulus effects in naïve rats (Holtzman, 1989). Therefore, both agonists were injected either i.p., s.c. or i.v..

Methods

Subjects

Male Sprague-Dawley rats (weighing approximately 300 g at the start of the study), obtained from Charles River Laboratories (Wilmington, MA) served as subjects after acclimation to the laboratory for at least one week. Food (Scored Bacon Lover Treats, BIOSERV, Frenchtown, NJ) and tap water were available in their home cages. After acclimation, weights of rats were maintained at approximately 320 g by adjusting their daily food ration. The animal housing room was temperature- and humidity-controlled and maintained on a 12:12-h light:dark cycle with lights on at 07:00 h. Care of the subjects was in accordance with the guidelines of the National Institutes of Health and the National Institute on Drug Abuse Intramural Research Program Animal Care and Use Program, which is fully accredited by AAALAC International.

Apparatus

Experimental sessions were conducted with rats placed in operant-conditioning chambers (modified ENV-203, Med Associates, St. Albans, VT) having inside measurements of 23.0 cm L $\times$ 29.0 cm W $\times$ 21.0 cm H. These chambers were enclosed within sound-attenuating cubicles equipped with a fan for ventilation and white noise to mask extraneous sounds. On the front wall of each chamber were two response levers, 5.0 cm from the midline and 4.0 cm above the grid floor. A downward displacement of a lever with a force approximating 20 g defined a response, which always activated a relay mounted behind the front wall of the chamber producing an audible “feedback” click. Three light-emitting diodes (LEDs) were located in a row above each lever. A receptacle for the delivery of food pellets was mounted behind a 5.0 $\times$ 5.0 cm opening in the front wall midline between the two levers and 2.0 cm above the floor.

Procedures

Rats were initially trained with food reinforcement to press both levers, and were eventually trained to press one after cocaine (10 mg/kg, i.p.), and the other after saline (i.p.) injection. Each response produced an audible click. The ratio of responses to food pellets (fixed ratio or FR) was gradually increased until, under the final conditions, the completion of 20 consecutive responses on the cocaine- or saline-appropriate lever produced a food pellet delivery. Incorrect responses reset the FR response requirement. The right- vs. left-assignment of cocaine- and saline-associated levers was counterbalanced among subjects.

Subjects were placed in chambers immediately after injection. There was a five min timeout period during which lights were off and responses produced an audible click, but had no other scheduled consequences. Following the timeout, the house light was turned on until

the completion of the FR 20 response requirement. Food presentation was followed by a 20-sec timeout during which all lights were off and responses had no scheduled consequences other than the feedback click. Sessions ended after 20 food presentations or 15 min, whichever occurred first. Cocaine or saline training sessions were scheduled in a double-alternation sequence (i.e., cocaine-saline-saline-cocaine). Training continued until subjects met the criteria on four consecutive sessions of 85% cocaine- or saline-appropriate responding over the entire session, as well as during the first FR of the session.

Once these criteria were met, testing began. Test sessions were conducted with the administration of different doses of cocaine, standard dopamine uptake inhibitors (WIN 35,428 and methylphenidate) or selective σ R agonists (PRE-084 and DTG) before sessions. Test sessions were identical to training sessions with the exception that completion of the FR requirement on either lever was reinforced. All data collection and programming of behavioral contingencies was accomplished with software from Med Associates, Inc (St. Albans, VT).

For habituation to i.v. injections, subjects were placed daily before sessions for several minutes into a flat bottom restrainer (model FB-LG, Braintree Scientific, Inc., MA) which measured 8.57 cm diameters $\times$ 21.59 cm. Subjects were intravenously injected with saline (1.0 ml/kg) inside the restrainer, removed from the restraint, and then given an i.p. injection of saline or cocaine (10 mg/kg) until the above training criteria were met. Subjects were tested as described above with i.v. injection of different doses of cocaine or DTG in a volume of 1.0 mg/ml administered in the restrainer, followed by an i.p. injection of saline (1.0 ml/kg) 5 min before sessions.

Drugs

The following drugs were used: (-)-cocaine hydrochloride (Sigma-Aldrich, St. Louis, MO, Molecular Weight: 339.8), WIN 35,428 ((-)-3 β -(4-Fluorophenyl)tropan-2 β -carboxylic acid methyl ester tartrate, NIDA, Drug Supply Program, Molecular Weight: 443.9), methylphenidate hydrochloride (NIDA, Molecular Weight: 269.8), PRE-084 hydrochloride (Tocris, Ballwin, MO, Molecular Weight: 353.9), and DTG (Sigma-Aldrich, Molecular Weight: 239.3). Drug pretreatments were administered by the i.p., s.c. or i.v. routes. Cocaine, WIN 35,428, and methylphenidate were administered i.p. five min before sessions. In addition, PRE-084 and DTG were administered i.p. or i.v. at five or 30 min before sessions or s.c. at 30 min before sessions. All drug solutions were prepared fresh daily in 0.9% NaCl, with the exception of DTG (initially dissolved in 1 N HCl and neutralized with 1 N NaOH). Pretreatment times and doses of drugs used in the present study were chosen based on published (Hiranita et al., 2010; Garcés-Ramírez et al., 2011) or preliminary data obtained in this laboratory.

Data analysis

The percentage of cocaine lever responding was calculated by dividing the total number of responses on the cocaine-associated lever by the total number of responses. Rate of responding was calculated by dividing the total number of responses by the session time (excluding timeout periods) and is expressed as percentage of saline (control) rate of responding. These data are shown as mean values ($\pm$ SEM) for groups of subjects at each drug dose. Response rate exclusion criteria were applied to the % cocaine lever selection data such that any dose at which more than half of the sample size did not respond was considered a potentially unreliable indication of lever selection and was removed from the analysis. Dose-effect curves for percent cocaine lever responding were analyzed using standard linear regression techniques, from which ED₅₀ values with 95% confidence limits (Snedecor and Cochran, 1967) were calculated. Only points on the linear part of the

ascending portions of the dose-effect curves were used. For compounds that did not fully substitute for cocaine standard analysis of variance was conducted to determine if drug substitution differed from saline vehicle controls. Comparisons were considered significant when $p < 0.05$.

Results

Cocaine produced a dose-dependent increase in the percentage of responses on the cocaine-appropriate lever (Fig. 1A and B, top panels, filled circles), with an ED_{50} value of 9.62 $\mu\text{mol/kg}$ (Table 1). Similar dose-dependent effects of the dopamine uptake inhibitors, WIN 35,428 and methylphenidate, were obtained (Fig. 1A, top panel, open circles and circles with cross hatch, respectively). WIN 35,428 was approximately 10-fold and methylphenidate 3-fold more potent than cocaine on a molar basis (Table 1). Cocaine did not affect response rates across the range of doses tested whereas both WIN 35,428 and methylphenidate decreased rates of responding at the highest doses tested (Fig. 1A, bottom panel).

In contrast to the dopamine uptake inhibitors, neither of the σR agonists, PRE-084 nor DTG, substituted for cocaine when administered i.p. at either 5 or 30 min before testing (Fig. 1B, top panel, open symbols). The % cocaine-appropriate responding was not statistically different from that obtained with vehicle (all F values < 1.43 ; NS). Both PRE-084 and DTG were studied at doses from those that had no effects on the rates of responding to those that decreased response rates to less than 50% of control response rates (Fig. 1B, bottom panel, open symbols). When tested 30 min after s.c. administration (Fig. 1C), the overall ANOVA for DTG was significant ($F_{4,20} = 3.78$; $p < 0.02$), though post-hoc comparisons indicated that effects at no dose were significantly different from vehicle. The effects of PRE-084 tested 30 min after s.c. administration were not significant ($F_{5,20} = 1.05$; NS). The highest dose of DTG decreased response rates to less than 50% of control, whereas PRE-084 administered s.c. had no effects on response rates up to 32 mg/kg (Fig. 1C, lower panel).

Intravenous injections of cocaine produced a dose-dependent increase in the percentage of responses on the cocaine-appropriate lever (Fig. 1D, top panels, open circles), with an ED_{50} value of 0.241 $\mu\text{mol/kg}$ (Table 1). The potency of i.v. cocaine was approximately forty-fold greater than that for the i.p. route. Across the range of doses of cocaine tested cocaine did not significantly affect response rates (Fig. 1D, bottom panels, open circles, $F_{4,12} = 0.41$; NS). In contrast, DTG did not substitute for cocaine when administered i.v. at 5 min before testing (Fig. 1D, top panel, open squares). The % cocaine-appropriate responding was statistically different from that obtained with vehicle ($F_{4,12} = 3.31$; $p < 0.05$). However, the subsequent post-hoc Bonferroni t -test indicated no significant differences in DTG dose (all t values < 2.90 ; all p values > 0.053). The highest dose of DTG decreased response rates to less than 50% of control rates (Fig. 1D, lower panel, open squares).

Discussion

The present study was initiated following studies showing that σR agonists were reinforcing in rats trained to self-administer cocaine (Hiranita et al., 2010) suggesting that the drugs might possess cocaine-like subjective effects. In contrast to the self-administration results, neither of the σR agonists tested, PRE-084 or DTG, produced cocaine-like discriminative effects different from vehicle across the range of behaviorally active doses in rats trained to discriminate cocaine (10 mg/kg) from saline injections. As expected based on previous reports (e.g., Colpaert et al., 1979; Witkin et al., 1991; Li et al., 2006), the standard dopamine uptake inhibitors, WIN 35,428 and methylphenidate, both fully substituted for cocaine.

While the previous self-administration results suggested that σ R agonists would produce cocaine-like discriminative effects, other studies have suggested otherwise. For example, in rats trained to discriminate injections of cocaine (10 mg/kg) from saline in a shock avoidance procedure (Ukai et al., 1997) s.c. injections of DTG (1 and 10 mg/kg, 30 minutes before sessions) were no different from vehicle (see also Cohen and Sanger, 1994). Additionally, two recent studies on substitution of another σ R agonist, SA 4503, in rats trained with food reinforcement to discriminate either cocaine (5.0 mg/kg; Rodvelt et al., 2011a) or methamphetamine (0.5 mg/kg; Rodvelt et al., 2011b) from saline also indicated a failure of that σ R agonist to fully reproduce the discriminative-stimulus effects of those psychomotor stimulant drugs.

The absence of cocaine-like discriminative-stimulus effects of both PRE-084 and DTG was also obtained in the present study with different pretreatment times (5 or 30 minutes before sessions). In addition, because the self administration of σ R agonists was obtained with i.v. injections different routes of administration (i.p., s.c., or i.v.) were studied. The absence of cocaine-like discriminative-stimulus effects at different pretreatment times and different routes of administration further substantiated the distinctiveness of the discriminative-stimulus or subjective effects of σ R agonists and those of psychomotor stimulants. Consistent with this suggestion are findings that rats trained to discriminate selective σ R agonists (Steinfels et al., 1988; Holtzman, 1989) did not show substitution with cocaine or other psychostimulants. Other studies using drug discrimination procedures have demonstrated that the σ R agonist, (+)-pentazocine, fully substituted in rats trained to discriminate drugs other than stimulants, ethanol (Hundt et al., 1998) or buprenorphine (Holtzman, 1997). Together these previous results are consistent with the suggestion of little, if any, overlap of cocaine-like and σ R-agonist discriminative-stimulus effects. Thus, the reinforcing effectiveness of the σ R agonists in rats with a history of cocaine self-administration in the previous study (Hiranita et al., 2010) probably did not result from subjective effects of σ R agonists that were similar to those of cocaine.

The standard dopamine uptake inhibitors, WIN 35,428 and methylphenidate, both fully reproduced cocaine-like discriminative-stimulus effects, as has been shown previously (Colpaert et al., 1979; Witkin et al., 1991; Li et al., 2006). Further, indirect agonists that release dopamine, such as d-amphetamine and methamphetamine, have been reported to produce full cocaine-like discriminative-stimulus effects and dopamine receptor antagonists block the discriminative-stimulus effects of cocaine (Barrett and Appel, 1989; Witkin et al., 1991; Terry et al., 1994). A previous study (Garcés-Ramírez et al., 2011) using in vivo microdialysis showed that both PRE-084 and DTG increase concentrations of dopamine in the nucleus accumbens shell, a brain region important for the actions of abused drugs (Pontieri et al., 1995; Tanda et al., 1997). However, the dose of PRE-084 that increased dopamine levels was approximately thirty-fold higher than the dose that maintained responding in rats trained to self-administer cocaine (Hiranita et al., 2010). Importantly, none of the selective σ R antagonists BD 1008 or BD 1063 antagonized the neurochemical effects of PRE-084 (Garcés-Ramírez et al., 2011) indicating that those effects were not σ R mediated. In contrast, the reinforcing effects of PRE-084 in self-administration studies were sensitive to the σ R antagonists (Hiranita et al., 2010). Thus it appears that there is a separation in the pharmacological mechanisms underlying the reinforcing effects of cocaine and σ R agonists, and it is likely that the separation of pharmacological mechanisms contributes to the differences in discriminative-stimulus effects.

In summary, the present study demonstrated dissimilarities in the discriminative-stimulus effects of cocaine and selective σ R agonists in rats. Those differences suggest that the reinforcing effects of the σ R agonists (Hiranita et al., 2010) are not based on substantial overlap of the subjective effects of the two classes of drugs. Previous studies suggest a

distinction between the neurochemical effects of cocaine and σ R agonists that may contribute to the differences in subjective effects of the two classes of drugs.

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Figure 1.

Substitution of the standard dopamine uptake inhibitors (WIN 35,428 and methylphenidate), and the standard σ R agonists (PRE-084 and DTG) in rats trained to discriminate injections of cocaine from saline. Horizontal axes, drug dose in mg/kg (log scale). Vertical axes: upper panels, percentage of responses on the cocaine-appropriate lever; lower panels, percentage of response rate after saline administration. Each point represents the mean $\pm$ SEM (N=5–18). The percentage of responses emitted on the cocaine-appropriate lever was considered unreliable, and not plotted, if less than half of the subjects responded at that dose. Panel A: Cocaine (filled circles), WIN 35,428 (open circles), and methylphenidate (circles with cross hatch). All three drugs were administered i.p. at 5 min before sessions. Panel B: Cocaine (filled circles), PRE-084 (open triangles down and up), and DTG (open squares and diamonds). Cocaine was administered i.p. at 5 min before sessions. PRE-084 and DTG were administered i.p. at either 5 or 30 min before sessions. Panel C: Saline (filled circles), PRE-084 (open triangles down), and DTG (open squares). All test compounds were administered s.c. at 30 min before sessions. Panel D: Saline (filled circles), cocaine (open circles), and DTG (open squares). All test compounds were administered i.v. at 5 min before sessions. Note that the dopamine uptake inhibitors dose-dependently produced cocaine-like responding and fully substituted for cocaine and that neither σ R agonist produced cocaine-like responding that different from vehicle.

TABLE 1

Comparisons of potencies and maximal effects of the dopamine uptake inhibitors and σ R agonists in substituting for cocaine and affecting rates of responding

Drugs	% Cocaine Response		Response Rates
	ED ₅₀ Value (μ mol/kg) and 95% CLs	Maximum Effect (% Cocaine Responding)	ED ₅₀ Value (μ mol/kg) and 95% CLs
Cocaine (i.p., 5' prior)	9.62 (7.96–11.7)	99.4 $\pm$ 0.220 @ 10 mg/kg	Nonsignificant linear regression
WIN 35,428 (i.p., 5' prior)	1.04 (0.678–1.55)	100 $\pm$ 0.00 @ 3.2 mg/kg	6.05 (2.51–4.26 $\times 10^6$)
Methylphenidate (i.p., 5' prior)	3.42 (2.33–4.89)	100 $\pm$ 0.00 @ 10 mg/kg	Nonsignificant linear regression
PRE-084 (i.p., 30' prior)	No substitution	26.7 $\pm$ 14.3 @ 32 mg/kg	106 (72.1–242)
DTG (i.p., 30' prior)	No substitution	28.6 $\pm$ 18.8 @ 17 mg/kg	60.6 (48.1–108)
PRE-084 (i.p., 5' prior)	No substitution	10.7 $\pm$ 10.7 @ 17 mg/kg	100 (78.8–136)
DTG (i.p., 5' prior)	No substitution	7.27 $\pm$ 4.11 @ 10 mg/kg	52.6 (47.2–58.1)
PRE-084 (s.c., 30' prior)	No substitution	2.02 $\pm$ 1.84 @ 1.0 mg/kg	Nonsignificant linear regression
DTG (s.c., 30' prior)	No substitution	25.8 $\pm$ 13.2 @ 10 mg/kg	35.3 (27.0–76.9)
Cocaine (i.v., 5' prior)	0.241 (0.126–0.400)	99.6 $\pm$ 0.205 @ 1.0 mg/kg	Nonsignificant linear regression
DTG (i.v., 5' prior)	No substitution	37.1 $\pm$ 20.0 @ 5.6 mg/kg	18.7 (15.0–25.7)