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SEROTONIN$_{1B}$ RECEPTOR LIGANDS IN THE NUCLEUS ACCUMBENS SHELL DO NOT AFFECT THE DISCRIMINATIVE STIMULUS EFFECTS OF AMPHETAMINE IN RATS

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Serotonin$_{1B}$ receptor ligands in the nucleus accumbens shell do not affect the discriminative stimulus effects of amphetamine in rats. M. FILIP, E. NOWAK, L. BARAN, E. PRZEGALIŃSKI. Pol. J. Pharmacol., 2001, 53, 449–457.

Enhanced dopamine neurotransmission particularly, in the target area of the mesolimbic system, i.e. the nucleus accumbens (NAc), seems to be critical for the behavioral effects of amphetamine in rodents. Nonetheless, recent findings have also demonstrated a modulatory role of 5-hydroxytryptamine (5-HT; serotonin) in these effects. In the present study, we examined whether 5-HT$_{1B}$ receptors in the NAc shell are engaged in the discriminative stimulus of amphetamine. To this end male Wistar rats were trained to discriminate amphetamine (1 mg/kg, *ip*) from saline (*ip*) in a two-lever, water reinforced fixed ratio (FR) 20 task. After acquiring the amphetamine-saline discrimination, rats were stereotaxically implanted with bilateral cannulae aimed at the NAc shell and then infused with selective 5-HT$_{1B}$ receptor ligands. The ability of these drugs to substitute for or to alter (enhance or antagonize) the discriminative stimulus effects of amphetamine was examined. When given systemically, amphetamine (0.125–1 mg/kg) produced a dose-dependent increase in drug-lever responding. In substitution studies, microinjection of the 5-HT$_{1B}$ receptor agonist CP 93129 (1–10 μg/side) or the 5-HT$_{1B}$ receptor antagonist GR 55562 (1–10 μg/side) into the NAc shell did not evoke amphetamine-lever responding. Combination tests of 5-HT$_{1B}$ receptor ligands demonstrated that local injection with fixed doses of CP 93129 (1 or 10 μg/side) or GR 55562 (1 or 10 μg/side) with the submaximal doses of amphetamine (0.125–0.5 mg/kg) did not modify dose-response curves of the psychostimulant, nor did it affect its ED$_{50}$ value.

Our results seem to exclude a role for the NAc shell 5-HT$_{1B}$ receptors in the control of the discriminative stimulus effects of amphetamine. These findings also show that pharmacological stimulation of those receptors does not affect the amphetamine discrimination in rats.

Key words: *5-HT$_{1B}$ receptors, amphetamine, CP 93129, GR 55562, discriminative stimulus effects, rats*

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INTRODUCTION

Several studies contribute brain dopamine neurotransmission in the behavioral effects of amphetamine. In fact, this psychostimulant augments the extracellular content of dopamine by promoting its reverse transport [38, 40] and such an increase appears mainly in a terminal region of the mesolimbic dopamine pathway, i.e. the nucleus accumbens (NAc, [21]). A vast body of evidence reveals that the latter brain structure is closely related to locomotor, reinforcing and discriminative stimulus properties of amphetamine [14, 25, 29, 41]. It is noteworthy, that the NAc has been subdivided into two subregions (the shell and core) on the basis of histochemical and connectional differences [19]. Furthermore, both parts of the NAc show also functional distinctions, especially to conventional rewards and to drugs of abuse [18, 25]. In fact, it has been demonstrated that – preferentially in the shell of NAc – amphetamine and other abused drugs increase dopamine neurotransmission [5, 17, 33], induce locomotor activation [13, 18] and are self-administered [11, 27].

Besides dopamine, amphetamine promotes also 5-hydroxytryptamine (5-HT; serotonin) release *via* a direct effect on the 5-HT transporter [36, 37]. Several findings indicate an involvement of 5-HT neurotransmission in the behavioral effects induced by amphetamine [9, 20, 22, 28, 43]. Interestingly, recent studies have shown that among 5-HT receptors, 5-HT_{1B} play a critical role in the expression of dopamine-mediated neurochemical and behavioral effects of amphetamine and other psychostimulants: 1) the transcript and protein for 5-HT_{1B} receptors are found at the level of the cell body and at the terminals of the dopamine mesolimbic system [1, 3]; 2) systemic activation of 5-HT_{1B} receptors enhances basal [2, 15] and drug-stimulated [30] extracellular dopamine levels in the NAc; 3) agonists of 5-HT_{1B} receptors increase locomotor and sensitizing effects of amphetamine [35] or cocaine [34] and reinforcing effects of the latter psychostimulant [31]; they also engender a dose-dependent leftward shift in the amphetamine (Filip et al., unpublished results) and cocaine dose-response curve in a drug discrimination model [6, 7, 12]. On the other hand, antagonists of 5-HT_{1B} receptors inhibit psychostimulant-induced locomotor hyperactivity [34, 35].

In the present study, we investigated the relationship between discriminative stimulus effects of amphetamine and 5-HT_{1B} receptors in the NAc shell. To that end we used a drug discrimination model in rats which models the subjective effects of amphetamine in humans [39] and employed the new and most selective 5-HT_{1B} receptor ligands, i.e. the agonist 1,4-dihydro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-5H-pyrrolo[3,2-b]pyridin-5-one (CP 93129, [24]) and the antagonist 3-(3-dimethylamino)propyl)-4-hydroxy-N-[4-(4-pyridinyl)-phenyl]benzamide (GR 55562, [42]). The 5-HT_{1B} receptor ligands were administered directly to the NAc shell. The latter subregion of the NAc expresses higher levels of mRNA and binding sites for 5-HT_{1B} receptors than the NAc core [1].

MATERIALS and METHODS

Animals

The experiment was performed on male Wistar rats (280–300 g). The animals were housed in groups of two to a cage at a room temperature of 20 ± 1°C on a 12 h light/dark cycle (the light on between 6.00–18.00 h). Although food (Labofeed pellets) was always available, the water that each animal received was restricted to the amount given during training sessions in the operant chambers, after test sessions (15 min), and on weekends. All the experiments were carried out in compliance with the Polish Animal Protection Bill of April 21, 1997, and with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Drugs

The following drugs were used (in parentheses: pre-session injection times, suppliers): (+)-amphetamine sulfate (–15 min; Sigma, USA), 1,4-dihydro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-5H-pyrrolo-[3,2-b]pyridin-5-one (CP 93129; –15 min; Pfizer, USA) and 3-[3-(dimethylamino)propyl]-4-hydroxy--N-[4-(4-pyridinyl)phenyl]benzamide dihydrochloride (GR 55562; –15 min; Tocris, UK). Amphetamine was injected intraperitoneally (*ip*) in a volume of 1 ml/kg. CP 93129 and GR 55562 were injected intracranially in a volume of 0.2 μl/side.

Apparatus

Commercially available, two-lever operant chambers (Med-Associates; USA) were used. Each chamber was equipped with a water dispenser mounted equidistant between two response levers on one

wall and contained in a light- and sound-attenuating shell. Illumination was provided by a 28-V house light; ventilation and masking noise were supplied by a fan. A computer was used to program and record all the experimental events.

Discrimination procedure

Rats were trained to discriminate amphetamine (1 mg/kg) from saline (0.9% NaCl). The drug or saline were administered *ip* 15 min before daily (Monday–Friday) sessions (30 min). The initial training ("errorless" training) began under a fixed ratio (FR) 1 schedule of continuous water reinforcement with only a stimulus-appropriate (drug or saline) lever presented. The ratio schedule was increased until all the animals responded reliably under an FR 20 schedule for each experimental condition. Half of the animals were reinforced for left-lever responses after drug administration and for right-lever responses after saline. The conditions were reversed for the remaining animals. To control possible development of position cues on the basis of olfactory stimuli, a pseudorandom relationship was maintained between the lever programmed to deliver reinforcement for each consecutive subject, run in the same experimental chamber [10]. During that phase of training, amphetamine and saline were administered in nonsystematic order, and neither training condition prevailed for more than three consecutive sessions.

When the responding stabilized on an FR 20 schedule, discrimination training started with both levers presented simultaneously. The rats were required to respond on the stimulus-appropriate (correct) lever to obtain reinforcement (water); there were no programmed consequences of responding on the incorrect lever. That phase of training continued until all the animals fulfilled the criterion (an individual mean accuracy of at least 80% correct responses before the first reinforcer during 10 consecutive sessions). After the rats acquired the amphetamine-saline discrimination, the training sessions were shortened from 30 to 15 min.

Test sessions were initiated once all the animals met the above-mentioned criterion, and were conducted once or twice a week. Amphetamine and saline sessions intervened between test sessions to maintain discrimination accuracy. Only rats that met an 80% performance criterion during the preceding amphetamine and saline sessions were used in the tests. During the test sessions, the animals were placed in chambers in the same manner as during training sessions. Upon completion of 20 responses on either lever, or after a session time (15 min) elapsed, a single reinforcer was delivered, and the animals were removed from the chamber. In the home cages all the rats were allowed 15 min of free access to water.

Several pharmacological manipulations were employed during test sessions. A systemic dose-response curve for amphetamine was established before and after surgical implantation of cannulae; rats were tested 15 min after an injection of amphetamine (0.125–1 mg/kg, *ip*). In intracranial substitution tests, lever selection was assessed 15 min after bilateral intracranial injection of sterile saline (0.9% NaCl; 0.2 μl/side), CP 93129 (1 and 10 μg/side) or GR 55562 (1 and 10 μg/side) paired with a systemic injection of saline (1 ml/kg, *ip*). Control tests were also conducted in which rats were tested for lever selection 15 min following administration of either saline or amphetamine (1 mg/kg, *ip*) which had been immediately preceded by intracranial injection of saline (0.2 μl/side). In combination tests, intracranial administration of CP 93129 (1 and 10 μg/side) or GR 55562 (1 and 10 μg/side) immediately preceded an *ip* injection of amphetamine (0.125–0.5 mg/kg) which produced < 80% amphetamine-lever responding when given alone ("potentiation"); rats were tested for lever selection 15 min later.

Cannulae implantation

After acquisition of the amphetamine-saline discrimination, rats were anesthetized with an intramuscular (*im*) injection of 100 mg/kg of ketamine and 65 mg/kg of xylazine in sterile saline (0.9% NaCl). With the upper incisor bar of a Kopf stereotaxic instrument positioned at –3.3 mm below the interaural line and using the intersection of the bregma and the longitudinal sutures as the origin, the bilateral 28-gauge guide cannulae (Plastics One Inc., USA) were positioned 2 mm above the nucleus accumbens shell (AP = –1.7 mm from bregma, ML = ± 0.5 mm, DV = –6 mm, [32]). The guide cannulae were fastened to the skull with stainless steel screws (Small Parts, USA) and cranioplastic cement (Plastics One Inc., USA). Each guide cannula was fitted with a 28-gauge stainless steel bilateral obturator (Plastics One Inc., USA). Rats received two injections of penicillin (10.000 units/kg, *im*) after surgery, and were allowed a 1-week recovery

period during which rats were handled and weighed daily.

Microinjection protocols

Following recovery, discrimination training was reinstated. After several weeks, the systemic dose-response curve for amphetamine was reestablished and did not differ from that established prior to surgery (data not shown); the post-surgical dose-response curve served as a control in the present experiment. During that period, rats were habituated to the brief confinement associated with the intracranial microinjection technique by removing the 28-gauge internal obturators, gently restraining the rats for approximately 3 min, and replacing the obturators. For each microinjection, the 28-gauge bilateral obturators were removed and two 33-gauge stainless steel bilateral internal cannulae (Plastics One Inc., USA) were positioned 2 mm below to the bilateral guide cannulae tips. The bilateral internal cannulae were attached to two 5-µl Hamilton syringes *via* PE-50 tubing (Small Parts, USA). A microsyringe drive (BAS, West Lafayette, USA) driven by a programmable controller (Bee Hive Controller, BAS) delivered a volume of 0.2 µl/side at a rate of 0.1 µl/min. Injection cannulae remained in place for an additional 1 min to allow for diffusion away from the cannulae tips.

Histology

At the completion of the study, rats were overdosed with chloral hydrate (800 mg/kg, *ip*), the brains were removed and stored in a 20% sucrose/10% formalin solution for at least 3 days before the sectioning. Brain sections (50 µm) were mounted onto gelatin-coated glass slides. The brain sections were defatted, stained with cresyl violet, cleared with xylene and cover-slipped. The cannulae placements were verified using a light microscope. Only those animals whose cannulae were within the shell of the NAc were included for statistical analysis (n = 19). No significant tissue damaged was evident upon histological examination of sections.

Statistical analyses

During training sessions, the accuracy (mean ± SEM) was defined as a ratio of correct responses to total responses before the delivery of the first reinforcer; during the test sessions, the performance (mean ± SEM) was expressed as a ratio of drug-lever responses to total responses before the delivery of the first reinforcer. Response rates (responses per second), regarded as a measure of behavioral disruption, were evaluated during the training and test sessions. For the training sessions, the response rate (mean ± SEM) was calculated as a total number of responses to either lever before completion of the first FR 20, divided by the number of seconds taken to complete the FR. During the test sessions, the response rate (mean ± SEM) was calculated as a total number of responses before completion of 20 responses on either lever, divided by the number of seconds taken to complete the FR 20. Only the data from animals that completed the FR 20 during the test sessions were used. Student's *t*-test for repeated measurements was used to compare the percentage of amphetamine-lever responding and response rates during the test sessions with the corresponding values of either the previous amphetamine sessions. The dose predicted to elicit a 50% drug-appropriate responding (ED_{50}) was calculated using Litchfield and Wilcoxon's method [23].

RESULTS

Figure 1 shows the distribution of injection sites in the shell of the NAc. Those rats which the cannulae placements were found outside the investigated brain area were discarded from the analyses.

Substitution studies

Acquisition of the amphetamine (1 mg/kg) *vs.* saline discrimination was reached in an average of 26 sessions (range: 21–40). After surgery, the criterion was met in 16 sessions (range: 10–21). Administration of systemic amphetamine (0.125–1 mg/kg) produced a dose-dependent increase in amphetamine-appropriate responding prior to (data not shown) and after surgical implantation of cannulae (Figs. 2–3); no differences were observed between the pre- (data not shown) and post-surgical amphetamine dose-response curves (Figs. 2–3). Drug-lever responding after 0.125, 0.25 and 0.375 mg/kg of amphetamine was significantly different from the previous amphetamine training session ($p < 0.05$); response rates after all test doses of amphetamine did not differ from that observed during the immediately previous amphetamine maintenance session ($p > 0.05$).

Control tests were also conducted to assure that the microinjection procedure did not interfere with the discrimination between amphetamine and saline. Systemic administration of saline engendered < 5% drug-lever responding (data not shown), as did intra-NAc shell microinjection of saline administered prior to a systemic injection of saline (Fig. 2); response rates did not vary between the control test and the previous maintenance saline session. Intra-shell NAc microinjection of saline did not alter the % amphetamine-lever responding seen after systemic injections of amphetamine (1 mg/kg); response rates did not vary between the control test and the previous maintenance amphetamine session (Figs. 2–3).

Intra-NAc shell infusion of CP 93129, 1 or 10 μg/side, evoked 0 or 17% drug-lever responding, respectively, values that were significantly different ($p < 0.05$) from the previous amphetamine training session; response rates of the animals were significantly decreased following CP 93129 (10 μg/side) (Fig. 2).

Following intra-NAc shell administration of GR 55562, 1 or 10 μg/side, no substitution for amphetamine was observed; those values were significantly different ($p < 0.05$) from the previous amphetamine training session; response rates were unaltered (Fig. 3).

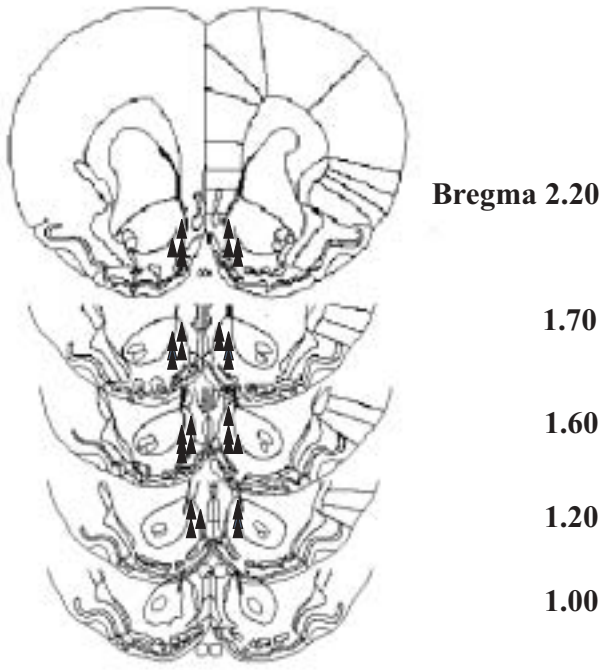

Fig. 1. The schematic diagram shows the sides of intra-NAc shell cannulae placements

Combination studies

Pretreatment with intra-NAc shell microinjection of CP 93129 (1 μg/side), neither affected the dose-response curve (0.125–0.5 mg/kg) (Fig. 2) nor changed the ED_{50} values for amphetamine performance (Tab. 1). CP 93129 (10 μg/side), given in combination with amphetamine (0.125–0.5 mg/kg), slightly shifted the amphetamine dose-response curve

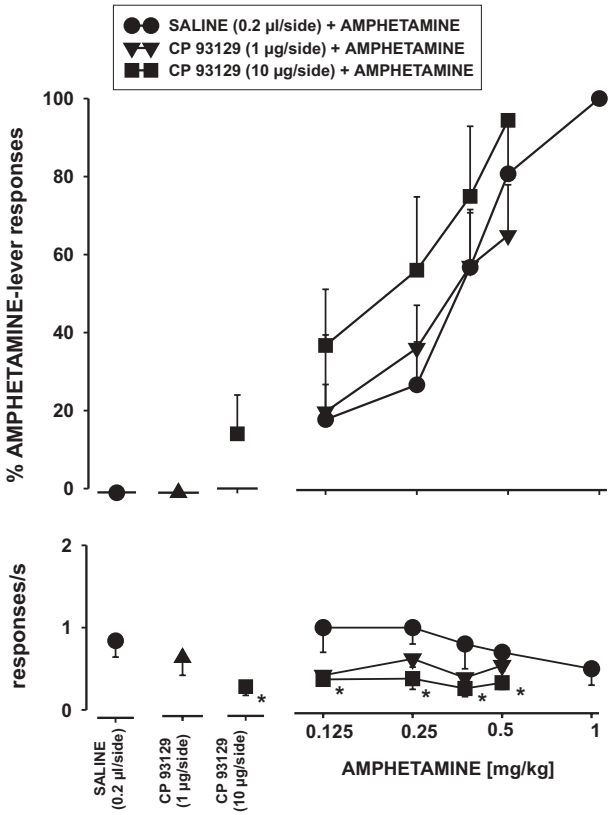

Fig. 2. Results of substitution and combination tests with intra-NAc shell microinjections of the 5-HT$_{1B}$ receptor agonist CP 93129 in rats trained to discriminate amphetamine (1 mg/kg) from saline. Symbols denote the mean percentage of amphetamine-lever responses (± SEM; top panels) or the mean response rate/min (± SEM; bottom panels). Left, symbol denotes performance after saline (0.2 μl/side, circle) or CP 93129 (1 μg/side, triangle, or 10 μg/side, squares). Right, symbols denote the performance of a group of animals administered different doses of amphetamine (0.125–1 mg/kg) following intra-NAc shell saline, 1 μg/side of CP 93129 or 10 μg/side of CP 93129. All data points represent the mean values of data from 7–10 rats of 10 rats. Asterisks represent response rates during test sessions that were significantly different from that observed after the previous amphetamine training session ($p < 0.05$)

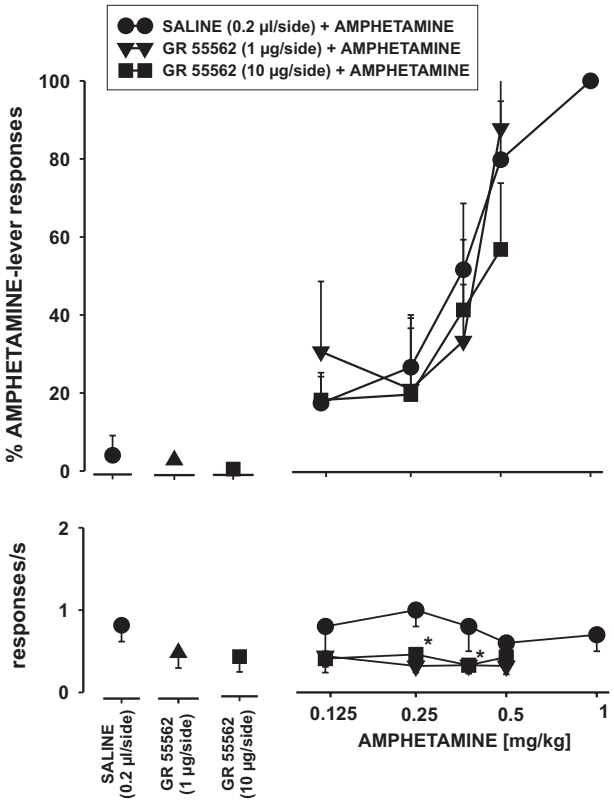

Fig. 3. Results of substitution and combination tests with intra-NAc shell microinjections of the 5-HT_{1B} receptor antagonist GR 55562 in rats trained to discriminate amphetamine (1 mg/kg) from saline. Left, symbol denote performance after saline (0.2 µl/side, circle) or GR 55562 (1 µg/side, triangle, or 10 µg/side, squares). Right, symbols denote the performance of a group of animals administered different doses of amphetamine (0.125–1 mg/kg) following intra-NAc shell saline, 1 µg/side of GR 55562 or 10 µg/side of GR 55562. All data points represent the mean values of data from 7–9 rats of 9 rats. Asterisks represent response rates during test sessions that were significantly different from that observed after the previous amphetamine training session ($p < 0.05$). For further explanation see Fig. 2

to the left (Fig. 2), however the ED_{50} values for amphetamine did not differ with or without CP 93129 (10 µg/side) pretreatment (Tab. 1). Response rates of the animals were significantly decreased following the combined administration of CP 93129 (10 µg/side) and amphetamine, 0.125–0.5 mg/kg (Fig. 2).

Combined administration of intra-NAc shell GR 55562 (1 or 10 µg/side) did not affect significantly the dose-response curve for amphetamine (0.125–0.5 mg/kg) (Fig. 3). Pretreatment with GR 55562 did not change the ED_{50} values for amphetamine performance (Tab. 1). Response rates of the animals were significantly decreased following GR 55562 (10 µg/side) and amphetamine, 0.25 and 0.375 mg/kg (Fig. 3).

Table 1. The ED_{50} values for amphetamine in rats pretreated with intra-NAc shell saline (0.2 µl/side), CP 93129 (1 or 10 µg/side) or GR 55562 (1 or 10 µg/side)

Pretreatment	ED_{50} (mg/kg) (95% C.L.)
Group 1	
Saline	0.29 (0.19–0.44)
CP 93129 (1 µg/side)	0.33 (0.26–0.41)
CP 93129 (10 µg/side)	0.19 (0.11–0.34)
Group 2	
Saline	0.33 (0.23–0.48)
GR 55562 (1 µg/side)	0.31 (0.06–1.51)
GR 55562 (10 µg/side)	0.58 (0.18–1.78)

Comparisons between all treatments in the group were not significant

DISCUSSION

A brain anatomical substrate underlying some behavioral effects of amphetamine and another psychostimulant cocaine has been found to be the NAc, a target of the mesolimbic dopamine system. In fact, the latter brain area seems to be directly involved in psychostimulant discriminative stimulus [8, 29, 44], locomotor [13, 17] and rewarding effects [11, 27]. Of the two NAc subregions, the shell seems to be tentatively related to the drug of abuse actions toward dopamine transmission [17, 33], reinforcement [11, 27] as well as locomotor stimulant effects of amphetamine [17] and cocaine [13]. Regarding anatomical distribution of 5-HT_{1B} receptors in the NAc, it was found that the shell – as compared to the core – contains higher levels of mRNA and binding sites for 5-HT_{1B} receptors by about 50 and 25%, respectively [1].

In the present study, we found that 5-HT_{1B} receptors in the NAc shell do not play a significant role in the amphetamine-induced discriminative stimulus effects in rats. In fact, using the behavioral procedure that models the subjective effects of amphetamine, we found that local injection of the 5-HT_{1B} receptor antagonist GR 55562 neither substituted nor – when co-administered – changed the

dose-response curve for amphetamine. The present study also shows that pharmacological stimulation of the accumbal shell 5-HT$_{1B}$ receptors does not influence the recognition of amphetamine in rats since intra-NAc shell infusion of the selective agonist CP 93129 neither substituted for amphetamine (when given alone) nor changed its discriminative performance (when combined with the psychostimulant).

It should be noted that 5-HT$_{1B}$ receptor agonist was used in the doses considered to be related with its efficacy to induce some 5-HT$_{1B}$ receptor-mediated functional responses in rats. Thus, when injected at a dose range of 10–16 μg into the paraventricular nucleus of the hypothalamus or into the hippocampus, CP 93129 was found to decrease food intake [24] or affect locomotor activity [4], respectively. Other experiments have demonstrated that intra-NAc injections with CP 93129 in doses of 1.25 and 2.5 μg reduced amphetamine-induced enhancement of responding for conditioned reward [14] or – when given intracerebroventricularly – it potentiated cocaine reinforcement in self-administration model [31]. On the other hand, intra-NAc shell administration of GR 55562 in a dose of 10 μg/side exerted protective effects against cocaine-induced hyperactivaton in rats (Przegaliński et al., in preparation).

Our present findings, which demonstrate that the NAc shell is not a locus of action for 5-HT$_{1B}$ receptors to control the discriminative stimulus effects of amphetamine, confirm some previous experiments with systemic administration of 5-HT$_{1B}$ receptor antagonists on psychostimulant-induced discrimination. In fact, we and other authors showed that neither GR 127935 [12, 26], GR 55562 [12] nor SB 216641 (Filip and Nowak, unpublished data) affected the latter behavioral effects of either cocaine or amphetamine in rats.

Similar to the studies on amphetamine, we recently observed that intra-NAc shell CP 93129 also was not able to modify the discriminative stimulus effects of cocaine (Papla et al., in preparation). It should be noted that, in contrast to the above experiments using microinjection procedure, systemic administration of some 5-HT$_{1B}$ receptor agonists enhance the psychostimulant-induced reward, discrimination, locomotion or sensitization. First, a non-selective agonist of 5-HT$_{1B}$ receptors RU 24969 was found to enhance the reinforcing effects of self-administered cocaine [31] and its discriminative stimulus effects [6]. Recent studies from our laboratory demonstrated that the selective 5-HT$_{1B}$ receptor agonist CP 94253 produced a leftward shift in the amphetamine (Filip and Nowak, unpublished results) and cocaine dose-response curves in drug discrimination model [12] as well as augmented both the locomotor activity effects and sensitization to those psychostimulants [34, 35].

In the light of the obtained negative results with intra-NAc shell injections of CP 93129 in the discriminative stimulus effects of amphetamine, it should be mentioned that the intra-NAc core injection of this agonist enhanced cocaine discrimination (Papla et al., in preparation). Whether the core subregion of the NAc is important to the effects of 5-HT$_{1B}$ receptor-stimulation on amphetamine discrimination was not addressed in the present paper, but some findings could partly support a role of the latter brain area to the instrumental behavior as well as to the engagement of 5-HT$_{1B}$ receptor control of conditioned reward of amphetamine. In fact, Hall et al. [16] found the NAc core is a significant brain component of the neural system mediating the impact of Pavlovian cues on instrumental responding in rats behavior. Furthermore, it was demonstrated that local stimulation of 5-HT$_{1B}$ receptors in the NAc with cannulae localized into the core subregion affected the responding for conditioned reward of amphetamine given either systemically or locally [14].

In conclusion, our results seem to exclude a role for the NAc shell 5-HT$_{1B}$ receptors in the control of the discriminative stimulus effects of amphetamine. These findings also show that pharmacological stimulation of those receptors does not affect the amphetamine discrimination in rats.

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