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Effects of serotonin (5-HT)$_{1B}$ receptor ligands on cocaine-seeking behavior in rats

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Abstract:
Numerous data indicated a significance for the brain dopaminergic pathways in the behavioral effects of cocaine, however recent research also demonstrated involvement of serotonin (5-HT) neurotransmission and particularly 5-HT$_{1B}$ receptors in the reinforcing, discriminative stimulus and sensitizing effects of cocaine. In order to substantiate a role of these receptors in incentive motivation for cocaine, we used the extinction/reinstatement model to examine the effects of the 5-HT$_{1B}$ receptor ligands on reinstatement of extinguished cocaine-seeking behavior and food-taking behavior. Rats trained to self-administer cocaine (0.5 mg/kg/infusion) subsequently underwent extinction procedures. They were then tested for the cocaine-primed or cocaine-associated cue-induced reinstatement of extinguished cocaine-seeking behavior. Other groups of rats were trained to self-administer food (sweet milk), and after extinction they were tested for the reinstatement of food-taking behavior induced by contingent food presentation. The 5-HT$_{1B}$ receptor antagonists SB 216641 (2.5–7.5 mg/kg) and GR 127935 (2.5–10 mg/kg) dose-dependently attenuated the cocaine (10 mg/kg)- and cocaine-associated cue-induced reinstatement of cocaine-seeking behavior whereas they failed to alter reinstatement of food-taking behavior. The 5-HT$_{1B}$ receptor agonist CP 94253 (2.5 or 5 mg/kg) combined with a subthreshold priming dose of cocaine (2.5 mg/kg) potentiated reinstatement of the drug seeking-behavior, but inhibited cocaine seeking induced by a submaximal dose (10 mg/kg) of cocaine or the cocaine-associated cue. Moreover, the 5-HT$_{1B}$ receptor agonist attenuated reinstatement of food-taking behavior. Facilitatory effect of CP 94253 on cocaine-seeking behavior and its inhibitory effect on food-taking behavior were blocked by SB 216641, but its inhibitory effect on cocaine-seeking behavior remained unaffected by this 5-HT$_{1B}$ receptor antagonist. Our results indicate that tonic activation of 5-HT$_{1B}$ receptors is involved in cocaine- and cue-induced reinstatement of cocaine-seeking behavior and that the inhibitory effects of 5-HT$_{1B}$ receptor antagonists on these phenomena are directly related to motivational aspects of cocaine abuse. The facilitatory 5-HT$_{1B}$ receptor-mediated effect of the 5-HT$_{1B}$ receptor agonist on cocaine seeking may be related to the earlier reported enhancement of the rewarding properties of cocaine, while its inhibitory effect on cocaine-seeking behavior, unrelated to the 5-HT$_{1B}$ receptor activation, may result from a general reduction of motivation.

Key words:
5-HT$_{1B}$ receptors, cocaine-seeking, food taking, rats

Introduction

Cocaine is one of the best known and powerful addictive substances and its abusers have a high rate of relapse to drug-seeking and drug-taking behavior following periods of abstinence [38, 41]. Incentive motivation for cocaine can be modeled in animals by using reinstatement procedures in which laboratory animals are trained to self-administer drugs and then undergo extinction training during which, in an operant version of this procedure, lever presses result in saline

delivery instead of cocaine. The reinstatement of extinguished lever responding as the operational measure of drug seeking has good face validity for withdrawal and relapse, because noncontingent priming injections of the drug or exposure to drug-paired cues or to stress [15, 16, 37, 61] model the behavioral patterns that lead to relapse in human drug addicts [9, 13, 15].

Cocaine inhibits dopamine (DA) reuptake by binding to the DA transporter [31] and elevates extracellular DA levels in the mesocorticolimbic system [33, 34, 67] which originates in the ventral tegmental area (VTA) and terminates in the nucleus accumbens (NAcc) and in the prefrontal cortex. However, cocaine inhibits also the noradrenaline transporter and serotonin (5-HT) transporter [31] and in this way enhances the extracellular norepinephrine and 5-HT levels, respectively [36]. Therefore, the question arises about the contribution of 5-HT to the behavioral effects of cocaine.

A number of studies have indicated that 5-HT plays a role in the modulating effects of cocaine and other psychostimulants [18, 40]. 5-HT fibers innervate both the VTA and NAcc, the key structures of the reward circuitry, and play a significant role in modulating the feedback between the DA projections from the VTA to the NAcc and γ-aminobutyric acid (GABA) projections from the NAcc to the VTA [43, 68, 69].

Serotonergic neurotransmission is mediated by at least 14 different receptor subtypes [23]. Recent findings have indicated that 5-HT$_{1B}$ receptors are strongly expressed in the mesocorticolimbic system [7, 56], which is particularly involved in the behavioral effects of cocaine. For example, 5-HT$_{1B}$ receptor activation increased the rewarding properties of this psychostimulant in fixed [45, 51] and progressive ratio schedules of self-administration [45] in rats. Consistent with this, Cervo et al. [11] have found that 5-propoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-pyrrolo-[3,2-b]pyridine hydrochloride (CP 94253; a 5-HT$_{1B}$ receptor agonist) enhances cocaine-induced conditioned place preference. Moreover, the stimulation of 5-HT$_{1B}$ receptors has also been found to increase reinforcing efficacy and discriminative signal of the psychostimulant amphetamine [24, 39] and to enhance cocaine-induced behavioral sensitization and cocaine discriminative cue [20–22, 50, 52, 53].

In contrast to the reinforcing, discriminative and sensitizing effects of cocaine, there is only one report suggesting an involvement of 5-HT$_{1B}$ receptors in cocaine-seeking behavior. Namely, Acosta et al. [1] demonstrated that the 5-HT$_{1B/1A}$ receptor agonist 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole (RU 24969) decreased cue- and cocaine-induced reinstatement of cocaine-seeking behavior. The inhibitory effects of RU 24969 were reversed by the 5-HT$_{1B}$ receptor antagonist N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-[1,2,4]oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide (GR 127935), supporting the hypothesis that the attenuation of cocaine-seeking behavior was mediated *via* 5-HT$_{1B}$ receptors.

In the present study we investigated the effects of the selective 5-HT$_{1B}$ receptor antagonists N-[3-[3-(dimethylamine)ethoxy]-4-methoxyphenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-carboxamide hydrochloride (SB 216641) [48] and GR 127935 [64], and the agonist CP 94253 [32] on cocaine-primed and cocaine-associated cue-induced reinstatement of extinguished cocaine-seeking behavior in rats trained to self-administer cocaine. Additionally, we investigated the effects of the 5-HT$_{1B}$ receptor ligands on the reinstatement of extinguished food-taking behavior induced by food presentation in rats trained to self-administer food.

Materials and Methods

Animals

Male Wistar rats (280–300 g) delivered by a licensed breeder (T. Górzkowska, Warszawa, Poland) were housed individually in standard plastic rodent cages in a colony room maintained at 20 ± 1°C and at 40–50% humidity under a 12-h light-dark cycle (lights on at 06:00). Animals had free access to food (Labofeed pellets) and water during the 7-day habituation period. Then, rats used in the cocaine self-administration and in the food self-administration procedures were maintained on limited food intake (20 g/rat/day) during initial training sessions (see below). All experiments were conducted during the light phase of the light-dark cycle (between 08:00–15:00) and were carried out in accordance with the National Institutes of *Health Guide for the Care and Use of Laboratory Animals* and with approval of the Bioethics Commission as compliant with the Polish Law (21 August 1997). The animals were experimentally naive.

Drugs

Cocaine hydrochloride (Sigma-Aldrich, USA), 5-propoxy-3(1,2,3,6-tetrahydro-4-pyridinyl)-1H-pyrrolo-[3,2-b]pyridine hydrochloride (CP 94253; Tocris, UK), N-{3-[3-(dimethylamine)-ethoxy]-4-methoxyphenyl}-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-(1,1'-biphenyl)-4-carboxamide hydrochloride (SB 216641; Tocris, UK) and N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-[1,2,4]oxadiazol-3-yl)-1,1'-biphenyl-4-carboxamide (GR 127935; Tocris, UK) were used. Cocaine was dissolved in sterile 0.9% NaCl, CP 94253 and SB 216641 were dissolved in distilled water, and GR 127935 was suspended in 20% β-cyclodextrin (Tocris, UK). Cocaine was given either *iv* (0.1 ml/injection) or *ip* (1 ml/kg). CP 94253 and SB 216641 were injected *ip*, while GR 127935 was injected *sc* in a volume of 1 ml/kg. CP 94253, SB 216641 and GR 127935 were administered at 30, 45 and 60 min before behavioral scoring, respectively. The doses of 5-HT_{1B} receptor ligands were chosen based upon their functional selectivity at 5-HT_{1B} receptors [20, 50, 65, 66].

Cocaine self-administration and extinction

Food restricted rats (20 g/rat/day) were trained to press the lever of standard operant conditioning chambers (Med-Associates, St. Albans, GA, USA) under a fixed ratio (FR) 5 schedule of food (condensed milk (1:1 v/v in distilled water; 0.1 ml)) reinforcement. Two days following lever-press training and free access to food, the rats were chronically implanted with a silastic catheter in the external right jugular vein, as described previously [17, 19]. Catheters were flushed every day with 0.1 ml of saline solution containing heparin (70 U/ml, Biochemie GmbH, Austria) and 0.1 ml solution of cephazolin (10 mg/ml; Biochemie GmbH, Austria). Catheter patency was tested periodically with the ultrashort-acting barbiturate anesthetic methohexital (10 mg/kg, *iv*; loss of consciousness within 5 s). However, no problems with catheter patency occurred.

After a 10-day recovery period, all animals were again food restricted (20 g/rat/day) and trained to lever press to FR 5 schedule of food reinforcement over a 2-h session. Then, subjects began lever pressing for cocaine reinforcement during 2-h daily sessions performed 6 days/week (maintenance). The house light was illuminated throughout each session. Each completion of five presses on the "active" lever complex (FR 5 schedule) resulted in a 5-s infusion of cocaine (0.5 mg/kg per 0.1 ml) and a 5-s presentation of a stimulus complex (activation of the white stimulus light directly above the "active" lever and the tone generator, 2000 Hz; 15 dB above ambient noise levels). The training dose of cocaine was selected based upon prior experiments [17, 19]. Following each injection, there was a 20-s time-out period during which responding was recorded but had no programmed consequences. Response on the "inactive" lever never resulted in cocaine delivery. Training and maintenance sessions occurred over a total of 16–18 days during which subjects met acquisition criteria that required the number of reinforcements and active lever presses over 6 consecutive maintenance sessions to vary by only 10%; this criterion was selected based on our prior experiments [17, 19]. The extinction procedure started on the following day. During extinction sessions subjects had 2-h daily training sessions with no delivery of cocaine or the presentation of the conditioned stimulus. Once they reached the extinction criteria (a minimum of 10 extinction days with the responding on the active lever below 10% of the level observed during maintenance during at least 3 consecutive days), rats were divided into separate groups to run reinstatement experiments.

Cocaine-primed reinstatement of cocaine-seeking behavior

After extinction training one group of animals (n = 7) served as subjects to establish dose-response relationship for reinstatement of cocaine-seeking behavior induced by three priming doses of the drug (2.5, 5 and 10 mg/kg, *ip*). Five groups of rats (n = 7–8 rats/group) were tested for reinstatement response induced by combination of 5-HT_{1B} receptor ligands and cocaine (10 mg/kg, *ip*). Finally, two separate groups of animals (n = 7–8 rats/group) were tested for reinstatement response induced by CP 94253 or by a combination of the 5-HT_{1B} receptor agonist and subthreshold dose (2.5 mg/kg, *ip*) of cocaine. During the reinstatement tests (2-h sessions), active lever presses on the FR 5 schedule resulted only in an intravenous injection of saline. Drug combinations were given in a randomized order in three reinstatement tests that each rat received, and test sessions were separated by at least two to three extinction sessions.

Cue-induced reinstatement of cocaine-seeking behavior

After extinction training, four separate groups of animals (n = 6–8 rats/group) served as subjects for reinstatement of cocaine-seeking behavior. They were tested for reinstatement response induced by 5-HT$_{1B}$ receptor ligands and the cue (tone + light previously paired with cocaine self-administration) which was presented during the reinstatement tests (2-h sessions) contingently to active lever presses. During the reinstatement tests, active lever presses on the FR 5 schedule resulted only in an intravenous injection of saline, as described previously [17, 19]. Drug combinations were given in a randomized order in three reinstatement tests that each rat received, and test sessions were separated by at least two to three extinction sessions.

Food self-administration and extinction

Food self-administration was conducted in a similar manner to cocaine self-administration, as described previously [17, 19]. Food-restricted rats (20 g/rat/day) were trained to press the lever of standard operant chambers (Med-Associates, St. Albans, GA, USA) under a FR 5 schedule of reinforcement (each completion of a FR 5 schedule on the "active" lever resulted in a delivery of the portion of sweetened condensed milk (1:1 v/v in distilled water; 0.1 ml)) in daily 2-h sessions. Following each reward – which was not connected with any cue – there was a 20-s time-out period during which responding was recorded but had no programmed consequences. Response on the "inactive" lever never resulted in food delivery. Training and maintenance sessions occurred over a total of 16–18 days during which subjects met acquisition criteria that required the number of reinforcements and active lever presses over 6 consecutive maintenance sessions to vary by only 10%. Once stable rates of responding were established, the extinction procedure started on the following day. During extinction sessions subjects had 2-h daily training sessions with no delivery of food. Once they reached the extinction criteria (a minimum of 10 extinction days with the responding on the active lever below 10% of the level observed during maintenance during at least 3 consecutive days), rats were divided into separate groups to run reinstatement experiments.

Reinstatement of food-taking behavior

After extinction training, four separate groups of animals (n = 6–8 rats/group) served as subjects for reinstatement of food-taking behavior, as described previously [17, 19]. They were tested for response reinstatement induced by 5-HT$_{1B}$ receptor ligands and a contingent presentation of food. During the reinstatement tests (2-h sessions) each completion of a FR 5 schedule on the "active" lever resulted in a delivery of the portion of sweetened milk (0.1 ml). Following each reward, there was a 20-s time-out period during which responding was recorded but had no programmed consequences. Response on the "inactive" lever never resulted in food delivery. Drug combinations were given in a randomized order in three reinstatement tests that each rat received, and test sessions were separated by at least two to three extinction sessions.

Statistical analyses

In reinstatement procedures of cocaine-seeking behavior or food-taking behavior, the number of responses on the active and inactive lever (including time out responding) for each group pretreated with several doses of cocaine or a 5-HT$_{1B}$ receptor ligand in combination with cocaine, cocaine associated cue or food was analyzed by separate one-way analyses of variance (ANOVAs) for repeated measures and where appropriate a *post-hoc* Dunnett's test was used to analyze differences between group means, while for a group pretreated with a dose of CP 94253 (2.5 mg/kg) a paired Student's *t*-test was used.

In combination experiments with the antagonists and the agonist of 5-HT$_{1B}$ receptors on reinstatement of cocaine-seeking behavior and food-taking behavior, the number of responses on the active and inactive lever (including time out responding) for each group was analyzed by two-way ANOVAs and where appropriate a *post-hoc* Newman-Keuls' test was used to analyze differences between group means.

Results

Acquisition of cocaine self-administration

Rats showed stable lever responding during the last 6 self-administration maintenance sessions with an ac-

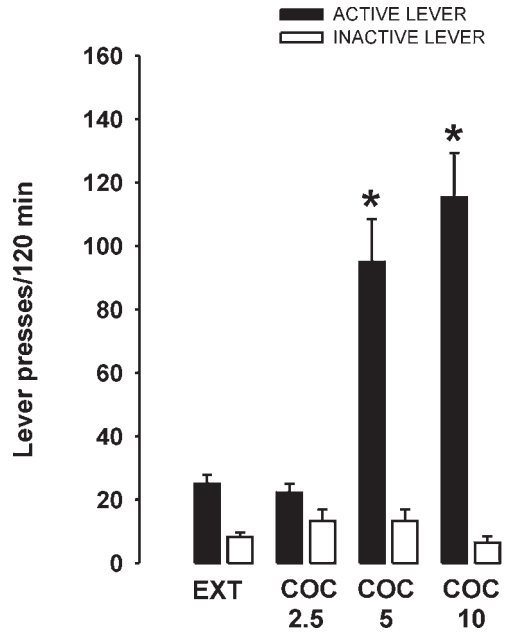

Fig. 1. The dose-response relationship for reinstatement of cocaine (COC)-seeking behavior induced by three priming doses of cocaine (2.5, 5 and 10 mg/kg, *ip*). Number of the active (black bars) and inactive (white bars) lever presses following cocaine priming injections are shown. The baseline extinction (EXT) responding is also presented. Each bar represent the mean (± SEM) of data from 7 rats. * $p < 0.001$ compared to EXT

quisition criterion requiring that the rate of active lever presses varied by less than 10%. The animals had self-administered 22–38 injections of cocaine with the daily mean cocaine intake between 11–19 mg/kg.

Cocaine-primed reinstatement of cocaine-seeking behavior

After 10 days of extinction (during which the active lever presses resulted in the *iv* delivery of saline without the presentation of cocaine-associated cue) the rats were tested for response reinstatement induced by cocaine.

A dose-response relationship for reinstatement of cocaine-seeking behavior induced by three priming doses of cocaine (2.5, 5 and 10 mg/kg, *ip*) is shown in Figure 1. Cocaine significantly altered the number of active [$F(3, 24) = 23.23$, $p < 0.001$], but not inactive [$F(3, 24) = 1.34$] lever presses. A significant effect was observed following cocaine 5 or 10 mg/kg.

The effects of 5-HT_{1B} receptor ligands on cocaine (10 mg/kg, *ip*)-primed reinstatement are shown in Figure 2. SB 216641 (5–7.5 mg/kg) significantly altered the number of active [$F(3, 28) = 6.28$, $p < 0.01$],

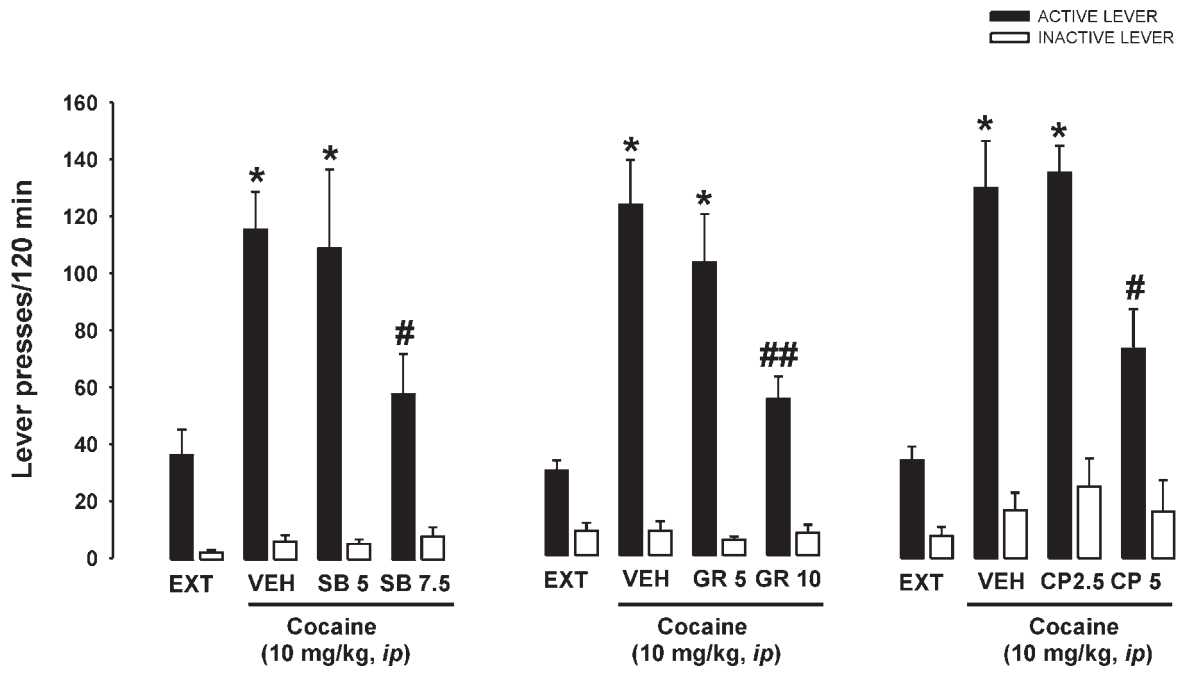

Fig. 2. Effects of the 5-HT_{1B} receptor antagonists SB 216641 (SB; left panel) and GR 127935 (GR; middle panel) and the agonist CP 94253 (CP; right panel) on the reinstatement of cocaine-seeking behavior induced by cocaine (10 mg/kg, *ip*). Number of the active (black bars) and inactive (white bars) lever presses following cocaine priming injections are shown for pretreatment with the corresponding vehicle (VEH), SB 216641 (5–7.5 mg/kg), GR 127935 (5–10 mg/kg) or CP 94253 (2.5–5 mg/kg). The baseline corresponding extinction (EXT) responding is also presented. Each bar represent the mean (± SEM) of data from 7–8 rats. * $p < 0.001$ compared to EXT; # $p < 0.05$, ## $p < 0.001$ compared to VEH

but not inactive [F(3, 28) = 1.27] lever presses. A significant decrease was observed following SB 216641, 7.5 mg/kg (Fig. 2, left panel). GR 127935 (5–10 mg/kg) significantly altered the number of active [F(3, 28) = 12.06, p < 0.001], but not inactive [F(3, 28) = 0.29] lever presses. A significant decrease was observed following GR 127935, 10 mg/kg (Fig. 2, middle panel). CP 94253 (2.5–5 mg/kg) significantly altered the number of active [F(3, 24) = 15.9, p < 0.001], but not inactive [F(3, 24) = 0.74] lever presses. A significant decrease was observed following CP 94253, 5 mg/kg (Fig. 2, right panel).

The effects of combination of SB 216641 (5 mg/kg) or GR 127935 (5 mg/kg) with CP 94253 (5 mg/kg) on cocaine (10 mg/kg)-induced reinstatement of cocaine seeking behavior are shown in Figure 3. A main effect for a SB 216641 + CP 94253 treatment combination was observed for active [F(1, 28) = 27.57, p < 0.001], but not for inactive [F(1, 28) = 0.77] lever presses. CP 94253 (5 mg/kg) produced a significant decrease in the response reinstatement on active lever induced by cocaine priming (p < 0.05). SB 216641 (5 mg/kg) did not affect the decrease in active lever presses following administration of CP 94253 (Fig. 3, left panel). A main effect for a GR 127935 + CP 94253 treatment combination was observed for active [F(1, 28) = 9.26, p < 0.001], but not for inactive [F(1, 28) = 0.29] lever presses. CP 94253 (5 mg/kg) produced a significant decrease in the response reinstatement on active lever induced by cocaine priming (p < 0.01). GR 127935 (5 mg/kg) did not affect the decrease in active lever presses following administration of CP 94253 (Fig. 3, right panel).

The effects of CP 94253 administered under saline extinction and effects of combination of 5-HT$_{1B}$ receptor ligands and subthreshold dose (2.5 mg/kg, *ip*) of cocaine are shown in Figure 4. Administration of CP 94253 (2.5 mg/kg, *ip*) under saline extinction did not produce reinstatement of cocaine-seeking behavior (Fig. 4, left panel). A main effect for a treatment combination was observed for active [F(1, 24) = 9.57, p < 0.01], but not for inactive [F(1, 24) = 0.0003] lever presses. Cocaine (2.5 mg/kg, *ip*) did not produce reinstatement of cocaine-seeking behavior, while pretreatment with CP 94253 (2.5 mg/kg, *ip*) in combination with cocaine (2.5 mg/kg, *ip*) produced a signifi-

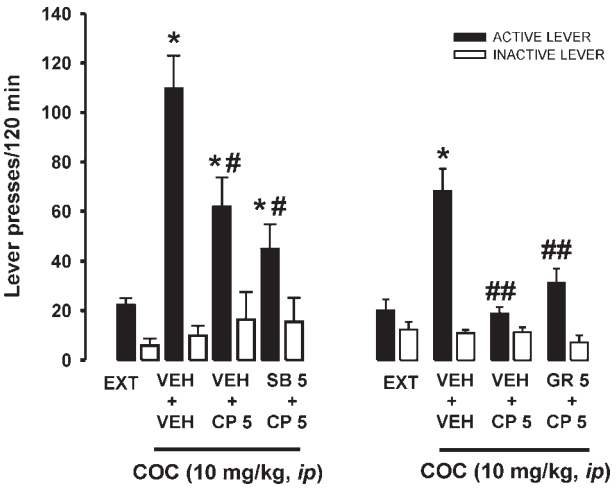

Fig. 3. Combination studies with the 5-HT$_{1B}$ receptor antagonists SB 216641 (SB) or GR 127935 (GR) injected before the 5-HT$_{1B}$ receptor agonist CP 94253 (CP) on the reinstatement of cocaine-seeking behavior induced by cocaine 10 mg/kg, *ip* SB 216641 (5 mg/kg; left panel) or GR 127935 (5 mg/kg; right panel) was given before CP 94253 (5 mg/kg). Number of the active (black bars) and inactive (white bars) lever presses following cocaine priming are shown for pretreatment with corresponding vehicle (VEH) + VEH, VEH + CP, SB + CP, GR + CP. The baseline corresponding extinction (EXT) responding for two different groups of rats is also presented. Each bar represent the mean (± SEM) of data from 8 rats. * p < 0.01 compared to EXT; # p < 0.05, ## p < 0.01 compared to VEH + VEH

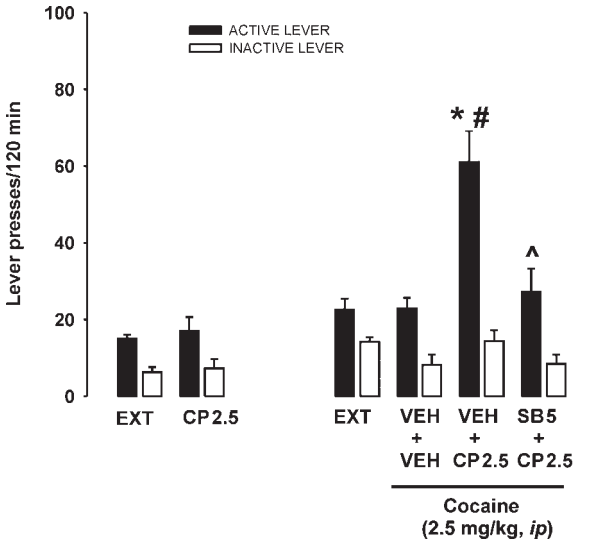

Fig. 4. Effect of the 5-HT$_{1B}$ receptor agonist CP 94253 (CP; 2.5 mg/kg) alone (left panel) or in combination with subthreshold dose of cocaine (2.5 mg/kg) on the reinstatement of cocaine-seeking behavior and blockade of its potentiating action by the 5-HT$_{1B}$ receptor antagonist SB 216641 (SB), 5 mg/kg (right panel). Number of the active (black bars) and inactive (white bars) lever presses following cocaine priming injections are shown for pretreatment with corresponding vehicle (VEH) + VEH, VEH + CP, SB + CP. The baseline extinction (EXT) responding is also presented. Each bar represent the mean (± SEM) of data from 7 rats. * p < 0.01 compared to EXT; # p < 0.01 compared to VEH + VEH; ^ p < 0.01 compared to VEH + CP

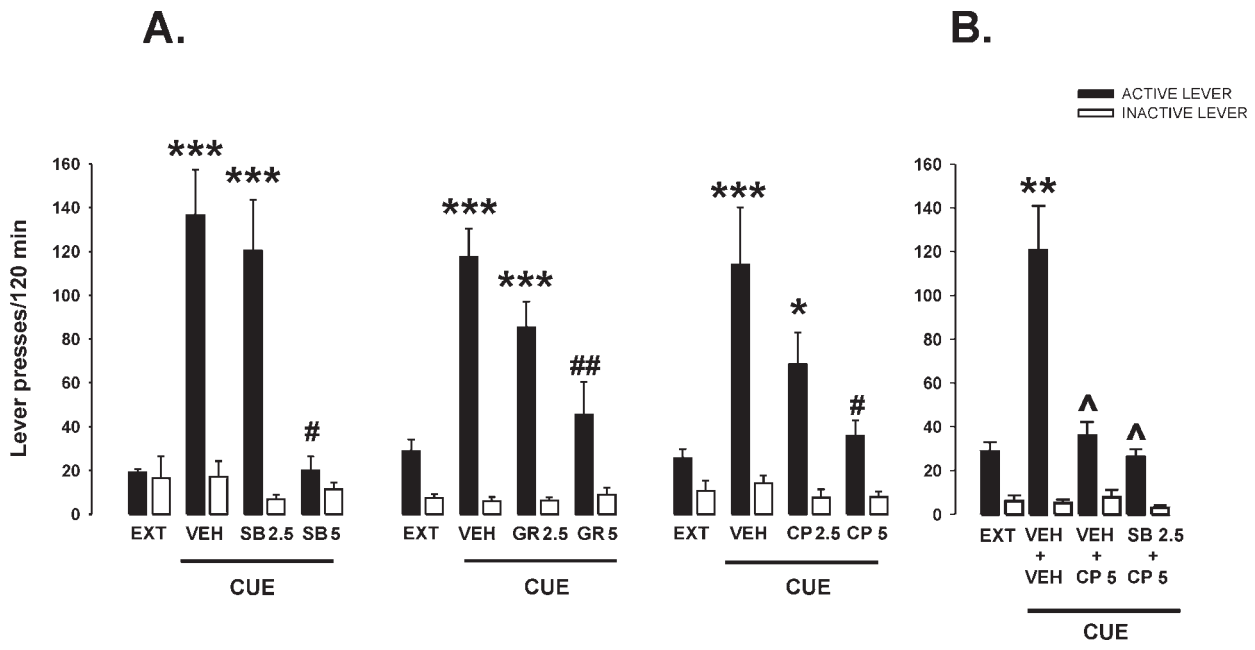

Fig. 5. Effects of 5-HT_{1B} receptor antagonists SB 216641 (SB; left **A** panel) and GR 127935 (GR; middle **A** panel) and the agonist CP 94253 CP; right **A** panel) and combination studies with SB 216641 plus CP 94253 **(B)** on the reinstatement of cocaine-seeking behavior induced by contingent presentation of cue. Number of the active (black bars) and inactive (white bars) lever presses following the cue are shown for pretreatment with the corresponding vehicle (VEH), SB 216641 (2.5–5 mg/kg), GR 127935 (2.5–5 mg/kg), CP 94253 (2.5–5 mg/kg) (A), VEH + VEH, VEH + CP 94253 (5 mg/kg), SB 216641 (2.5 mg/kg) + CP (5 mg/kg) (B). The baseline corresponding extinction (EXT) responding is also presented. Each bar represent the mean (± SEM) of data from 6–7 (A) or 8 rats (B). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared to EXT; # $p < 0.05$, ## $p < 0.001$ compared to VEH; ^ $p < 0.01$ compared to VEH + VEH

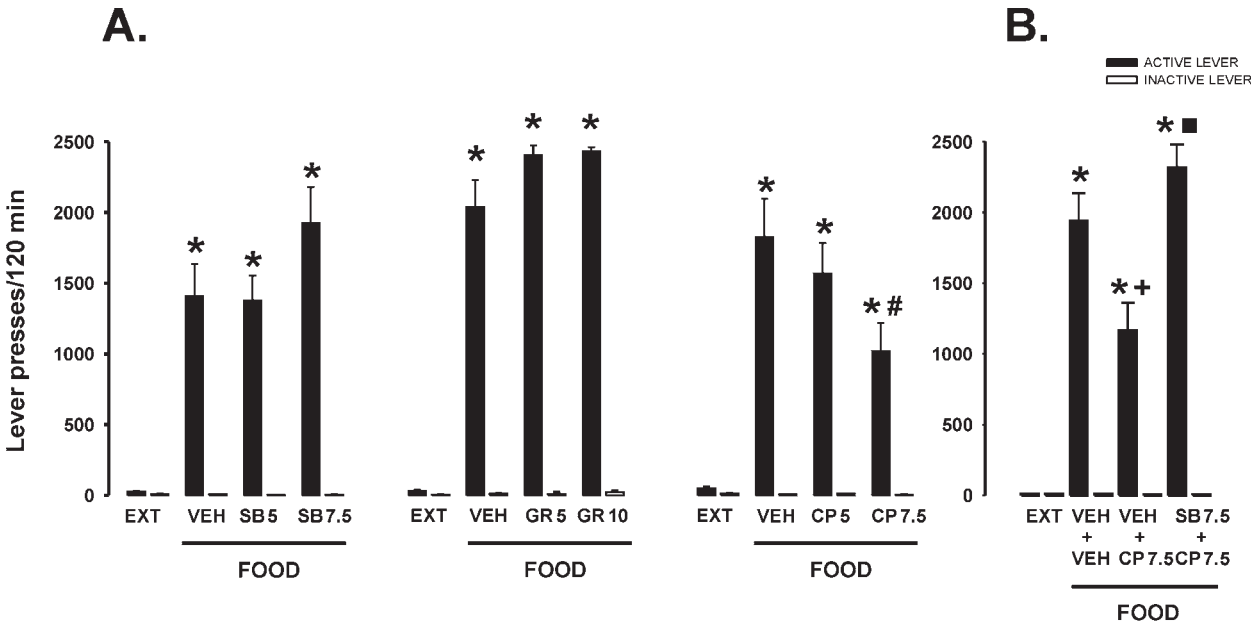

Fig. 6. Effects of 5-HT_{1B} receptor antagonists SB 216641 (SB; left **A** panel) and GR 127935 (GR; middle **A** panel) and the agonist CP 94253 CP; right **A** panel) and combination studies with SB 216641 plus CP 94253 **(B)** on the reinstatement of food-taking behavior induced by contingent presentation of food. Number of the active (black bars) and inactive (white bars) lever presses following the food presentation are shown for pretreatment with the corresponding vehicle (VEH), SB 216641 (5–7.5 mg/kg), GR 127935 (5–10 mg/kg), CP 94253 (5–7.5 mg/kg) (A), VEH + VEH, VEH + CP 94253 (7.5 mg/kg), SB 216641 (7.5 mg/kg) + CP (7.5 mg/kg) (B). The baseline corresponding extinction (EXT) responding is also presented. Each bar represent the mean (± SEM) of data from 6–8 (A) or 8 rats (B). * $p < 0.01$ compared to EXT; # $p < 0.05$ compared to VEH; + $p < 0.01$ compared to VEH + VEH; ■ $p < 0.01$ compared to VEH + CP

cant increase in active lever presses. SB 216641 (5 mg/kg) antagonized the increase in active lever presses following administration of CP 94253 + cocaine (Fig. 4, right panel).

Cue-induced reinstatement of cocaine-seeking behavior

After 10 days of extinction (during which the active lever presses resulted in the *iv* delivery of saline without the presentation of cocaine-associated cue) the rats were tested for response reinstatement induced by the cue. During cue-induced reinstatement tests (Fig. 5), rats responded more often on the active lever in relation to the inactive lever and to the extinction period.

The effects of 5-HT$_{1B}$ receptor ligands on the cue-induced reinstatement are shown in Figure 5A. SB 216641 (2.5–5 mg/kg) significantly altered the number of active [$F(3, 20) = 13.26$, $p < 0.01$], but not inactive [$F(3, 20) = 0.79$] lever presses. A significant decrease was observed following SB 216641, 5 mg/kg (Fig. 5A, left panel). GR 127935 (2.5–5 mg/kg) significantly altered the number of active [$F(3, 24) = 11.6$, $p < 0.001$], but not inactive [$F(3, 24) = 0.37$] lever presses. A significant decrease was observed following GR 127935, 5 mg/kg (Fig. 5A, middle panel). CP 94253 (2.5–5 mg/kg) significantly altered the number of active [$F(3, 24) = 6.47$, $p < 0.01$), but not inactive [$F(3, 24) = 0.72$] lever presses. A significant decrease was observed following CP 94253, 5 mg/kg (Fig. 5A, right panel).

The effects of combination of CP 94253 (5 mg/kg) with SB 216641 (2.5 mg/kg) on cocaine-associated cue-induced reinstatement of cocaine seeking behavior are shown in Figure 5B. A main effect for a treatment combination was observed for active [$F(1, 28) = 21.4$, $p < 0.001$), but not for inactive [$F(1, 28) = 0.48$] lever presses. CP 94253 produced a significant decrease in the response reinstatement on active lever induced by the cocaine-associated cue ($p < 0.01$). SB 216641 did not affect the decrease in active lever presses following administration of CP 94253 (5 mg/kg) and presentation of the cue.

Acquisition of food self-administration

Rats showed stable lever responding during the last 6 self-administration maintenance sessions with an acquisition criterion requiring that the rate of active lever presses varied by less than 10%. Rats responded significantly more frequently on the active lever than on the inactive lever ($p < 0.05$), independently of food self-administration test day.

Reinstatement of food-taking behavior

After 10 days of extinction the rats were tested for response reinstatement induced by the contingent presentation of food. During food-induced reinstatement tests (Fig. 6) rats responded more often on the active lever in relation to the inactive lever and to the extinction period.

The effects of 5-HT$_{1B}$ receptor ligands on reinstatement of food-taking behavior are shown in Figure 6A. SB 216641 (5–7.5 mg/kg) significantly altered the number of active [$F(3, 20) = 17.92$, $p < 0.001$], but not inactive [$F(3, 20) = 1.85$] lever presses. However, the individual dose groups of pretreatment with SB 216641 (5–7.5 mg/kg) in combination with food did not indicate a significant alteration in the reinstatement (Fig. 6A, left panel). GR 127935 (5–10 mg/kg) significantly altered the number of active [$F(3, 28) = 123.27$, $p < 0.001$], but not inactive [$F(3, 28) = 0.99$] lever presses. However, data from the individual dose groups of pretreatment with GR 127935 (5–10 mg/kg) in combination with food did not indicate a significant alteration in the reinstatement (Fig. 6A, middle panel). CP 94253 (5–7.5 mg/kg) significantly altered the number of active [$F(3, 20) = 15.65$, $p < 0.01$], but not inactive [$F(3, 20) = 2.53$] lever presses. A significant decrease was observed following CP 94253, 7.5 mg/kg (Fig. 6A, right panel).

Figure 6B shows the effects of combination of SB 216641 (7.5 mg/kg) with CP 94253 (7.5 mg/kg) on food-induced reinstatement of food-taking behavior. A main effect for a treatment combination was observed for active [$F(1, 20) = 6.45$, $p < 0.05$], but not for inactive [$F(1, 20) = 0.004$] lever presses. CP 94253 (7.5 mg/kg) produced a significant decrease in the response reinstatement on active lever induced by food ($p < 0.01$). SB 216641 antagonized the decrease in active lever presses following administration of CP 94253 and presentation of food (Fig. 6B).

Discussion

The results of the present study indicate for the first time that the 5-HT$_{1B}$ receptor antagonists (SB 216641

and GR 127935) significantly reduced or even almost completely blocked cocaine-primed or cocaine-associated cue-induced reinstatement of cocaine-seeking behavior, respectively. Since these antagonists failed to alter cocaine or food-maintained responding in the self-administration procedures, locomotor activity [51] or reinstatement of food-taking behavior (the present study), their effects on cocaine-seeking seem to be unrelated to motor artifacts and specific for the inhibition of incentive motivation for an artificial reinforcer (cocaine), but not for a natural reward. It is also noteworthy that almost complete blockade of cocaine-associated cue-induced reinstatement of cocaine-seeking was produced by 1.5–2 times lower doses of the antagonists than those necessary to inhibit cocaine-primed cocaine-seeking behavior. Since the conditioned-cued reinstatement models better simulate relapses in humans than the cocaine-primed reinstatement procedures [13, 30], the stronger inhibitory effects of SB 216641 and GR 127935 on cocaine-associated cue-induced reinstatement indicate that the 5-HT_{1B} receptor antagonists can be considered to be a potential therapeutic strategy for preventing relapse.

SB 216641 displays high affinity for 5-HT_{1B} receptors but its affinity at 5-HT_{1D} and other examined 5-HT receptors is at least 25 times lower. This antagonist has been reported to be a selective partial agonist of 5-HT_{1B} receptors in the cloned high receptor expression systems [48], but it fails to demonstrate any intrinsic activity in native tissues and functions as a silent antagonist of these receptors [27, 48, 57]. GR 127935 has high affinity for 5-HT_{1B} and 5-HT_{1D} receptors and in functional studies behaves as an antagonist of those receptors [23, 46]. Specifically, a number of papers have indicated that SB 216641 and GR 127935 administered at doses of 2 or 3–4 mg/kg, respectively, antagonized several behavioral or neurochemical effects induced by 5-HT_{1B} receptor agonists [1, 11, 12, 14, 25, 27, 28, 45, 51].

In our experiments we found that the doses of the 5-HT_{1B} receptor antagonists which inhibited cocaine- or cue-induced reinstatement of cocaine-seeking behavior were higher than those reported to be effective in blocking 5-HT_{1B} receptors. SB 216641 and GR 127935 were effective at doses of 5–7.5 mg/kg and 5–10 mg/kg, respectively, but not at lower doses. The latter finding supports earlier results of Acosta et al. [1] who reported that GR 127935 administered at a low dose of 3 mg/kg was ineffective in affecting cocaine-seeking behavior. It should be remembered, however, that the withdrawal from repeated treatment with cocaine (sensitization, discrimination or self-administration paradigms) induces up-regulation [49] and functional supersensivity [42] of 5-HT_{1B} receptors. Consequently, in our experiments on animals trained to self-administer cocaine and then exposed to cocaine or the cue priming following a 10-day extinction, higher doses of SB 216641 and GR 127953 were required to block 5-HT_{1B} receptors than those used in cocaine-naive animals. Taken together, our results on inhibitory effects of SB 216641 and GR 127935 on cocaine-primed and cue-induced reinstatement of cocaine seeking behavior suggest that both phenomena depend on the tonic activation of 5-HT_{1B} receptors. This conclusion, at least in the case of cocaine priming, is not unexpected, considering that the psychostimulant inhibits 5-HT reuptake and increases the extracellular 5-HT concentration [6].

Another finding of this paper shows the bi-directional effect of the selective 5-HT_{1B} receptor agonist CP 94253 [32] on the cocaine-primed reinstatement of cocaine seeking behavior. This compound had inhibitory or facilitatory influence depending on the priming dose (10 mg/kg or 2.5 mg/kg *ip*, respectively) of the psychostimulant. Actually, CP 94253 at a dose of 5 mg/kg inhibited cocaine-seeking behavior induced by the high-dose (10 mg/kg) psychostimulant challenge or by cocaine-associated cue. These effects were unexpected since CP 94253 and other 5-HT_{1B} receptor agonists enhance rather than inhibit the discriminative stimulus and reinforcing effects of cocaine [8, 20, 45, 51]. As the agonist reduced also reinstatement of food-taking behavior (the present study), produced satiety effect and reduced the frequency and duration of feeding behavior [35], its inhibitory effect on the cocaine-seeking behavior does not seem to be specific but related to general inhibitory effect on motivation for appetitive stimuli. It is, however, noteworthy that the higher dose of CP 94253 (7.5 mg/kg) was required to inhibit food-taking behavior than that (5 mg/kg) able to reduce cocaine-seeking.

In contrast to the reinstatement of food-taking behavior, the inhibitory effect of CP 94253 on cocaine-seeking behavior seems to be also unspecific in terms of its receptor activity. In fact, whereas the CP 94253-induced inhibition of reinstatement of food-taking behavior was blocked by SB 216641, the 5-HT_{1B} receptor agonist-induced inhibition of cocaine-primed or cue-induced reinstatement of cocaine-seeking behavior was not affected by SB 216641 (5 or 2.5 mg/kg,

respectively) and/or GR 127935 (5 mg/kg). However, it cannot be excluded that these doses were ineffective in blocking the 5-HT$_{1B}$ receptors, but either antagonist administered at 1.5–2 times higher doses inhibited cocaine seeking behavior and therefore they could not be used in combination with the inhibitory dose of the 5-HT$_{1B}$ receptor agonist. Nevertheless, the dose of 5 mg/kg of SB 216641 was sufficient to block the facilitatory effect of CP 94253 on the reinstatement of cocaine seeking behavior (see below). Our above observations differ from the results of Acosta et al. [1] who found that GR 127935 (administered at a dose of 3 mg/kg) blocked the inhibitory response of the 5-HT$_{1B/1A}$ receptor agonist RU 24969 on the reinstatement of cocaine-seeking behavior induced by 10 mg/kg of cocaine or cocaine-associated cue, and concluded that the stimulation 5-HT$_{1B}$ receptors was responsible for the inhibitory effects of RU 24969.

Since the dose of 10 mg/kg of cocaine may be close to the ceiling effect for the reinstatement of cocaine-seeking behavior, we also examined how CP 94253 affected cocaine-seeking behavior after the subthreshold priming dose (2.5 mg/kg) of the psychostimulant. Thus, the combination of the dose of CP 94253 (2.5 mg/kg), which *per se* did not induce reinstatement of cocaine-seeking behavior, with the subthreshold priming dose of cocaine, evoked the effect similar to that produced by higher doses of cocaine (5–10 mg/kg) given alone. Moreover, we have also found that the potentiating effect of the 5-HT$_{1B}$ receptor agonist was almost totally blocked by SB 216641. The latter observation shows that, in contrast to the unspecific inhibitory effect of CP 94253 when high priming cocaine dose (10 mg/kg) was given – the potentiating activity of the 5-HT$_{1B}$ receptor agonist at the subthreshold priming dose of the psychostimulant depends on 5-HT$_{1B}$ receptor stimulation. Importantly, the potentiating effect of CP 94253 is supported by earlier observations showing that the 5-HT$_{1B}$ receptor agonist enhances rewarding properties of cocaine [45, 51] and facilitates the effect of low doses of cocaine in the conditioned place preference paradigm, with the latter effect being antagonized by GR 127935 [11].

A large body of evidence indicates that DA plays a role in cocaine-seeking behavior [5, 58, 60, 61, 63] and that the NAcc shell is the brain structure involved in this phenomenon [2–4, 59]. Furthermore, a number of reports have indicated that 5-HT$_{1B}$ receptors may be regarded as modulators of the mesoaccumbal DA system. Indeed, this system contains both 5-HT$_{1B}$ receptor transcript and protein [7, 47]. These receptors act not only as autoreceptors inhibiting 5-HT release [29, 62], but also as inhibitory heteroreceptors present on nerve terminals of different neurotransmitter pathways, including DA-ergic ones [54, 55]. Nevertheless, the results of the *in vivo* experiments indicate that the stimulation of 5-HT$_{1B}$ receptors indirectly, *via* inhibition of GABA release, leads to an increase in basal and cocaine-induced extracellular DA concentrations in the NAcc [26, 43, 44, 69]. The above mechanism can be responsible for the potentiating effect of CP 94253 on the reinstatement of cocaine-seeking behavior induced by a subthreshold priming dose of the psychostimulant. At the same time, Castanon et al. [10] suggested that the blockade of 5-HT$_{1B}$ receptors increased GABA input in the VTA, and, consequently reduced the output of DA in the NAcc. In the light of the above suggestion, our results showing the inhibitory effects of the 5-HT$_{1B}$ receptor antagonists (SB 216641 and GR 127935) on cocaine-seeking behavior seem to be in conformity with the hypothesis of Castanon et al. [10]. On the other hand, the inhibitory effect of CP 94253 on the reinstatement of cocaine-seeking behavior evoked by the high priming dose (10 mg/kg) of the psychostimulant cannot be interpreted in terms of 5-HT$_{1B}$ receptor – accumbal DA interaction since the above behavioral effect of the 5-HT$_{1B}$ receptor agonist seems to be unrelated to activation of these receptors.

In conclusion, our findings indicate that the 5-HT$_{1B}$ receptor antagonists (SB 216641 and GR 127935) attenuate reinstatement of cocaine seeking behavior, while the agonist CP 94253 facilitates or inhibits this phenomenon depending on the priming dose of the psychostimulant (subthreshold or submaximal, respectively). While the effect of the antagonists is directly related to motivational aspects of cocaine abuse, the inhibitory effect of the agonist results from a general decrease in motivation. On the other hand, the facilitatory effect of CP 94253 may be due to the enhancement of rewarding properties of cocaine induced by the 5-HT$_{1B}$ receptor agonist. Moreover, the inhibitory effects of SB 216641 or GR 127935 and facilitatory effect of CP 94253 seem to be due to the blockade or stimulation of 5-HT$_{1B}$ receptors, respectively, while the importance of the stimulation of 5-HT$_{1B}$ receptors for the inhibitory effect of CP 94253 remains an open question.

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