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Effects of the 5-$HT_{2C/2B}$ Antagonist SB 206553 on Hyperactivity Induced by Cocaine

Andrew C. McCreary, Ph.D., and Kathryn A. Cunningham, Ph.D.

Serotonin (5-HT) appears to play a modulatory role in the behavioral effects of cocaine, although the impact of 5-HT_{2C} receptors in this control has not been fully established. The aim of the present study was to establish whether acute pretreatment with the selective 5-$HT_{2C/2B}$ antagonist SB 206553 (1, 2, and 4 mg/kg IP) altered hyperactivity induced by cocaine (15 mg/kg, IP) using an open field activity system which recorded central, peripheral, and rearing activity. Pretreatment with 1 and 2 mg/kg of SB 206553 attenuated cocaine-induced central and peripheral activity, respectively; rearing was also attenuated by the latter dose. However, the 4-mg/kg dose of SB 206553 significantly enhanced the effects of cocaine on peripheral activity. Based upon the present observations and an interpretation of previous research to implicate 5-HT_{2C} receptor control of the dopamine (DA) mesoaccumbens pathways in behavior, a thorough and systematic analysis of the role of 5-HT_{2C} (and 5-HT_{2B}) receptors in psychostimulant-induced behaviors is warranted. ***[Neuropsychopharmacology 20:556–564, 1999]*** *© 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

KEY WORDS: *Cocaine; Hyperactivity; SB 206553; Serotonin; 5-HT_{2C}; 5-HT_{2B}*

The behavioral effects of cocaine in rodents include the stimulation of locomotor activity and stereotypy as well as convulsions at higher doses (Scheel-Kruger et al. 1977; McCreary and Marsden 1993). Cocaine also serves as a positive reinforcer for operant behavior (de Wit and Wise 1977) and elicits interoceptive stimulus effects easily discriminable from saline (Callahan et al. 1994). The locomotor stimulant effects have been linked to the inhibition of dopamine (DA) reuptake (Koe 1976) and a subsequent enhancement of DA activation via both DA D_1 and D_2 receptors (Scheel-Kruger et al. 1977; McCreary and Marsden 1993; White et al. 1998). The elevated DA neurotransmission, particularly within the mesoaccumbens pathway originating from DA soma in the ventral tegmental area (VTA) and terminating in the nucleus accumbens (NAc), is especially important in mediating the locomotor, discriminative stimulus and reinforcing effects of cocaine (for review, Amalric and Koob 1993).

Despite the pronounced involvement of DA in its *in vivo* effects, cocaine is not a selective DA reuptake inhibitor as it binds to 5-hydroxytryptamine (5-HT) and norepinephrine (NE) transporters and inhibits the reuptake of 5-HT and NE with at least equal potency and efficacy as that of DA reuptake (Koe 1976). Recent studies of the locomotor stimulant, reinforcing and stimulus effects of cocaine suggest that enhanced 5-HT transmission and subsequent stimulation of 5-HT receptors play a modulatory role in the *in vivo* effects of cocaine (for reviews, see Cunningham and Callahan 1994; Walsh and Cunningham 1997).

The exact contribution of specific 5-HT receptors to the behavioral profile of cocaine has not yet been fully elucidated, largely due to the multiplicity of 5-HT receptors in mammalian systems and the lack of selective

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Received May 13, 1998; revised August 20, 1998; accepted September 3, 1998.

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/99/$–see front matter
PII S0893-133X(98)00087-6

ligands for each of the respective receptor subtypes. At least 14 5-HT receptor subtypes have been shown to exist, although the operational characteristics are unknown for some receptors (Hoyer and Martin 1997). The 5-HT_{2C} receptor subtype (formerly 5-HT_{1C}) has received attention as a possible therapeutic target in psychiatric conditions such as psychoses and anxiety (Kennett 1993) and evidence suggests that this receptor is important in the serotonergic regulation of the mesolimbic DA system. The transcript for the 5-HT_{2C} receptor is richly expressed in DA somatic and terminal field regions, including the VTA and NAc (Hoffman and Mezey 1989; Eberle-Wang et al. 1997). Although not yet established for the VTA, 5-HT_{2C} mRNA was localized in γ-aminobutyric acid (GABA), but not DA, neurons in the substantia nigra suggesting that the influence of 5-HT_{2C} receptors on DA cell bodies may be indirect (Eberle-Wang et al. 1997). In keeping with the distribution of mRNA, ligand binding studies have demonstrated labeling of 5-HT_{2C} receptors in the VTA and NAc (Pazos and Palacios 1985; Mengod et al. 1990).

Mesolimbic DA circuits appear to be under a modulatory influence of 5-HT_{2C} receptors at the level of both the VTA and NAc. For example, systemic and microiontophoretic administration of the 5-$HT_{2C/1B}$ agonist meta-chlorophenylpiperazine (mCPP) decreased the firing rate of VTA DA neurons; the systemic actions of mCPP were antagonized by the 5-$HT_{2/1A}$ antagonist mesulergine, which alone increased firing rates of a subpopulation of these cells (Prisco et al. 1994; Prisco and Esposito 1995). Although 5-$HT_{2C/2B/1B}$ ligands failed to alter the firing characteristics of DA neurons in the substantia nigra (Kelland et al. 1990; but see Stanford and Lacey 1996), the activity of VTA DA neurons is reported to increase following administration of the 5-$HT_{2C/2B}$ antagonists SB 200646A (Ashby and Minabe 1996) or SB 206553 (Lejeune et al. 1997). These results suggest that 5-$HT_{2C/2B}$ receptors may tonically inhibit cell firing of DA neurons in the VTA. In keeping with this possibility, preliminary microdialysis studies have shown that systemic injection of the 5-$HT_{2C/2B}$ antagonist SB 206553 (Lejeune et al. 1997; Spampinato et al. 1997) or the 5-$HT_{2/1A}$ receptor antagonist mesulergine (Spampinato et al. 1997) enhanced basal DA overflow in the NAc.

Consonant with the observation that 5-HT_{2C} receptor activation may dampen DA activity in mesolimbic circuits, pretreatment with the 5-$HT_{2C/2B/1B}$ agonists mCPP and MK 212 effectively attenuated the stimulus effects of cocaine (Callahan and Cunningham 1995). Both mCPP (Nader and Barrett 1990) and the 5-HT_2 antagonist ritanserin (Meert and Janssen 1992; Howell and Byrd 1995) altered rates of responding for cocaine in self-administration tasks. The ability of selective 5-HT_{2C} antagonists to affect hyperactivity induced by cocaine has not been analyzed, however, non-selective 5-$HT_{1/2}$ antagonists have been shown to enhance cocaine-induced hyperactivity (Scheel-Kruger et al. 1977; Berman et al. 1982; Herges and Taylor 1998; but see Reith 1990 and Peltier et al. 1994). Since 5-HT_{2C} antagonists appear to increase the activity of a subpopulation of VTA DA neurons (Prisco et al. 1994; Prisco and Esposito 1995; Ashby and Minabe 1996; Lejeune et al. 1997) and 5-HT_{2C} agonists induce hypomotility (Lucki et al. 1989; Kennett 1993; Kennett et al. 1996), a 5-HT_{2C} antagonist would be predicted to increase the locomotor activation observed after cocaine administration. To test this hypothesis, we assessed the ability of the 5-$HT_{2C/2B}$ antagonist SB 206553 (Forbes et al. 1995; Kennett et al. 1996) to modulate spontaneous and acute cocaine-induced locomotor activation. The doses of SB 206553 (1–4 mg/kg) chosen for this study encompass those doses that effectively inhibit mCPP-induced hypermotility (ID_{50} = 1.1 mg/kg; G. Kennett, personal communication), increase cell firing of DA VTA neurons (Lejeune et al. 1997) and increase DA release in the NAc (Lejeune et al 1997; Spampinato et al. 1997).

MATERIALS AND METHODS

Animals

Male Sprague–Dawley rats (Harlan Sprague–Dawley, Indianapolis, IN, USA) weighing 225–250 g were housed (4 rats/cage) for 1 week prior to experimentation in a temperature (21 ± 2°C) and humidity (40–50%) controlled environment with food and tap water available *ad libitum*, except during experimental sessions. Lighting was maintained under a 12-hr light-dark cycle (lights on 07:00–19:00 hrs). All experimental procedures were performed between 08:00 and 14:00 hrs.

Apparatus

Behavioral activity was monitored and quantified using an open field activity system (San Diego Instruments, San Diego, CA, USA). Housed within sound attenuating enclosures, each chamber was a 40 cm × 40 cm × 40 cm clear Plexiglas enclosure containing a 4 × 4 photobeam matrix located 4 cm from the floor surface; interruptions of these photobeams resulted in counts of activity in the peripheral and central fields of the chamber. Another horizontal row of 16 photobeams located 16 cm from the floor provided a measure of rearing activity. Video cameras, located above the chambers, provided the ability to observe activity of animals continuously without disrupting behavior. Separate counts of peripheral, central, and rearing activity were made by the control software (Photobeam Activity

Software, San Diego Instruments, San Diego, CA, USA) and stored for subsequent statistical evaluation.

Behavioral Procedures

Three separate groups of rats (n = 8 rats/group) were habituated to the activity monitors for 2 hr per day on the 2 days prior to the start of the experiment. On test days, rats were removed from the chamber at the termination of a 30-min habituation period, injected intraperitoneally (IP) with the vehicle [45% (w/v) β-cyclodextrin; 2 ml/kg] or SB 206553 (1, 2, and 4 mg/kg) and returned to the activity monitor. Saline (1 ml/kg, IP) or cocaine (15 mg/kg, IP) was injected 30 min later. Locomotor activity was subsequently recorded in 5-min time epochs for a total of 45 min. The three doses of the antagonist (1, 2, or 4 mg/kg) were tested in three separate groups of rats using a within subjects design in which each rat in the respective group (n = 8) received each of the following treatments: vehicle + saline, SB 206553 + saline, vehicle + cocaine, and SB 206553 + cocaine. Drug combinations were tested in the same order for each group of rats and tests occurred 48 hr apart; injections of cocaine were at least 96 hr apart. All experiments were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* and local Animal Care and Use Committee approval.

Drugs

β-cyclodextrin (2-hydroxypropyl-β-cyclodextrin) was obtained from RBI (Natick, MA, USA), SB 206553 (5-methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-f]indole) from Smith-Kline Beecham Pharmaceuticals (Harlow, Essex, UK) and cocaine HC1 from the National Institute on Drug Abuse (NIDA; Bethesda, MD, USA). Cocaine was dissolved in 0.9% saline and SB 206553 in 45% β-cyclodextrin with mild heating. Verification that the compounds were dissolved was made visually. All doses were calculated based on the weight of the salts. The drugs were administered IP in a volume of 1 ml/kg (saline, cocaine) or 2 ml/kg (vehicle, SB 206553).

Statistical Analyses

Data are presented and analyzed as mean total peripheral, central, and rearing activity over the 45-min session time (± SEM). The main effect of drug treatments were analyzed using a repeated measures, one-way analysis of variance. Subsequent *a priori* comparisons between means of total peripheral, central, or rearing activity (45 min) were made using Fisher's least-significant difference test (The SAS system for Windows, Version 6.12). All statistical analyses were conducted with an experimentwise error rate of $\alpha = 0.05$.

RESULTS

Effects of SB 206553 (1 mg/kg) on Basal and Cocaine-induced Locomotor Activity

A significant main effect of pretreatment was observed for central ($F_{(3,28)} = 19.60$, $p < .0001$), peripheral ($F_{(3,28)} = 21.93$, $p < .0001$), and rearing activity ($F_{(3,28)} = 4.01$, $p < .0172$). *A priori* analyses revealed that 1 mg/kg of SB 206553 did not alter central, peripheral, or rearing activity compared to vehicle + saline (Figure 1). Significant increases in horizontal, central, and rearing activity were observed following pretreatment with cocaine (15 mg/kg) compared with vehicle + saline ($p < .05$). SB 206553 significantly attenuated cocaine-induced central, but not peripheral or rearing, activity ($p < .05$).

Effects of SB 206553 (2 mg/kg) on Basal and Cocaine-induced Locomotor Activity

A significant main effect of pretreatment was observed for central ($F_{(3,28)} = 6.78$, $p < .001$), peripheral ($F_{(3,28)} = 5.60$, $p < .004$), and rearing activity ($F_{(3,28)} = 10.89$, $p < .0001$). *A priori* analyses revealed that 2 mg/kg of SB 206553 did not alter activity levels compared to vehicle + saline (Figure 2). Significant increases in central, peripheral, and rearing activity were observed after cocaine administration (15 mg/kg) compared with vehicle + saline ($p < .05$). SB 206553 significantly attenuated cocaine-induced peripheral and rearing activity ($p < .05$).

Effects of SB 206553 (4 mg/kg) on Basal and Cocaine-induced Locomotor Activity

A significant main effect of pretreatment was observed for total central ($F_{(3,28)} = 12.45$, $p < .0001$), peripheral ($F_{(3,28)} = 25.36$, $p < .0001$), but not rearing activity ($F_{(3,28)} = 2.45$, $p < .08$). *A priori* analyses revealed that 4 mg/kg of SB 206553 did not alter activity levels compared to vehicle + saline (Figure 3). Significant increases in central, peripheral, and rearing activity occurred following pretreatment with cocaine (15 mg/kg) compared with vehicle + saline ($p < .05$). SB 206553 significantly enhanced cocaine-induced peripheral activity ($p < .05$).

DISCUSSION

The present results demonstrate that the 5-$HT_{2C/2B}$ receptor antagonist SB 206553 differentially altered cocaine-induced hyperactivity dependent on the dose of the antagonist used, such that a potentiation was observed at the highest dose (4 mg/kg) and an attenuation at the lower doses of SB 206553 (1 and 2 mg/kg). The alterations in cocaine-induced hyperactivity in-

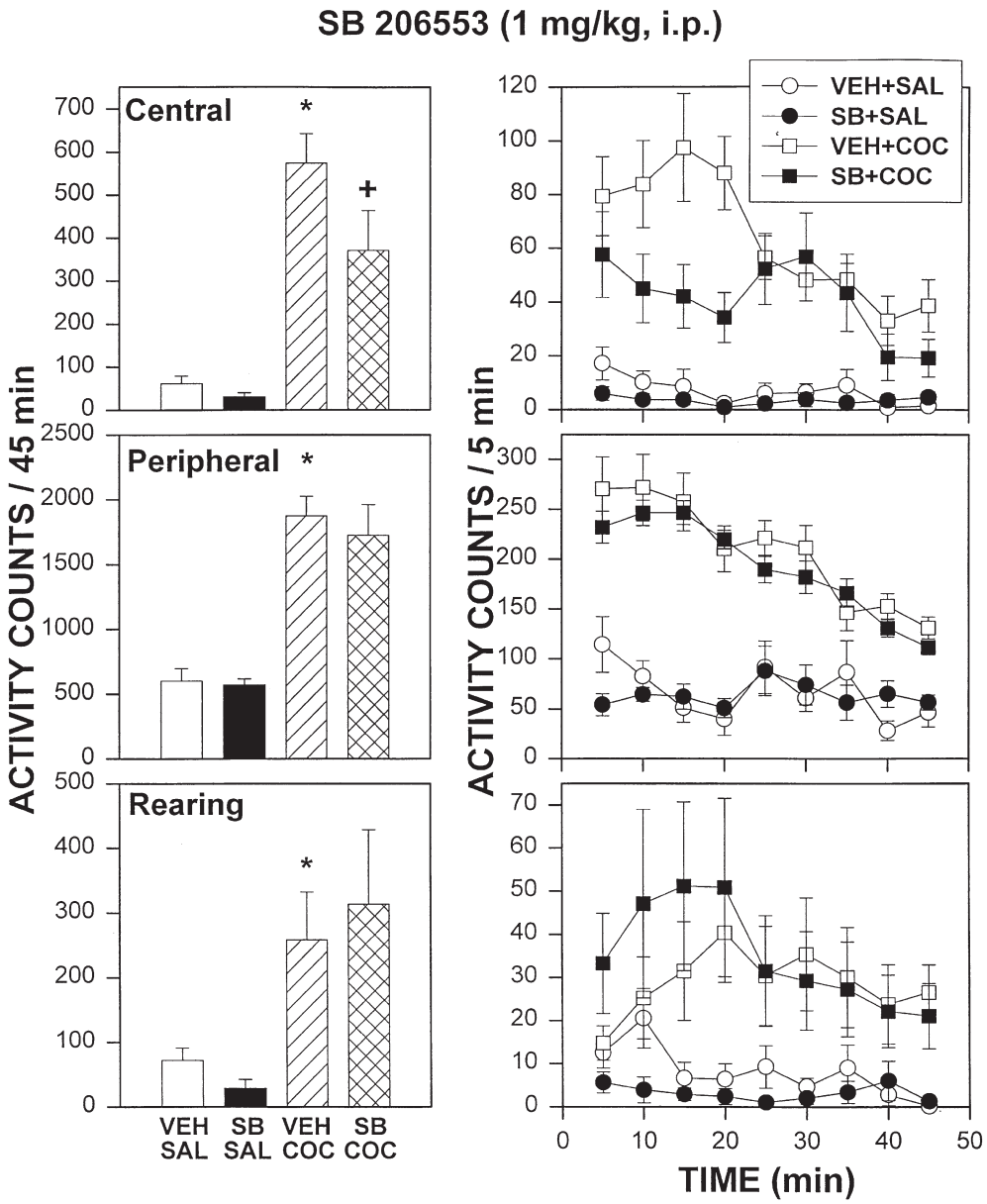

Figure 1. Effects of SB 206553 (1 mg/kg, IP) on hyperactivity induced by cocaine (15 mg/kg, IP). **Left panel**: Total activity. Rats (n = 8) received either vehicle + saline (VEH + SAL; open bars), SB 206553 + saline (SB + SAL; filled bars), vehicle + cocaine (VEH + COC; hatched bars) or SB 206553 + cocaine (SB + COC; cross-hatched bars) as two injections spaced 30 min apart. Data are presented as mean total activity (±SEM) summed over the 45-min test session. Separate counts of central (top), peripheral (middle), and rearing activity (bottom) are presented. Asterisks represent activity levels that differed significantly from vehicle + saline, while the plus (+) symbol represents activity levels that differed significantly from vehicle + cocaine for a given behavioral measure ($p < .05$). **Right panel**: Time course of activity. Data from the same group of animals are presented as mean activity counts (±SEM) in each 5-min bin over the 45-min test session beginning immediately after the second injection of either saline or cocaine. Symbols are as indicated: VEH + SAL (open circles), SB + SAL (closed circles), VEH + COC (open squares), SB + COC (closed squares).

duced by SB 206553 were not as robust as those observed after pretreatment with the DA D_1-like receptor antagonist SCH 23390 (McCreary and Marsden 1993) or the DA D_2 receptor antagonist eticlopride (White et al. 1998) suggesting that the contribution of 5-HT$_{2C}$ receptors to cocaine-induced hyperactivity may be at least secondary to that of dopaminergic systems.

Based upon behavioral, neurochemical, and electrophysiological observations that 5-HT$_{2C}$ receptors may modulate DA neurotransmission, the aim of the present

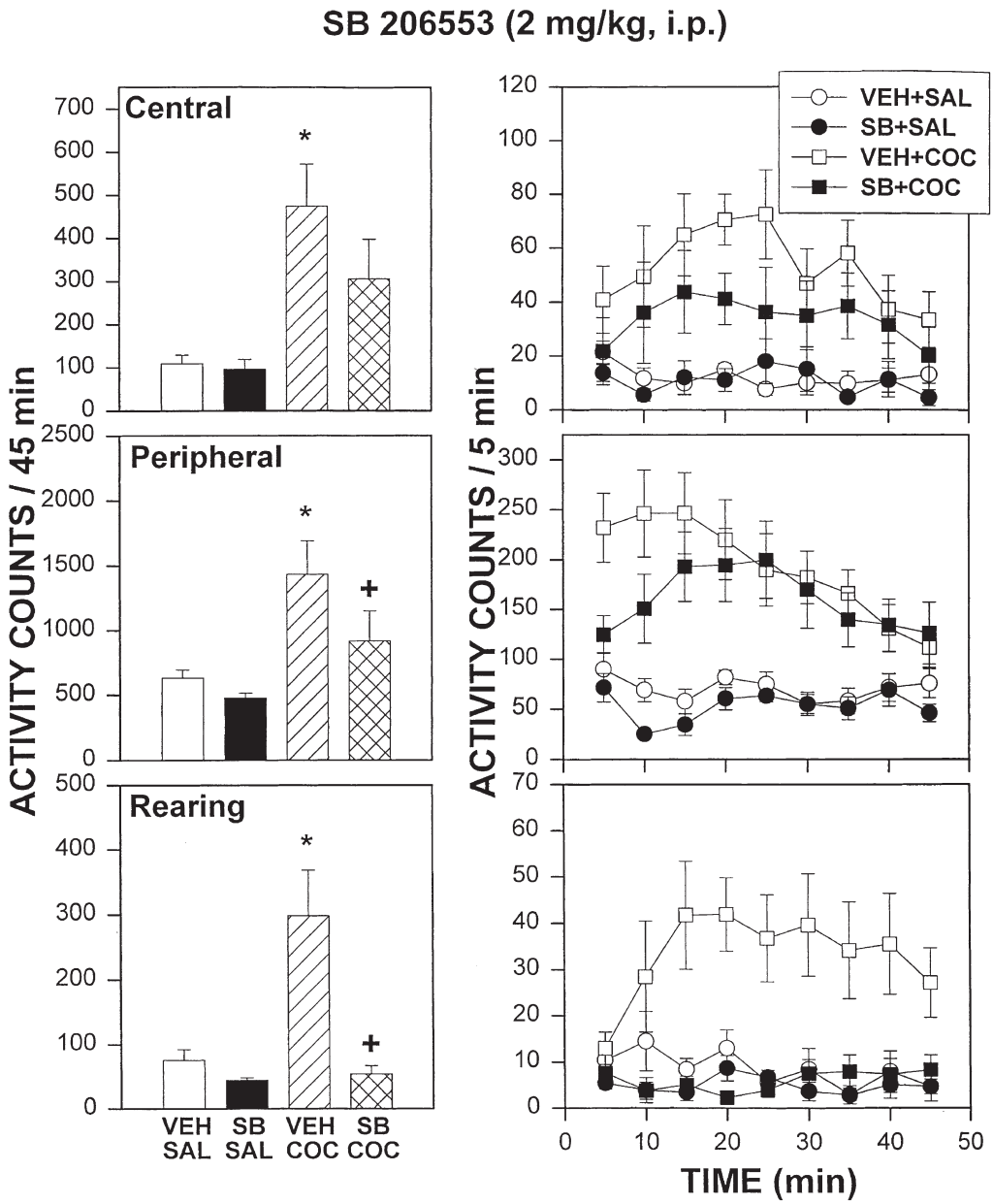

Figure 2. Effects of SB 206553 (2 mg/kg, IP) on hyperactivity induced by cocaine (15 mg/kg, IP). See Figure 1 for explanation of symbols.

study was to establish whether acute pretreatment with a selective 5-HT_{2C} antagonist would increase the locomotor activation observed after acute administration of cocaine. Consistent with a previous observation that oral administration of SB 206553 did not alter basal locomotor activity (Kennett et al. 1996), peripheral, central, and rearing activity were unaltered following IP administration of SB 206553 (1–4 mg/kg). However, a significant potentiation of cocaine-induced peripheral hyperactivity was observed at the highest dose of SB 205663 administered (4 mg/kg); a trend toward increased central activity was also observed. This enhancement of cocaine-induced locomotor activity seen after 4 mg/kg of SB 206553 may be related to activation of 5-HT_{2C} receptors that control the activity of DA VTA neurons. Increased activity of DA VTA neurons due to antagonism of 5-HT_{2C} receptors in the VTA may result in enhanced release of DA in terminal regions such as the NAc. In preliminary microdialysis studies, SB 206553 enhanced DA overflow in the NAc at doses similar to the highest dose (4 mg/kg, IP) used in the present study (Lejeune et al. 1997; Spampinato et al. 1997). Thus, the highest dose of SB 206553 may increase hyperactivity induced by cocaine due to an activation of DA neurotransmission in the mesoaccumbens pathway. While exogenous stimulation of 5-HT_{2C} receptors

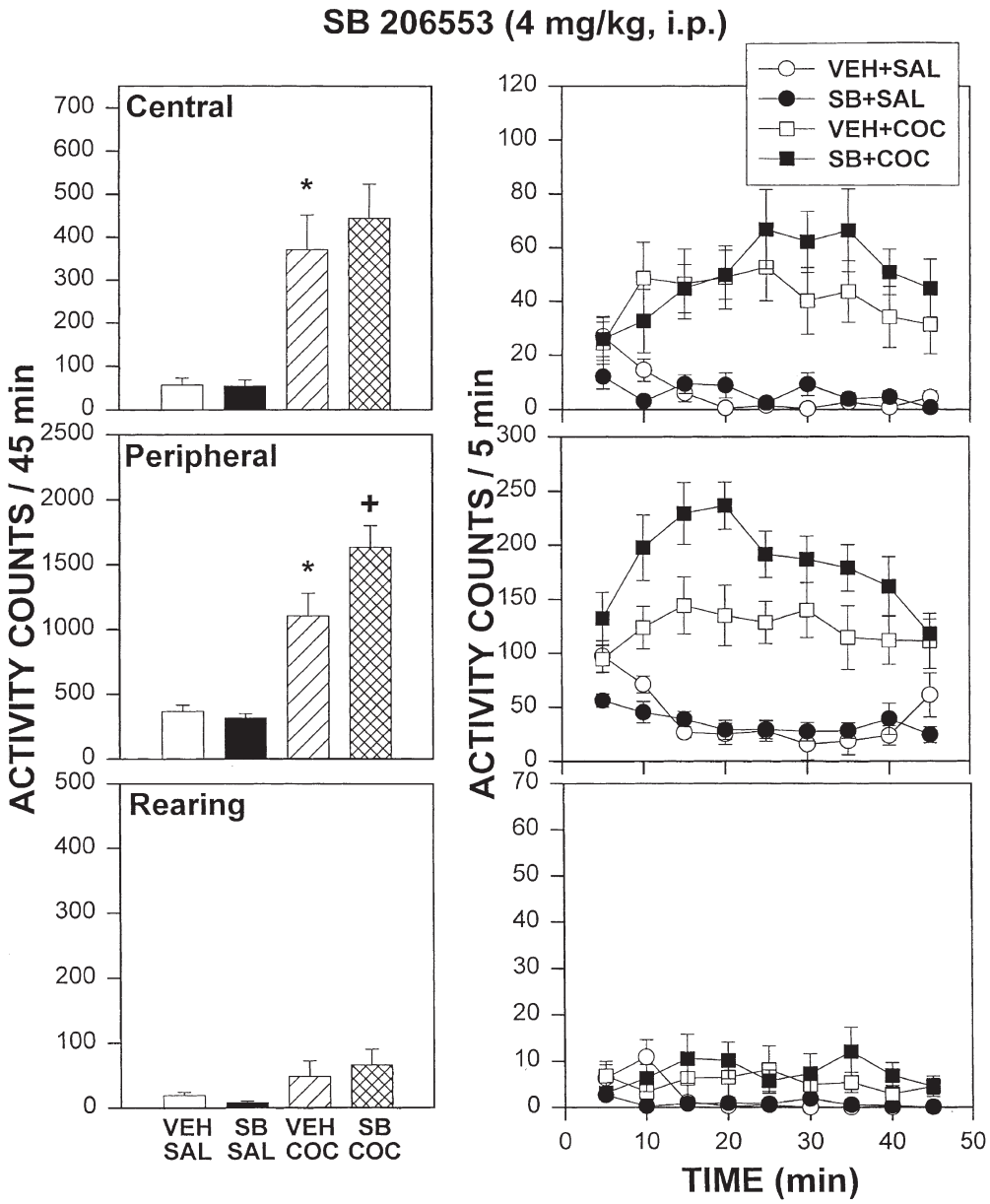

Figure 3. Effects of SB 206553 (4 mg/kg, IP) on hyperactivity induced by cocaine (15 mg/kg, IP). See Figure 1 for explanation of symbols.

appears to result in hypolocomotion (Lucki et al. 1989; Kennett 1993; Kennett et al. 1996), the tonic nature of 5-HT$_{2C}$ receptor control of the DA mesoaccumbens pathway is questionable since systemic administration of SB 206553 did not alter locomotion on its own (present results; Kennett et al. 1996). However, Filip and Cunningham (1998) have collected preliminary data to suggest that 5-HT$_{2C}$ receptors in the shell of the NAc may exert an inhibitory tone on locomotion since microinjection of the selective 5-HT$_{2C}$ antagonist RS 102221 into the shell of the NAc enhanced basal levels of activity.

Increases in synaptic 5-HT concentration as a consequence of the inhibition of 5-HT reuptake in the VTA following systemic administration of cocaine may result in stimulation of 5-HT$_{2C}$ receptors and contribute to the inhibitory actions of cocaine on DA VTA neurons (Einhorn et al. 1988) as well as the behavioral activation induced by cocaine. Antagonism of the indirect inhibitory actions of cocaine on 5-HT$_{2C}$ receptors in the VTA may account for the ability of the highest dose of SB 206553 to enhance cocaine-induced hyperactivity. Observations from other studies of the locomotor stimulant effects of cocaine are in general agreement with the hypothesis that antagonism of at least one of the three 5-HT$_2$ receptor subtypes modulates the *in vivo* effects of psychostimulants. Non-selective 5-HT antagonists which preferentially bind to 5-HT$_2$ receptors such as metergoline and cyproheptadine were reported to increase

cocaine-induced hyperactivity or to unmask more intense DA stereotypies such as gnawing and biting in rats (Scheel-Kruger et al. 1977; Berman et al. 1982), although the 5-$HT_{2/1A/1D}$ antagonist methysergide did not alter cocaine behaviors in mice (Reith 1990). Herges and Taylor (1998) have recently reported that methysergide potentiated, while the 5-$HT_{2A/2C}$ antagonist ketanserin differentially increased (0.1 mg/kg) and decreased (1 mg/kg) cocaine-induced locomotor hyperactivity, consistent with the reduction seen after a high dose of the 5-HT_2 antagonist ritanserin (10 mg/kg; Peltier et al. 1994).

The potentiative effects of SB 206553 on cocaine-induced hyperactivity in the present study are presumably due to its actions to antagonize 5-HT_{2C} receptors. SB 206553 displays a high affinity (pK_i = 7.92) for cloned human 5-HT_{2C} receptors expressed in HEK 293 cells and is a potent antagonist of 5-HT-stimulated phosphoinositide hydrolysis in these cells (Kennett et al. 1996). Unlike many compounds previously employed to antagonize 5-HT_{2C} receptors, SB 206553 has little affinity for the 5-HT_{2A} receptors (pK_i = 5.8) or for DA D_2, D_3, or D_4 receptors expressed in HEK 293 cells ($pK_i < 5$; Kennett et al. 1996). On the other hand, SB 206553 displays high affinity for the 5-HT_{2B} receptor as measured in the rat stomach fundus preparation (pA_2 = 8.89; Kennett et al. 1996). Although only modest levels of 5-HT_{2B} receptors are found in brain, 5-HT_{2B}-like immunoreactivity has been localized to the lateral septum, medial amygdala, hippocampus, and cerebellum (Duxon et al. 1997a). This pattern of 5-HT_{2B} receptor distribution differs from that observed for the 5-HT_{2C} receptor (Hoffman and Mezey 1989; Mengod et al. 1990; Pazos and Palacios 1985; Duxon et al. 1997a; Eberle-Wang et al. 1997; Sharma et al. 1997). Furthermore, systemic administration of the putative 5-HT_{2B} receptor agonist BW 723C86 induced the immediate early gene product FOS in a pattern that overlapped the localization of 5-HT_{2B} receptor immunoreactivity (Duxon et al. 1996; Duxon et al. 1997a), but was very distinct from the pattern of FOS expression observed following systemic administration of mCPP (Duxon et al. 1996). These findings suggest that the 5-HT_{2B} receptor in brain may play a functional role in rats. Indeed, recent behavioral studies with the putative 5-HT_{2B} receptor agonist BW 723C86 have supported this hypothesis. For example, BW 723C86 was shown to increase food consumption and reduce grooming in rats (Kennett et al. 1997) and, following microinjection into the medial amygdala, BW 723C86 elicited anxiolysis in the social interaction model (Duxon et al. 1997b).

Based upon its potential functional role in the rat and the affinity of SB 206553 for 5-HT_{2B} receptors, antagonism of 5-HT_{2B} receptors may contribute to SB 206553-induced alterations of cocaine-evoked hyperactivity. Although direct comparisons of functional and binding data are problematic, the attenuation of cocaine-evoked hyperactivity observed following administration of the two lowest doses of SB 206553 (1 and 2 mg/kg) could be related to the greater affinity of SB 206553 for 5-HT_{2B} receptors (pA_2 = 8.89) over 5-HT_{2C} receptors (pK_i = 7.92; Kennett et al. 1996), such that the lowest doses of SB 206553 might preferentially block 5-HT_{2B} receptors, many of which are found in the periphery (Wainscott et al. 1993). To date, however, no empirical evidence exists in support of a role for either central or peripheral 5-HT_{2B} receptors in psychostimulant-evoked hyperactivity.

The dose-dependent inhibitory and potentiative effects of SB 206553 may also reflect subtle regional distinctions in 5-HT_{2C} receptor regulation of DA mesoaccumbens function. Both pre- and postsynaptic populations of 5-HT_{2C} receptors appear to exist. The postsynaptic localization has been confirmed with the demonstration that classical denervation supersensitivity of 5-HT_{2C} receptors develops following depletion of 5-HT with the 5-HT neurotoxin 5,7-dihydroxytrypamine (5,7-DHT). For example, 5-HT_{2C} receptor ligand binding (Conn et al. 1987), 5-HT_{2C}-like immunoreactivity (Sharma et al. 1997) and the behavioral consequences of 5-HT_{2C} receptor stimulation (Lucki et al. 1989) are increased following 5,7-DHT pretreatment. While these findings are consistent with a postsynaptic localization of 5-HT_{2C} receptors, 5-HT_{2C} receptor mRNA has also been demonstrated in serotonergic cell body regions: the dorsal, linear, obscurus, pallidus, and magnus raphe nuclei (Hoffman and Mezey 1989). In contrast to the denervation supersensitivity reported in other brain regions after 5,7-DHT pretreatment (above), 5-HT_{2C}-like immunoreactivity in the thoracic dorsal spinal cord, midbrain, and brainstem was reduced after 5,7-DHT pretreatment (Sharma et al. 1997). These data suggest an additional population of 5-HT_{2C} receptors found on 5-HT nerve terminals. Thus, both pre- and postsynaptic 5-HT_{2C} receptors may contribute differentially to the present observation that SB 206553 can dose-dependently decrease and increase cocaine-induced hyperactivity. Preliminary findings from our laboratory suggest that the inhibitory effects of systemic administration of the 5-$HT_{2C/2B}$ antagonist SB 206553 on cocaine-induced behavior may be related to actions at either/both pre- or postsynaptic 5-HT_{2C} receptors in the NAc as we have found that the 5-HT_{2C} antagonist RS 102221 injected into the shell of the NAc dose-dependently attenuated cocaine-induced hyperactivity (Filip and Cunningham 1998).

In summary, the 5-$HT_{2C/2B}$ antagonist SB 206553 dose-dependently attenuated (1 and 2 mg/kg) or potentiated (4 mg/kg) the hyperactivity induced by cocaine. Based upon the present observations and an interpretation of previous research to implicate 5-HT_{2C} receptor control of the DA mesoaccumbens pathways

in behavior, a thorough and systematic analysis of the role of 5-HT_{2C} (and 5-HT_{2B}) receptors in psychostimulant-induced behaviors is warranted and awaits the availability of selective compounds.

ACKNOWLEDGMENTS

We gratefully acknowledge Michael Bankson for technical assistance, Smith-Kline Beecham Pharmaceuticals (Harlow, Essex, UK), and the National Institute on Drug Abuse (NIDA) for gifts of drugs used in this study, and NIDA for financial support (DA 06511 and DA 00260). We thank Malgorzata Filip for her helpful review of the manuscript and Yvette Ruiz for her assistance with the preparation of the references.

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