Serotonin$_{1B}$ Receptor Stimulation Enhances Cocaine Reinforcement

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The effects of serotonin$_{1B}$ [5-hydroxytryptamine$_{1B}$ (5-HT$_{1B}$)] receptor activation on cocaine reinforcement were investigated using intravenous cocaine self-administration by rats. The 5-HT$_{1B}$ receptor agonists 5-methoxy-3-1,2,3,6-tetrahydro-4-pyridinyl-1H-indole (RU 24969) (0.3–3 mg/kg), 3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3,2-b]pyridine (CP 94,253) (0.3–3 mg/kg), and 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-b]pyridine (CP 93,129) (3 and 10 μg, i.c.v.) each dose-dependently reduced the self-administration of a cocaine dose on the descending limb of the fixed-ratio 5 (FR-5) cocaine dose–effect function, in a manner similar to the effect produced by increasing the unit dose of cocaine. In addition, each of these 5-HT$_{1B}$ agonists lowered the threshold dose of cocaine that supported self-administration. These results are consistent with a 5-HT$_{1B}$ agonist-induced potentiation of cocaine reinforcement. On a progressive ratio schedule of reinforcement, RU 24969 and CP 94,253 dose-dependently (0.3–3 mg/kg) increased the highest completed ratio for cocaine self-administration, again by producing behavioral alterations similar to those induced by increasing the unit dose of cocaine. The effect of CP 94,253 was dose-dependently blocked by the 5-HT$_{1B/1D}$ receptor partial agonist 2′-methyl-4′-(5-methyl[1,2,4]oxadiazol-3-yl)-biphenyl-4-carboxylic acid[4-methodoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide (GR 127,935) (0.3–10 mg/kg) but was unaffected by the 5-HT$_{1A}$ receptor antagonist 4-iodo-*N*-[2-[4-(methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-benzamide (p-MPPI; 1–10 mg/kg). Self-administration behavior was not maintained when either RU 24969 or CP 94,253 was substituted for cocaine, indicating that these 5-HT$_{1B}$ agonists do not produce significant reinforcing effects alone. Together, these findings indicate that 5-HT$_{1B}$ receptor stimulation facilitates the reinforcing properties of cocaine. These results are in opposition to recent findings with 5-HT$_{1B}$ receptor knock-out mice and may have important ontogenic implications in the area of drug abuse research.

Key words: cocaine; self-administration; 5-HT$_{1B}$; 5-HT$_{1A}$; RU 24969; CP 94,253; CP 93,129; GR 127,935; 8-OH-DPAT; p-MPPI; progressive ratio

It is well established that the reinforcing effects of cocaine and other psychostimulants are dependent on the ability of these drugs to enhance extracellular dopamine (DA) concentrations in the mesocorticolimbic system (Wise, 1984; Koob and Bloom, 1988; Kuhar et al., 1991). However, cocaine also elevates extracellular serotonin [5-hydroxytryptamine (5-HT)] and norepinephrine levels (Chen and Reith, 1994; Li et al., 1996), suggesting that monoaminergic systems other than DA could play some role in the mediation of cocaine reinforcement.

There is increasing evidence implicating a serotonergic component in the behavioral effects of cocaine in rats and monkeys (Carroll et al., 1990a,b; Loh and Roberts, 1990; Spealman, 1993) as well as in humans (Walsh et al., 1994; Aronson et al., 1995; Satel et al., 1995; Buydens-Branchey et al., 1997). Acute cocaine administration dramatically alters the electrophysiological activity of both 5-HT and DA neurons (Cunningham, 1995; White et al., 1995), and chronic cocaine exposure produces pronounced decrements in both 5-HT and DA neuronal activity (Cunning-

ham, 1995; White et al., 1995) and 5-HT and DA efflux (Parsons et al., 1991, 1995; Weiss et al., 1995). Moreover, the combined stimulation of 5-HT and DA receptors is required to mimic the effects of cocaine on striatal gene expression (Bhat et al., 1992; Bhat and Baraban, 1993) and on the firing rate of DA cells in the nucleus accumbens (White et al., 1993). However, in contrast to what is known about dopaminergic mechanisms, relatively little is known about the contribution of serotonergic mechanisms to the behavioral and physiological effects of cocaine.

Serotonin neurotransmission is mediated by at least 14 different 5-HT receptor subtypes (Hoyer et al., 1994). Recent findings suggest that serotonin$_{1B}$ (5-HT$_{1B}$) receptors, in particular, play some role in the mediation of the reinforcing and subjective effects produced by psychostimulants. For example, 5-HT$_{1B}$ receptor agonists potentiate the reinforcing effects of a selective DA uptake inhibitor (Parsons et al., 1996), enhance the discriminative cue produced by cocaine, and partially substitute for the discriminative stimulus properties of cocaine (Callahan and Cunningham, 1995, 1997). In addition, 5-HT$_{1B}$ receptors mediate the cocaine-induced reduction in ventral tegmental area GABA release (Cameron and Williams, 1994) and contribute to cocaine-induced striatal c-*fos* expression (Lucas et al., 1997). These findings suggest an involvement of 5-HT$_{1B}$ receptors in the behavioral, neurochemical, and cellular effects produced by cocaine.

To test the hypothesis that 5-HT$_{1B}$ receptors play a role in the mediation and/or modulation of cocaine reinforcement, we investigated the effects of the putative 5-HT$_{1B}$ receptor agonists

5-methoxy-3-1,2,3,6-tetrahydro-4-pyridinyl-1H-indole (RU 24969), 3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3,2-b]pyridine (CP 94,253), and 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-b] pyridine (CP 93,129) on intravenous cocaine self-administration in rats. Alterations in cocaine reinforcement were assessed by examining shifts in the cocaine dose–effect function using both a low fixed-ratio schedule (FR-5) and a progressive ratio schedule of cocaine reinforcement. The ability of the selective 5-HT$_{1B/1D}$ receptor partial agonist 2′-methyl-4′-(5-methyl[1,2,4]oxadiazol-3-yl)-biphenyl-4-carboxylic acid[4-methodoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide (GR 127,935) or the selective 5-HT$_{1A}$ receptor antagonist 4-iodo-*N*-[2-4-(methoxy-phenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-benzamide (p-MPPI) to alter the effects of CP 94,253 on cocaine reinforcement was also investigated. The reinforcing effects of intravenous RU 24969 and CP 94,253 self-administration were also explored.

MATERIALS AND METHODS

Subjects

Male Wistar rats (Charles River Laboratories, Wilmington, MA; *n* = 80) weighing 250–275 gm after delivery were housed in groups of two to three in a humidity- and temperature-controlled (22°C) vivarium on a 12 hr light/dark cycle (lights off at 10 A.M.). Animals were provided with food and water *ad libitum* throughout the course of the study, with the exception of 1 week of food restriction during operant training (see self-administration training). All behavioral procedures began between 1 to 3 hr after the onset of the dark phase. All procedures were conducted in strict adherence to the *National Institutes of Health Guide for the Care and Use of Laboratory Animals*.

Drugs

RU 24969 was generously provided by Roussel UCLAF (Romainville, France). CP 94,253 and CP 93,129 were generously provided by Pfizer (Groton, CT). GR 127,935 was generously provided by GlaxoWellcome (Stevenage, United Kingdom). Cocaine HCl was obtained from the National Institute on Drug Abuse (Washington, DC). (±)-8-Hydroxy-dipropylaminotetralin (8-OH-DPAT) and p-MPPI were purchased from Research Biochemicals (Natick, MA). All drugs were dissolved in 0.9% saline (CP 94,253, GR 127,935, and p-MPPI required gentle heating). All doses refer to the weights of the respective salts, and all test drugs were administered subcutaneously in a volume of 0.6 ml/kg [with the exception of CP 93,129 that was administered intracerebroventricularly because this compound does not penetrate the blood–brain barrier].

Intracerebroventricular surgery

Animals that were to receive CP 93,129 pretreatments were anesthetized (*n* = 7; 1.0–1.5% halothane), mounted in a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA), and implanted with a sterilized stainless steel guide cannula (made from a 23 gauge needle to a length of 7 mm) lowered to 1 mm above the lateral cerebral ventricle [from bregma: posterior, −0.6 mm; lateral +1.4 mm; and ventral −3.2 mm (from skull); atlas of Paxinos and Watson (1986)]. The cannula was secured to the skull with stainless steel screws and cranioplastic cement. Dummy stylets made of 0.011 inch wire that extended to the tip of the cannulae were inserted to prohibit cannula blockade and entry of foreign particles. All animals were allowed 7 d of recovery before returning to cocaine self-administration testing.

Intracerebroventricular drug administration

Injectors (made from 30 gauge needles; 8 mm in length) were connected to 70 cm lengths of polyethylene-10 tubing that were calibrated and marked for 2 µl volumes and filled with drug solution. Ten minutes before the cocaine self-administration sessions, the dummy stylet was removed from the cannula, and the injector was lowered into the ventricle via the guide cannula. By raising the tubing above the animal's head, gravity was used to deliver 2 µl of drug solution over a 30–60 sec period. Injectors were left in place for 30 sec after drug delivery and were then replaced with a dummy stylet.

Intravenous cocaine self-administration

Surgery. Rats were anesthetized with a halothane/oxygen vapor mixture (1.0–1.5%) and prepared with chronic intravenous catheters as described previously (Caine et al., 1993) with minor modifications (Emmett-Oglesby and Lane, 1993; Parsons et al., 1996). All animals were allowed to recover for a minimum of 7 d before the start of cocaine self-administration training. Catheters were flushed daily with sterile physiological saline containing heparin (30 USP units/ml).

Apparatus. The self-administration chambers consisted of operant boxes enclosed in sound-attenuating, ventilated environmental cubicles (chambers and cubicles manufactured in-house). Each operant chamber was equipped with a single retractable lever (Model E21–03; Coulbourn Instruments, Allentown, PA) that was extended into the chamber at the start of the session. Drug infusions were delivered by a syringe pump equipped with a 5 rpm motor (Model A; Razel Scientific Instruments, Stanford, CT) activated for 4 sec to deliver drug in a volume of 0.1 ml via a stainless steel liquid swivel and a polyethylene tube attached to the catheter on the animal's back.

Self-administration training. Before surgery, rats were food restricted (20 gm per rat per day) and allowed to press a lever for 0.45 mg food pellets (Bio-Serve, Frenchtown, NJ). After stable responding maintained by food 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 were then surgically prepared with chronic jugular catheter implants as described above. After a 7 d recovery period, cocaine self-administration training began in daily 3 hr sessions, 6 d per week, in which lever pressing was reinforced by infusion of 0.25 mg of cocaine on an FR-5 schedule of reinforcement. With the exception of the first self-administration session, all sessions commenced with two non-contingent infusions of cocaine. The lever was then extended, after which time the completion of each ratio requirement resulted in an injection signaled immediately by a cue light that was located above the lever and that remained lit for a 20 sec "timeout" period, during which responses were recorded but not reinforced. Self-administration training sessions continued until the total number of drug infusions per session stabilized to within ±10% for 3 consecutive days (baseline criterion). The integrity of the intravenous catheter was tested whenever an animal not receiving drug pretreatments deviated substantially from baseline self-administration performance. 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, IN) was administered through the catheter, and the animal was observed. Animals that did not exhibit prominent signs of anesthesia (pronounced loss of muscle tone) within 3 sec of intravenous injection were later anesthetized with halothane, and the faulty catheter was examined for leaks and repaired, or the animal was recatheterized in the contralateral jugular vein.

Experiment I: effects of the 5-HT$_{1B}$ agonists RU 24969, CP 94,253, and CP 93,129 on FR-5 cocaine self-administration. After the baseline criterion was met with the training dose of cocaine, the effect of RU 24969 pretreatment (1 mg/kg) on the cocaine self-administration dose–effect function was examined using cocaine doses of 0, 0.015, 0.03, 0.06, 0.125, and 0.25 mg per infusion. All animals (*n* = 8) were tested with each cocaine dose using a within-subject experimental design for dose, with different doses tested between sessions. The order of cocaine dose presentation was randomized between animals. A stability criterion of three consecutive self-administration sessions with less than ±10% variation in the total number of infusions earned was established for each cocaine dose [including the 0 dose (saline)] before pretreatment tests with RU 24969 or vehicle. To examine the dose dependency of the effects of RU 24969 on cocaine self-administration, we also pretreated animals with RU 24969 (0.3 and 3.0 mg/kg) before the self-administration of the 0.125 mg dose of cocaine per infusion (a dose on the descending limb of the dose–effect function). Thus, after completion of this experiment, all rats received both saline and RU 24969 (1.0 mg/kg) pretreatments before the self-administration of all cocaine doses in the dose–effect determination, in addition to receiving 0.3 and 3.0 mg/kg doses of RU 24969 before the self-administration of cocaine (0.125 mg/infusion). Pretreatments were administered 15 min before testing and were given in a randomized order between animals.

Two separate groups of animals (*n* = 7 per group) were used to investigate the dose-dependent effects of CP 94,253 and CP 93,129 on responding for a dose of cocaine on the descending limb of the dose–effect function (0.125 mg/infusion). In addition, a dose of cocaine found to be too low to maintain responding (0.03 mg/infusion) was made

available after pretreatment with a midrange dose of either 5-HT$_{1B}$ agonist. Animals in the first group were pretreated with saline or CP 94,253 (0.3, 1, or 3 mg/kg) before the self-administration of cocaine (0.125 mg/infusion) and with CP 94,253 (1 mg/kg) before the self-administration of cocaine (0.03 mg/infusion). Animals in the second group received saline or CP 93,129 (3 or 10 μg, i.c.v.) before the self-administration of cocaine (0.125 mg/infusion) and CP 93,129 (3 μg) before the self-administration of cocaine (0.03 mg/infusion). Baseline criterion for stable self-administration was met before each test day (as described above). All animals in each group were tested with each of the 5-HT$_{1B}$ pretreatment doses, which were administered in a randomized order between animals. CP 94,253 was administered 15 min before testing, and CP 93,129 was administered 10 min before testing.

Experiment II: effects of the 5-HT$_{1B}$ agonists RU 24969 and CP 94,253 and of the 5-HT$_{1A}$ agonist 8-OH-DPAT on progressive ratio cocaine self-administration. For this schedule of reinforcement, the response requirement (i.e., the number of lever responses required to receive a drug infusion or "ratio") was increased in the following manner. For each of the first eight cocaine infusions, the ratio was increased by 1; for each of the next eight infusions, the ratio was increased by 2; and for each of the next eight cocaine infusions, the ratio was increased by 4. Thereafter, the ratio was increased by 8 for each cocaine infusion (Caine and Koob, 1995). A 20 sec timeout period followed all cocaine infusions in which responses were recorded but had no programmed consequence. Sessions on this schedule were terminated when >1 hr had elapsed since the last self-administered cocaine infusion. The breaking point was defined as the highest completed ratio in a session (see Data analyses). The effect of the cocaine unit dose on the breaking point was tested with cocaine doses of 0.125, 0.25, and 0.5 mg/infusion using a within-subjects design (*n* = 7). Cocaine doses were tested in separate sessions, and the order of dose presentation was randomized between animals. A cocaine dose of 0.125 mg/infusion was used for all subsequent pretreatment tests. Separate groups of animals were then pretreated with either RU 24969 (0, 0.3, 1.0, and 3.0 mg/kg; *n* = 7), CP 94,253 (0, 0.3, 1.0, and 3.0 mg/kg; *n* = 9), or 8-OH-DPAT (0, 0.03, 0.1, and 1.0 mg/kg; *n* = 7) 15 min before the start of progressive ratio cocaine self-administration (0.125 mg/infusion). The 0 dose for each drug was 0.9% saline. The pretreatment order was randomized between animals. Before cocaine doses were changed or drug pretreatment tests were conducted, animals had to meet the baseline criterion of three consecutive self-administration sessions with less than ±10% variation in the total number of infusions earned.

Experiment III: effects of the 5-HT$_{1B}$ partial agonist GR 127,935 and of the 5-HT$_{1A}$ antagonist p-MPPI on CP 94,253-induced alterations in progressive ratio cocaine self-administration. Separate groups of animals received either GR 127,935 (0, 0.3, 1, 3, and 10 mg/kg; *n* = 9) or p-MPPI (0, 1, 3, and 10 mg/kg; *n* = 7) before either CP 94,253 (1 mg/kg) or saline, followed by cocaine self-administration (0.125 mg/infusion) on a progressive ratio schedule. The 0 dose for each drug was 0.9% saline. GR 127,935 and p-MPPI were administered 25 min before the self-administration sessions, and CP 94,253 was administered 15 min before the sessions. Pretreatment doses were randomized between animals, and all animals in each group received all pretreatments. Before cocaine doses were changed or drug pretreatment tests were conducted, animals were required to meet the stability criterion of three consecutive self-administration sessions with less than ±10% variation in the total number of infusions earned.

Experiment IV: intravenous self-administration of the 5-HT$_{1B}$ agonists RU 24969 and CP 94,253. Separate groups of animals (*n* = 6/group) were trained to self-administer cocaine (0.25 mg/infusion) as described above, and stable responding for cocaine was established. To determine "behaviorally active" intravenous doses of the 5-HT$_{1B}$ agonists for use in subsequent self-administration tests, we added either RU 24969 or CP 94,253 to the self-administered cocaine solution of each respective group. Doses of 0.003 mg of each 5-HT$_{1B}$ agonist per infusion were tested first and were increased in subsequent test sessions in half-log increments until 5-HT$_{1B}$ agonist doses were found that reduced cocaine self-administration by 50%. The test sessions were limited to 90 min and were separated by at least three daily sessions in which cocaine was self-administered alone.

After a behaviorally active dose of each agonist was established (i.e., a dose that reduced cocaine self-administration by 50%), the ability of each agonist alone to maintain FR-5 self-administration behavior was investigated. The doses tested were the behaviorally active dose, one dose below and two doses above the behaviorally active dose (incremented by half-log concentrations), and saline. 5-HT$_{1B}$ agonist test

sessions were 3 hr in duration and were separated by at least three daily sessions in which cocaine was self-administered alone.

Data analyses. All data from the FR-5 cocaine self-administration experiments were subjected to repeated measures ANOVA with drug pretreatment as the within-subjects factor and with the total number of self-administered infusions per session as the dependent measure. For experiments examining RU 24969-induced changes in the cocaine self-administration dose–effect function, cocaine and RU 24969 pretreatment doses were used as the two factors in a two-way ANOVA with repeated measures on both factors. A significant interaction effect was explored using simple main effects to determine significant effects of RU 24969 at different cocaine doses. A leftward shift of the dose–effect function was defined by a significant cocaine dose × RU 24969 interaction, in the presence of both an RU 24969-induced increase in the self-administration of cocaine doses on the ascending limb and an RU 24969-induced decrease in the self-administration of cocaine doses on the descending limb of the dose–effect function. For the examination of the dose-dependent effects of 5-HT$_{1B}$ agonist pretreatment (RU 24969, CP 94,253, and CP 93,129) on the self-administration of a single cocaine dose, the effects of agonist pretreatment were analyzed by one-way ANOVA. Comparisons of individual 5-HT$_{1B}$ agonist doses with saline pretreatment were subsequently determined by Fisher's partial least squares *post hoc* test.

The dependent measure in the progressive ratio experiments was the total number of infusions obtained per session. Although the breaking point (i.e., the highest completed ratio) has been used as the dependent variable in progressive ratio studies (Hodos, 1961), this measure can be problematic for statistical analyses because the assumption of homogeneity of variance is often violated (Depoortere et al., 1993; Woolverton, 1995; Rowlett et al., 1996). Alternately, the number of infusions obtained per session is a natural logarithmic function of the highest completed ratio, and thus this measure does not violate the assumption of homogeneity of variance. Alterations in the breaking point for cocaine self-administration are also presented in the Results and in the figures as a qualitative measure of changes in behavioral output. However, breaking points were not used for statistical comparisons.

The effects of a drug pretreatment or various unit doses of self-administered cocaine on the total number of cocaine infusions obtained per session were analyzed by repeated measures ANOVA, followed where appropriate by Fisher's partial least squares *post hoc* test. To examine the effects of the 5-HT$_{1B}$ antagonist GR 127,935 on CP 94,253-induced alterations in progressive ratio cocaine self-administration, we used the antagonist and agonist doses as the two factors in a two-way ANOVA with repeated measures. A significant main interaction was explored using simple effects to determine significant effects of different GR 127,935 doses on CP 94,253-induced alterations in cocaine self-administration. This same approach was used to examine the effect of the 5-HT$_{1A}$ receptor antagonist p-MPPI on CP 94,253-induced alterations in progressive ratio cocaine self-administration.

RESULTS

Experiment I: effects of the 5-HT$_{1B}$ agonists RU 24969, CP 94,253, and CP 93,129 on FR-5 cocaine self-administration

Cocaine self-administration on the FR-5 schedule produced a characteristic inverted U-shaped dose–effect function (Fig. 1). Pretreatment with RU 24969 (1 mg/kg) produced a leftward shift of the cocaine dose–effect function. RU 24969 produced a significant overall main effect [$F_{(1,7)}$ = 12.8; $p < 0.001$] and a significant cocaine dose × RU 24969 interaction [$F_{(4,28)}$ = 12.71; $p < 0.0001$] when compared with saline pretreatment. The self-administration of cocaine doses on the ascending limb of the dose–effect function was increased by RU 24969 [$F_{(1,7)}$ = 14.5; $p < 0.01$ for the 0.03 mg of cocaine/infusion dose; $F_{(1,7)}$ = 8.35; $p < 0.05$ for the 0.06 mg of cocaine/infusion dose] (also Table 1), whereas RU 24969 reduced the total intake of cocaine doses on the descending limb of the dose–effect function [$F_{(1,7)}$ = 13.6; $p < 0.01$ for the 0.125 mg of cocaine/infusion dose; $F_{(1,7)}$ = 5.5; $p < 0.05$ for the 0.25 mg of cocaine/infusion dose] by increasing the time interval between drug infusions. Self-administration was not reliably maintained when saline was substituted for cocaine
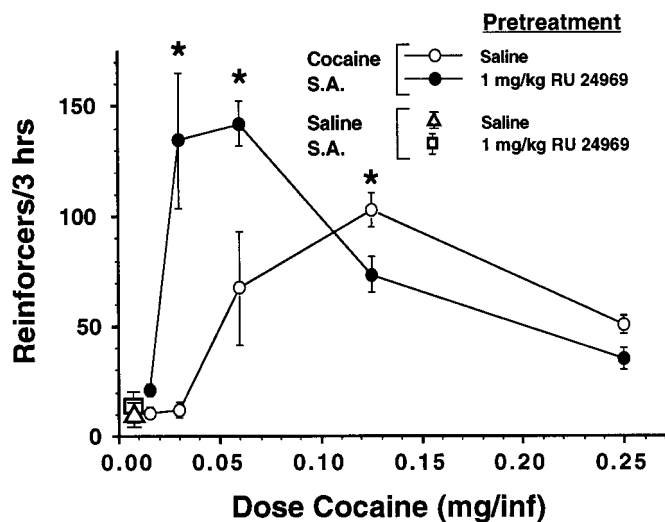
Figure 1. Effects of RU 24969 pretreatment (1 mg/kg, s.c.) on the cocaine self-administration dose–effect function on an FR-5 schedule of reinforcement (*n* = 8). *Open circles* are data obtained after saline pretreatment, and *filled circles* are data obtained after RU 24969 pretreatment. *Symbols* adjacent to the *vertical axis* represent the effects of either saline (*open triangle*) or RU 24969 (1 mg/kg; *open square*) pretreatment on lever pressing for intravenous saline infusions. *Asterisks* denote significant effects (*p* < 0.05) of RU 24969 versus saline pretreatments on the self-administration of individual cocaine doses. *S.A.*, Self-administration.

Table 1. Effect of 5-HT$_{1B}$ agonist pretreatment on the FR-5 self-administration of a subthreshold dose of cocaine (0.03 mg/infusion)

	Number of cocaine infusions per 3 hr	
Pretreatment	Vehicle	Agonist
RU 24969 (1 mg/kg, s.c.)	12 ± 3	135 ± 31*
CP 94,253 (1 mg/kg, s.c.)	10 ± 2	133 ± 12*
CP 93,129 (10 µg, i.c.v.)	11 ± 2	143 ± 13*

Data are the total number of cocaine infusions (mean ± SEM) obtained per 3 hr session after pretreatment with either RU 24969 (1 mg/kg, s.c.; *n* = 8), CP 94,253 (1 mg/kg, s.c.; *n* = 7), or CP 93,129 (10 µg, i.c.v.; *n* = 7) along with the number of cocaine infusions obtained after vehicle pretreatment for each respective group.

*Significant 5-HT$_{1B}$ agonist-induced increase (*p* < 0.05) in responding for cocaine compared to saline pretreatment.

(Fig. 1), and there was no significant effect of RU 24969 on responding for saline compared with that obtained with vehicle pretreatment [$F_{(1,7)}$ = 0.312; NS].

The dose-dependent effects of RU 24969 on FR-5 cocaine self-administration were examined using a cocaine dose on the descending limb of the self-administration dose–effect function (0.125 mg/infusion) (Fig. 2*A*). RU 24969 dose-dependently (0.3, 1, and 3 mg/kg) reduced the total number of cocaine infusions obtained in a 3 hr session [$F_{(3,28)}$ = 9.284; *p* < 0.0005] by increasing the interinfusion interval without disrupting the regular pattern of drug intake [shown as the slope of the cumulative reinforcers per unit-time curve in Fig. 2*A*; $F_{(3,28)}$ = 4.165; *p* < 0.05]. Although the 0.3 mg/kg dose of RU 24969 did not significantly reduce cocaine self-administration, both the 1 and 3 mg/kg doses produced significant reductions in cocaine intake compared with that obtained with saline-pretreated animals (*p* < 0.05 for each dose), with the 3 mg/kg dose producing significantly greater reductions than the 1 mg/kg dose (*p* < 0.05). Saline did not support self-administration when substituted for cocaine, and

there was no significant effect of any RU 24969 dose on responding for saline compared with that obtained with saline pretreatment [$F_{(3,28)}$ = 0.031; NS; data not shown]. RU 24969 did not alter the number of responses made during the 20 sec timeout period that followed each cocaine infusion relative to that obtained with saline pretreatment [$F_{(3,31)}$ = 0.329; NS].

CP 94,253 also altered cocaine self-administration in a manner consistent with a dose-dependent leftward shift of the cocaine dose–effect function. On the descending limb of the cocaine dose–effect function (0.125 mg of cocaine/infusion), CP 94,253 dose-dependently reduced cocaine intake [$F_{(3,24)}$ = 5.264; *p* < 0.01] by increasing the time interval between cocaine infusions [$F_{(3,24)}$ = 4.203; *p* < 0.01; Fig. 2*B*]. The total number of self-administered cocaine infusions was significantly lower after pretreatment with either 1 or 3 mg/kg CP 94,253 compared with that obtained with saline-pretreated controls (*p* < 0.05 for each dose). CP 94,253 (1 mg/kg) also significantly enhanced the self-administration of a subthreshold dose of cocaine on the ascending limb of the cocaine dose–effect function [0.03 mg of cocaine/infusion; $F_{(1,13)}$ = 109.502; *p* < 0.0001; see Table 1]. There was no significant effect of any CP 94,253 dose on the number of lever presses occurring during the 20 sec timeout period that followed each cocaine infusion [$F_{(3,27)}$ = 0.513; NS] or on responding for saline self-administration [$F_{(3,24)}$ = 0.085; NS; data not shown] relative to that obtained with saline pretreatment.

Similar effects were observed after the intracerebroventricular administration of CP 93,129 (3 and 10 µg). On the descending limb of the cocaine dose–effect function (0.125 mg of cocaine/infusion), CP 93,129 dose-dependently reduced cocaine intake [$F_{(2,18)}$ = 8.007; *p* < 0.005] by increasing the time interval between cocaine infusions [$F_{(2,18)}$ = 6.281; *p* < 0.01; Fig. 2*C*]. Both doses of CP 93,129 produced a significant reduction (*p* < 0.05) in the total number of cocaine infusions obtained relative to that obtained with saline-pretreated controls. CP 93,129 (10 µg, i.c.v.) also significantly enhanced the self-administration of a subthreshold dose of cocaine on the ascending limb of the cocaine dose–effect function [0.03 mg of cocaine/infusion; $F_{(1,13)}$ = 104.04; *p* < 0.0001; see Table 1]. There was no significant effect of the intracerebroventricular injection procedure on cocaine intake [$F_{(1,12)}$ = 0.217; NS], as demonstrated by the similar patterns of cocaine intake between animals given saline (2 µl, i.c.v.) and animals that received no intracerebroventricular infusion before the self-administration session (Fig. 2*C*). Neither dose of CP 93,129 altered the number of lever presses occurring during the 20 sec timeout period that followed each cocaine infusion [$F_{(2,10)}$ = 0.13; NS] or the responding for saline self-administration relative to saline pretreatment [$F_{(2,18)}$ = 0.02; NS; data not shown].

All doses of RU 24969, CP 94,253, and CP 93,129 produced stable reductions in cocaine self-administration (0.125 mg/infusion) for the duration of the 3 hr session, as shown by the slopes of the cumulative reinforcer records in Figure 2, *A–C*.

For comparison, the effect of increasing unit cocaine doses on the descending limb of the cocaine dose–effect function is shown in Figure 2*D*. Cocaine intake was dose-dependently reduced [$F_{(2,21)}$ = 60.18; *p* < 0.0001] by increasing unit doses of cocaine (0.125, 0.25, and 0.5 mg/infusion). This was a result of a stable, dose-dependent increase in the time interval between cocaine infusions [$F_{(2,21)}$ = 46.062; *p* < 0.0001]. Thus, RU 24969, CP 94,253, and CP 93,129 each produced alterations in cocaine self-administration that were similar to the effects of increasing the unit dose of cocaine in saline-pretreated animals.
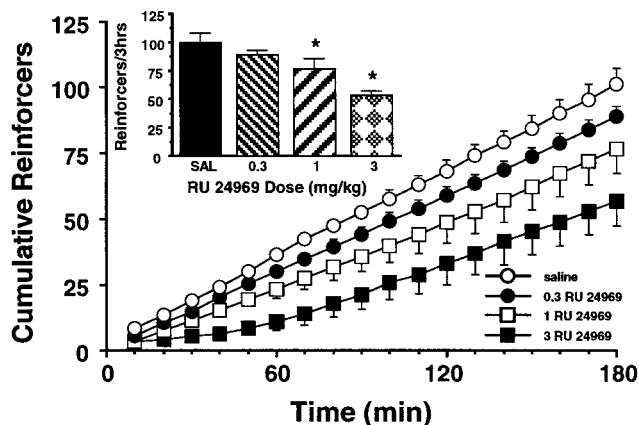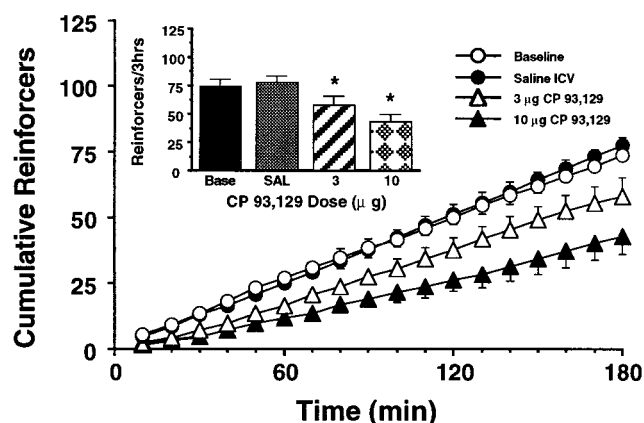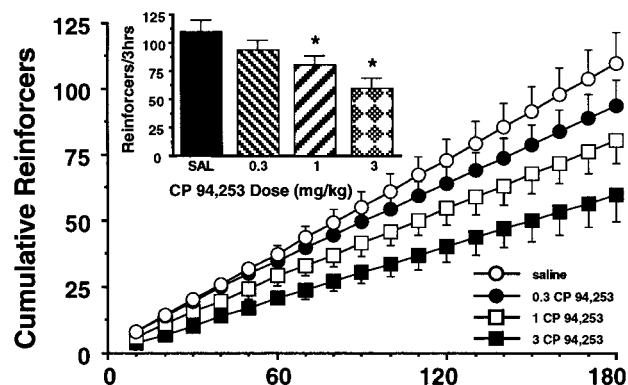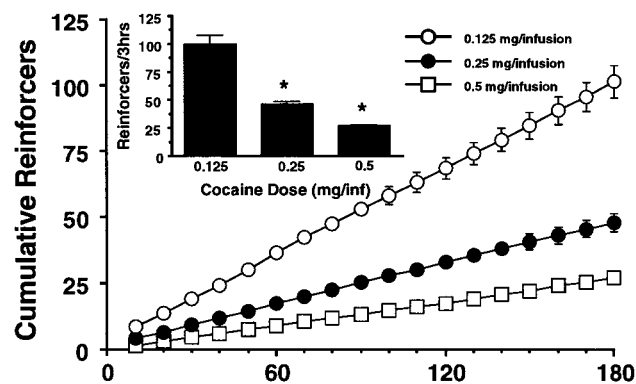
Figure 2. Dose-dependent effects of RU 24969 (*A*; $n = 8$), CP 94,253 (*B*; $n = 7$), and CP 93,129 (*C*; $n = 7$) pretreatment on the self-administration of a cocaine dose on the descending limb of the FR-5 cocaine–effect function (0.125 mg of cocaine/infusion). Each 5-HT$_{1B}$ agonist dose-dependently reduced the total number of self-administered cocaine infusions obtained in a 3 hr session (see *insets*) by producing stable increases in the time interval between infusions (shown by the decreasing slopes of the cumulative reinforcer per time curves; *D*). *A, B,* The pretreatment doses of RU 24969 and CP 94,253 are denoted by the following *symbols*: *open circles*, saline (*SAL*); *filled circles*, 0.3 mg/kg; *open squares*, 1 mg/kg; and *filled squares*, 3 mg/kg. *C,* The following *symbols* denote data collected after intracerebroventricular pretreatment with the following doses of CP 93,129: *open circles,* no intracerebroventricular (*ICV*) injection; *filled circles,* 2 μl of saline; *open triangles,* 3 μg of CP 93,129; and *filled triangles,* 10 μg of CP 93,129. *Asterisks* denote significant differences from saline pretreatment ($p < 0.05$). *D,* For comparison, the effect of increasing unit doses of cocaine on self-administration behavior in saline-pretreated animals is shown ($n = 8$). *Inset,* Increasing doses of cocaine dose-dependently reduced the total number of cocaine reinforcers obtained in a 3 hr session by increasing the interval between infusions. The different cocaine doses are denoted by the following *symbols: open circles,* 0.125 mg/infusion; *filled circles,* 0.25 mg/infusion; and *open squares,* 0.5 mg/infusion. *Asterisks* denote significant differences in cocaine intake compared with the intake of the 0.125 mg of cocaine/infusion dose ($p < 0.05$). Comparison of these findings to those in *A–C* suggests that 5-HT$_{1B}$ agonist pretreatment altered FR-5 cocaine self-administration in a manner similar to increasing the unit dose of cocaine.

Experiment II: effects of the 5-HT$_{1B}$ agonists RU 24969 and CP 94,253 and the 5-HT$_{1A}$ agonist 8-OH-DPAT on progressive ratio cocaine self-administration

In saline-pretreated animals, increasing unit cocaine doses produced a dose-dependent increase in the total number of cocaine infusions obtained in a progressive ratio session [Fig. 3*C*; main effect of cocaine dose; $F_{(2,18)} = 4.921$; $p < 0.05$]. The breaking points (i.e., the highest completed ratio) per session were 90 ± 9, 148 ± 10, and 214 ± 15 for the 0.125, 0.25, and 0.5 mg of cocaine/infusion doses, respectively. Because the time required to reach the breaking point increased significantly with increasing cocaine doses [$F_{(2,18)} = 21.413$; $p < 0.0001$], the 0.125 mg of cocaine/infusion dose was used for subsequent tests with 5-HT$_1$ agonist pretreatments to ensure that the effects of the pretreatment drug persisted for the duration of the sessions (see FR-5 schedule results). With the 0.125 mg of cocaine/infusion dose,

breaking points were reached in <2.5 hr in 40 of the 46 rats tested on this schedule.

RU 24969 dose-dependently increased the total number of cocaine infusions (0.125 mg/infusion) obtained per session [Fig. 3*A*, *inset*; main effect of RU 24969 dose; $F_{(3,24)} = 13.141$; $p < 0.0001$; $n = 7$]. Relative to the control condition, the 0.3, 1, and 3 mg/kg doses of RU 24969 each significantly increased total cocaine intake ($p < 0.05$). Both the 1 and 3 mg/kg doses of RU 24969 produced significantly greater cocaine intake than did the 0.3 mg/kg dose ($p < 0.05$), although the 1 and 3 mg/kg doses were not significantly different from each other. The breaking point for this dose of cocaine was 108 ± 16 after saline pretreatment. RU 24969 increased the breaking point to 167 ± 14, 239 ± 25, and 252 ± 14 for the 0.3, 1, and 3 mg/kg doses, respectively. In addition to potentiating the breaking point of responding for cocaine, RU 24969 dose-dependently increased the time taken to
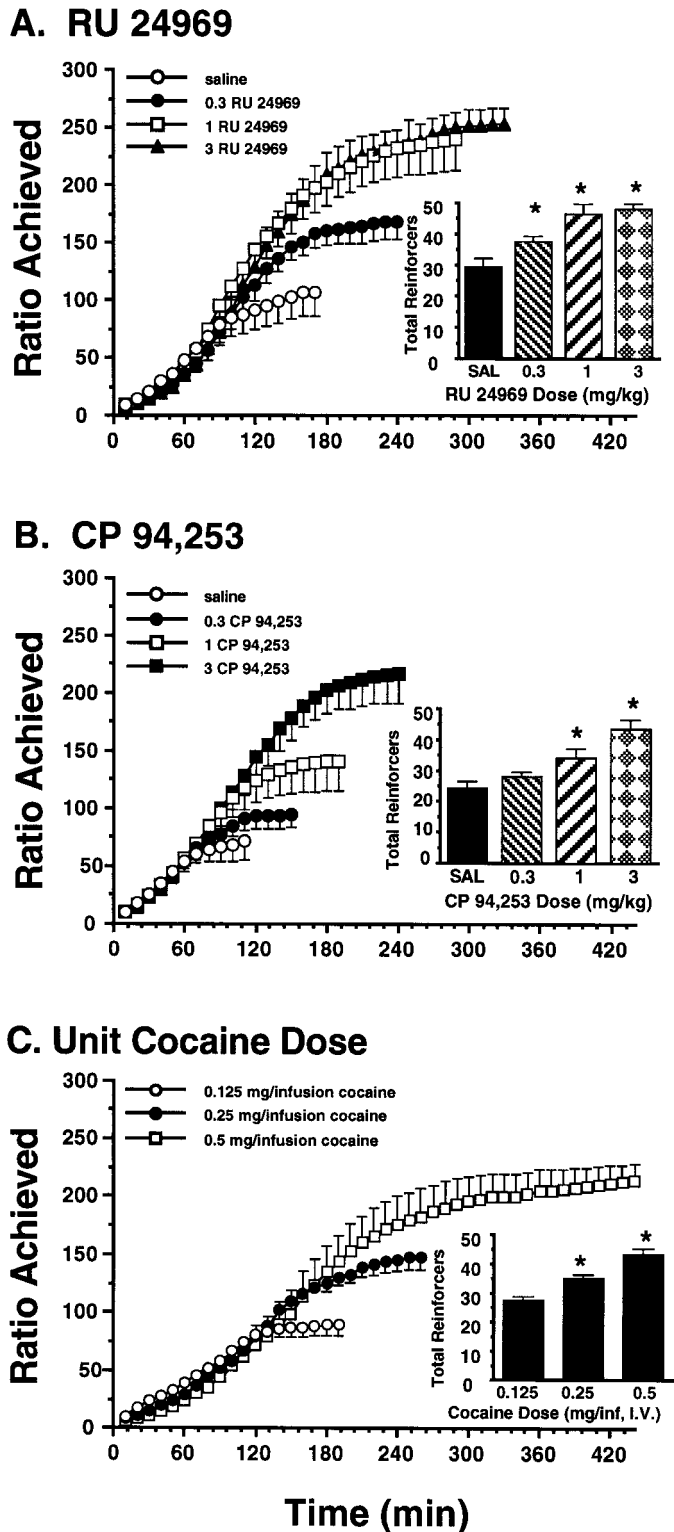
A. RU 24969

B. CP 94,253

C. Unit Cocaine Dose

Time (min)

Figure 3. Effects of RU 24969 (*A*; *n* = 7) and CP 94,253 (*B*; *n* = 9) pretreatments on cocaine self-administration (0.125 mg/infusion) on a progressive ratio schedule of reinforcement. Both 5-HT$_{1B}$ receptor agonists dose-dependently increased the highest completed ratio of responding for cocaine. *A*, *B*, The RU 24969 and CP 94,253 pretreatment doses are denoted by the following *symbols*: *open circles*, saline (*SAL*); *filled circles*, 0.3 mg/kg; *open squares*, 1 mg/kg; and *filled triangles* (*A*) and *squares* (*B*), 3 mg/kg. *Insets*, The total number of cocaine infusions obtained per 3 hr session are shown. *Asterisks* denote significant differ-
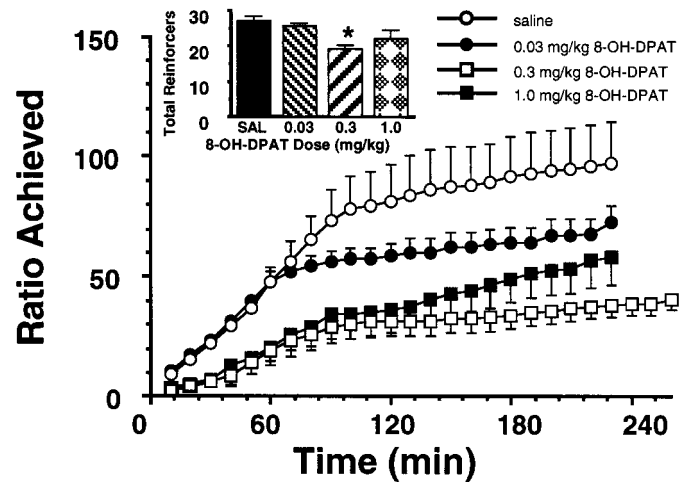

Figure 4. Effects of pretreatment with the selective 5-HT$_{1A}$ receptor agonist 8-OH-DPAT on progressive ratio cocaine self-administration (0.125 mg/infusion; *n* = 7). In contrast to the effects of 5-HT$_{1B}$ agonist pretreatment, 8-OH-DPAT reduced the highest completed ratio of responding for cocaine. The pretreatment doses of 8-OH-DPAT are denoted by the following *symbols*: *open circles*, saline (*SAL*); *filled circles*, 0.03 mg/kg; *open squares*, 0.3 mg/kg; and *filled squares*, 1 mg/kg. *Inset*, The total number of cocaine infusions obtained in a 3 hr session is shown. An *asterisk* denotes a significant difference in the number of cocaine infusions compared with that obtained with saline ($p < 0.05$). Five of the seven saline-pretreated animals reached the breaking point of responding for cocaine in <2 hr, whereas two animals took substantially longer to reach the breaking point.

reach the breaking point of responding [$F_{(3,24)} = 10.102$; $p < 0.0005$], similar to the effect of increasing the unit dose of self-administered cocaine (compare Fig. 3*A* with *C*).

CP 94,253 also dose-dependently increased the total number of cocaine infusions (0.125 mg/infusion) obtained per session [Fig. 3*B*, *inset*; main effect of CP 94,253 dose; $F_{(3,32)} = 10.833$; $p < 0.0001$; *n* = 9]. Relative to the control condition, the 1 and 3 mg/kg doses of CP 94,253 produced significant elevations in total cocaine intake ($p < 0.05$). The 3 mg/kg dose of CP 94,253 produced significantly greater effects than did either the 0.3 or 1 mg/kg doses ($p < 0.05$). The breaking point of responding was 71 ± 16 after saline pretreatment. CP 94,253 increased the breaking point to 94 ± 12, 141 ± 26, and 216 ± 25 for the 0.3, 1, and 3 mg/kg doses, respectively. CP 94,253 also dose-dependently increased the time taken to reach the breaking point of responding [$F_{(3,32)} = 28.266$; $p < 0.0001$], similar to the effect of increasing the unit dose of self-administered cocaine (compare Fig. 3*B* with *C*).

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ences in cocaine intake compared with saline ($p < 0.05$). *C*, For comparison, the effect of increasing unit doses of cocaine on progressive ratio schedule self-administration in saline-pretreated rats is shown (*n* = 7). Increasing unit doses of cocaine dose-dependently increased the highest completed ratio of responding for cocaine. The unit cocaine doses are denoted by the following *symbols*: *open circles*, 0.125 mg/infusion; *filled circles*, 0.25 mg/infusion; and *open squares*, 0.5 mg/infusion. *Inset*, The total numbers of cocaine infusions obtained in a 3 hr session are shown. *Asterisks* denote significant differences in the total number of cocaine infusions obtained compared with that obtained with the 0.125 mg/infusion dose ($p < 0.05$). Comparison of these findings to those in *A* and *B* suggests that 5-HT$_{1B}$ agonist pretreatment altered cocaine self-administration on a progressive ratio schedule in a manner similar to increasing the unit dose of cocaine.
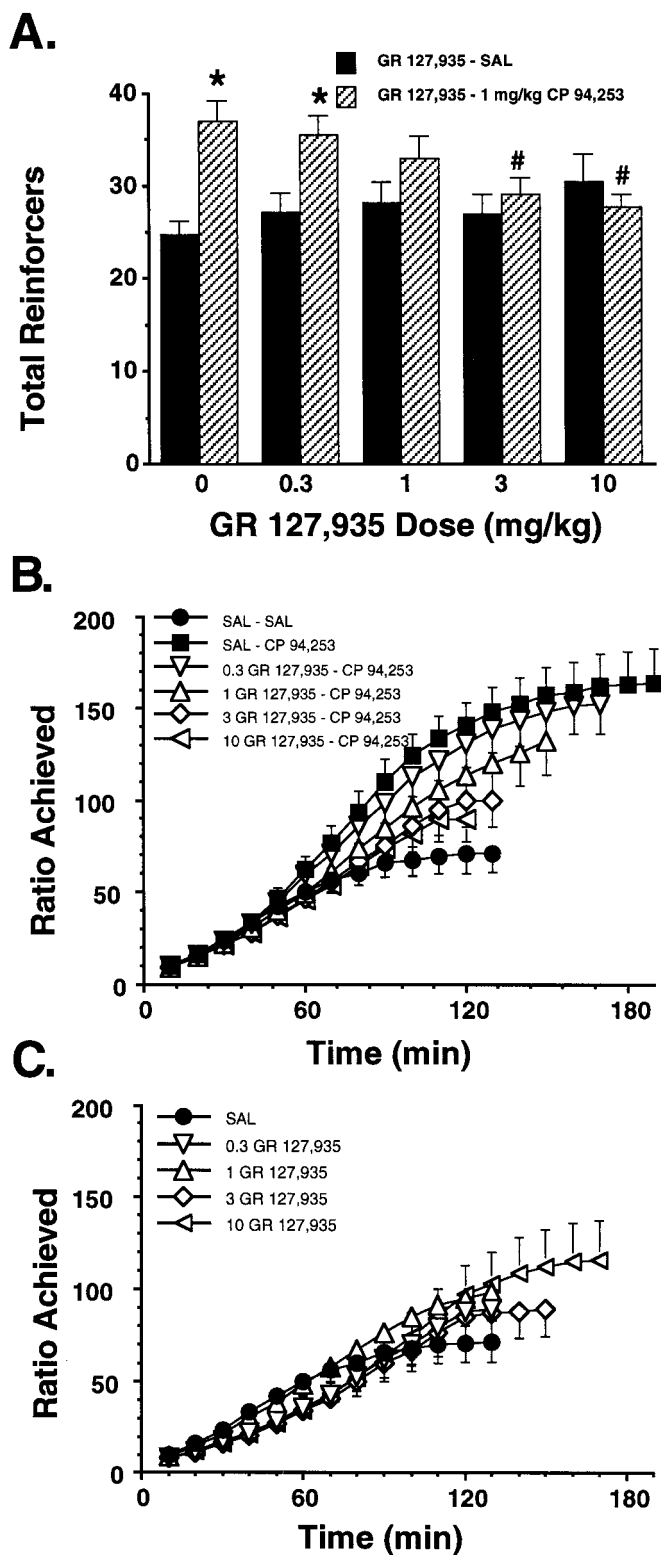
A.

B.

C.

To investigate a potential contribution of 5-HT$_{1A}$ receptor activation to the effects produced by either RU 24969 or CP 94,253, we treated a separate group of animals ($n = 7$) with the selective 5-HT$_{1A}$ agonist 8-OH-DPAT (Glennon and Dukat, 1991; Hoyer et al., 1994) before progressive ratio cocaine self-administration sessions. In contrast to RU 24969 and CP 94,253, 8-OH-DPAT produced a significant reduction in cocaine intake (Fig. 4, *inset*). There was a significant main effect of 8-OH-DPAT on the total number of cocaine infusions per session [$F_{(3,20)} = 4.294$; $p < 0.05$], with a significant reduction in cocaine intake after the 0.3 mg/kg dose of 8-OH-DPAT ($p < 0.05$) and trends toward reductions with the 0.03 and 1.0 mg/kg doses. The breaking points were 97 ± 17, 73 ± 7, 41 ± 4, and 58 ± 11 for the 0, 0.03, 0.1, and 1 mg/kg doses of 8-OH-DPAT, respectively. Unlike the effects produced by different unit cocaine doses, there were no significant effects of 8-OH-DPAT pretreatment on the time taken to reach the breaking point of responding [$F_{(3,24)} = 0.272$; NS].

Experiment III: effects of the 5-HT$_{1B}$ partial agonist GR 127,935 and the 5-HT$_{1A}$ antagonist p-MPPI on CP 94,253-induced alterations in progressive ratio cocaine self-administration

The selective 5-HT$_{1B/1D}$ receptor partial agonist GR 127,935 (Skingle et al., 1996; Pauwels, 1997) dose-dependently (0.3, 1, 3, and 10 mg/kg) blocked the ability of 1 mg/kg CP 94,253 to increase responding for cocaine on a progressive ratio schedule [significant interaction between CP 94,253 pretreatment and GR 127,935 dose; $F_{(4,32)} = 10.997$; $p < 0.0001$; $n = 9$]. The increase in cocaine intake induced by CP 94,253 was significantly reduced ($p < 0.05$) by pretreatment with the 3 and 10 mg/kg doses of GR 127,935 (Fig. 5A). In addition, GR 127,935 dose-dependently reduced the CP 94,253-induced increase in the time taken to reach the breaking point of responding [Fig. 5B; $F_{(4,40)} = 10.571$; $p < 0.0001$] in a manner similar to that of decreasing the unit dose of self-administered cocaine (compare Figs. 5B with 3C). There was no significant effect of GR 127,935 pretreatment alone (0.3, 1, and 10 mg/kg) on cocaine intake [Fig. 5A; $F_{(4,32)} = 1.948$; NS] or on the time taken to reach the breaking point of responding [Fig. 5C; $F_{(4,40)} = 1.642$; $p = $ NS].

Pretreatment with the selective 5-HT$_{1A}$ receptor antagonist p-MPPI (Kung et al., 1994; Thielen et al., 1996) induced a dose-dependent (1, 3, and 10 mg/kg) decrease in cocaine self-administration both when animals were pretreated with 1 mg/kg CP 94,253 [$F_{(3,18)} = 8.082$; $p < 0.001$] and when animals were pretreated with saline [$F_{(3,18)} = 24.188$; $p < 0.0001$; Fig. 6; $n = 7$].

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Figure 5. Effects of the selective 5-HT$_{1B/1D}$ receptor partial agonist GR 127,935 on the potentiation of progressive ratio cocaine self-administration induced by CP 94,253 ($n = 9$). *A*, GR 127,935 dose-dependently reversed the enhancement of cocaine self-administration produced by 1 mg/kg CP 94,253 but did not alter cocaine self-administration when coadministered with saline. *Asterisks* denote a significant effect of CP 94,253 on cocaine intake in the presence of GR 127,935 compared with the cocaine intake after pretreatment with the respective dose of GR 127,935 alone. *Number signs* denote a significant

GR 127,935-induced reduction in the effect of CP 94,253 on cocaine intake compared with that obtained by CP 94,253 pretreatment alone. *B*, The effect of coadministration of GR 127,935 and CP 94,253 on the profile of responding for cocaine is shown. CP 94,253 pretreatment increased both the highest completed ratio of responding for cocaine and the duration of responding for cocaine. Both effects of CP 94,253 were dose-dependently blocked by GR 127,935. The pretreatment doses are denoted by the following *symbols*: *filled circles*, saline (*SAL*) and saline; *filled squares*, saline and 1 mg/kg CP 94,253; *open inverse triangles*, 0.3 mg/kg GR 127,935 and 1 mg/kg CP 94,253; *open triangles*, 1 mg/kg GR 127,935 and 1 mg/kg CP 94,253; *open diamonds*, 3 mg/kg GR 127,935 and 1 mg/kg CP 94,253; and *open leftward triangles*, 10 mg/kg GR 127,935 and 1 mg/kg CP 94,253. *C*, GR 127,935 itself produced no alteration in either the breaking point of responding for cocaine or in the duration of cocaine self-administration. The pretreatment doses are denoted by the following *symbols*: *filled circles*, saline; *open inverse triangles*, 0.3 mg/kg GR 127,935; *open triangles*, 1 mg/kg GR 127,935; *open diamonds*, 3 mg/kg GR 127,935; and *open leftward triangles*, 10 mg/kg GR 127,935.

However, p-MPPI produced no significant effect on the CP 94,253-induced potentiation of cocaine self-administration [interaction between CP 94,253 pretreatment and p-MPPI dose; $F_{(3,18)}$ = 0.123; NS; Fig. 6A]. Although animals self-administered significantly less cocaine when pretreated with a combination of 10 mg/kg p-MPPI and 1 mg/kg CP 94,253 than when pretreated with 1 mg/kg CP 94,253 alone ($p < 0.05$), the 10 mg/kg dose of p-MPPI also produced a significant reduction in cocaine self-administration when this antagonist was administered alone ($p < 0.05$). Thus, relative to the cocaine intake after pretreatment with each respective dose of p-MPPI alone, CP 94,253 potentiated cocaine intake to a similar degree regardless of the dose of coadministered p-MPPI. When coadministered with CP 94,253, p-MPPI produced no significant alteration in the time taken to reach the breaking point relative to pretreatment with CP 94,253 alone [$F_{(3,24)}$ = 1.459; p = 0.2507; Fig. 6B]. However, when administered alone, p-MPPI induced a dose-dependent increase in the time taken to reach the breaking point [$F_{(3,24)}$ = 3.903; $p < 0.05$], despite a dose-dependent reduction in breaking point (Fig. 6C).

Experiment IV: intravenous self-administration of the 5-HT$_{1B}$ agonists RU 24969 and CP 94,253

Inclusion of either RU 24969 or CP 94,253 (0.01–0.1 mg/infusion) in the self-administered cocaine solution (0.25 mg/infusion) resulted in a dose-dependent decrease in the total number of drug infusions obtained in a 90 min test session (data not shown). This reduction in the number of cocaine infusions obtained per time resulted from a stable increase in the time interval between cocaine infusions, similar to the effects produced when either 5-HT$_{1B}$ agonist was administered as an intraperitoneal pretreatment (Fig. 2). A dose of 0.1 mg/infusion of either 5-HT$_{1B}$ agonist was required to reduce cocaine intake by 50%.

In subsequent test sessions, the ability of saline or 0.03, 0.1, 0.3, and 1.0 mg/infusion of either RU 24969 or CP 94,253 alone to maintain FR-5 self-administration was examined in 3 hr sessions in separate groups of animals (n = 6/group). Neither agonist, at any dose, supported self-administration behavior for longer than 90 min (Fig. 7). Moreover, of all doses of both agonists tested, only the 0.1 mg/infusion dose of CP 94,253 produced a significant increase in the total number of self-infusions obtained relative to

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However, p-MPPI did not alter the ability of CP 94,253 to potentiate cocaine self-administration as shown by a significant increase in cocaine intake after coadministration of p-MPPI and CP 94,253 compared with the cocaine intake obtained after pretreatment with the respective dose of p-MPPI alone (denoted by *asterisks*). *B*, The effect of coadministration of p-MPPI and CP 94,253 on the profile of responding for cocaine is shown. CP 94,253 pretreatment increased both the highest completed ratio of responding for cocaine and the duration of responding for cocaine. p-MPPI did not alter the effects of CP 94,253 on the duration of responding for cocaine but decreased the CP 94,253-induced potentiation of responding for cocaine relative to saline/CP 94,253 pretreatment [note, however, that p-MPPI also reduced responding for cocaine when administered alone (see *C*)]. The *symbols* in *B* correspond to the following pretreatment doses: *filled circles*, saline (*SAL*) and saline; *filled squares*, saline and 1 mg/kg CP 94,253; *open inverse triangles*, 1 mg/kg p-MPPI and 1 mg/kg CP 94,253; *open diamonds*, 3 mg/kg p-MPPI and 1 mg/kg CP 94,253; and *open triangles*, 10 mg/kg p-MPPI and 1 mg/kg CP 94,253. *C*, p-MPPI itself dose-dependently reduced the breaking point of responding for cocaine and dose-dependently increased the duration of cocaine self-administration. The pretreatment doses are denoted by the following *symbols*: *filled circles*, saline; *open inverse triangles*, 1 mg/kg p-MPPI; *open diamonds*, 3 mg/kg p-MPPI; and *open triangles*, 10 mg/kg p-MPPI.
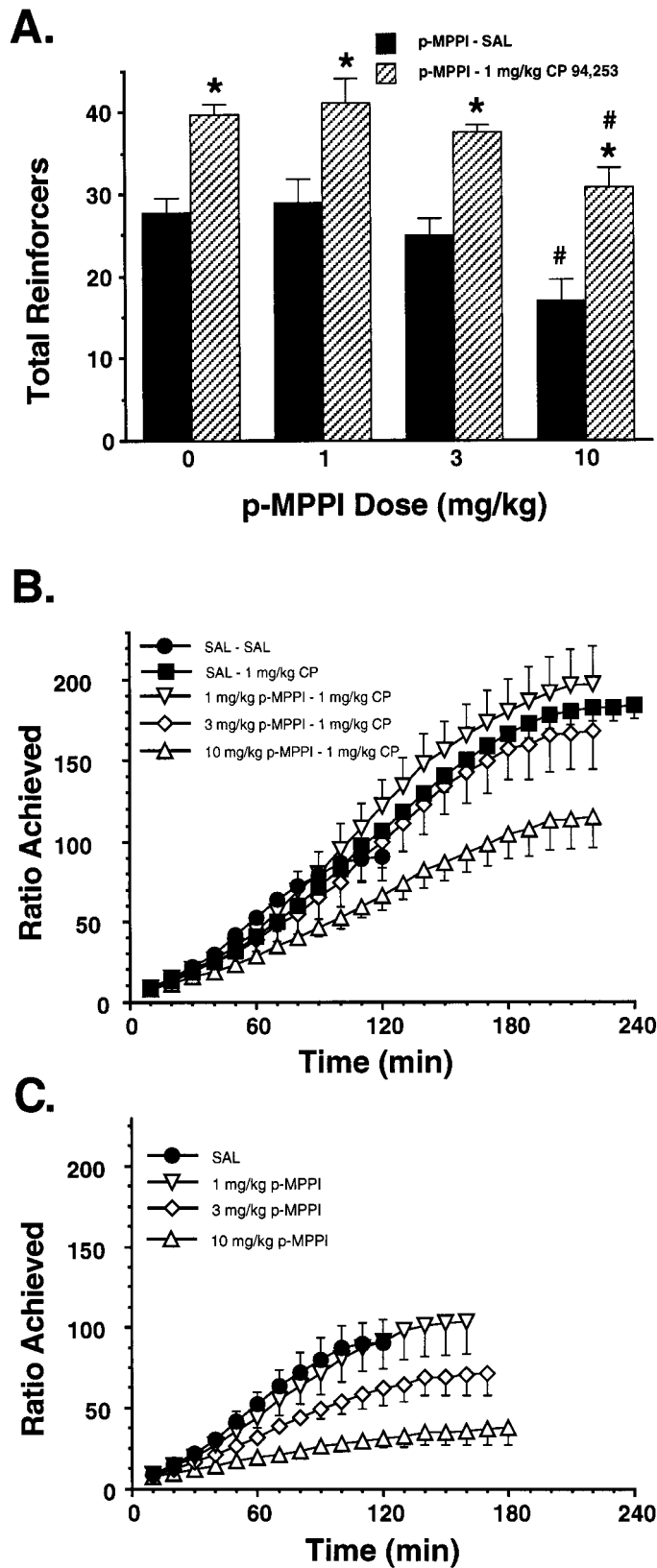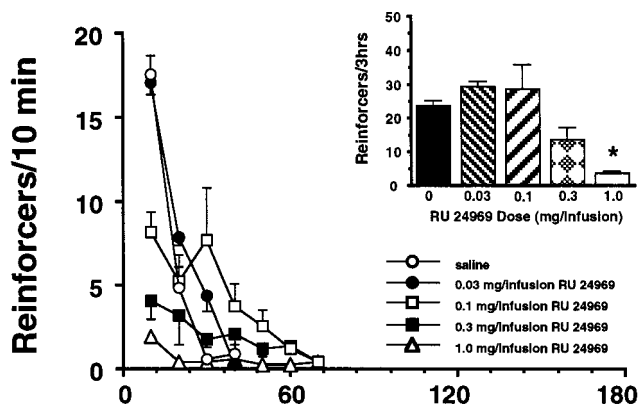
Figure 6. Effects of the selective 5-HT$_{1A}$ receptor antagonist p-MPPI on the potentiation of progressive ratio cocaine self-administration induced by 1 mg/kg CP 94,253 (n = 7). *A*, p-MPPI pretreatment induced a significant and dose-dependent decrease in cocaine self-administration in both saline- and CP 94,253-pretreated animals (denoted by *number signs*).
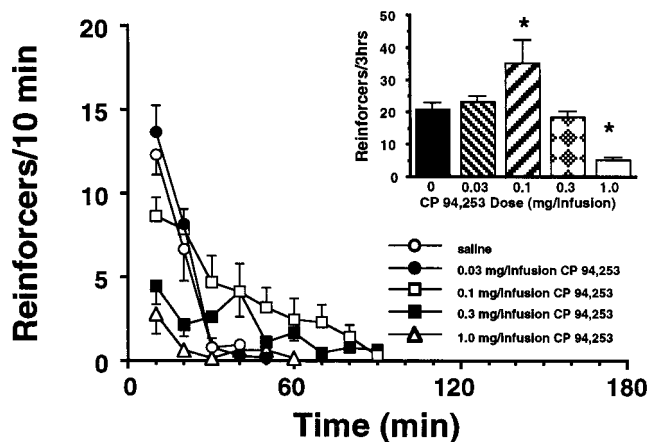
A: RU 24969

B: CP 94,253

Figure 7. The intravenous self-administration of RU 24969 (*A*; *n* = 6) and CP 94,253 (*B*; *n* = 6) on an FR-5 schedule of reinforcement. Both 5-HT$_{1B}$ agonists dose-dependently reduced the burst-like extinction behavior observed with saline self-administration (*t* = 10 min) and dose-dependently increased the duration of operant responding. The infusion doses of RU 24969 and CP 94,253 are denoted by the following *symbols*: *open circles*, saline; *filled circles*, 0.03 mg; *open squares*, 0.1 mg; *filled squares*, 0.3 mg; and *open triangles*, 1.0 mg. *Insets* in *A*, *B*, Although CP 94,253 produced an inverted U-shaped drug intake dose–effect function, RU 24969 did not. However, neither agonist supported self-administration behavior for longer than 90 min. *Asterisks* denote significant differences in drug intake compared with that obtained with saline self-administration (*p* < 0.05).

that obtained with saline self-administration (*p* < 0.05). Both RU 24969 and CP 94,253 dose-dependently increased the duration of lever-pressing activity relative to saline [$F_{(4,29)}$ = 6.585; *p* < 0.001 for RU 24969; $F_{(4,29)}$ = 9.469; *p* < 0.0001 for CP 94,253] and decreased the high rates of burst-like responding observed during the first minutes of saline self-administration (i.e., "extinction"-like responding). These alterations in the patterning of responses suggest that these agonist doses were behaviorally active. Informal visual observations made during self-administration indicated that infusions of either RU 24969 or CP 94,253 at doses of 0.1 mg/infusion and higher induced fairly robust motor activation

during the early portion of the sessions (*t* = 20–40 min). However, as self-administration progressed (*t* = 40–90 min) this motor activation was supplanted by mild flat body posture and spontaneous tail flicks.

DISCUSSION

RU 24969, CP 94,253, and CP 93,129 each altered FR-5 cocaine self-administration in a manner consistent with a leftward shift of the cocaine dose–effect function. Pretreatment with each 5-HT$_{1B}$ agonist lowered the threshold dose of cocaine that supported cocaine self-administration (Table 1). Moreover, each 5-HT$_{1B}$ agonist produced a dose-dependent decrease in the intake of cocaine doses on the descending limb of the dose–effect function by increasing the interval between infusions (Fig. 2*A–C*), similar to the effect produced by increasing the unit dose of self-administered cocaine (Fig. 2*D*). This latter finding, coupled with the observation that none of the agonists altered responding for saline self-administration or the number of lever presses occurring during a 20 sec timeout period after each cocaine infusion, indicates that the effects of the 5-HT$_{1B}$ agonists were not produced by a nonspecific increase in lever-pressing activity. This observation is particularly important given that 5-HT$_{1B}$ receptor activation increases motor activity (Callaway and Geyer, 1992; Cheetham and Heal, 1993; Ramboz et al., 1996). Thus, RU 24969, CP 94,253, and CP 93,129 each induced alterations in FR-5 cocaine self-administration that are consistent with an enhancement of the reinforcing properties of cocaine (Woods et al., 1978, 1987; Bergman et al., 1990; Caine and Koob, 1995).

The effects of RU 24969 and CP 94,253 on progressive ratio cocaine self-administration were also evaluated. The breaking point of responding on this schedule is presumed to reflect the maximum effort an animal will expend to receive a drug infusion and thus serves as a measure of the reinforcing efficacy of the drug (Depoortere et al., 1993; Markou et al., 1993; Richardson and Roberts, 1996; Rowlett et al., 1996). Treatments that increase the breaking point of responding have been interpreted as enhancing the rewarding efficacy of the self-administered drug (Roberts et al., 1989; Ranaldi et al., 1996; Rodefer and Carroll, 1996). Both RU 24969 and CP 94,253 dose-dependently increased the breaking point of responding for cocaine self-administration (Fig. 3*A,B*) and produced alterations in the pattern of drug intake that were similar to the effect produced by increasing the unit dose of cocaine in saline-pretreated animals (Fig. 3*C*). Thus, RU 24969 and CP 94,253 each altered progressive ratio cocaine self-administration in a manner consistent with a potentiation of cocaine reinforcement.

There are at least three lines of evidence that suggest a specific involvement of 5-HT$_{1B}$ receptors in the potentiation of cocaine reinforcement. First, the selective 5-HT$_{1B/1D}$ receptor partial agonist GR 127,935 dose-dependently attenuated the effect of CP 94,253 on responding for cocaine (Fig. 5). Second, although CP 94,253 displays a moderate affinity for 5-HT$_{1A}$ receptors, the selective 5-HT$_{1A}$ receptor antagonist p-MPPI did not alter the ability of CP 94,253 to increase the breaking point of responding for cocaine (Fig. 6). In addition, the selective 5-HT$_{1A}$ receptor agonist 8-OH-DPAT induced opposite effects on cocaine self-administration from those produced by the 5-HT$_{1B}$ receptor agonists (Figs. 3, 4). These findings indicate that 5-HT$_{1A}$ receptors are not involved in the potentiation of cocaine reinforcement by CP 94,253. It is interesting, however, that both the 5-HT$_{1A}$ agonist 8-OH-DPAT and the 5-HT$_{1A}$ antagonist p-MPPI decreased the breaking point of responding for cocaine. An expla-

nation for this is presently unclear, although it is possible that this reflects a differential selectivity of these ligands for distinct 5-HT$_{1A}$ receptor subtypes (De Vry, 1995) and/or for 5-HT$_7$ receptors (Tsou et al., 1994; Ying and Rusak, 1997). It is noteworthy that each of the 5-HT$_{1B}$ agonists altered the pattern of cocaine self-administration in a manner similar to the effect produced by increasing the unit cocaine dose, whereas the 5-HT$_{1A}$ receptor ligands produced effects that were dissimilar to those produced by changes in cocaine dose. This provides qualitative evidence that 5-HT$_{1B}$ receptor stimulation alters the reinforcing properties of cocaine, whereas 5-HT$_{1A}$ receptor manipulations produce nonspecific effects on cocaine self-administration. Third, the three putative 5-HT$_{1B}$ agonists presently tested display similar affinities for and potencies at 5-HT$_{1B}$ receptors, but they differ considerably in their activities at other 5-HT receptor subtypes (Macor et al., 1990; Koe et al., 1992a,b). Thus, the comparable effects of these agonists on cocaine self-administration point to an involvement of 5-HT$_{1B}$ receptors. Moreover, RU 24969, CP 94,253, CP 93,129, and GR 127,935 have extremely low affinity for dopaminergic, adrenergic, muscarinic, benzodiazepine, or opiate receptors (Tricklebank et al., 1986; Van Wijngaarden et al., 1990; Koe et al., 1992a,b; Skingle et al., 1996). Together, these observations suggest a specific involvement of 5-HT$_{1B}$ receptors in the presently observed potentiation of cocaine reinforcement.

Although the neural mechanisms via which 5-HT$_{1B}$ agonists facilitate cocaine reinforcement are unknown, at least two hypotheses can be proposed. First, because serotonergic lesions increase the reinforcing effects of cocaine (Carroll et al., 1990b; Loh and Roberts, 1990; Richardson and Roberts, 1991), it is possible that 5-HT$_{1B}$ receptor agonists facilitate cocaine reward by reducing 5-HT release via 5-HT$_{1B}$ autoreceptor activation. However, doses of the 5-HT$_{1A}$ agonist 8-OH-DPAT that significantly reduce 5-HT levels (Blier and De Montigny, 1987; Lum and Piercey, 1988; Chen and Reith, 1995) did not enhance the reinforcing effects of either cocaine (Fig. 4) or the dopamine uptake inhibitor 1-[2-[bis(4-fluorphenyl)methoxy]ethyl-4-(3-phenylpropyl)piperazine (GBR 12909) (Parsons et al., 1996). This suggests that acute reductions in 5-HT release do not potentiate stimulant reinforcement. A second potential mechanism is a 5-HT$_{1B}$ receptor-mediated regulation of neurotransmitter systems that modulate the activity of mesoaccumbens dopamine neurons. Examples of this mechanism are the 5-HT$_{1B}$ receptor regulation of both the GABAergic projections to the ventral tegmental area and the substantia nigra (Johnson et al., 1992; Cameron and Williams, 1994; Gongora-Alfaro et al., 1997; Parsons et al., 1998) and the hippocampoaccumbens glutamate projection (Boulenguez et al., 1996). In addition, the reinforcing properties of cocaine may be altered independently of mesolimbic dopamine neurotransmission (Zito et al., 1985; Hubner and Koob, 1990; Robledo and Koob, 1993) by a 5-HT$_{1B}$ receptor regulation of the activity of the accumbopallidal GABA projection (Bruinvels et al., 1993, 1994).

It cannot be determined from the present experiments whether the stimulation of 5-HT$_{1B}$ receptors by the indirect 5-HT agonist properties of cocaine contributes to the reinforcing effects produced by this psychostimulant. Although GR 127,935 was developed as an antagonist at 5-HT$_{1D/1B}$ receptors (Skingle et al., 1993), recent evidence suggests that this ligand displays partial agonist properties both *in vitro* and *in vivo* (for review, see Pauwels, 1997). Thus, although GR 127,935 reduced the effect of a full 5-HT$_{1B}$ agonist on cocaine self-administration (Fig. 5*A*), it

may not have induced sufficient 5-HT$_{1B}$ receptor inactivation itself to eliminate a contribution of these receptors to cocaine reinforcement. This hypothesis is supported by the recent finding that the 5-HT$_{1B}$ receptor partial agonist 7-trifluromethyl-4(4-methyl-1-piperazinyl)-pyrrolo[1,2-a]quinoxaline (CGS 12066B) (Cheetham and Heal, 1993) enhances the reinforcing effects of the selective DA uptake inhibitor GBR 12909 but not the reinforcing effects of cocaine (Parsons et al., 1996). This latter observation suggests that the stimulation of multiple 5-HT receptor subtypes during cocaine self-administration masks or counters a mild enhancement of reinforcement produced by partial 5-HT$_{1B}$ receptor activation. Thus, although it is clear from the present experiments that 5-HT$_{1B}$ receptor agonists potentiate the reinforcing effects of cocaine, final conclusions on the relative contribution of 5-HT$_{1B}$ receptors in the mediation of cocaine reinforcement await the development of selective full-efficacy 5-HT$_{1B}$ receptor antagonists.

It is interesting that neither RU 24969 nor CP 94,253 supported self-administration behavior when they were substituted for cocaine (Fig. 7), suggesting that 5-HT$_{1B}$ receptor stimulation alone is not sufficiently rewarding to support operant responding. Thus the effects of RU 24969 and CP 94,253 on cocaine self-administration may reflect a facilitation of cocaine reinforcement rather than a summation of independent reinforcement produced by the 5-HT$_{1B}$ agonists and cocaine, respectively. This interpretation is supported by recent reports that 5-HT$_{1B}$ agonists potentiate the interoreceptive cue produced by cocaine at doses that do not produce substantial cocaine-appropriate responding on their own (Callahan and Cunningham, 1995, 1997). Analogously, RU 24969 was recently found to enhance the ability of cocaine to elevate nucleus accumbens dopamine levels at doses that when administered alone do not alter accumbens dopamine (Parsons et al., 1998). Thus, rather than mediating reward, 5-HT$_{1B}$ receptors may play a modulatory role with regard to stimulant reinforcement. It should be noted, however, that behaviors characteristic of 5-HT$_{1A}$ receptor activation were apparent during the 5-HT$_{1B}$ agonist self-administration sessions [i.e., flat body posture and spontaneous tail flicks (Smith and Peroutka, 1986; O'Connell and Curzon, 1996)]. Thus it is possible that the effects of 5-HT$_{1B}$ receptor stimulation were confounded by concurrent 5-HT$_{1A}$ receptor activation. Accordingly, selective 5-HT$_{1B}$ receptor agonists are required to fully assess the efficacy of 5-HT$_{1B}$ receptor-mediated reinforcement.

In an effort to circumvent the pharmacological limitations of the 5-HT$_{1B}$ receptor ligands currently available, two recent reports have examined cocaine self-administration in transgenic mice lacking 5-HT$_{1B}$ receptors and in their wild-type counterparts (Rocha et al., 1997, 1998). Although no major differences between strains were observed with self-administration on a fixed-ratio schedule, the breaking point of responding for cocaine on a progressive ratio schedule was significantly higher in the 5-HT$_{1B}$ "knock-out" animals than in the wild-types. This latter finding suggests that cocaine has a greater reward value in mice lacking 5-HT$_{1B}$ receptors. However, as noted by Rocha et al. (1998), behaviors observed in 5-HT$_{1B}$ knock-out mice do not always reflect behaviors observed in wild-type mice treated with 5-HT$_{1B}$ receptor antagonists. This implies that compensatory mechanisms may develop in the 5-HT$_{1B}$ knock-out animals that render them more sensitive to the effects of cocaine. Accordingly, it may be prudent to use caution when interpreting results obtained with knock-out mice. It is important, however, to recog-

nize that differences observed between knock-out and wild-type mice may have ontogenic implications in the area of drug abuse.

In conclusion, 5-HT$_{1B}$ receptor activation was found to potentiate the reinforcing properties of cocaine. It is likely that the serotonergic regulation of stimulant reinforcement is dependent on the net balance of effects produced by individual 5-HT receptor subtypes (Parsons et al., 1996; Walsh and Cunningham, 1997). Because recent reports indicate that extended cocaine exposure alters the function of various 5-HT receptor subtypes (Cunningham et al., 1992; Baumann et al., 1993; Baumann and Rothman, 1995, 1996; Simms and Gallagher, 1996), including an upregulation of 5-HT$_{1B}$ receptor function (Levy et al., 1992; L. H. Parsons, P. Sanna, and G. F. Koob, unpublished observations), the present observations allow for a potential involvement of 5-HT$_{1B}$ receptors in the development of cocaine dependence.

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