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ORIGINAL INVESTIGATION

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Serotonin$_{1B}$ receptor stimulation enhances dopamine-mediated reinforcement

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Abstract The effect of 5-HT$_{1B}$ receptor stimulation on dopamine-mediated reinforcement in rats was investigated using intravenous self-administration of the selective dopamine uptake inhibitor GBR-12909 on an FR5 schedule of reinforcement. Pretreatment with the 5-HT$_{1A/1B}$ receptor agonist CGS-12066B (1–10 mg/kg, IP) dose-dependently reduced the self-administration of GBR-12909 (83 μg/injection) by increasing the interval between drug injections, consistent with a enhancement of the reinforcing effects of GBR-12909. Additionally, CGS-12066B pretreatment (3 mg/kg, IP) shifted the dose-effect function for GBR-12909 self-administration to the left. Pretreatment with the selective 5-HT$_{1A}$ receptor agonist 8-OH-DPAT (0.03–1.0 mg/kg, SC) had no significant effect on GBR-12909 self-administration (83 μg/injection), indicating that the effect of CGS-12066B is not mediated by the 5-HT$_{1A}$ receptor. Finally, CGS-12066B pretreatment (1–10 mg/kg, IP) did not alter the self-administration of cocaine (0.03–0.5 mg/injection), suggesting that the simultaneous stimulation of multiple 5-HT receptor subtypes by the indirect 5-HT agonist properties of cocaine may mask the effect of 5-HT$_{1B}$ receptor stimulation on DA-mediated reinforcement.

Key words 5-HT$_{1B}$ receptors · GBR-12909 · CGS-12066B · Self-administration · 8-OH-DPAT · Cocaine

Introduction

A large body of evidence indicates that the reinforcing effects of cocaine and other psychostimulants are dependent on the ability of these drugs to enhance dopamine (DA) neurotransmission in the mesocorticolimbic system (Roberts et al. 1977, 1980; Wise 1984; Ritz et al. 1987; Koob and Bloom 1988; Kuhar et al. 1991). However, in addition to increasing interstitial DA concentrations, psychostimulants also elevate extracellular serotonin (5-HT) and norepinephrine (NE) levels (Koe 1976), suggesting that monoaminergic systems other than DA may also contribute to the reinforcing and addictive properties of these drugs.

There is increasing evidence that both dopaminergic and serotonergic neurotransmission are involved in mediating the behavioral and neurophysiological effects of cocaine. In humans, depletion of the 5-HT precursor tryptophan attenuates both the euphorigenic and anxiogenic effects of intranasal cocaine (Aronson et al. 1995) as well as cue-induced craving for cocaine (Satel et al. 1995). In rats, the reinforcing properties of cocaine self-administration are altered by the manipulation of both the dopaminergic (Koob 1992) and serotonergic systems (Carroll et al. 1990a, b; Loh and Roberts 1990; Richardson and Roberts 1991; McGregor et al. 1993; Peltier and Schenk 1993; Spealman 1993). Moreover, repeated cocaine exposure produces cross-tolerance to the cocaine analogue WIN 35,428, a compound that like cocaine, has affinity for the 5-HT uptake transporter (Rudnik and Wall 1991). However, cocaine does not produce cross-tolerance to GBR-12909 (Katz et al. 1993), a DA reuptake inhibitor which does not have appreciable affinity for the 5-HT transporter (Heikkila and Manzino 1984; Anderson 1989). Acute cocaine exposure dramatically alters the electrophysiology of both the dopaminergic and serotonergic systems (for review see Cunningham 1995; White et al. 1995), and chronic exposure to cocaine results in pronounced decrements in both DA and 5-HT activity (for review see Cunningham 1995; Weiss et al. 1995; White et al. 1995). The simultaneous involvement of these systems in the neurophysiological effects of cocaine is demonstrated by the findings that the *combined* stimulation

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of both DA and 5-HT receptors are required to mimic the effects of cocaine on striatal gene expression (Bhat and Baraban 1993) and nucleus accumbens (NAcc) electrophysiology (White et al. 1993). Together, these findings suggest that in addition to DA, 5-HT is also involved in mediating or modulating the behavioral and neurophysiological effects of cocaine.

Based on anatomical and pharmacological evidence, it may be hypothesized that serotonergic neurotransmission affects the reinforcing properties of cocaine by modulating dopaminergic activity. For example, a dense serotonergic innervation is found in the ventral tegmental area (VTA) (Conrad et al. 1974; Azmitia and Segal 1978; Phelix and Broderick 1995), and these 5-HT neurons have been shown to form direct synaptic contact on DA cells bodies in this region (Parent et al. 1981; Hervé et al. 1987). These DA cells project to the NAcc and are implicated in mediating cocaine reward (Koob and Bloom 1988) and motivated behaviors (Wise and Bozarth 1987). Elevations in VTA 5-HT levels have been shown to increase both the local release of DA (Beart and McDonald 1982) and dopaminergic activity in the NAcc (Guan and McBride 1989). Moreover, DA release from nigrostriatal, mesoaccumbal and mesocortical DA terminals is potentiated by the local application 5-HT or specific 5-HT agonists (Benloucif and Galloway 1991; Chen et al. 1991, 1992; Nissbrandt et al. 1992; Benloucif et al. 1993; Galloway et al. 1993; Parsons and Justice 1993; Chen and Reith 1994; Yadid et al. 1994; however, see Chen and Reith 1995). While the specific 5-HT receptor(s) involved in this interactive process have not yet been clearly identified, the 5-HT_{1B} and 5-HT_{1D} receptor subtypes have been the most commonly implicated (see above references).

While the literature suggests an involvement of 5-HT in the modulation of the reinforcing effects of cocaine, ligands specific for individual 5-HT receptor subtypes have proven ineffective at altering behaviors maintained by cocaine administration. 5-HT receptor antagonists do not alter either cocaine self-administration (Peltier and Schenk 1991; Lacosta and Roberts 1993) or the stimulus properties of cocaine (Colpaert et al. 1976; McKenna and Ho 1980; Paris and Cunningham 1991; Baker et al. 1993; Peltier et al. 1994). Moreover, neither direct (Colpaert et al 1979; McKenna and Ho 1980; Winters and Slifer 1989) nor indirect 5-HT receptor agonists (McKenna and Ho 1980; Cunningham and Callahan 1991; Baker et al. 1993) generalize to cocaine in discrimination tests.

One possible explanation for the negative findings with specific 5-HT receptor ligands relates to the fact that as indirect agonists, cocaine and other psychostimulants induce a non-specific stimulation of all 15 of the 5-HT receptor subtypes identified so far (Hoyer et al. 1994). Because these individual receptors have differing and sometimes opposing effects on neuronal transmission (for review see Hoyer et al. 1994), the effect(s) of individual 5-HT receptor stimulation or blockade on psychostimulant reinforcement may be masked in studies using an indirect agonist as a reinforcer. Thus, the purpose of the present experiment was to examine the effect of 5-HT_{1B} receptor stimulation on GBR-12909 self-administration. GBR-12909 is a potent inhibitor of DA uptake which displays little affinity for the 5-HT and NE reuptake transporters (Heikkila and Manzino 1984; Anderson 1989). Thus, GBR-12909 self-administration provides a model of reinforcement mediated primarily via DA neurotransmission. The effect of 5-HT_{1B} receptor stimulation (by the agonist CGS-12066B) was examined in view of neurochemical evidence indicating a stimulatory role for this receptor on DA neurotransmission (Benloucif and Galloway 1991; Nissbrandt et al. 1992; Benloucif et al. 1993; Galloway et al. 1994). For comparison, the effect of 5-HT_{1B} receptor stimulation on cocaine self-administration was also examined.

Materials and methods

Subjects

Twenty-five male albino Wistar rats (Charles River, Kingston, Calif. USA weighing 220–260 g upon arrival) were habituated to the animal colony for 1 week with food and water available ad libitum, and were handled daily. All animals were group housed (two or three/cage) and maintained on a reverse 12-h light/dark cycle (lights on at 10 p.m.) in a humidity and temperature controlled (22°C) vivarium. All behavioral procedures began between 1 and 3 h after the onset of the dark phase (approximately 12:30 p.m.) and were conducted using a within-subject design. Data are presented from all animals that completed an experimental design. All procedures were conducted in strict adherence to the *National Institutes of Health Guide for the Care and Use of Laboratory Animals*.

Surgery

Rats were anesthetized with a halothane/oxygen vapor mixture (1.0–1.5%) and implanted with chronic intravenous catheters as previously described (Emmett-Oglesby and Lane 1992) with minor modifications (Caine et al. 1993). Briefly, the catheters consisted of a 12 cm length of silastic tubing fitted to a guide cannula (Plastics One, Roanoke Va., USA) bent at a right angle and encased in dental cement anchored with a 3 cm square of durable mesh. The catheter tubing was passed subcutaneously from the animal's back to the right jugular vein which was punctured with a 26-gauge needle. Silastic tubing (37 mm) was inserted into the vein, and tied gently with suture thread. All animals were allowed to recover for a minimum of 7 days before being given access to drug self-administration. Catheters were flushed daily with sterile physiological saline containing heparin (30 USP units/ml) and streptokinase (0.67 mg/ml).

Catheter patency

The integrity of a catheter was tested whenever an animal not receiving drug pretreatments displayed behavior outside baseline parameters. If intravenous blood could not be readily withdrawn via

the catheter, 0.1 ml of the ultra-short-acting barbiturate anesthetic Brevital Sodium (1% methohexital sodium, Eli lilly, Indianapolis, Ind., USA) was administered through the catheter and the animal was observed. Animals with patent catheters exhibited prominent signs of anesthesia (pronounced loss of muscle tone) within 3 s of IV injection. Animals with faulty catheters were recatheterized on the opposite jugular vein. Data collected from animals that did not complete all the tests in an experimental design were excluded.

Apparatus

Self-administration chambers consisted of operant boxes equipped with a single retractable lever which was extended approximately 1 inch into the chamber at the start of the session. A light above the lever signaled delivery of a drug injection. A food hopper was located to the left of the lever. Drug infusions were delivered by a syringe pump equipped with a 5 rpm motor (Razel Scientific Instrumnets, Model A, Stanford, Conn., USA) activated for 4 s to deliver drug in a volume of 0.1 ml through a polyethylene tube attached to the catheter on the animals' back via a stainless steel liquid swivel.

Self-administration training

Prior to surgery, rats were food restricted (20 g chow/rat per day) and operantly trained to press a lever for 0.45-mg food pellets (Bio-Serve, Frenchtown, N.J., USA). Once stable responding on a fixed ratio 5 (FR 5) schedule of reinforcement was achieved the animals were given ad libitum access to food for the remainder of the experiment. The animals then received chronic jugular catheter implants. Following surgery, animals were divided into two groups, each of which was then trained to self-administer either GBR-12909 or cocaine, respectively, on an FR5 schedule of reinforcement. Thus, GBR-12909 self-administering animals in this experiment were not exposed to cocaine at any time. The animlas were allowed a post-operative recovery period of 7 days, after which they were allowed to acquire drug self-administration by autoshaping, 3 h per day, 6 days a week. The training doses of each drug were 83 μg/injection GBR-12909 and 0.25 mg/injection cocaine. The daily 3-h self-administration sessions were continued until the total number of drug infusions per session stabilized to within ± 10% for 3 consecutive days (baseline criterion). With the exception of the first self-administration session, all sessions commenced with two non-contingent infusions of the drug dose for that session. The lever was then extended after which time the completion of each FR 5 resulted in an injection signaled immediately by a cue light, which remained lit for a 20-s timeout period, during which responses were recorded but not reinforced.

Experimental design

After baseline criteria were met in each group for the training doses of GBR-12909 and cocaine, the dose-effect functions for each drug and the effect of CGS-12066B pretreatment on these dose-effect functions were established. The criterion for the start of unit dose or drug interaction tests was three consecutive self-administration sessions with less than ± 10% variation in the total number of injections earned. Dose-effect functions (GBR-12909; 0, 10.4, 20.75, 41.5, 83, 166 μg per injection: Cocaine; 0, 0.03, 0.06, 0.125, 0.25, 0.5 mg per injection) were generated using a within-subject counter-balanced design (n = 7–12 for all experiments). On one of the final baseline criterion days for each dose of self-administered drug, a control injection of saline (0.6 ml/kg, IP) was administered 15 min prior to the self-administration session. Because CGS-12066B also has affinity for the 5-HT_{1A} receptor (Hoyer et al. 1994) the effect of 8-OH-DPAT pretreatment on the self-administration of 83 μg/injection GBR-12909 was also investigated. CGS-12066B (IP) and 8-OH-DPAT (SC) pretreatments were adminsered 15 min prior to testing in a volume of 0.6 ml/kg.

Drugs

GBR-12909 HBr was generously provided by Novo Nordisk A/S (The Netherlands) and was dissolved in 0.9% saline by sonication and gentle heating. Cocaine HCl was obtained from Sigma (St Louis, Mo., USA) and was dissolved in 0.9% saline. CGS-12066B maleate was obtained from Research Biochemicals International (RBI, Natick, Mass., USA) and was dissolved in 20 μl 0.1 N HCl, then diluted 100-fold with 0.9% saline. All GBR-12909 and CGS-12066B solutions were made fresh daily. All doses refer to the weights of the respective salts.

Statistics

All results were analyzed using a repeated measures analysis of variance (ANOVA) with the drug pretreatment (either CGS-12066B or 8-OH-DPAT) as the within-subject factor. For experiments involving a single dose of self-administered GBR-12909 or cocaine, the effects of the serotonin agonist pretreatment were analyzed by one-way ANOVA followed by Fisher's PLS test to compare various doses of agonist pretreatment with vehicle treatment. For experiments examining the effects of CGS-12066B pretreatment on the drug self-administration dose-effect function, drug dose (GBR-12909 or cocaine) and CGS-12066B pretreatment dose were analyzed by a two-way ANOVA with repeated measures. To identify significant effects of CGS-12066B at different doses of either GBR-12909 or cocaine, simple effects ANOVA was used. A shift of the dose-effect function was defined by a significant drug (GBR-12909 or cocaine) dose × CGS-12066B interaction, in the presence of significant simple effects of CGS-12066B to increase self-administration on the ascending limb of the dose-effect function, as well as to decrease self-administration on the descending limb. Differences were considered significant at $P < 0.05$.

Results

Effect of CGS-12066B on GBR-12909 self-administration

The training dose of GBR-12909 (83 μg/injection) maintained stable, titrated (i.e. stable and regular inter-injection intervals) self-administration behavior with a mean drug intake of 43.7 ± 5.5 (mean ± SEM) injections per 3-h session. The average weight of the animals was 0.51 ± 0.01 kg; thus the training dose of GBR-12909 corresponded to 163 μg/kg per injection. Pretreatment with the 5-HT_{1B} agonist CGS-12066B (1–10 mg/kg, IP; n = 9) dose-dependently reduced GBR-12909 self-administration by increasing the time interval between reinforcers [$F(3,24) = 5.339$, $P < 0.01$], without disrupting stable drug intake (Fig. 1). Both 3 mg/kg and 10 mg/kg CGS-12066B produced significant decreases in GBR-12909 self-administration ($P < 0.05$).

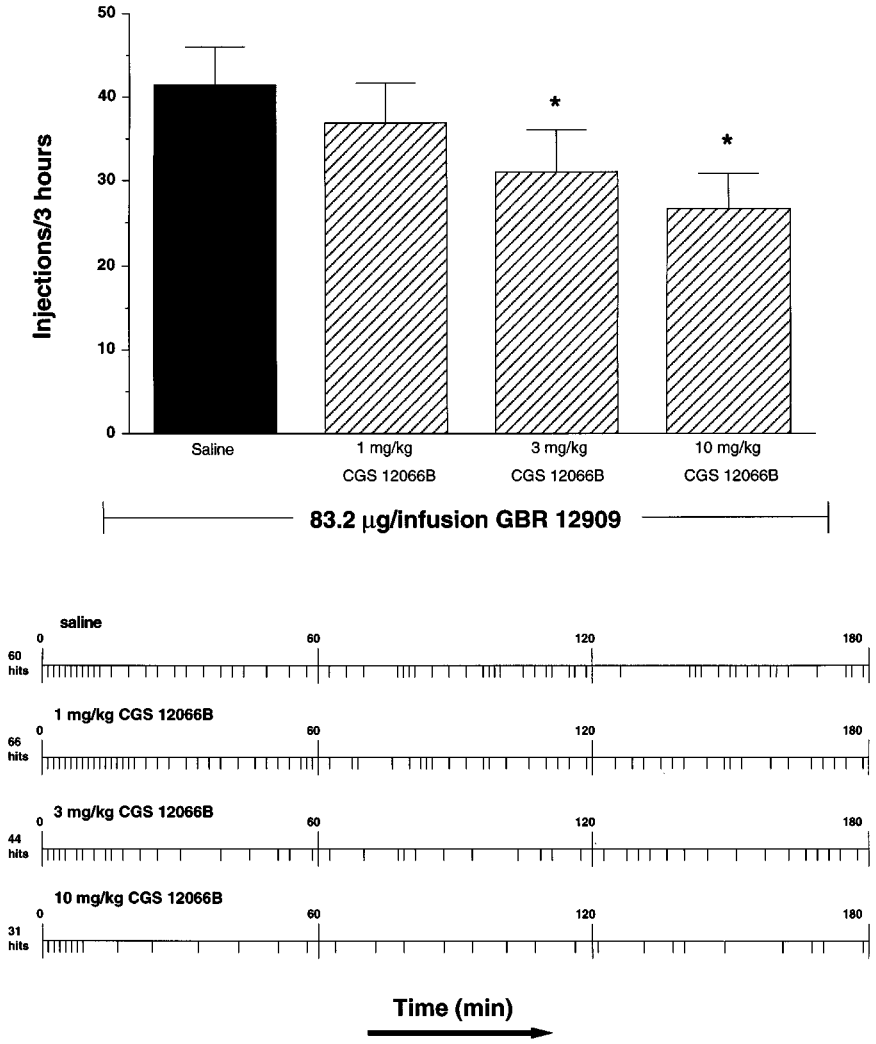

Fig. 1 Effect of pretreatment with the 5-HT_{1B} agonist CGS-12066B (1–10 mg/kg, IP) on the self-administration of the training dose (83 μg/injection) of GBR-12909 ($n = 9$). *Top panel*: CGS-12066B pretreatment dose-dependently reduced the amount of self-administered GBR-12909 in a 3-h session. *Asterisks* denote significant differences from vehicle control, by pairwise comparison following overall main effects by ANOVA. *Bottom panel*: event record of reinforcer delivery for one rat self-administering GBR-12909 after pretreatment with vehicle or CGS-12066B (1–10 mg/kg, IP). Each *horizontal line* represents a separate 3-h self-administration session, with time progressing from the left to the right. Each *vertical tick mark* denotes delivery of a single reinforcer following completion of an FR5

GBR-12909 self-administration produced an inverted U-shaped dose-effect function [$F(4,44) = 15.402$, $P < 0.0001$] characteristic of psychostimulant self-administration. Pretreatment with CGS-12066B (3 mg/kg, IP; $n = 12$) produced a significant GBR-12909 dose × CGS-12066B interaction [$F(4,44) = 2.9$, $P < 0.05$]. Simple main effects tests indicated that CGS-12066B pretreatment shifted the GBR-12909 dose-effect function to the left (Fig. 2); the minimum effective dose of GBR-12909 to maintain self-administration was lowered [$F(1,11) = 4.9$ and 11.2; $P < 0.05$ and $P < 0.01$ for the 10 and 21 μg/injection doses of GBR-12909, respectively], while at the same time the self-administration of higher doses was decreased [$F(1,11) = 14.5$, 11.2 and 0.9; $P < 0.05$, $P < 0.006$ and NS for the 42, 83 and 166 μg/injection doses of GBR-12909, respectively]. There was no significant effect of saline pretreatment on GBR-12909 self-administration. Self-administration was not reliably maintained when saline was substituted for GBR-12909 (Fig. 2), and there was no significant effect of CGS-12066B on responding for saline [$F(1,11) = 0.258$, NS].

Effect of 8-OH-DPAT on GBR-12909 self-administration

In a separate group of animals ($n = 7$), the effect of pretreatment with the selective 5-HT_{1A} receptor agonist 8-OH-DPAT (0.03, 0.1 and 1.0 mg/kg, SC) on the self-administration of GBR-12909 (83 μg/injection)

Table 1 Effect of 8-OH-DPAT pretreatment on the self-administration of GBR-12909 (83 μg/injection; $n = 7$). The number of GBR-12909 self-injections for each hour of the 3-h sessions is shown. There was no effect of 8-OH-DPAT pretreatment at any dose (0.03, 0.1 and 1.0 mg/kg, SC) on the self-administration of GBR-12909

8-OH-DPAT pretreatment dose (mg/kg, IP)	Number of GBR-12909 Injections (mean ± SEM)		
	Hour 1	Hour 2	Hour 3
Saline	21 ± 1.7	12 ± 2.0	12 ± 1.3
0.03	19 ± 2.2	14 ± 1.0	13 ± 1.7
0.1	18 ± 2.2	11 ± 2.7	14 ± 2.6
1.0	19 ± 1.1	11 ± 2.4	12 ± 2.1

Table 2 Effect of CGS-12066B pretreatment on the self-administration of cocaine with cocaine doses on the ascending (0.06 mg/injection) and descending (0.25 mg/injection) limb of the dose-effect function (n = 7). The number of cocaine self-injections for each hour of the 3-h sessions is shown. There was no effect of CGS-120666B pretreatment at any dose (1.0, 3.0, 10 mg/kg, IP) on cocaine self-administration at either of the cocaine doses examined

CGS-12066B pretreatment dose (mg/kg, IP)	Cocaine dose (mg/inj, IV)	Number of cocaine injections (mean ± SEM)		
		Hour 1	Hour 2	Hour 3
Saline	0.25	20 ± 1.1	14 ± 1.1	13.8 ± 1.3
1.0	0.25	19 ± 1.4	13 ± 0.9	12 ± 0.8
3.0	0.25	20 ± 1.3	14 ± 0.9	13 ± 0.7
10.0	0.25	19 ± 1.2	14 ± 0.9	13 ± 0.9
Saline	0.06	36 ± 10.5	29 ± 11.8	21 ± 10.8
1.0	0.06	38 ± 9.8	27 ± 12.0	22 ± 11.5
3.0	0.06	34 ± 10.5	30 ± 11.2	25 ± 11.8
10.0	0.06	37 ± 11.2	27 ± 10.5	23 ± 11.5

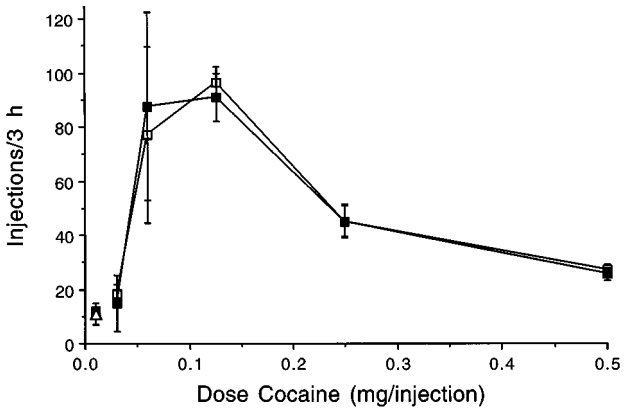

Fig. 3 Effect of pretreatment with CGS-12066B (3 mg/kg, IP) on the cocaine self-administration dose-effect function (n = 7). *Symbols* adjacent to the *vertical axis* represent the effect of saline (□) or CGS-12066B (■) pretreatment on saline self-administration (cocaine dose = 0)

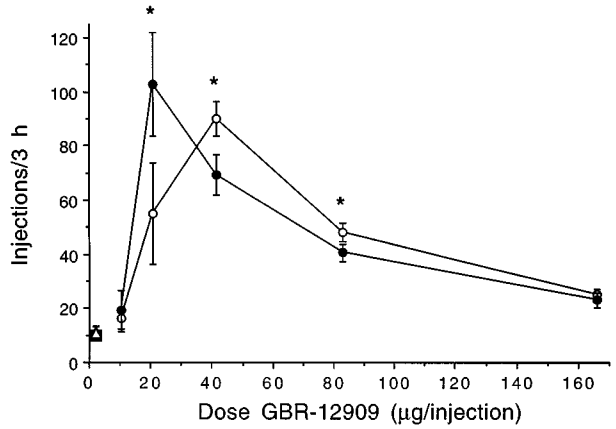

Fig. 2 Effect of pretreatment with CGS-12066B (3 mg/kg, IP) on the GBR-12909 self-administration dose-effect function (n = 12). *Symbols* adjacent to the *vertical axis* represent the effect of saline (○) or CGS-12066B (●) pretreatment on saline self-administration (GBR dose = 0). *Asterisks* denote significant simple main effects of CGS-12066B following significant CGS-12066B × GBR-12909 main interaction by two-way ANOVA

was investigated. There was no effect of 8-OH-DPAT on GBR-12909 self-administration at any of the pretreatment doses tested [F(3,18) = 0. 514; NS; see Table 1].

Effect of CGS-12066B on cocaine self-administration

Cocaine at the training dose of 0.25 mg/injection also maintained stable, titrated self-administration with a mean drug intake of 48.7 ± 6.1 injections per 3-h session. Pretreatment with the 5-HT_{1B} agonist CGS-12066B (1–10 mg/kg, IP; n = 7) had no significant effect on the self-administration of this dose of cocaine [F(3,18) = 2.06, NS; see Table 2]. These same doses of the 5-HT_{1B} agonist also failed to modify the self-administration of a lower dose of cocaine (0.06 mg/injection) [F(3,18) = 1.98, NS; see Table 2].

Cocaine self-administration produced a characteristic inverted U-shaped dose-effect function [F(4,24) = 7.1, $P < 0.001$] (n = 7). Pretreatment with CGS-2066B (3 mg/kg, IP) had no significant effect on the cocaine dose-effect function as demonstrated by a lack of a significant cocaine dose × CGS-12066B main interaction [F(4,24) = 0.253, NS; Fig. 3]. There was also no significant effect of saline pretreatment on cocaine self-administration. Self-administration was not reliably maintained when saline was substituted for cocaine (Fig. 3), and there was no significant effect of CGS-12066B on responding for saline [F(1,6) = 0.477, NS].

Discussion

5-HT_{1B} receptor stimulation was found to enhance DA-mediated reinforcement as demonstrated by a significant leftward shift of the GBR-12909 self-administration dose-effect function (Fig. 2). Pretreatment with the 5-$HT_{1A/1B}$ receptor agonist CGS-12066B not only decreased the self-administration of GBR-12909 on the descending limb of the dose-effect function (by increasing the inter-injection interval), but also lowered the minimum dose of GBR-12909 which maintains self-administration on a fixed-ratio schedule (Fig. 2). Moreover, this 5-HT_{1B} receptor-induced potentiation of GBR-12909 reinforcement was dose-dependent, as indicated by the progressive decrease in the self-administration of GBR-12909 with increasing doses of CGS-12066B (Fig. 1). The 5-HT_{1A} receptor-selective agonist 8-OH-DPAT did not alter GBR-12909 self-administration, suggesting that 5-HT_{1A} receptors are not involved in the potentiating actions of CGS-12066B. Finally, there was no effect of CGS-12066B

pretreatment on cocaine self-administration (Fig. 3), suggesting that the stimulation of other 5-HT receptor subtypes by the indirect agonist effects of cocaine may mask the potentiating effects of 5-HT_{1B} receptor stimulation.

GBR-12909 maintained stable, dose-dependent self-administration, in agreement with previous reports of its self-administration by rats (Roberts 1993) and monkeys (Kleven et al. 1988; Bergman et al. 1989; Howell and Byrd 1991). Reinforcing actions of GBR-12909 would be expected based on reports indicating that this uptake inhibitor substitutes for the discriminative properties of cocaine in rats (Cunningham and Callahan 1991; Witkin et al. 1991) and monkeys (Melia and Spealman 1991) and cross-sensitizes to the locomotor-stimulant effects of cocaine (Baldo and Kelley 1991). Similar to cocaine (Markou and Koob 1991), GBR-12909 also lowers the threshold for electrical brain stimulation reward (Rompré and Bauco 1990). These findings suggest that GBR-12909 and cocaine share many of the same properties, and likely activate the same neurochemical pathway, namely the mesocorticolimbic DA system.

In the present study, rats that had no prior psychostimulant exposure readily acquired GBR-12909 self-administration (83 μg/injection; FR5) with an acquisition timecourse similar to cocaine self-administration (0.25 mg/injection; FR5). While the dose range of self-administered GBR-12909 was much lower in the present study than that previously investigated in rats (Roberts 1993), a similar dose of GBR-12909 in each of these studies produced comparable amounts of drug intake (8.36 injections/h with a dose of 325 μg/kg per injection presently versus approximately eight injections/h with a dose of 375 μg/kg per injection (Roberts 1993). Additionally, the present finding that similar amounts of drug intake are maintained both by cocaine and a 3-fold lower dose of GBR-12909 (0.25 mg/injection versus 83 μg/injection respectively) is in agreement with previous findings using an FR schedule of reinforcement in rats (Roberts 1993).

Stimulation of 5-HT_{1B} receptors by the 5-HT_1 receptor agonist CGS-12066B produced a leftward shift of the GBR-12909 dose effect function (Fig. 2), suggesting that stimulation of these receptors facilitates DA-mediated reinforcement. This finding is supported by recent studies indicating that 5-HT_{1B} receptor stimulation enhances DA efflux in the striatum and limbic forebrain (Benloucif and Galloway 1991; Nissbrandt et al. 1992; Benloucif et al. 1993; Galloway et al. 1993), increases locomotor activity (Green et al. 1984; Oberlander et al. 1986; Tricklebank et al. 1986; Cheetham and Heal 1993), produces a cocaine-like stimulus in rats (Callahan ad Cunningham 1995), and shifts the cocaine discrimination dose-effect function to the left (Callahan and Cunningham 1995).

CGS-12066B has been reported to display selectivity for 5-HT_{1B} receptors (Schoeffter and Hoyer 1989; Middlemiss and Hutson 1990), but it also has appreciable affinity for 5-HT_{1A} receptors (Neale et al. 1987; Schoeffter and Hoyer 1989; Macor et al. 1990). Thus the effect of 5-HT_{1A} receptor stimulation on GBR-12909 self-administration was also investigated. Over a wide dose range, pretreatment with the selective 5-HT_{1A} receptor agonist 8-OH-DPAT (Glennon and Dukat 1991; Hoyer et al. 1994) had no significant effect on GBR-12909 self-administration. The doses of 8-OH-DPAT examined encompass the low-dose inhibition of dorsal and median raphé neuronal firing which results in decreased 5-HT efflux in the VTA (0.03 mg/kg, IP; Blier and DeMontigny 1987; Lum and Piercey 1988; Chen and Reith 1995) and higher dose induction of the "serotonin syndrome" (1.0 mg/kg, IP; Arvidsson et al. 1981; Dourish et al. 1985). The lack of effect of 8-OH-DPAT suggests that 5-HT_{1A} receptors are not involved in the stimulatory effects of CGS-12066B on GBR-12909 reinforcement. While CGS-12066B also has an affinity for 5-HT_{2C} receptors (Schoeffter and Hoyer 1989), Callahan and Cunningham (1995) have recently provided evidence that this receptor subtype induces opposite effects on the discriminative properties of cocaine as does the 5-HT_{1B} receptor subtype (i.e. inhibition versus potentiation), suggesting that 5-HT_{2C} stimulation might inhibit psychostimulant reinforcement. In support of this finding, the 5-HT_{2C} receptor agonist mCPP (Schoeffter and Hoyer 1989) dose-dependently *increases* the self-administration of GBR-12909 (83 μg/injection; Parsons et al., unpublished findings). Coupled with the observation that CGS-12066B has minimal affinity for both D_1 and D_2 dopamine receptors and α_1-, α_2-, or β-adrenergic receptors (Neale et al. 1987), these findings suggest that the potentiation of GBR-12909 reinforcement by CGS-12066B observed here is likely to result from the stimulation of 5-HT_{1B} receptors.

One possible mechanism for the facilitory action of CGS-12066B on GBR-12909 self-administration is a 5-HT_{1B} receptor-induced increase in DA efflux. This effect could occur via a reduction in the inhibitory input to mesoaccumbens DA neurons, since 5-HT_{1B} (rat) or 5-HT_{1D} (guinea pig) receptor stimulation has recently been shown to inhibit the release of GABA onto A10 DA neurons (Johnson et al. 1992; Cameron and Williams 1994). These findings are in agreement with the distribution of 5-HT_{1B} receptors which are abundant in the substantia nigra and the VTA in rats, where they appear to be localized on the terminals of GABAergic afferents emanating from the caudate-putamen and NAcc (Boschert et al. 1993). This proposed mechanism may correlate with the observations that local administration of 5-HT into the VTA increases mesoaccumbens DA release via interactions with 5-HT_{1B} receptors (Guan and McBride 1988) and that mesocortical DA efflux is potentiated by the peripheral pretreatment with 5-HT_{1B} agonists (Nissbrandt et al. 1992). In addition, DA efflux is increased by local

administration of 5-HT_{1B} receptor agonists (Benloucif and Galloway 1991; Benloucif et al. 1993; Galloway et al. 1993), although the mechanism for this effect has not been fully characterized. Thus, stimulation of 5-HT_{1B} receptors by CGS-12066B may enhance DA neurotransmission both in the cell body and terminal regions, which may produce the presently observed leftward shift of the GBR-12909 self-administration dose-effect function.

An alternate mechanism by which 5-HT_{1B} receptor stimulation potentiates GBR-12909 reinforcement may be via a reduction in 5-HT efflux. There is ample evidence that 5-HT_{1B} receptors function as terminal (Middlemiss 1985, 1986; Engel et al. 1986; Limberger et al. 1991) and somatodendritic (Davidson and Stamford 1995; Pineyro et al. 1995) autoreceptors, and several reports suggest an inverse relationship between extracellular 5-HT levels and the reinforcing effects of psychostimulants. For example, depletion of extracellular 5-HT in the forebrain by 5,7-dihydroxytryptamine enhances the reward magnitude of cocaine (Loh and Roberts 1990), while increased synaptic availability of 5-HT inhibits cocaine self-administration (Carroll et al. 1990a, b) and decreases the breaking point of a progressive ratio schedule in cocaine self-administering rats (Richardson and Roberts 1991). Thus, in the present study, pretreatment with CGS-12066B may result in decreased basal 5-HT efflux which results in the enhancement of the reinforcing properties of GBR-12909. However, since 8-OH-DPAT also decreases 5-HT efflux (Chen and Reith 1995), this argument is weakened by the lack of effect of this 5-HT_{1A} receptor agonist on GBR-12909 self-administration. Moreover, clinical reports indicate that tryptophan depletion attenuates the acute euphoria induced by cocaine in humans (Aronson et al. 1995). It is possible, however, that the differential locations of 5-HT_{1A} (somatodendritic, post-synaptic in terminal fields; Hall et al. 1985; Verge et al. 1986) and 5-HT_{1B} (primarily pre-synaptic in terminal fields; Engel et al. 1986; Hamon et al. 1990; Limberger et al. 1991) receptors may be significant with regard to the differential effects of these receptors on GBR-12909 reinforcement.

Unlike GBR-12909 self-administration, cocaine self-administration was unaltered by 5-HT_{1B} receptor stimulation (Fig. 3). The median dose of CGS-12066B (3 mg/kg) was tested on the entire cocaine dose-effect function, as were various doses of CGS-12066B (1–10 mg/kg) both on the ascending and descending limbs of the cocaine dose-effect function. In all situations examined, CGS-12066B was ineffective at modulating cocaine self-administration on a fixed ratio schedule of reinforcement. It should be noted, however, that modulations of some phenomena such as motivation are more apparent on schedules of reinforcement other than the fixed ratio (Loh and Roberts 1990). It may be possible that positive effects of CGS-12066B on cocaine self-administration would be observed on a different schedule of reinforcement such as a progressive ratio.

Nonetheless, the present finding that CGS-12066B enhances the reinforcing effects of GBR-12909 self-administration but does not alter cocaine self-administration suggests that the effects of 5-HT_{1B} receptor stimulation on DA-mediated reinforcement are somehow less apparent in the presence of the indirect 5-HT and/or NE agonist properties of cocaine. One explanation for this effect is that the simultaneous stimulation of multiple 5-HT receptor subtypes in the presence of cocaine masks or counters the effect of 5-HT_{1B} receptor stimulation. While the infleunce of other 5-HT receptor subtypes on reinforcement is not clear, recent findings by Callahan and Cunningham (1995) indicate that while 5-HT_{1B} receptor stimulation facilitates the stimulus effects of cocaine, 5-HT_{2C} receptor stimulation is inhibitory on this process. If the stimulus properties of a drug predict the drug's reinforcing properties, it may be that the concurrent stimulation of the 5-HT_{2C} receptor during cocaine self-administration reverses or blocks the effects of 5-HT_{1B} receptor stimulation. It should be noted, however, that while the 5-HT_{1B} agonist RU 24969 produced a leftward shift of the cocaine dose-effect curve in drug discrimination tests, CGS-12066B was ineffective (Callahan and Cunnigham 1995). The differential effects of these agonists on cocaine discrimination may reflect their affinities for the 5-HT_{1B} and 5-HT_{2C} receptors, since the selectivity of RU 24969 for the 5-HT_{1B} receptor versus the 5-HT_{2C} receptor is greater than the selectivity of CGS-12066B for these receptors (Schoeffter and Hoyer 1989). The selectivities of these compounds for the 5-HT_{1B} receptor versus the 5-HT_{1A} receptor may also be important in light of reports that suggest a synergistic action of these receptors (Berendsen and Broekkamp 1990; Layer et al. 1992). CGS-12066B has also been found to have weak agonist efficacy in behavioral tests (Cheetham and Heal 1993) and thus it may be that the differential effects of CGS-12066B and RU 24969 on cocaine discrimination reflects a difference in potency at the 5-HT_{1B} receptor, rather than different selectivities for various 5-HT receptor subtypes. It is possible that a more potent and selective 5-HT_{1B} agonist than CGS-12066B, such as RU 24969, would have greater effects on GBR-12909 self-administration and would also potentiate the reinforcing properties of cocaine, a hypothesis supported by preliminary studies in rats (Parsons et al., unpublished observations).

An alternate explanation for the lack of effect of CGS-12066B on cocaine self-administration is that 5-HT_{1B} receptors are already maximally stimulated during cocaine self-administration (via cocaine-induced increases in synaptic 5-HT levels), making the addition of a 5-HT_{1B} agonist inconsequential. However, under these circumstances it would be expected that CGS-12066B would positively effect sub-threshold doses of cocaine without any effect at doses higher on the dose-

effect function, an effect which was not observed in the present study. Additionally as noted above, preliminary studies indicate that the more potent 5-HT_{1B} agonist RU 24969 produces a leftward shift of the cocaine self-administration dose-effect function (Parsons et al. unpublished observations). Together these findings suggest that 5-HT_{1B} receptors are not maximally stimulated during cocaine self-administration.

While the involvement of 5-HT_{1B} receptors in the acute reinforcing effects of cocaine is not clear at the present time, it is possible that the role of this receptor in mediating the behavioral effects of cocaine may be more pronounced following chronic cocaine exposure. Extended cocaine self-administration results in robust decrements in ambient extracellular 5-HT levels (Parsons et al. 1995) and a substantial literature indicates an inverse relationship between 5-HT levels and 5-HT_{1B} binding density and/or sensitivity (Weissmann et al. 1986; Offord et al. 1988; Van de Kar et al. 1989; Crino et al. 1990; Frankfurt et al. 1993; Manrique et al. 1993, 1994; Pranzatelli and Razi 1994). Thus it may be that 5-HT_{1B} receptor function is enhanced following chronic cocaine exposure, a proposal which is supported by recent endocrinological studies (Levy et al. 1992). An involvement of 5-HT_{1B} receptors in the motor sensitizing effects of repeated cocaine exposure may also be inferred from the finding that 5-HT_{1B} "knock-out" mice do not develop the increase in cocaine-induced stereotyped behaviors that wild type control animals do after chronic cocaine administration (Scearce et al. 1995).

In addition to reports of alterations in 5-HT_{1B} receptor function specifically, there is substantial evidence that repeated cocaine exposure results in a general alteration of 5-HT function. Extended exposure to cocaine has been shown to result in significant decrements in 5-HT neuronal activity (Cunningham 1995) and alterations in 5-HT receptor sensitivity (Cunningham et al. 1992; Baumann et al. 1993; King et al. 1993; Levy et al. 1994; Baumann and Rothman 1995). Coversely, repeated cocaine exposure enhances the cocaine-induced elevations of both 5-HT (Parsons and Justice 1993) and DA (Kalivas and Duffy 1990; Pettit et al. 1990; Parsons and Justice 1993) in several brain regions and results in an enhanced ability of exogenous 5-HT to elevate NAcc DA levels (Parsons et al. 1995; but see Galloway and Suchowski 1995). Together, these findings indicate that chronic cocaine exposure results in altered serotonergic function, both within the 5-HT neurotransmitter system itself and potentially also *between* the serotonergic system and the dopaminergic system. A possible functional significance of these alterations may be inferred from the finding that repeated cocaine exposure produces cross-tolerance to the cocaine analogue WIN 35,428, but does not produce cross-tolerance to GBR-12909 (Katz et al. 1993). Because WIN 35,428 has affinity for the 5-HT uptake transporter (Rudnick and Wall 1991) and produces similar effects on serotonergic activity as cocaine (Cunningham and Lakoski 1990) while GBR-12909 does not (Heikkila and Manzino 1984; Anderson et al. 1989), these findings may suggest a serotonergic component in the processes of cocaine tolerance. However, a contribution of NE neurotransmission to the cross-tolerance between cocaine and WIN 35,428 cannot be ruled out.

In summary, 5-HT_{1B} receptor stimulation was found to enhance the reinforcing effects of the selective DA uptake inhibitor GBR-12909. However, there was no effect of 5-HT_{1B} receptor stimulation on the self-administration of cocaine, suggesting that the simultaneous stimulation of other 5-HT receptor subtypes by the indirect agonist properties of cocaine masks the stimulatory effects of 5-HT_{1B} receptor stimulation. The 5-HT_{1B} receptor is the rat homologue of the 5-HT_{1D} receptor in humans (Hartig et al. 1992 for review), and these species specific receptor homologues are differentiated by a single amino acid (Oksenberg et al. 1992; Parker et al. 1993). Given the remarkable similarities between these receptors, the present finding of a stimulatory role of the 5-HT_{1B} receptor on DA-mediated reinforcement in rats may have direct relevance to the mechanisms of stimulant reinforcement and motivation in humans.

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