



Role of serotonin (5-HT)₂ receptors in cocaine self-administration and seeking behavior in rats

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Abstract:

Previous studies have indicated a role of serotonin (5-HT)₂ receptors in modulation of the behavioral effects of cocaine. In the present study, the efficacy of SR 46349B (a 5-HT_{2A} receptor antagonist) or SDZ SER-082 (a 5-HT_{2C} receptor antagonist) in altering cocaine seeking behavior was examined in rats. Rats were trained to press a lever for cocaine (0.5 mg/kg/infusion, *iv*) paired with the cue (light + tone). After stabilization of self-administration response, the animals underwent daily extinction sessions during which responding had no consequences. The cocaine seeking behavior was reinstated by cocaine priming (10 mg/kg, *ip*) or by presentation of the cue. Neither SR 46349B (0.25–1 mg/kg) nor SDZ SER-082 (0.25–1 mg/kg) altered the maintenance of cocaine self-administration. SR 46349B (0.5–1 mg/kg) decreased responding to the cocaine priming dose and reduced cue-induced reinstatement, while SDZ SER-082 failed to alter both cue- and cocaine priming-induced reinstatement. These findings indicate that 5-HT_{2A} and 5-HT_{2C} receptors are not significant to cocaine rewarding effects. However, they show the importance of 5-HT_{2A} receptors (but not 5-HT_{2C} receptors) in cocaine-priming- and cue-provoked reinstatement. Since drugs that reduce cocaine seeking also alleviate cocaine craving, 5-HT_{2A} receptor antagonists may be considered to be of possible clinical application for the treatment of cocaine dependence.

Key words:

cocaine, 5-HT₂ receptors, reinstatement, self-administration

Introduction

A number of studies indicate the importance of dopamine (DA) neurotransmission in cocaine rewarding effects and in reinstatement of cocaine-seeking behavior [44, 62]. Thus, antagonists of the DA D₁-like and D₂-like receptors attenuate the cocaine-induced reinforcement in a self-administration model [4, 8, 40] or cocaine seeking behavior [30, 61]. Pharmacological stimulation of DA D₁-like receptors produces downward shifts in cocaine dose-effect functions [3, 10, 45] and decreases the ability of cocaine to

reinstatement drug-seeking behavior in rats [30, 55], while DA D₂-like receptor agonists have been found to maintain self-administration behavior [7, 8, 63], produce leftward shifts in cocaine dose-effect function [3, 9] and augment the cocaine-induced reinstatement of seeking behavior [30, 55].

In addition to its ability to block the reuptake of DA, cocaine blocks the reuptake of serotonin (5-HT) and norepinephrine [31, 47], therefore, 5-HT neurotransmission is also significant to altering cocaine reinforcement. For example, a decrease in 5-HT neurotransmission by 5,7-dihydroxytryptamine (a specific 5-HT neurotoxin) or by para-chlorophenylalanine

(p-CPA; an inhibitor of the tryptophan hydroxylase) increases motivation for cocaine [33, 50] and enhances cocaine-evoked reinstatement of seeking behavior [58, 59], while p-CPA attenuates cocaine seeking in a cocaine-free state, i.e. during extinction or after exposure to environment associated with the cocaine self-administration [58, 59]. A decrease in cocaine self-administration was found following enhancement of 5-HT neurotransmission by dietary supplementation with L-tryptophan, a 5-HT precursor [13, 37] or by administration of fluoxetine, a 5-HT uptake inhibitor [12, 43, 48; but in contrast see: 46, 57]. Fluoxetine also decreased cocaine-seeking behavior during extinction [2], and this 5-HT uptake inhibitor or fenfluramine (a 5-HT releaser/inhibitor) reduced cocaine seeking behavior after presentation of a cocaine self-administration environment [2, 6].

Recent studies indicate that, of 16 brain 5-HT receptors [27], 5-HT_{2A} and 5-HT_{2C} receptors may play an important regulatory role in the DA neurotransmission [15, 18, 25, 53] and behavioral effects of cocaine [11, 19–23, 35, 38]. Regarding cocaine rewarding effects, the 5-HT_{2C} receptor antagonist SB 242084 was found to enhance responding to cocaine under a low dose regimen [23] while the 5-HT_{2C} receptor agonist, RO 60-0175, reduced cocaine-induced reinforcing effects [26]. Preferential 5-HT_{2A} receptor antagonists (e.g. M100907, ketanserin, ritanserin) did not alter cocaine self-administration [23, 32, 42] or cocaine-induced reductions in brain self-stimulation reward thresholds [60]. Furthermore, 5-HT_{2A} receptor blockade [23] or pharmacological stimulation of 5-HT_{2C} receptors [26] attenuated cocaine-induced reinstatement of seeking behavior.

In the present study, self-administration procedures were employed to study whether the selective blockade of 5-HT_{2A} or 5-HT_{2C} receptors altered the reinstatement of cocaine-seeking behavior induced by cocaine priming or by a cocaine-associated cue. An extinction/reinstatement model in self-administration procedures was used as it seems to be the most adequate animal model for studying the craving and relapse phenomena [16, 24, 34]. Moreover, we evaluated the effects of SR 46349B, a 5-HT_{2A} receptor antagonist (IC₅₀ = 6 nM for 5-HT_{2A} receptors and > 16-fold 5-HT_{2A}/5-HT_{2C} receptor selectivity [49]), or SDZ SER-082, a 5-HT_{2C} receptor antagonist (K_D = 15 nM for 5-HT_{2C} receptors and > 42-fold 5-HT_{2C}/5-HT_{2A} receptor selectivity [41]) on respond-

ing maintained by cocaine under a fixed ratio (FR) 5 schedule of reinforcement.

Materials and Methods

Animals

Male Wistar rats (Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland) weighing 250–280 g at the beginning of the experiment were used. The rats were housed individually 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) and had free access to tap water and rodent chow. After a week quarantine, the animals were deprived of water for 18 h, then trained to press a lever for 2 h daily for water reinforcement on a FR 1 schedule of reinforcement. On the third day of the training, the number of responses required to produce reinforcement was increased to a final value of five (a 5-response FR schedule of reinforcement). During this phase of training, the amount of water each animal received was restricted to that given during daily training sessions and after sessions for 10 min.

All experiments were conducted during the light phase of the light-dark cycle (between 07:00–15:00 h) and were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Bioethics Commission as compliant with the Polish Law (August 21, 1997).

Surgery

Two days following lever-press training and free access to water, the rats were anesthetized with ketamine HCl (75 mg/kg, *ip*, Bioketan, Biowet, Puławy, Poland) and xylazine (5 mg/kg, *ip*, Sedazin, Biowet, Puławy, Poland) and chronically implanted with a silastic catheter in the external jugular vein, as described previously by McFarland and Kalivas [36]. For catheter implantation, a guide cannula (C313G, Plastics One Inc., Wallingford, USA), was attached to microrenathane tubing (MRE-040, Sandown Chemicals Ltd., Hampton, UK) and polypropylene mesh (Bard Mesh, Davol Inc., Cranston, USA) by dental cement. Then, it was inserted under the skin between

the shoulder blades and exited the skin *via* a dermal biopsy hole (3 mm). The other end of the tubing was threaded under the skin, inserted 3 cm into the right jugular vein, and then sutured securely to the underlying muscles. Catheters were flushed each day with 0.1 ml of saline solution containing heparin (70 U/ml, Biochemie, Austria) and 0.1 ml of solution of cephalozolin (10 mg/ml Biochemie GmbH, Kundl, Austria). Catheter patency was tested periodically, or whenever an animal displayed behavior outside baseline parameters, with the ultrashort-acting barbiturate anesthetic methohexital (10 mg/kg, *iv*) for loss of consciousness within 5 s.

Apparatus

Cocaine self-administration experiments were conducted in twelve standard operant chambers (MedAssociates, St. Albans, USA). Each chamber was equipped with a 24-V house light, located on the ceiling, two retractable levers on one wall, a water-filled dispenser mounted equidistantly between the levers, a white circular stimulus lamp illuminated by a 24-V bulb above each lever and a tone generator. Lever pressing on one of the levers (defined as “active”) resulted in drug delivery to the animal when the schedule (FR 5) requirements were met, whereas pressing on the other lever (defined as “inactive”) were recorded but not reinforced. Completion of each FR 5 produced *iv* infusions of cocaine through liquid swivel (Instech, Plymouth Meeting, USA) *via* an infusion pump (Model 3.33 RPM, MedAssociates, St. Albans, USA). The position of the “active” and “inactive” levers remained unchanged throughout the study. A house light was on during the experimental sessions. The operant chambers were enclosed in ventilated, sound-attenuating cubicles (MedAssociates, St. Albans, USA) and controlled by an IBM compatible computer using the MedAssociates MED-PC software package.

Cocaine self-administration procedure

Rats were allowed 10 days to recover before the start of the experiments. Initially, all animals deprived of water for 18 h were trained in one 2-h session to press the lever on an FR 5 schedule for water reinforcement. Then, subjects (N = 8–9 rats/group) began lever pressing for cocaine reinforcement and from that time

they were given water *ad libitum* throughout the remaining period of the experiment. Rats were given access to cocaine during 2-h daily sessions performed 6 days/week (maintenance). Each completion of an FR 5 schedule (i.e. 5 lever presses) on the “active” lever resulted in an infusion of cocaine (0.5 mg/kg over 5 s). Injection speed was adjusted according to the weight of each rat. A tone (2000 Hz; 15 dB above ambient) and illumination with the stimulus light directly above the “active” lever (i.e. the conditioned stimulus) was presented for 5 s, concurrently with a successful response for cocaine delivery. 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. Each training trial lasted for 2 h or until the subject had self-administered 25 infusions of cocaine. An arbitrary acquisition criterion required that the number of active lever presses varied by 10% or less over the course of 3 consecutive maintenance days.

Effects of 5-HT₂ receptor antagonists on cocaine self-administration

Once stable rates of responding were established, separate groups of rats were pretreated with either appropriate vehicle, SR 46349B (0.25–1 mg/kg) or SDZ SER-082 (0.25–1 mg/kg) before the test sessions. The order of injections was counterbalanced according to a Latin square design, and test sessions were separated by at least two-three baseline days of cocaine self-administration.

Effects of 5-HT₂ receptor antagonists on reinstatement of cocaine seeking behavior induced by cocaine priming

After the 18 days of self-administration, the rats were subjected to extinction trials for 10 days. During extinction, the animals had 2-h daily training sessions; however, active lever presses now resulted in neither the delivery of cocaine (saline was substituted for cocaine) nor the presentation of the conditioned stimulus. Rats remained in extinction until the responding on the active lever fell below 10% of the level observed during maintenance. After extinction, the rats were tested for response reinstatement induced by cocaine (10 mg/kg, *ip*). During reinstatement test (2 h session), active lever presses on the FR

5 schedule resulted only in an *iv* injection of saline and no cocaine was delivered. Separate groups of rats were pretreated with either appropriate vehicle, SR 46349B (0.5–1 mg/kg) or SDZ SER-082 (0.5–1 mg/kg) before *ip* injections of either saline or cocaine (10 mg/kg). Drug combinations were given in a randomized order and test sessions were separated by at least two–three extinction sessions.

Effects of 5-HT₂ receptor antagonists on reinstatement of cocaine seeking behavior induced by a cue associated with cocaine self-administration

After extinction (see above), the rats were tested for response reinstatement induced by a cue (tone + light) associated with cocaine *iv* infusions during the maintenance of cocaine self-administration. During reinstatement test (2-h session), active lever presses on the FR 5 schedule resulted only in a delivery of a tone and turning on the stimulus light directly above the

correct lever (i.e. the conditioned stimulus) presented concurrently with an *iv* injection of saline and not cocaine. Separate groups of rats were pretreated with either appropriate vehicle, SR 46349B (0.5–1 mg/kg) or SDZ SER-082 (0.5–1 mg/kg) before presentation of the conditioned stimulus (the cue). Drug combinations were given in a randomized order and test sessions were separated by at least two extinction sessions.

Drugs

Cocaine hydrochloride (Merck, Darmstadt, Germany), SDZ SER-082 [(+)-*cis*-4,5,7a,8,9,10,11,11a-octahydro-7H-10-methylindolo(1,7-BC)(2,6) naphthyridine fumarate, Tocris Cookson, Bristol, UK] and SR 46349B [1(Z)-[2-(dimethylamino)ethoxyimino]-1(2-fluorophenyl)-3-(4-hydroxyphenyl)-2(E)-propene, Sanofi, France] were used. Cocaine and SDZ SER-082 were dissolved in sterile 0.9% NaCl, SR 46349B was dissolved in

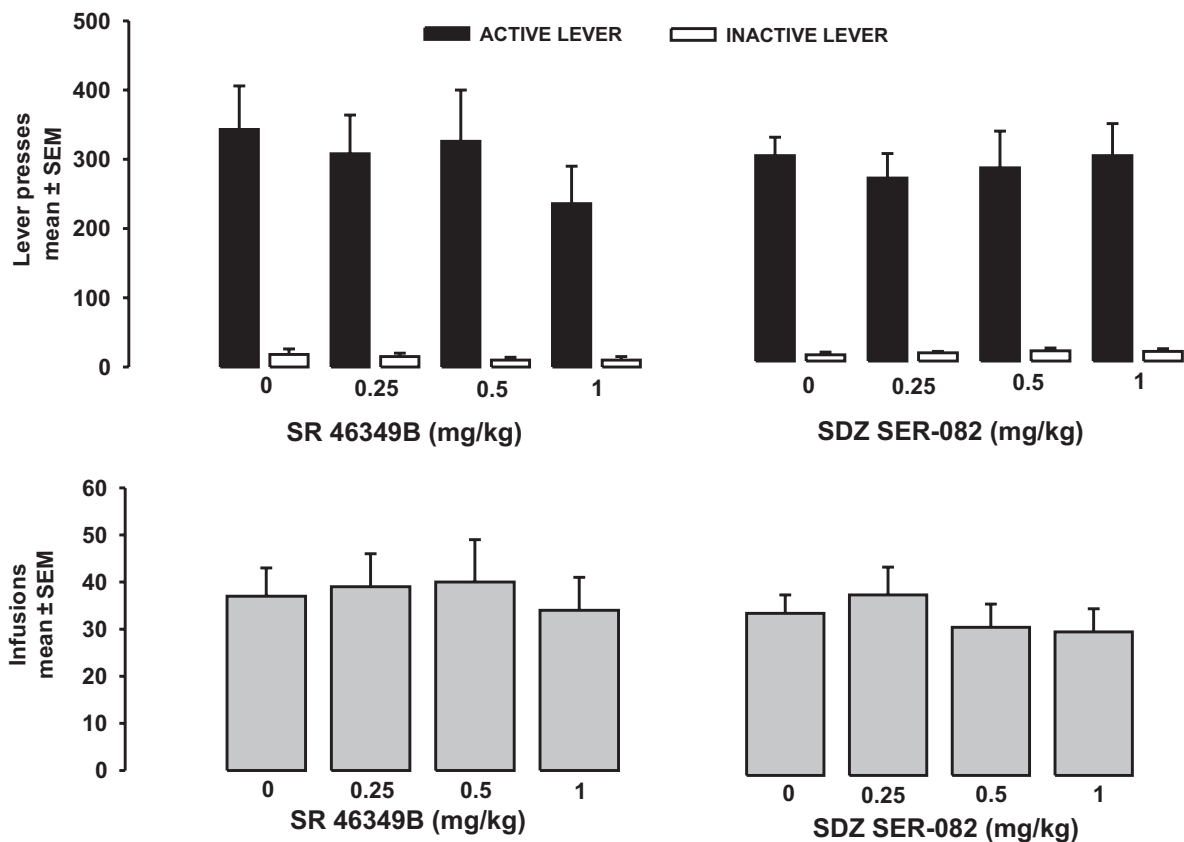


Fig. 1. Effects of SR 46349B and SDZ SER-082 on cocaine self-administration in rats responding under a FR 5 schedule of reinforcement. *Upper panels.* Effects of SR 46349B (0.25–1 mg/kg) and SDZ (0.25–1 mg/kg) on active (associated with cocaine self-administration) and inactive lever presses (mean ± SEM). *Lower panels.* Effects of SR 46349B (0.25–1 mg/kg) and SDZ (0.25–1 mg/kg) on number of infusions (mean ± SEM)

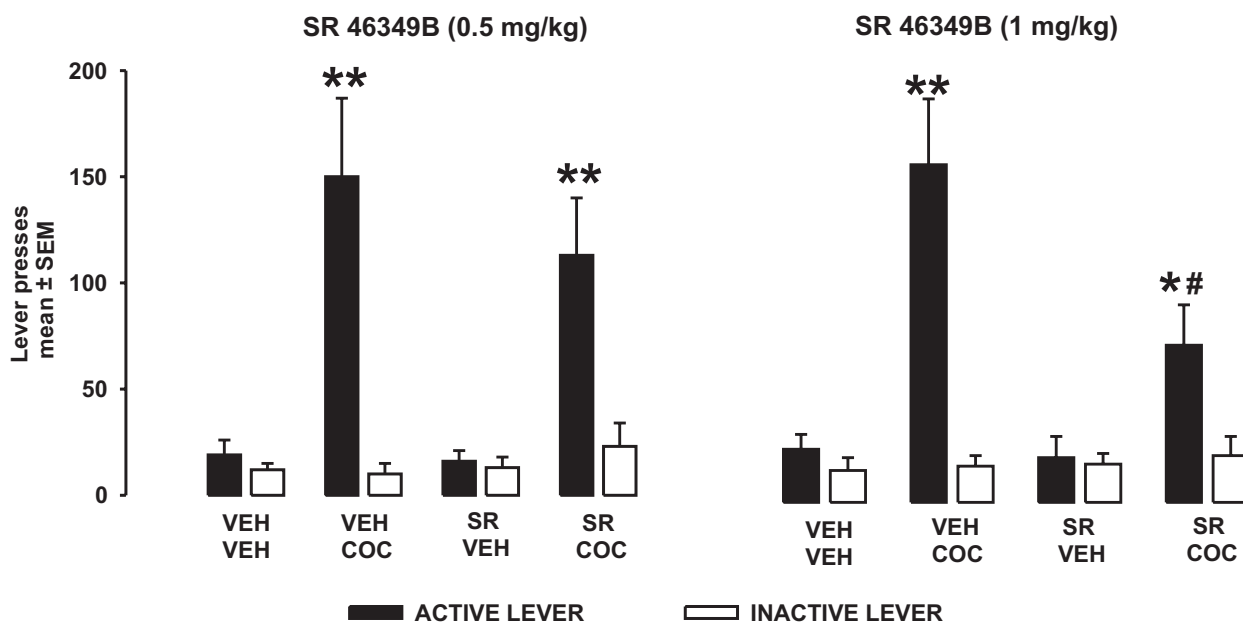


Fig. 2. Effects of SR 46349B on the reinstatement of cocaine seeking behavior induced by cocaine priming. Number of active (i.e. previously associated with cocaine self-administration) and inactive lever presses (mean \pm SEM) following SR 46349B administration at 0.5 mg/kg (*left*) or 1 mg/kg (*right*), in combination with cocaine (10 mg/kg, *ip*) or saline (*ip*). * $p < 0.05$, ** $p < 0.001$ vs. vehicle-vehicle; # $p < 0.05$ vs. vehicle-cocaine (Newman-Keuls' test)

2–3 drops of ethanol and diluted as required in distilled water. Cocaine was given either *iv* (0.05 ml/in-fusion) or *ip* (1 ml/kg). SDZ SER-082 and SR 46348B were injected either *ip* or *sc*, respectively, in a volume of 1 ml/kg.

Data analysis

During maintenance of cocaine self-administration, the number of responses on the active and inactive lever and the number of infusions were analyzed by a one-way analysis of variance (ANOVA) for repeated measures, with the dose of the 5-HT₂ receptor antagonist and cocaine serving as factors. During reinstatement of cocaine seeking behavior induced by cocaine priming, the number of responses on the active and inactive lever was analyzed *via* a two-way ANOVA for repeated measures for the factors of pre-treatment (vehicle vs. a dose of 5-HT₂ receptor antagonist), treatment (vehicle vs. cocaine), and the pre-treatment \times treatment interaction. *Post hoc* Newman-Keuls test was used to analyze preplanned, pairwise comparisons. During reinstatement of cocaine seeking behavior induced by the presentation of the cue, the

number of responses on the active and inactive lever were analyzed *via* a one-way analysis of variance (ANOVA) for repeated measures, with the dose of the 5-HT₂ receptor antagonist and cue serving as factors. *Post hoc* Dunnett's test was used to analyze differences between group means. The criterion for statistically significant differences was set at $p < 0.05$.

Results

Rats showed stable responding on levers 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%. The animals had self-administered 33–38 infusions of cocaine with the daily mean cocaine intake between 17–19 mg/kg. Rats responded significantly more frequently on the active lever than on the inactive lever ($p < 0.05$), independently of self-administration test day (Fig. 1).

Effects of 5-HT₂ receptor antagonists on cocaine self-administration

SR 46349B (0.25–1 mg/kg) did not change the number of active ($F_{3,28} = 0.54$) or inactive lever presses ($F_{3,28} = 1.51$). The number of cocaine infusion also remained unaltered ($F_{3,28} = 0.26$) (Fig. 1).

SDZ SER-082 (0.25–1 mg/kg) failed to alter the number of active ($F_{3,32} = 0.08$) or inactive lever presses ($F_{3,32} = 2.37$) or the number of cocaine infusion ($F_{3,32} = 0.49$) (Fig. 1).

Effects of 5-HT₂ receptor antagonists on reinstatement of cocaine seeking behavior induced by cocaine priming

After 10 days of extinction trials during which active lever presses resulted in the *iv* delivery of saline without the presentation of the conditioned stimulus (cue), the rats were tested for response reinstatement induced by cocaine (10 mg/kg, *ip*). During cocaine-primed reinstatement test, rats responded more often on the active lever in relation to the inactive lever ($p < 0.05$) and to the extinction period ($p < 0.05$). The responses on the inactive lever were not different across the days (Figs. 2–3).

Effects of SR 46349B (0.5 mg/kg). A main effect of treatment ($F_{1,28} = 20.29$, $p < 0.001$), but not pre-

treatment ($F_{1,28} = 0.64$) or a pretreatment \times treatment interaction ($F_{1,28} = 0.82$), was observed for total active lever responding. SR 46349B at 0.5 mg/kg neither altered the cocaine-primed reinstatement nor did it evoke reinstatement of seeking behavior when given alone (Fig. 2). There was no significant main effect of pretreatment ($F_{1,28} = 2.22$), treatment ($F_{1,28} = 0.73$) or a pretreatment \times treatment interaction ($F_{1,28} = 1.84$) observed for total inactive lever responding.

Effects of SR 46349B (1 mg/kg). A main effect of pretreatment ($F_{1,28} = 4.6$, $p < 0.05$), treatment ($F_{1,28} = 20.51$, $p < 0.001$) and a pretreatment \times treatment interaction ($F_{1,28} = 3.88$, $p < 0.05$) was observed for total active lever responding. SR 46349B at 1 mg/kg attenuated the cocaine-primed reinstatement and did not evoke reinstatement of seeking behavior, when given alone (Fig. 2). There was no significant main effect of pretreatment ($F_{1,28} = 2.22$), treatment ($F_{1,28} = 0.73$) or a pretreatment \times treatment interaction ($F_{1,28} = 1.84$) observed for total inactive lever responding.

Effects of SDZ SER-082 (0.5 mg/kg). A main effect of treatment ($F_{1,28} = 28.71$, $p < 0.001$), but not pretreatment ($F_{1,28} = 1.28$) or a pretreatment \times treatment interaction ($F_{1,28} = 0.93$), was observed for total active lever responding. SDZ SER-082 at 0.5 mg/kg did not alter the cocaine-primed reinstatement. This dose of the drug also did not evoke reinstatement of seeking behavior, when given alone (Fig. 3). There

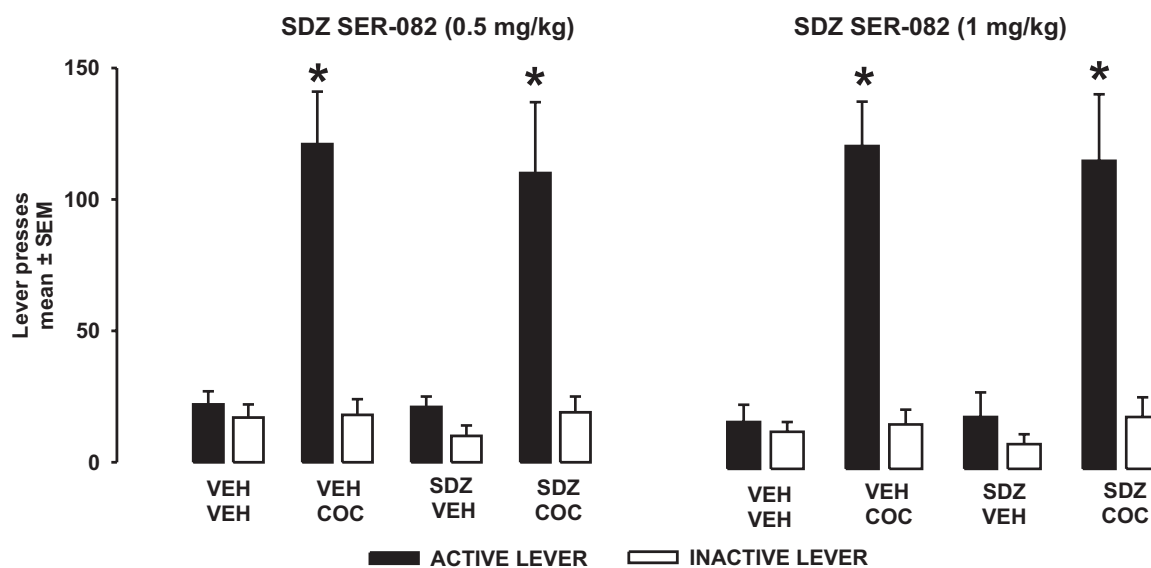


Fig. 3. Effects of SDZ SER-082 on the reinstatement of cocaine seeking behavior induced by cocaine priming. Number of active (i.e. previously associated with cocaine self-administration) and inactive levers presses (mean \pm SEM) following SDZ SER-082 administration at 0.5 mg/kg (left) or 1 mg/kg (right), in combination with cocaine (10 mg/kg, *ip*) or saline (*ip*). * $p < 0.001$ vs. vehicle-vehicle (Newman-Keuls' test)

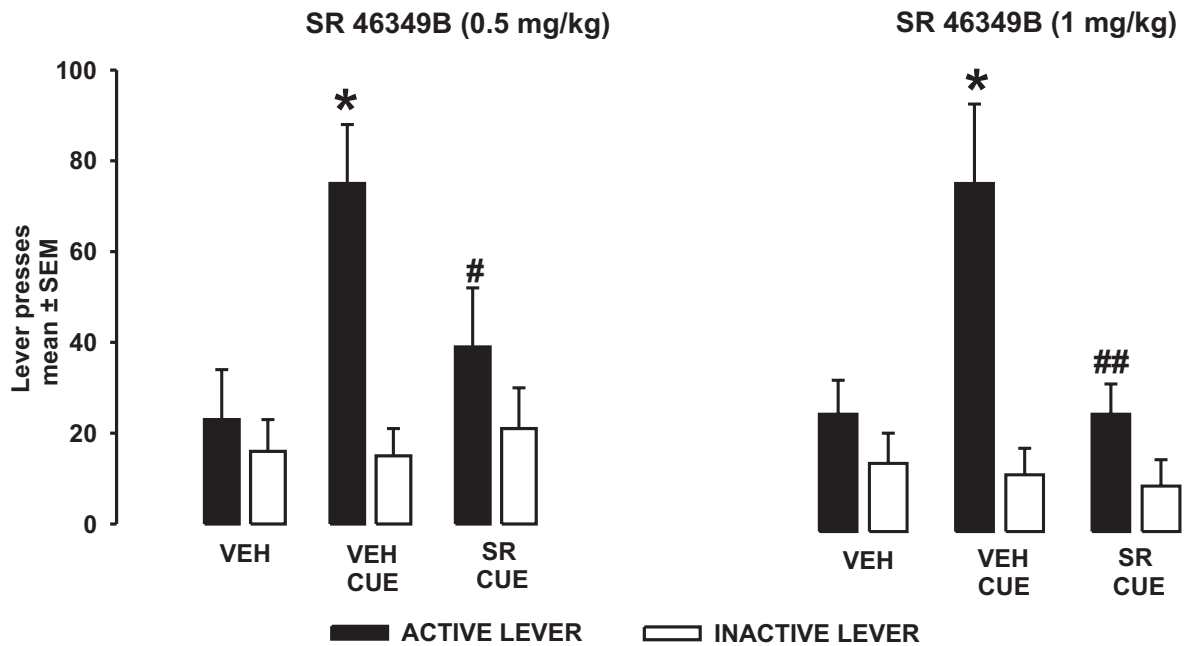


Fig. 4. Effects of SR 46349B on the reinstatement of cocaine seeking behavior induced by a cue associated with cocaine self-administration. Number of active (i.e. previously associated with cocaine self-administration) and inactive levers presses (mean \pm SEM) following SR 46349B administration at 0.5 mg/kg (*left*) or 1 mg/kg (*right*), in combination with the cue. * $p < 0.001$ vs. vehicle; # $p < 0.05$, ## $p < 0.01$ vs. vehicle-cue (Dunnett's test)

was no significant main effect of pretreatment ($F_{1,28} = 0.16$), treatment ($F_{1,28} = 4.31$) or a pretreatment \times treatment interaction ($F_{1,28} = 0.01$) observed for total inactive lever responding.

Effects of SDZ SER-082 (1 mg/kg). A main effect of treatment ($F_{1,28} = 32.38$, $p < 0.001$), but not pretreatment ($F_{1,28} = 0.91$) or a pretreatment \times treatment interaction ($F_{1,28} = 0.83$), was observed for total active lever responding. SDZ SER-082 at 1 mg/kg neither altered the cocaine-primed reinstatement nor did it evoke reinstatement of seeking behavior, when given alone (Fig. 3). There was no significant main effect of pretreatment ($F_{1,28} = 0.05$), treatment ($F_{1,28} = 4.11$) or a pretreatment \times treatment interaction ($F_{1,28} = 0.33$) observed for total inactive lever responding.

Effects of 5-HT₂ receptor antagonists on reinstatement of cocaine seeking behavior induced by the cue associated with cocaine self-administration

After 10 days of extinction trials during which active lever presses resulted in the *iv* delivery of saline without the presentation of the conditioned stimulus (cue), the rats were tested for response-reinstatement in-

duced by the presentation of the cue paired previously with cocaine infusions. During the cue-induced reinstatement test, the rats responded more frequently on the active lever in relation to the inactive lever ($p < 0.05$) and to extinction period ($p < 0.05$). The responses on the inactive lever were not different across the days (Figs. 4–5).

Effects of SR 46349B (0.5 mg/kg). A main effect of treatment ($F_{2,21} = 16.35$, $p < 0.001$) was observed for total active lever responding. SR 46349B at 0.5 mg/kg attenuated the response reinstatement induced by the presentation of the cue (Fig. 3). There was no significant main effect of treatment ($F_{2,21} = 0.69$) observed for total inactive lever responding.

Effects of SR 46349B (1 mg/kg). A main effect of treatment ($F_{2,21} = 20.12$, $p < 0.001$) was observed for total active lever responding. SR 46349B at 1 mg/kg reduced the response reinstatement induced by the presentation of the cue to the level that was not different from vehicle-treated control (Fig. 4). There was no significant main effect of treatment ($F_{2,21} = 1.13$) observed for total inactive lever responding.

Effects of SDZ SER-082 (0.5 mg/kg). A main effect of treatment ($F_{2,21} = 18.03$, $p < 0.001$) was observed for total active lever responding. SDZ SER-082 at

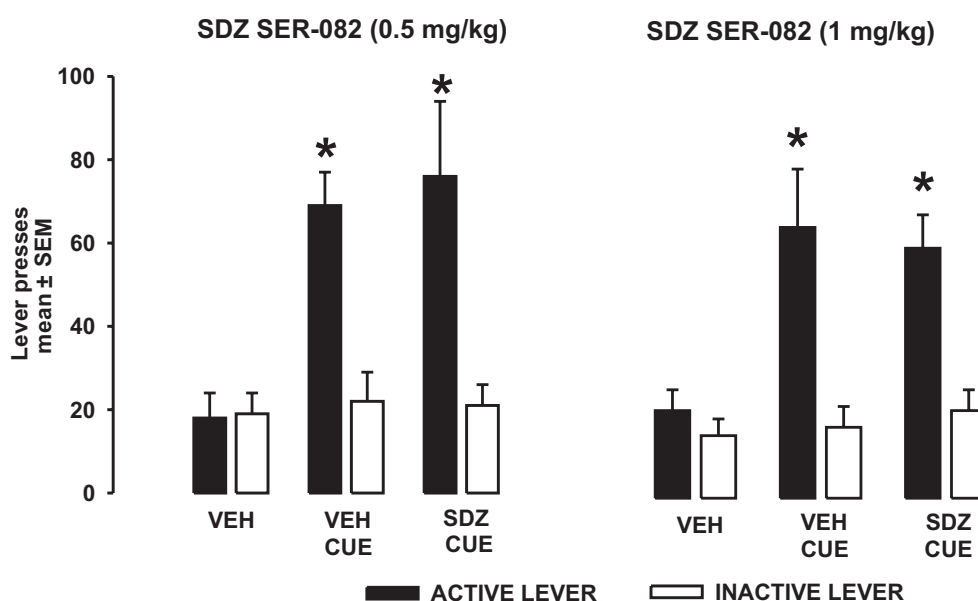


Fig. 5. Effects of SDZ SER-082 on the reinstatement of cocaine seeking behavior induced by a cue associated with cocaine self-administration. Number of active (i.e. previously associated with cocaine self-administration) and inactive levers presses (mean \pm SEM) following SDZ SER-082 administration at 0.5 mg/kg (*left*) or 1 mg/kg (*right*), in combination with the cue. * $p < 0.001$ vs. vehicle (Dunnett's test)

0.5 mg/kg failed to alter the response reinstatement induced by the presentation of the cue (Fig. 5). There was no significant main effect of treatment ($F_{2,21} = 0.54$) observed for total inactive lever responding.

Effects of SDZ SER-082 (1 mg/kg). A main effect of treatment ($F_{2,21} = 15.22$, $p < 0.001$) was observed for total active lever responding. SDZ SER-082 at 1 mg/kg did not alter the response reinstatement induced by the presentation of the cue (Fig. 5). There was no significant main effect of treatment ($F_{2,21} = 0.97$) observed for total inactive lever responding.

Discussion

The present study demonstrated that 5-HT_{2A} receptors, but not 5-HT_{2C} ones, played a significant role in cocaine-seeking behavior in rats. In fact, SR 46349B, a 5-HT_{2A} receptor antagonist, reduced the cocaine- or cocaine-associated cue-induced reinstatement of cocaine-seeking, while SDZ SER-082, a 5-HT_{2C} receptor antagonist, was inactive in those models. Moreover, we observed that neither SR 46349B nor

SDZ SER-082 affected cocaine self-administration maintained on the FR 5 schedule.

The failure of 5-HT_{2A} or 5-HT_{2C} receptor blockade to control cocaine self-administration is not likely to be due to an inadequate dosing since SR 46349B or SDZ SER-082 were used in a dose range that induced a functional blockade of the respective receptors [25, 41, 49, 54] and altered hyperlocomotor effects of cocaine [19]. In line with the present findings, other preferential 5-HT_{2A} receptor antagonists (e.g. M100907, ketanserin, ritanserin) have not changed cocaine self-administration [23, 32, 42] or cocaine-induced reductions in brain self-stimulation reward thresholds [60]. Similarly to our results with SDZ SER-082, another 5-HT_{2C} receptor antagonist, SB 242984, caused no alterations in the responding for cocaine infusion at doses ranging between 0.25–0.5 mg, however, some enhancing effects of SB 242084 limited to cocaine low-dose infusion (0.125 mg) were observed [23]. Despite the observation that blockade of 5-HT_{2C} receptors failed to alter responding for cocaine, the 5-HT_{2C} receptor agonist, RO 60-0175, was found to suppress cocaine-maintained responding [26] what provides evidence of a role of pharmacological stimulation of 5-HT_{2C} receptors in this behavior. However, it should be stressed that RO 60-0175 reduced food-

maintained responding, when administered in the same dose-range that suppressed cocaine self-administration [26], what may indicate that 5-HT_{2C} receptor stimulation causes a nonspecific motivational deficit for different classes of reinforcers.

The present paper also reports that SR 46349B given before the priming dose of cocaine dose-dependently decreased effectiveness of cocaine in reinstating the lever responding. Since the reinstatement was initiated by *ip* cocaine administration by an experimenter, the question arises whether SR 46349B directly altered the incentive motivational effects of cocaine or other processes (e.g. stimulant effects of cocaine or anxiety) were involved. In fact, it has been demonstrated that SR 46349B exerted an inhibitory influence on cocaine locomotor hyperactivation [19], but it is unlikely that this antagonist attenuated cocaine-primed reinstatement by a disruption of operant behavior since the effective doses of SR 46349B did not reduce lever pressing during maintenance of cocaine self-administration (present paper), or basal locomotor activity [19] and lever pressing during reinstatement tests (present paper), when the drug was given alone. Similarly, it should not be expected that potential anxiolytic activity of SR 46349B accounted for its inhibitory effects on the cocaine-induced reinstatement of seeking behavior since much higher doses (> 5 mg/kg) of SR 46349B than those used in this study reduced inhibitory avoidance representing learned fear in the T-maze test [39]. In the elevated-plus maze test, SR 46349B (1–10 mg/kg) either did not demonstrate anxiolytic action [14] or even its anxiogenic effects were detected [56]. It should also be added that 5-HT_{2C} rather than 5-HT_{2A} receptor antagonists possess anxiolytic-like activity in rodent models [28, 29, 39], and SDZ SER-082, in the same dose-range (0.5–1 mg/kg) as used in the present paper, reduced inhibitory avoidance in the T-maze test [39] while it did not alter the cocaine- or the cue-induced reinstatement of cocaine seeking (present paper; see below).

The priming effect of cocaine might also serve as a discriminative stimulus and indirectly influence motivation by signaling the availability of cocaine [16, 52]. SR 46349B and other 5-HT_{2A} receptor antagonists reduced discriminative stimulus effects of cocaine in rats [38, Filip, Bubar and Cunningham, unpublished observations], thus, it is possible that SR 46349B reduced the priming effect of cocaine by blocking the discriminative stimulus properties of co-

caine. However, SR 46349B reduced the cocaine-paired cue-induced reinstatement evident as a decrease in responding following vehicle (in a cocaine-free state), and this effect was even more potent than the influence of the drug on the cocaine priming effect. Therefore, it is postulated that antagonistic effects of SR 46349B on the reinstatement of cocaine seeking can be attributed to its specific diminishing action on the sensitivity to the incentive motivational effects of cocaine and to the conditioned reinforcement induced by the cocaine-paired cues.

The role of 5-HT_{2A} receptors in controlling the reinstatement of cocaine-seeking behavior is strongly supported also by other recent studies showing that the selective 5-HT₂ receptor antagonist M100907 attenuated the cocaine-induced reinstatement of responding [23], while nonselective 5-HT_{2A/2C} receptor blockers ketanserin or ritanserin were inactive in this respect [5, 51]. The mechanism by which 5-HT_{2A} receptors control cocaine-seeking behavior is likely mediated through modulation of DAergic neurotransmission. In fact, the mesolimbic DA release is thought to play a role in cocaine-primed reinstatement of cocaine-seeking behavior [1, 30, 61] and microdialysis assays suggest that 5-HT_{2A} receptors are engaged in controlling of DA neurotransmission under “stimulated” conditions [15, 53].

In contrast to the evidence that 5-HT_{2A} receptors are critical for mediating cocaine-primed and in cue-induced reinstatement, the present study failed to show a role of 5-HT_{2C} receptors in reinstatement of cocaine seeking. The finding that the selective 5-HT_{2C} receptor antagonist, SDZ SER-082, did not alter cocaine-primed reinstatement is consistent with the previous research which showed that another 5-HT_{2C} receptor antagonist, SB 242084, did not change the responding after priming with cocaine [5, but see also 23]. The present results and those of Burmeister et al. [5] contrast with the previous findings that 5-HT_{2C} receptors exert an inhibitory influence on the mesolimbic DA neurotransmission [17, 18] and on cocaine-induced hyperactivation [19, 23, 35]. On the other hand, pharmacological stimulation of 5-HT_{2C} receptors attenuates cocaine-induced reinstatement [26] and hyperactivation after acute and repeated cocaine administration [19]. The lack of inhibitory effect of SDZ SER-082 on the cocaine-induced reinstatement of seeking behavior may suggest that withdrawal from repeated cocaine exposure during self-administration might alter the function of 5-HT_{2C}

receptors and/or their “downstream” signaling. Such hypothesis seems to be supported by our recent observation that 5-HT_{2C} receptor sensitivity is reduced during withdrawal from repeated cocaine administration [19].

The present findings indicate that 5-HT_{2A} and 5-HT_{2C} receptors are not significant to cocaine rewarding effects. However, they show the importance of 5-HT_{2A} receptors (but not 5-HT_{2C} receptors) in cocaine-primed and cue-induced reinstatement. Since drugs that reduce cocaine seeking also reduce cocaine craving [2, 24], 5-HT_{2A} receptor antagonists may be considered to be of possible clinical application for the treatment of cocaine dependence.

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