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Differential Effects of the 5-HT_{2A} Receptor Antagonist M100,907 and the 5-HT_{2C} Receptor Antagonist SB242,084 on Cocaine-induced Locomotor Activity, Cocaine Self-administration and Cocaine-induced Reinstatement of Responding

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These studies investigated the effects of antagonists selective for the 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptor subtypes on behaviors elicited or maintained by cocaine. The selective 5-HT_{2A} receptor antagonist M100,907 (0.5 mg/kg, SC) attenuated the locomotor activity elicited by 10 mg/kg cocaine, whereas the selective 5-HT_{2C} receptor antagonist SB242,084 (0.5 mg/kg IP) potentiated the locomotor stimulant effect of 10 mg/kg cocaine. The selective 5-HT_{2B} antagonist SB215,505 (3 mg/kg PO) did not alter cocaine-induced locomotor activity. In a second series of experiments, the effects of M100,907 and SB242,084 were examined in rats self-administering cocaine intravenously according to a progressive ratio schedule. M100,907 (0.5–2 mg/kg) did not alter responding for cocaine at an infusion dose of 0.25 mg. Similarly M100,907 (0.5 mg/kg) failed to alter responding for cocaine at infusion doses of 0.0625, 0.125 and 0.25 mg. SB242,084 (0.5–1 mg/kg) increased responding for cocaine with the infusion dose set at 0.125 mg. Examination of the effects of SB242,084 (0.5 mg/kg) on the cocaine dose response curve revealed significant increases in responding at the lowest doses of 0.0625 and 0.125 but not 0.25 mg. After completion of the self-administration experiments responding was extinguished. M100,907 (0.5 mg/kg) attenuated the ability of experimenter administered cocaine (10 mg/kg and 20 mg/kg) to reinstate lever pressing, whereas the priming effect of cocaine (10 mg/kg) was enhanced by SB242,084. These results indicate distinct, and in some cases opposite, effects of a 5-HT_{2A} compared with a 5-HT_{2C} receptor antagonist on various cocaine-mediated behavioral effects.
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The behavioral effects of cocaine are mediated in part by increased activity of the mesolimbic dopamine (DA) system. Cocaine binds to a site on the DA transporter (McElvain and Schenk 1992) and inhibits re-uptake of released DA into presynaptic terminals. Cocaine elevates extracellular levels of DA (Di Ciano et al. 1995; Pettit and Justice 1991) and this is critical for the behav-

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ioral effects of cocaine. Thus, the locomotor activating effect of cocaine is abolished in rats with 6-OHDA lesions of the mesolimbic pathway (Kelly and Iversen 1976), and similar lesions abolish self-administration of cocaine (Roberts et al. 1977; Pettit et al. 1984). DA receptor antagonists injected into the nucleus accumbens also block cocaine-induced hyperactivity (Neisewander et al. 1995), and disrupt cocaine self-administration (Maldonado et al. 1993).

Although much of the work directed at understanding the neurochemical bases of the behavioral effects of cocaine has focused on DA, other neurotransmitters are likely involved. Cocaine inhibits the 5-hydroxytryptamine (5-HT, serotonin) transporter (Koe 1976) leading to enhanced levels of extracellular 5-HT (Bradberry et al. 1993), and cocaine self-administration is affected by treatments which alter 5-HT function. Increasing 5-HT availability, either by blocking re-uptake (Carroll et al. 1990; Richardson and Roberts 1991) or by administration of the 5-HT precursor L-tryptophan (McGregor et al. 1993) reduces responding for cocaine, whereas 5-HT depletion increases responding for cocaine (Loh and Roberts 1990; Roberts et al. 1994). One issue that is unresolved by previous work is which of the multiple 5-HT receptor sub-types (Boess and Martin 1994; Barnes and Sharp 1999) may be involved in modifying the behavioral effects of cocaine. Few studies have examined the effect of selective 5-HT receptor agonists on cocaine self-administration. One study (Peltier and Schenk 1993) found that the 5-HT_{1A} receptor agonist 8-OH-DPAT induced a modest reduction of cocaine self-administration, but this effect was seen at only one dose of cocaine. Recently, we reported that the 5-HT_{2C} receptor agonist Ro 60-0175 (Martin et al. 1998) dose-dependently reduced the hyperactivity induced by cocaine, cocaine self-administration on fixed and progressive ratio schedules, and the priming effect of cocaine to reinstate responding (Grottick et al. 2000).

The 5-HT_{2C} receptor is found in a variety of forebrain structures, including cortical, amygdala, hippocampal, striatal/accumbens regions, as well as monoaminergic cell body areas such as the locus coeruleus, substantia nigra, and ventral tegmental area (VTA) (Pompeiano et al. 1994; Abramowski et al. 1995; Eberle-Wang et al. 1997). Eberle-Wang et al. (1997) demonstrated the presence of 5-HT_{2C} mRNA within inhibitory GABA-ergic interneurons making direct synaptic contact with dopaminergic cell bodies in both the VTA and substantia nigra. Electrophysiological studies have shown that Ro60-0175–induced activation of 5-HT_{2C} receptors within the VTA inhibits DAergic cell body firing, likely through an enhancement of GABA function (Di Matteo et al. 2000; Di Giovanni et al. 2001). An important consequence of this is a reduction of extracellular DA in the nucleus accumbens (Di Matteo et al. 2000). One interpretation of our previous findings of reduced cocaine-induced behaviors by Ro60-0175 is that activation of 5-HT_{2C} receptors by this compound counters cocaine-induced elevations in synaptic DA levels leading to a reduction in the behavioral effects of cocaine.

The selective 5-HT_{2C} receptor antagonist, SB242,084, seems to exert an opposite effect to Ro60-0175 on indices of mesolimbic DA function (Kennett et al. 1997). Thus, SB242,084 increases VTA cell firing and DA release in the nucleus accumbens (Di Matteo et al. 1999). This pattern of results implies a degree of endogenous serotonergic tone to this pathway. Given our previous findings with Ro60-0175 on the behavioral effects of cocaine (Grottick et al. 2000), one objective of the present experiments was to investigate the effects of treatment with the 5-HT_{2C} receptor antagonist SB242,084 on locomotor activity induced by cocaine, cocaine self-administration and the response-reinstating effects of cocaine.

Receptors of the 5-HT_{2A} sub-type are particularly prominent in cortical areas but are also found in DA-rich areas such as the striatum, substantia nigra, and ventral tegmental area (Pompeiano et al. 1994; Lopez-Gimenez et al. 1997; Doherty and Pickel 2000). It is not surprising then that the activity of DA systems and the effects of psychomotor stimulants can be modulated by manipulating 5-HT_{2A} receptor function. Although the selective 5-HT_{2A} antagonist M100,907 (formerly MDL100,907; Kehne et al. 1996) does not influence the spontaneous firing rate of dopaminergic neurons, nor alter basal levels of DA release (Kehne et al. 1996), it reverses the effects of amphetamine on the firing rate of VTA neurons, and attenuates DA release by methylenedioxymethamphetamine (MDMA) (Schmidt et al. 1995). In behavioral studies, M100,907 attenuates the hyperactivity induced by amphetamine (Moser et al. 1996) and cocaine (O'Neill et al. 1999; McMahon and Cunningham 2001). This profile of 5-HT_{2A} receptor antagonists appears opposite to that induced by 5-HT_{2C} receptor antagonists. Therefore an additional aim of these studies was to compare the effects of M100,907 with those of SB242,084 on the same behavioral effects of cocaine.

To complete these investigations, we included the 5-HT_{2B} receptor preferring antagonist SB215,505 (Kennett et al. 1998; Reavill et al. 1999) in certain studies. Despite a developmental role in cardiac function (Nebigil et al. 2000), the involvement of this receptor in central nervous system function is unclear (Barnes and Sharp 1999). Accordingly we examined SB215,505 at a pharmacologically active dose (Kennett et al. 1998) against cocaine-induced hyperlocomotion.

MATERIALS AND METHODS

Tests of locomotor activity were conducted at Hoffmann-La Roche, Basel, Switzerland, while experiments involving cocaine self-administration were conducted

at the Centre for Addiction and Mental Health, Toronto, Canada. In each case, all experiments complied with the appropriate local and national guidelines relating to animal experimentation.

Animals and Housing

Adult male Sprague-Dawley rats were used in all studies (source: RCC Ltd., Fullinsdorf, Switzerland, for Roche; Charles River, St. Constant, Quebec, Canada, for CAMH). The animals weighed approximately 280–340 g at the time of surgery and testing and were housed either individually (self-administration studies) or in groups of four (all other studies) in polycarbonate cages with sawdust bedding. Water was freely available; food was freely available for rats in the locomotor activity studies except during testing. For rats in the self-administration studies, food availability varied as described below. The housing room was maintained at a constant temperature of 22 ± 2°C, under a 12/12-h light-dark cycle (lights on: 6 A.M. at Roche; 8 A.M. at CAMH). All testing was conducted under the light phase of the animals' light/dark cycle.

Locomotor Activity Testing

Rats were first handled, given sham injections and habituated to the test apparatus (36 × 24 × 19 cm; Benwick Electronics, UK) for three daily 2-h sessions before experiments were started. A repeated measures design was used for all activity studies, which were of 90 min duration. A washout period of three days was used between each treatment cycle. Total activity counts for the session was the dependent measure.

Cocaine Self-administration Procedures

Rats were anesthetized with 75 mg/kg ketamine and 5 mg/kg xylazine. A catheter constructed of silastic tubing was surgically implanted in the right jugular vein. The terminal end of the catheter consisted of a 22-gauge guide cannula (Plastics One, Roanoke, VA) and was anchored subcutaneously between the scapulae with a small piece of Marlex mesh. This arrangement allowed the catheter to be quickly attached and detached from the drug delivery line by means of a small plastic nut cemented to the end of a stainless steel tether encasing the drug delivery line.

Testing was conducted in 16 operant chambers measuring 28 cm long, 21 cm wide and 21 cm high (MED Associates Inc., St. Albans, VT). Each chamber contained a food pellet dispenser, two response levers 4.5 cm wide and 7 cm above the floor of the chamber and a stimulus light located 6 cm above each lever. A counterbalanced arm held a fluid swivel above the ceiling of the chamber. The inlet port of the swivel was attached to a syringe mounted on a motor driven syringe pump (Razel) located outside the chamber by a length of Tygon tubing. The outlet port of the swivel was connected to the animal's catheter by a length of Tygon tubing, encased in a stainless steel tether. Each chamber was illuminated by a house light and housed in a sound-attenuating box equipped with a ventilating fan. The apparatus was controlled, and the data collected, by a 386SX IBM-type computer.

Before surgery, rats were first trained to lever press for food (45 mg Noyes pellets). Rats were food restricted (15 g per day) and placed in the operant chambers where each response on the left lever delivered food according to a FR1 schedule. Rats were allowed a maximum of 100 pellets during daily 30 min sessions. Any rats failing to obtain 100 pellets by the third day of training were placed in the operant boxes overnight and allowed 300 food pellets delivered according to the FR1 schedule. A water dish was also placed inside the operant chamber during this session. Thereafter, rats were placed in the chamber only during the 30 min session during the daytime. Using this procedure all rats were responding for 100 pellets within seven days. Thereafter rats were maintained on 20 g of food per day. Rats then underwent surgery to implant an intravenous catheter as described above. Six days after surgery rats were placed in the operant chambers for a 3-h drug self-administration session. The session began with illumination of the houselight and 5 s later a non-contingent infusion of 0.25 mg cocaine (dissolved in 0.1 ml sterile saline) was delivered over a period of 5 s. The infusion was accompanied by illumination of the stimulus light above the lever. This light remained illuminated for 20 s, during which period responses were recorded but had no programmed consequences. For the remainder of the session cocaine was available according to an FR1 schedule. Once responding was stable, usually within 7–10 days, a progressive ratio (PR) schedule was implemented in which the number of responses required to obtain an infusion increased for successive infusions. The progression was derived from the equation: response ratio = $(5 \times e^{(0.2 \times \text{infusion no.})} - 5)$, and yielded response ratios of 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118 etc. (e.g. Arnold and Roberts 1997; Loh and Roberts 1990). Sessions lasted until a period of 1 h without an infusion elapsed, or were a maximum of 5 h in length. The number of infusions earned before this breaking-point was recorded. After 12 days on this schedule responding was stable, defined as three consecutive days with breaking-points not varying by more than two steps. Drug testing was then initiated with specific details of the testing procedures provided below in the description of the relevant experiment.

Drugs and Injections

M100,907 ((±)2,3-dimethoxyphenyl-1-[2-4-(piperidine)-methanol]), and SB242,084 (6-chloro-5-methyl-1-[2-(2-

methylpyridyl-3-oxy)-pyrid-5-yl carbomyl] indoline) were synthesized at the Chemistry department at F. Hoffmann-La Roche Ltd., Basel. SB215,505 (6-chloro-5-methyl-1-(5-quinolylcarbamoyl) indoline) was generously provided by SmithKline Beecham Pharmaceuticals, Harlow, UK. M100,907 was dissolved in 0.9% saline solution containing 0.3% Tween and injected sc 30 min before test onset. SB242,084 was prepared in 0.9% saline solution containing 8% hydroxypropyl-β-cyclodextrin and 25 mM citric acid and injected by the IP route. SB215,505 was dissolved in a solution of 0.3% Tween in saline, and injected PO 60 min before test at a volume of 5 ml/kg. All drug doses are expressed as that of the base. Cocaine hydrochloride was supplied either through the Chemistry department (Roche) or BDH Inc. Toronto, Ontario, Canada (CAMH). Cocaine was dissolved in sterile saline and injected IP for the locomotor activity studies. In self-administration studies the cocaine solution was passed through a 0.22 μm filter prior to intravenous infusion. For the initial locomotor activity tests doses, routes of injection and pretreatment times for the antagonists were based on a consideration of previous reports showing blockade of 5-HT_{2A} receptors by M100,907 (Krebs-Thomson et al. 1998; Sipes and Geyer 1995), blockade of 5-HT_{2B} receptors by SB215,505 (Kennett et al. 1998), and blockade of 5-HT_{2C} receptors by SB242,084 (Grottick et al. 2000).

Statistical Analysis

Data were analyzed by 1-, 2-, or 3-way repeated measures ANOVA using Statistica software. All post-hoc comparisons were carried out with Neuman Keuls tests. For the cocaine self-administration studies the main dependent variable was the number of infusions earned prior to a breaking-point of 1 h without an earned infusion.

Experiments 1a, 1b, and 1c. Effects of M100,907, SB215,505 and SB242,084 on Cocaine-induced Locomotor Activity

Three groups of rats (n = 12 per group) were used to test the effects of 0.5 mg/kg M100,907, 3 mg/kg SB215,505 and 0.5 mg/kg SB242,084 on the locomotor stimulant effects of 3 and 10 mg/kg cocaine. These doses were based on both published and in-house data to likely be pharmacologically selective for each target receptor (Kehne et al. 1996; Kennett et al. 1997, 1998; Reavill et al. 1999; Higgins et al. 2001). Within each experiment, all rats were tested under all six possible combinations of the antagonist and its vehicle, and cocaine and saline. The order of injections was counterbalanced, and at least three drug-free days intervened between successive tests. M100,907 or its vehicle was injected SC 30 min prior to cocaine, SB242,084 or its vehicle was injected IP 30 min prior to cocaine, and SB215,505 or its vehicle was injected PO 60 min before cocaine. Cocaine was injected IP 5 min before the animals were placed into the activity monitors, and activity was measured for the subsequent 90 min.

Experiment 2a. Effects of M100,907 on Cocaine Self-administration

In this experiment, rats (n = 8) were trained to self-administer cocaine under the PR schedule with the infusion dose of cocaine held constant at 0.25 mg in 0.1 ml saline. When breaking-points were stable rats were injected with vehicle, 0.5, 1 or 2 mg/kg M100,907 30 min prior to self-administration sessions. The order of injections was counterbalanced, and at least three days intervened between successive tests. Rats were allowed to self-administer cocaine as usual on these days.

Experiment 2b. Effects of 0.5 mg/kg M100,907 on the Cocaine Self-administration Dose-response curve

A further group of rats (n = 13) were trained to self-administer cocaine at the 0.25 mg infusion dose under the PR schedule. Once responding had stabilized, they were then injected with either vehicle or 0.5 mg/kg M100,907 prior to a self-administration session. Successive drug doses were spaced at least three days apart. Following this regimen each rat was shifted to a different dose of cocaine (0, 0.0625 or 0.125 mg/infusion) until responding was again stable for three consecutive days and were tested following injections of vehicle or 0.5 mg/kg M100,907 spaced at least three days apart. This procedure was repeated until each animal had been tested with both M100,907 and vehicle injections at each dose of cocaine.

Experiment 3a. Effects of SB242,084 on Cocaine Self-administration

Rats (n = 8) were trained to self-administer cocaine under the PR schedule with the infusion dose of cocaine held constant at 0.25 mg in 0.1 ml saline. When breaking-points were stable the rats were injected with vehicle, 0.25, 0.5 or 1 mg/kg SB242,084 30 min prior to self-administration sessions. On these test days the infusion dose of cocaine was reduced to 0.125 mg in 0.1 ml infusate. This was done to reduce breaking-points and to avoid possible ceiling effects on self-administration behavior which would make it difficult to detect any increase in breaking-points which we predicted from the results of Experiment 1c. The order of injections was counterbalanced, and at least three days intervened between successive tests. Rats were allowed to self-administer cocaine as usual at the 0.25 mg infusion dose on these days.

Experiment 3b. Effects of 0.5 mg/kg SB242,084 on the Cocaine Self-administration Dose-response Curve

Rats (n = 12) were trained to self-administer cocaine at the 0.25 mg infusion dose under the PR schedule. They were then injected with vehicle or 0.5 mg/kg SB242,084 spaced at least 72 h apart. After this each rat was transferred to a different dose of cocaine (0, 0.0625 or 0.125 mg/infusion) until responding was stable for three consecutive days and were tested again following injections of 0.5 mg/kg SB242,084 or vehicle spaced at least 72 h apart. This procedure was repeated until each animal had been tested with SB242,084 and its vehicle at each dose of cocaine.

Experiment 4a. Effect of 0.5 mg/kg M100,907 on response-reinstatement Induced by Cocaine

Following completion of experiments 2a and 2b, the rats (n = 8 and 13 respectively) were placed into extinction during which no responses were reinforced by cocaine infusions. In these 3-h sessions every response on the left lever was accompanied by the drug-associated light stimulus for a period of 20 s; responses on the right lever had no programmed consequences. We have found previously that the degree of responding induced by experimenter-administered cocaine injections can be relatively high in rats previously self-administering cocaine on a progressive ratio. If responding during this period were accompanied by saline infusions this could lead to excessive fluid intake and so for this reason during extinction and tests for reinstatement the syringe pumps were turned off. After approximately two weeks all rats were making less than 15 responses per 3-h session. At this point the effects of 0.5 mg/kg M100,907 on the response reinstating effects of cocaine (20 mg/kg IP) was examined. On each of four test days rats were tested under one of the four possible drug combinations with M100,907 or its vehicle administered SC 30 min before cocaine or its vehicle. Responding was then measured for the next 3 h. Drug combinations were administered in a randomized order with approximately equal numbers of rats tested under each treatment combination on any given test day. Successive test days were 48–72 h apart and on the intervening days the usual 3-h extinction tests were conducted. The results from the two groups of rats were pooled. One rat died before completion of this phase; a second rat showed consistently high responding during extinction and was not included in this experiment. The final sample size was 19. Following completion of the four treatment cycles, the remaining 11 rats from experiment 2b were tested on two further occasions with vehicle followed by 10 mg/kg cocaine, and 0.5 mg/kg M100,907 followed by vehicle.

Experiment 4b. Effects of 0.5 mg/kg SB242,084 on Response-reinstatement Induced by Cocaine

The rats from experiments 3a and 3b (n = 8 and 11 respectively) were used for this experiment. The procedure was similar to that described for experiment 4a, except that rats were treated with 0.5 mg/kg SB242,084 or its vehicle IP 30 min before 10 mg/kg cocaine or its vehicle. Again data from the two groups of rats were pooled. One rat failed to complete the study; consequently the final sample size was 18.

RESULTS

Experiments 1a, 1b, and 1c. Effects of M100,907, SB215,505 and SB242,084 on Cocaine-induced Locomotor Activity

Figure 1 shows the effects of the three 5-HT_2 receptor antagonists on cocaine stimulated activity. Analysis of variance on the total activity scores revealed a significant main effect of cocaine treatment in each experiment ($F_{2,22} \geqslant 11.6$, $p < .01$). The main effect of antagonist treatment was significant for M100,907 ($F_{1,11} = 18.5$, $p < .01$) and SB242,084 ($F_{1,11} = 9.6$, $p < .01$) but not for SB215,505 ($F_{1,11} = 0.1$, $p > .9$). None of the interaction terms were significant (largest $F_{2,22} = 1.7$, $p > .2$). Post-hoc testing confirmed that the 10 mg/kg dose of cocaine significantly increased activity above control levels and that this effect was attenuated by M100,907 and enhanced by SB242,084. The lower panels of Figure 1 show the time courses of changes in activity. In the case of M100,907 a significant attenuation of the effect of 10 mg/kg cocaine was found at 10, 20 and 30 min intervals ($p < .05$, Newman-Keuls). For the experiment involving SB242,084 the effect of 10 mg/kg cocaine was significantly increased by this antagonist at each of the first four time intervals ($p < .05$, Newman-Keuls).

Experiments 2a and 2b. Effects of M100,907 on Cocaine Self-administration

The upper panel of Figure 2, panel A, shows that M100,907 (0.5–2 mg/kg) did not alter cocaine self-administration at any of the doses tested ($F_{3,21} = 1.2$, $p > .3$). As shown by Figure 2, panel B, lowering the infusion dose of cocaine-induced a dose-dependent reduction in the number of cocaine infusions earned ($F_{3,36} = 46.2$, $p < .001$). Neither the main effect of Antagonist ($F_{1,12} = 1.6$, $p > .2$) nor the Antagonist X Cocaine interaction were significant ($F_{3,36} = 0.3$, $p > .7$). Thus M100,907 did not alter responding for cocaine.

Experiments 3a and 3b. Effects of SB242,084 on Cocaine Self-administration

Figure 2, panel C, shows that SB242,084 (0.25–1 mg/kg) induced a dose-dependent increase in breaking-points

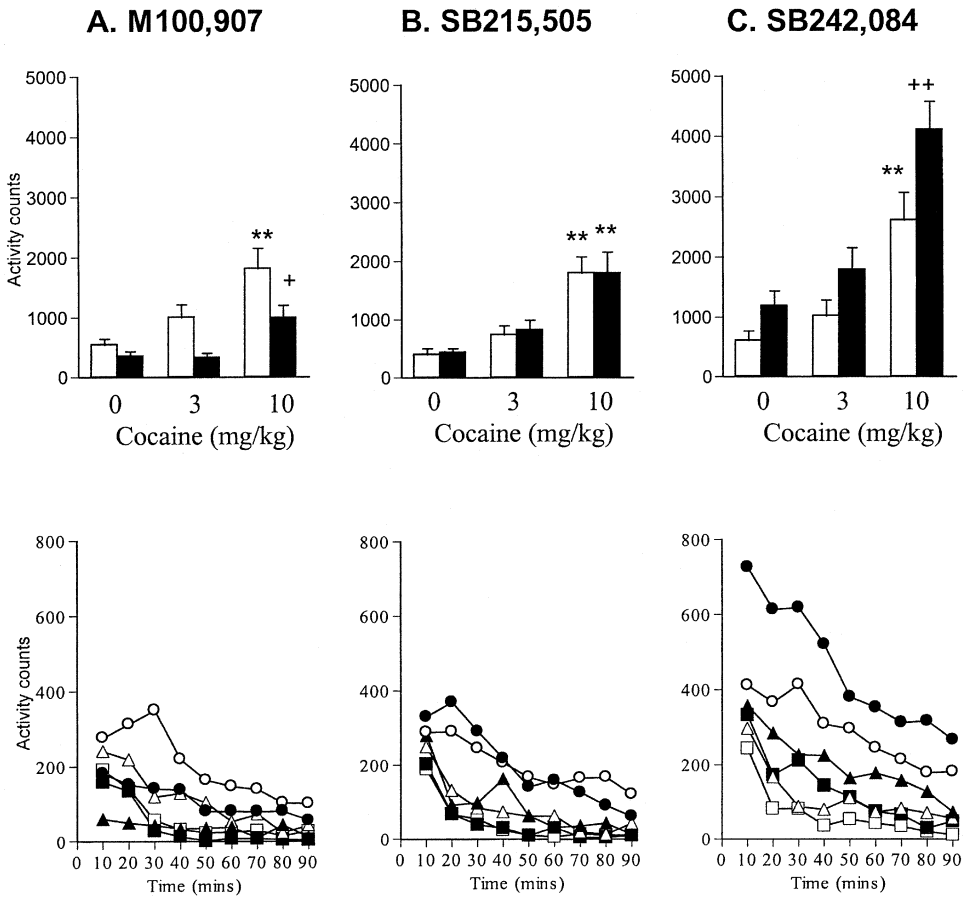

Figure 1. The effects of (A) M100,907 (0.5 mg/kg SC), (B) SB215,505 (3 mg/kg, PO), and (C) SB242,084 (0.5 mg/kg IP) on locomotor activity following injection with 3 and 10 mg/kg cocaine or vehicle (IP) 5 min before locomotor activity recording. Each experiment was conducted in a different group of 12 rats. Within each experiment rats were tested with all six possible drug combinations administered in a counterbalanced order. The upper panels show mean (+ SEM) activity counts for the 90 min session. $^{**}p < .01$ compared with vehicle/vehicle combination; $^{+}p < .05$ compared with vehicle/10 mg/kg condition; $^{++}p < .01$ compared with vehicle/10 mg/kg cocaine condition. Open bars = vehicle pre-treatment, filled bars = antagonist pre-treatment. The lower panel shows the time course of changes in activity following drug treatment. Open symbols represent vehicle pretreatment, and filled symbols represent antagonist pretreatment; triangles = saline, squares = 3 mg/kg cocaine and circles = 10 mg/kg cocaine. For clarity SEMs are not depicted.

when the cocaine dose was set at 0.125 mg on test days ($F_{3,21} = 5.5$, $p < .01$). This effect was apparent at both the 0.5 and 1 mg/kg doses of SB242,084. Responding for the maintenance dose of 0.25 mg cocaine was stable across days. Thus on the days immediately prior to each of the test sessions the number of infusions ranged from 15.8 ± 0.8 to 16.3 ± 1.2 infusions.

In experiment 3b systematic reduction of the cocaine infusion dose resulted in a dose dependent reduction in breaking points [$F(3,30) = 92.8$, $p < 0.001$]. Both the main effect of antagonist treatment [$F(1,10) = 41.7$, $p < 0.001$] and the cocaine dose × antagonist interaction were significant [$F(3,30) = 3.9$, $p < 0.02$]. Post-hoc testing showed the SB242,084 (0.5 mg/kg) significantly increased the break-points when the infusion dose was 0.0625 and 0.125 mg per infusion (Figure 2D).

Experiments 4a and 4b. Effects of M100,907 and SB242,084 on Cocaine-induced Reinstatement of Responding

Figure 3, panel A, illustrates the effects of M100,907 (0.5 mg/kg) on reinstatement of responding induced by 20 mg/kg cocaine. Responding was generally increased by cocaine ($F_{1,18} = 18.5$, $p < .001$) and this effect was directed toward the previously active lever (Cocaine X Lever interaction ($F_{1,18} = 15.6$, $p < .001$). There was a significant interaction between Cocaine and M100,907 ($F_{1,18} = 13.88$, $p < .001$) but this varied as a function of Lever (overall 3-way interaction, $F_{1,18} = 14.7$, $p < .001$). Thus, tests of simple interactions revealed that the interaction between Cocaine and M100,907 was found for responses on the previously active lever ($F_{1,18} = 14.7$, $p < .01$) but not the previously inactive lever ($F_{1,18} = 0.9$, $p >$

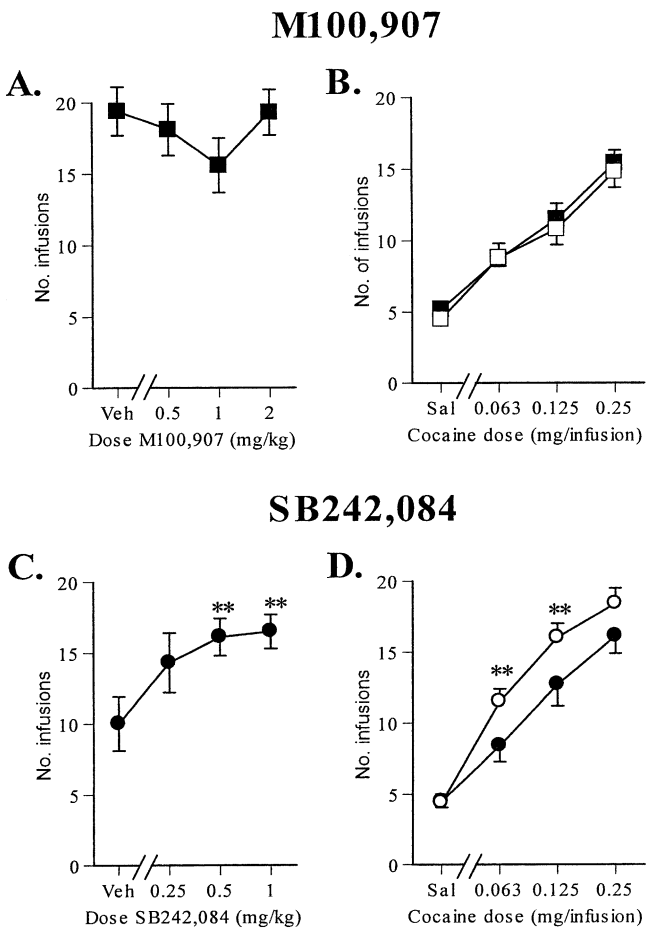

Figure 2. A. Effects of 0, 0.5, 1 and 2 mg/kg M100,907 on cocaine self-administration with the infusion dose of cocaine set at 0.25 mg (n = 8). Injections of M100,907 were made in a counterbalanced fashion with at least three days between successive tests. B. The effects of pre-treatment with 0.5 mg/kg M100,907 (□) or vehicle control (■) on cocaine self-administration across a range of doses of cocaine (n = 13). C. The effects of 0, 0.25, 0.5, and 1 mg/kg SB242,084 on cocaine self-administration with the infusion dose of cocaine set at 0.125 mg (n = 8). Injections of SB242,084 were made in a counterbalanced fashion with at least three days between successive tests. $^{**}p < .01$ compared with vehicle condition. D. The effects of pre-treatment with 0.5 mg/kg SB242,084 (○) or vehicle control (●) on cocaine self-administration across a range of doses of cocaine (n = 12). $^{**}p < .01$ compared with vehicle treatment within the same cocaine dose condition. In each experiment cocaine was delivered according to a progressive ratio schedule. Sessions lasted until a period of one hour had elapsed without an earned infusion of cocaine

.3). Post-hoc comparisons between means showed that cocaine significantly elevated responding on the active lever, and that this effect was significantly attenuated by M100,907. Essentially the same profile of responding was obtained with the lower dose of cocaine tested in a subset of these animals (Figure 3, panel B). The overall 3-way interaction was significant ($F_{1,10} = 8.5$, $p < .02$). The M100,907 X Cocaine interaction was clearly not significant for inactive lever responses ($F_{1,10} = 1.1$, $p > .3$), but was of borderline significance for active lever responses ($F_{1,10} = 4.8$, $p = .05$). Again the post-hoc tests showed that M100,907 (0.5 mg/kg) significantly attenuated the response reinstating effect of 10 mg/kg cocaine. In both experiments responding under the M100,907 was significantly greater than under the vehicle treatment, thus M100,907 attenuated but did not completely reverse the effect of cocaine at either dose.

The effects of SB242,084 (0.5 mg/kg) on reinstatement of responding induced by cocaine are shown in Figure 3, panel C. The analysis of variance confirmed that responding was enhanced by cocaine ($F_{1,17} = 28.1$, $p < .0001$), and that this effect was confined to the active lever (Cocaine X Lever interaction, $F_{1,17} = 25.3$, $p < .001$). The overall 3-way interaction was significant ($F_{1,17} = 8.2$, $p < .02$) and tests of simple interactions indicate that this is best explained by the fact that the interaction between SB242,084 and cocaine treatment was significant for responses on the previously active lever ($F_{1,17} = 7.4$, $p < .02$) and not the previously inactive lever ($F_{1,17} = 0.01$, $p > .9$). Specific post-hoc comparisons revealed that cocaine significantly increased responding on the previously active lever, and that this effect was enhanced by SB242,084. The antagonist alone did not significantly alter responding.

DISCUSSION

M100,907 and SB242,084 had opposite effects on cocaine-induced locomotor activity. Thus, 5-HT_{2A} receptor blockade with M100,907 attenuated cocaine-induced locomotion, whereas 5-HT_{2C} receptor blockade with SB242,084 enhanced cocaine-induced activity. Our result with M100,907 replicates the findings of O'Neill et al. (1999) and McMahon and Cunningham (2001). Recently it was demonstrated that the mixed 5-$HT_{2B/2C}$ receptor antagonist SB206,553 modified the locomotor activity induced by cocaine (McCreary and Cunningham 1999). At doses of 1 and 2 mg/kg this compound attenuated cocaine-induced locomotion, but at 4 mg/kg it potentiated the effect of cocaine. Our results are consistent with the latter finding and clearly suggest that 5-HT_{2C} rather than 5-HT_{2B} receptor blockade potentiates the effects of cocaine on locomotor activity since SB215,505 failed to alter cocaine-stimulated locomotion. The apparent lack of effectiveness of SB215,505 is unlikely to be due to inappropriate dose or route of administration since a previous report indicates that SB215,505 prevented the anxiolytic effect of the 5-HT_{2B} receptor agonist BW 723C86 (Kennett et al. 1998). Thus, these results imply that 5-HT_{2B} receptor blockade may not influence cocaine-mediated hyperlocomotion.

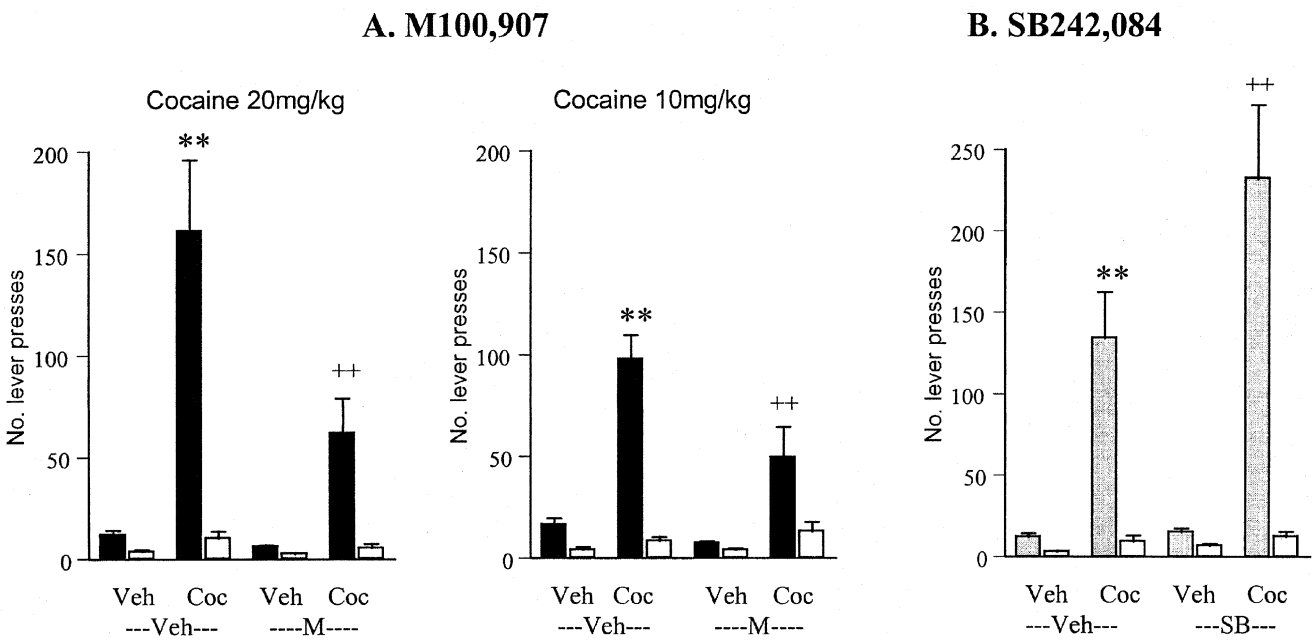

Figure 3. Left panel under A. M100,907. The effect of 0.5 mg/kg M100,907 on the priming effect of 20 mg/kg cocaine. Lever pressing of rats from experiments 2a and 2b was extinguished after completion of the self-administration studies. Once responding was at a stable low level, they were tested for the response-reinstating effects of 20 mg/kg cocaine. All rats were tested under the four possible drug combinations spaced at 48–72 h intervals. Responding was measured on the previously active lever (i.e. the lever that previously delivered cocaine: filled bars), and an inactive lever (open bars). A total of 19 rats completed this study. Right panel under A. M100,907. The effect of 0.5 mg/kg M100,907 on the priming effect induced by 10 mg/kg cocaine. These data were derived from 11 rats from experiment 2b. The data obtained under the vehicle-vehicle and M100,907-vehicle treatments were those derived from the experiment involving 20 mg/kg cocaine. B. The effect of 0.5 mg/kg SB242,084 on the priming effect induced by 10 mg/kg cocaine. The data were obtained from rats also used for Experiments 3a and 3b (n = 18) following a period of extinction. $^{**}p < .01$ compared with active lever response under vehicle-vehicle treatment; $^{++}p < .01$ compared with active lever response under vehicle-cocaine treatment.

Although McCreary and Cunningham (1999) reported that some doses of the 5-$HT_{2B/2C}$ receptor antagonist SB206,553 attenuated the locomotor activity induced by cocaine, we did not see any evidence for a biphasic effect of the more selective antagonist SB242, 084 on cocaine self-administration. However, the use of two drugs differing in selectivity for 5-HT_{2B} and 5-HT_{2C} receptors, SB206,553 versus SB242,084 and two different behaviors, locomotion versus self-administration, make it difficult to speculate on this seeming discrepancy between the two studies.

Despite having little effect on locomotor behavior or terminal DA efflux under basal conditions, M100,907 reduces these parameters under conditions where the DA systems are activated (Schmidt et al. 1995), suggesting that serotonin acting through the 5-HT_{2A} receptor has a permissive role in these processes. Such a role for 5-HT_{2A} receptor activation is highly likely in the case of cocaine, which elevates synaptic 5-HT levels (Bradberry et al. 1993). Recently, McMahon et al. (2001) reported that direct injections of M100,907 into the VTA, but not the nucleus accumbens, attenuated the locomotor stimulant effect of cocaine. This finding, coupled with the demonstration that 5-HT_{2A} receptors are localized to a subset of DA neurons in the VTA (Doherty and Pickel 2000), suggests that the VTA is one area where 5-HT_{2A} receptors could potentially play a role in the expression of cocaine-stimulated locomotion. It is also possible that cortical 5-HT_{2A} receptors (Pompeiano et al. 1994; Lopez-Gimenez et al. 1997) could influence subcortical DA function via modulation of glutamatergic cortico-striatal circuits (Schmidt et al. 1995), thereby altering cocaine-stimulated locomotor activity.

Recent studies have reported that 5-HT_{2C} receptor blockade resulting from treatment with SB242,084 activates midbrain DA neurons leading to increased extracellular DA levels (Di Matteo et al. 1999). Cocaine acts primarily to inhibit the DA transporter, and thus would be expected to lead to greater levels of extracellular DA in situations where the DA system is already activated. Given that the locomotor stimulant effects of cocaine are mediated via increased DA (Kelly and Iversen 1976) this could provide a neurochemical mechanism for the observed potentiation of cocaine-induced locomotor activity by SB242,084.

The profile of effects of M100,907 and SB242,084 on cocaine self-administration did not completely mirror those on cocaine-induced locomotion. In keeping with its potentiating effect on cocaine-induced locomotion, SB242,084 similarly enhanced self-administration of cocaine. However, M100,907 failed to alter cocaine self-administration. This failure of M100,907 to alter cocaine self-administration was observed at the same dose (0.5 mg/kg), and higher (1–2 mg/kg), than that which attenuated cocaine-induced locomotion. M100,907 was also ineffective over a range of cocaine infusion doses that supported differing levels of self-administration. It is important to note that over this dose range M100,907 reverses behavioral effects of the 5-$HT_{2A/2C}$ agonist DOI (Krebs-Thomson et al. 1998; Sipes and Geyer 1995) indicating a functional blockade of 5-HT_{2A} receptors at these doses. The lack of effect of M100,907 on the reinforcing effectiveness of cocaine is consistent with the failure of this drug to block cocaine-induced reductions in brain-stimulation reward thresholds (Tsibulsky et al. 1995), and the lack of effectiveness of ketanserin to alter cocaine self-administration under the same PR schedule as used here (Lacosta and Roberts 1993). Ketanserin shows reasonable selectivity (approximately 2–10-fold) for the 5-HT_{2A} over the 5-HT_{2C} receptor, although this drug does have appreciable affinity for adrenergic α_1 receptors (Lopez-Gimenez et al. 1997). The differing effects of M100,907 on cocaine-induced locomotion versus self-administration provide an interesting dissociation between these two behaviors. A similar dissociation has been noted with amphetamine-dependent behaviors: M100,907 attenuates amphetamine induced locomotion, but does not alter the ability of amphetamine to lower thresholds for brain stimulation reward (Moser et al. 1996; Tsibulsky et al. 1995). Thus, it appears that 5-HT_{2A} receptor blockade has a differential impact on motor versus reinforcement or reward-related behaviors. More particularly, 5-HT_{2A} receptor stimulation may contribute to the expression of the locomotor-stimulant effect of cocaine but not the reinforcing effect of cocaine.

In the PR schedule, increasing the dose of cocaine resulted in a linear increase in the number of cocaine infusions, and in parallel an increase in the final response ratio that animals were willing to complete. The fact that SB242,084 increased responding for cocaine clearly suggests an increase in the reinforcing efficacy of cocaine in the presence of 5-HT_{2C} receptor blockade. Again, it is possible that a heightened dopaminergic tone following SB242,084 pre-treatment sets the stage for an increased effect of cocaine on extracellular DA leading to an increase in the reinforcing strength of cocaine, i.e. an effect equivalent to increasing the unit dose of cocaine. The fact that SB242,084 did not significantly increase self-administration of the highest cocaine dose could indicate that this interactive effect occurs only within certain limits. Rats depleted of 5-HT show increased responding for cocaine on a PR schedule (Loh and Roberts 1990), and so the present results suggest that this could be due to impaired serotonergic transmission through 5-HT_{2C} receptors. However, 5-HT depleted rats also showed enhanced responding for food, and during extinction (Roberts et al. 1994). In the present experiments SB242,084-treated rats showed normal responding during extinction, when saline was substituted for cocaine, suggesting that 5-HT_{2C} receptor blockade and 5-HT depletion may not be functionally equivalent in terms of their impact on cocaine self-administration. The potentiating effect of SB242,084 on responding for cocaine is opposite to the effect of the 5-HT_{2C} receptor agonist Ro60-0175 which reduced responding for cocaine on the same PR schedule (Grottick et al. 2000). Thus, it appears that 5-HT_{2C} receptors can exert bi-directional modulation of cocaine self-administration. Cocaine is an inhibitor of the 5-HT transporter (Koe 1976) and leads to an accumulation of extracellular 5-HT (Bradberry et al. 1993). One implication of the opposing effects of 5-HT_{2C} receptor stimulation versus blockade is that 5-HT accumulation following cocaine infusions may serve as a limiting factor for cocaine self-administration via 5-HT_{2C} receptor activation. This hypothesis is strengthened by the finding that Ro 60-0175 reduces extracellular levels of DA in the nucleus accumbens (Di Matteo et al. 2000).

In the final series of studies SB242,084 again potentiated the effect of cocaine, this time increasing the effectiveness of cocaine to reinstate responding on a lever that previously delivered cocaine. The interactive mechanisms between SB242,084 and cocaine as outlined above could also be operative here. Interestingly M100,907 attenuated the priming effect of cocaine, an effect consistent with its action on cocaine-induced locomotion, but not cocaine reinforcement. The mechanisms involved in mediating the priming effect of cocaine are not understood, although a number of accounts have been offered. One possibility is that following a period of drug abstinence a priming injection may serve as a discriminative stimulus that signals that drugs are available (de Wit and Stewart 1981, 1983; Schenk and Partridge 1999). This would be especially relevant in situations where self-administration sessions were initiated with a non-contingent injection of the drug, which was the case in the present studies. Evidence to support this argument derives from observations that priming effects are generally drug-class specific. Thus, following systemic injection psychomotor stimulants generally show "cross-priming" effects within their class, but not to opiates and vice versa (de Wit and Stewart 1981, 1983). M100,907 reduces the discriminative stimulus effects of cocaine in rats trained to discriminate between saline and cocaine in a two-lever operant task (McMahon and Cunningham 2001). Thus,

it is possible that M100,907 reduces the priming effect of cocaine by diminishing the discriminative stimulus properties of cocaine. The fact that responding for cocaine was not altered by M100,907 could indicate that the 5-HT_{2A} receptor-mediated component of the discriminative stimulus effect of cocaine plays a negligible role in the reinforcing effectiveness of cocaine. Indeed, it is noteworthy that M100,907 attenuated, rather than abolished, the discriminative stimulus (McMahon and Cunningham 2001), and priming effects of cocaine. Other studies clearly demonstrate that other neurochemical mechanisms contribute to the cue-effects of cocaine (e.g. Callahan et al. 1991) and presumably also the reinforcing effect of cocaine (Caine and Koob 1994).

In summary, M100,907 and SB242,084 exerted different effects on cocaine-induced locomotion, cocaine-mediated reinforcement, and cocaine-induced reinstatement of responding. The 5-HT_{2C} receptor antagonist consistently enhanced the effects of cocaine in all three paradigms, effects that may be attributable to an increase in the endogenous tone of mesolimbic DA neurons. In contrast, 5-HT_{2A} receptor blockade attenuated the effects of cocaine to stimulate locomotor activity, and to reinstate responding, but did not alter the reinforcing efficacy of cocaine. Thus, 5-HT_{2A} receptors are involved in some but not all of the behavioral effects of cocaine. The results demonstrate further the complex modulation that 5-HT neurons appear to exert over DA-dependent functions, and also demonstrate that a full understanding of the interactions between these two systems will necessarily have to take into account differential effects mediated via specific 5-HT receptor sub-types.

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