Modulatory role of 5-HT$_{1B}$ receptors in the discriminative signal of amphetamine in the conditioned taste aversion paradigm

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Abstract:

Drugs of abuse, such as amphetamine (AMPH), share the ability to activate the mesolimbic dopamine (DA) system. The behavioral effects of AMPH are largely mediated by increased DA neurotransmission in the nucleus accumbens. However, there is evidence that serotonin (5-hydroxytryptamine – 5-HT) systems may regulate forebrain DA function. We examined the role of 5-HT$_{1B}$ receptors on the discriminative stimulus properties of AMPH using conditioned taste aversion (CTA) as the drug discrimination procedure. Male Wistar rats were deprived of water and trained in the CTA procedure. They received the administration of AMPH (1.0 mg/kg) before a 10 min period of access to saccharin solution and followed by an injection of LiCl; on alternate days, rats received saline before and after the access to saccharin solution. In generalization and combination tests, the training dose of AMPH was substituted by 5-HT$_{1B}$ receptor ligands RU24969 (5-HT$_{1B}$ agonist: 0.1, 0.3 and 1.0 mg/kg), CP94253 (5-HT$_{1B}$ agonist: 1.0, 3.0 and 5.6 mg/kg) and GR127935 (5-HT$_{1B}$ antagonist: 0.3, 1.0 and 3.0 mg/kg) or a combination of RU24969 (0.1, 0.3 and 1.0 mg/kg), CP94253 (1.0, 3.0 and 5.6 mg/kg) or GR127935 (0.3, 1.0 and 3.0 mg/kg) with AMPH (0.3 mg/kg) or GR127935 (0.3, 1.0 and 3.0 mg/kg) and CP94253 (5.6 mg/kg) with AMPH (0.3 mg/kg). The results showed that 5-HT$_{1B}$ agonists RU24969 and CP94253 produced partial generalization of 48% and 60%, respectively, and the 5-HT$_{1B}$ antagonist GR127935 neither substituted for AMPH nor affected the discriminative cue of AMPH; however, when RU24969 or CP94253 were administered in combination with AMPH, they increased the discriminative cue of AMPH. This effect was reversed by the administration of 5-HT$_{1B}$ antagonist GR127935. These data suggest that 5-HT$_{1B}$ receptors play a modulatory role in the discriminative cue of AMPH.

Key words:
amphetamine, drug discrimination, 5-HT$_{1B}$ receptors

Introduction

Cocaine and amphetamine (AMPH) are indirect monoamine agonists that exhibit affinity for dopamine (DA; cocaine: K_i = 478 nM; AMPH: K_i = 34 nM), norepinephrine (NE; cocaine: K_i = 779 nM; AMPH: K_i = 38.9 nM) and serotonin (5-HT; cocaine: K_i = 304 nM; AMPH: K_i = 3830 nM) transporters involved in neurotransmitter reuptake and vesicular storage systems [32]. Cocaine is a reuptake inhibitor of DA, NE and 5-HT, thereby increasing synaptic level of these neurotransmitters. AMPH acts on DA, NE and 5-HT transporters at synaptic vesicles to promote an increase in the cytoplasmic concentration of monoamines, and also reverses the direction of membrane

monoamine transporters, facilitating the efflux of the neurotransmitters to the synaptic cleft [6, 19, 32].

The mesolimbic DA system, in particular the projection from ventral tegmental area (VTA) to the nucleus accumbens (NAcc), is an important locus for the production of locomotor, reinforcing, rewarding and discriminative stimulus effects of cocaine and AMPH [5, 8, 21, 27]. Administration of AMPH or cocaine rapidly increases DA neurotransmission by interfering with proper DA transporter function facilitating DAergic signaling in limbic areas [21, 22].

Recent evidence suggests that 5-HT neurotransmission also plays a modulatory role in some behavioral effects of psychostimulants [7, 34]. Although 7 families of 5-HT receptors ($5-HT_1 - 5-HT_7$) with at least 16 subtypes have been identified [18], several studies indicate that the $5-HT_{1B}$ receptor subtype might play an important role in modulating some abuse-related behavioral effects of cocaine and AMPH. For example, pretreatment with the $5-HT_{1B}$ receptor agonist RU24969 produced a leftward shift of cocaine self-administration dose-effect function, although cocaine self-administration was not maintained when RU24969 was substituted for cocaine [25]. Przegaliński et al. [28] reported that microinjection of CP93129 ($5-HT_{1B}$ receptor agonist) into the accumbens shell, but not in the core, produced an enhancement of the cocaine-induced locomotor activity, although CP93129 administrated alone did not produce any changes in locomotor activity. However, it has been reported that microinjection of CP93129 into VTA increases basal locomotor activity [29].

In drug discrimination studies, the administration of the RU24969 in rats trained to discriminate cocaine from saline elicits a dose-dependent partial substitution and the administration of RU24969 in combination with cocaine produced a leftward shift in the cocaine dose-response curve [3]. Similar results were obtained with the selective $5-HT_{1B}$ receptor agonist CP94253 [10]. However, microinjections of CP93129 into the NAcc shell in combination with systemic administration of AMPH did not modify discriminative stimulus effects of AMPH [9]. On the other hand, Przegaliński et al. [30] reported that the locomotor hyperactivity induced by AMPH was increased by CP94593 and inhibited by SB216641 ($5-HT_{1B}$ antagonist) during the development phase but not during the expression phase of sensitization. Similarly, microinjections of CP93129, a $5-HT_{1B}$ agonist, into VTA enhanced AMPH-induced hyperactivity, and the

pretreatment with GR55562, a $5-HT_{1B}$ antagonist, blocked the effects of CP93129, but when either CP93129 or GR55562 were administrated alone, neither affected basal locomotor activity [24].

According to previous data indicating a modulatory role of $5-HT_{1B}$ receptors in behavioral effects of AMPH or cocaine, the activation of $5-HT_{1B}$ receptors produces an enhancement of psychostimulant-induced effects while pretreatment with $5-HT_{1B}$ antagonist reduces these effects. Drug discrimination studies have also been used to identify whether $5-HT_{1B}$ receptors are involved in cocaine-induced stimulus effects. Since AMPH acts through a slightly different mechanism than cocaine to increase DA in limbic areas (see above), it is important to evaluate whether $5-HT_{1B}$ receptor-related ligands that modulate cocaine-induced stimulus effects might also be able to modulate the discriminative signal of AMPH. Therefore, the present study was designed to obtain evidence of the role of $5-HT_{1B}$ receptor ligands in the discriminative signal of AMPH using a conditioned taste aversion (CTA) paradigm.

Materials and Methods

Animals

Eight male Wistar rats, 120 days old and weighing 200–250 g at the start of the experiment, were obtained from the breeding colony of the FES-Iztacala-UNAM, México. They were housed individually in stainless steel cages with food (Teklad LM485 Rat Diet by Harlan) freely available, and were maintained under a 12 h light/dark cycle with lights on at 08:00 h, and a temperature of $21 \pm 1°C$. Rats had access to liquid solutions through one or two inverted graduated cylinders placed in the front wall of the cage. Animal care and handling procedures were conducted in accordance with the Official Mexican Norm (NOM-062-ZOO-1999: Technical specifications for the production, care, and use of laboratory animals) and were approved by local bioethical committee.

Drugs

The drugs used were: d-amphetamine sulfate was from Sigma-Aldrich, St. Louis MO, USA, RU24969 hemisuccinate, CP94253 hydrochloride and GR127935

hydrochloride were obtained from Tocris (Ballwin, MO, USA) and LiCl (Baker, Mexico D.F. Mexico). All drugs were dissolved in water and were administered *ip* (1 ml/kg). LiCl was administered at a dose of 0.34 mEq (2.0 ml/kg of a 0.177 M solution). Saccharin solution (Elly-Lilly, Mexico D.F. Mexico) at 0.15% (w/v) was dissolved in distilled water and made up daily.

Discrimination procedure

Subjects were trained for 7 days to drink daily water within a 20 min period. Thereafter, they were trained to drink a saccharin solution within 10 min sessions for 2 days. For training in the CTA procedure, subjects underwent drug- or saline-trials as follows: *Drug trials*. After AMPH (1.0 mg/kg, *ip*) administration, subjects were placed in the experimental-cages, where 30 min later they had a 10 min period of access to an inverted graduate cylinder with saccharin solution. Immediately thereafter, subjects received an *ip* injection of LiCl, and were returned to their home-cages. *Saline trials*. After the administration of isotonic saline (1.0 ml/kg, *ip*), subjects were placed in the experimental cages where 30 min later they had access to saccharin solution for 10 min. Immediately thereafter, rats received isotonic saline, and were returned to their home-cages.

Subjects received a total of 11 drug- and 11 saline-trials. Drug- and saline-trials were separated by 2 days; on those days the rats remained in their home-cages and had access to tap water for 30 min a day. Drug and saline trials alternated randomly, with the restriction that drug trials did not occur on more than two consecutive occasions.

Generalization and combination tests with 5-HT$_{1B}$ ligands

Tests were carried out on a 4-day cycle. On the first day, the subjects had a drug trial as previously described. On the second day, the subjects remained in their home cages and had a 30-min period of free access to tap water. On the third day, the rats had a saline trial as previously described. Finally, on the fourth day the subjects received a particular dose of AMPH, a dose of a study drug or a combination of two or three drugs; thereafter, they had a two-bottle test for 10 min; one bottle had tap water and the other had saccharin solution. No saline or LiCl was admin-istered on these occasions. The dose and time intervals between administration and testing for each drug were selected according to literature; AMPH: 0.1–1.0 mg/kg, 30 min [16]; RU24969: 0.1–1.0 mg/kg, 30 min [3]; CP94253: 1.0–5.6 mg/kg, 30 min [30]; GR127935: 0.3–3.0 mg/kg, 30 min [1]. The dose to be tested was chosen randomly and the cycle was repeated until all doses of the substitution drug had been evaluated; the order of testing the drugs was also randomized. The training dose of AMPH (see figures) was evaluated (on the full 4-day cycle that ended in the two bottle test) immediately after the training period, and was then repeated before the evaluation of the various doses of each drug tested (including before the occasion when several doses of AMPH were tested, in order to have an independent estimation of the full dose response curve). To examine the effects of 5-HT$_{1B}$ receptor ligands on discriminative signal engendered by a dose of AMPH which produced partial generalization (39%) to the training dose of AMPH, doses of RU24969 (0.1–1.0 mg/kg, 31 min) or CP94253 (1.0–5.6 mg/kg, 31 min) or GR127935 (0.3–3.0 mg /kg, 31 min) or GR127935 (0.3–3.0 mg/kg, 32 min) + CP94253 (5.6 mg/kg, 31 min) were administered in combination with AMPH (0.3 mg/kg, 30 min).

Statistical analysis

During acquisition, saccharin intake in drug and saline trials was recorded and compared using two-way ANOVA with drug-saline condition as the first factor and trial number (only the last three trials of each conditions were analyzed) as the second factor. During the two-bottle generalization tests, water and saccharin intake were recorded and a saccharin preference was calculated according to the formula A/(A + B), where A was saccharin intake and B was water intake. With this formula, an index of 0.0 indicates a strong aversion to saccharin, while 1.0 indicates strong preference for saccharin. Preference data were analyzed using one-way ANOVA. Preference data from combination tests were analyzed using one-way ANOVA for repeated measures. When ANOVAs were significant, the Dunnett test (p < 0.05) was used for a posteriori comparison. For the description of generalization tests, the following criteria were used: full substitution: $\geq$ 80%; partial substitution: < 80% and > 30%; no substitution: $\leq$ 30%.

Results

Acquisition of the discriminative stimulus properties of AMPH

Rats learned to discriminate between AMPH and saline solution (Fig. 1). No differences [F (2, 21) = 2.099, p > 0.05] were observed between saccharin intake in baseline sessions, the first drug trial and the first saline trial. When AMPH was followed by saccharin-LiCl pairings, a reduction of saccharin intake was observed. Two-way ANOVA revealed significant differences between the last 3 drug trials and the last 3 saline trials; these differences were related to drug-saline trial [F(1, 42) = 39.041, p < 0.0001] since the effects of trial number [F(2, 42) = 0.244, p > 0.05] and the interaction [F(2, 42) = 0.644, p > 0.05] were not significant.
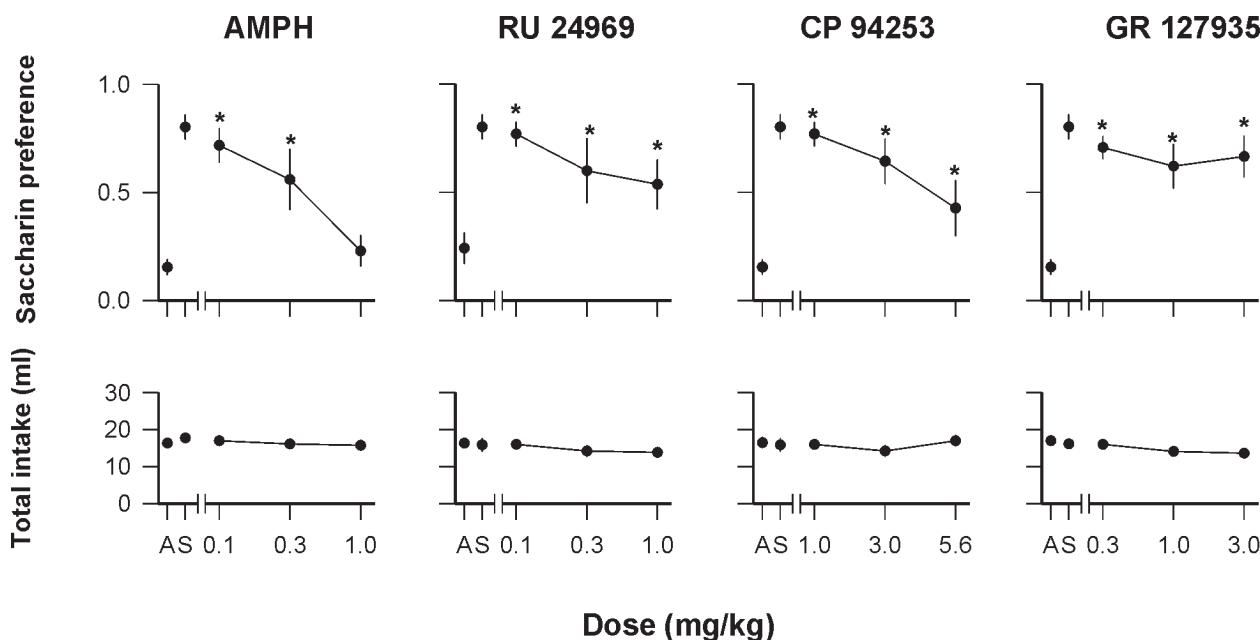
Generalization tests with AMPH

Figure 2 (AMPH) shows that administration of different doses of AMPH evaluated in the two-bottle test induced a dose-dependent stimulus control; the 1.0 mg/kg dose administered during the evaluation of the

dose response curve replicated the stimulus control exerted by the training dose of AMPH. One-way ANOVA revealed significant differences [F(4, 35) = 12.036, p < 0.0001]. Dunnett test revealed that the condition where 1.0 mg/kg of AMPH was adminis-
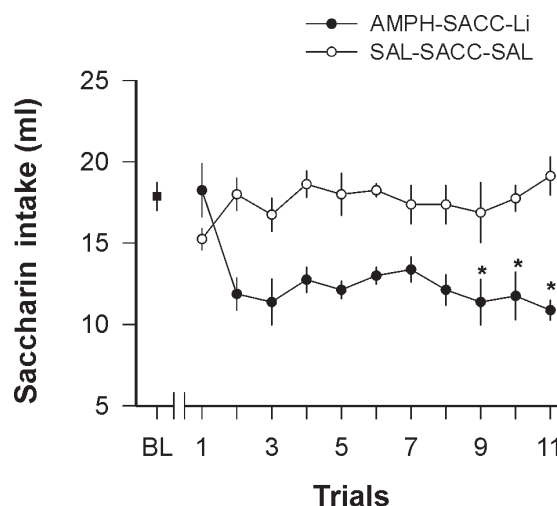
Fig. 1. Acquisition of AMPH-saline discrimination using CTA procedure. All points represent the mean ± SEM from the same group of 8 rats. BL – baseline saccharin consumption; AMPH – amphetamine; SACC – saccharin, Li – LiCl and SAL – saline

Fig. 2. Top: Saccharin preference (discrimination index) during generalization tests with AMPH, RU24969, CP94253 and GR127935. Points are the means ± SEM of 8 rats. Asterisks indicate significant differences (Dunnett test, p < 0.05) between saccharin preference observed after the training dose of AMPH and that observed after the different doses of AMPH, RU24969, CP94253 or GR127935. Bottom: Total liquid intake during the corresponding sessions
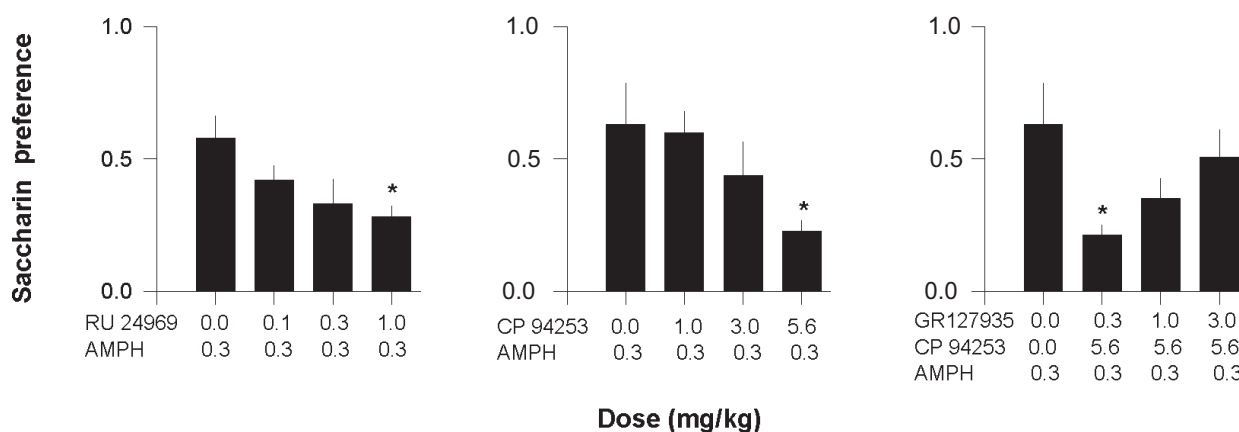
Fig. 3. Saccharin preference during combination tests with the 5-HT$_{1B}$ receptor ligands + AMPH in rats trained to discriminate AMPH (1.0 mg/kg) from saline. Bars are the mean ± SEM of 8 rats. Asterisks indicate significant differences (Dunnett test, p < 0.05) between saccharin preference observed after 5-HT$_{1B}$ receptor ligands + AMPH and that observed after saline + AMPH (0.3 mg/kg)

tered was not different from the training dose of AMPH.

Generalization tests with 5-HT$_{1B}$ receptor ligands

Figure 2 shows that the highest tested dose of RU-24969 (1.0 mg/kg) and CP94253 (5.6 mg/kg) produced only a partial generalization (48% and 60%, respectively) in the AMPH-trained rats (their preference for saccharin was almost halfway of that observed after the training drug and saline). One-way ANOVA revealed a significant differences for RU24969 [F(4, 35) = 7.898, p < 0.0001] and CP94253 [F(4, 35) = 12.036, p < 0.001]. Figure 2 also shows the results of the substitution test with GR127935. It can be observed that this antagonist did not substitute for AMPH [F(4, 35) = 12.121, p < 0.0001]. Dunnett tests revealed that saccharin preference with all doses of the 5-HT$_{1B}$ ligands was different from that seen with the training dose of AMPH.

Combination tests with 5-HT$_{1B}$ receptor ligands + AMPH

Figure 3 shows the results of the substitution test with RU24969 + AMPH. Administration of a fixed dose of AMPH (0.3 mg/kg) in combination with various doses of RU24969 produced a dose-dependent increase in the discriminative signal of AMPH [F(3, 21) = 3.449, p < 0.05]. The condition where 1.0 mg/kg of RU24969 was administered with AMPH (0.3 mg/kg) was different from saline + 0.3 mg/kg of AMPH

(Dunnett test). Similarly, the combination of various doses of CP94253 with a fixed dose of AMPH produced a dose-dependent increase in the discriminative cue of AMPH [F(3, 21) = 3.683, p < 0.05]. *Post-hoc* analysis revealed that this effect was due to the combination of 5.6 mg/kg of CP94253 and 0.3 mg/kg of AMPH (Dunnett test). When GR127935 was given, it did not affect the discriminative signal produced by AMPH [F(3, 21) = 1.009, p > 0.05]. However, as shown in Figure 3, administration of GR127935 dose-dependently reduced the effects of CP94253 on AMPH-induced discriminative signal [F(3, 21) = 3.538, p < 0.05].

Liquid intake in generalization tests

The total intake of liquids was not disrupted during administration of AMPH [F(4, 35) = 0.769], RU-24969 [F(4, 35) = 1.925], CP94253 [F(4,35) = 1.259], GR127935 [F(4, 35) = 1.006], RU24969 + AMPH [F(3, 21) = 1.001], CP94253 + AMPH [F(3, 21) = 1.101], GR127935 + AMPH [F(3, 21) = 0.978] and GR127935 + CP 94253 + AMPH [F(3, 21) = 1.007].

Discussion

The aim of the present study was to examine the effects of 5-HT$_{1B}$ receptor ligands on AMPH discrimination in rats using CTA as the drug discrimination procedure. We found that rats were able to discrimi-

nate AMPH from saline after 11 drug- and 11 saline-trials. These results are similar to those obtained in previous studies using AMPH as the training drug in a CTA paradigm [16]. We also found in generalization and combination tests that RU24969 and CP94253 induced partial generalization. Although RU24969 is not a selective 5-HT$_{1B}$ agonist [17], it is a common pharmacological ligand employed in behavioral and pharmacological studies [1, 3, 14, 25, 35]. In the present study, systemic administration of RU24969 in combination with a medium dose of AMPH increased the AMPH-induced discriminative signal (Fig. 3). On the other hand, CP94253 is a high-affinity agonist at the 5-HT$_{1B}$ receptor subtype [20] which also increased the AMPH-induced discriminative signal. These observations suggest that 5-HT$_{1B}$ receptor subtype may be involved in the modulation of the discriminative signal of AMPH. The selective antagonists of specific receptor subtypes are often used to confirm the mechanism associated with agonist-induced changes in some behavior. In the present study, the systemic administration of GR127935, a highly selective antagonist [4] reduced the effects of CP-94253 on the AMPH-induced discriminative signal. It should be noted that systemic administration of GR-127935 did not affect the AMPH-induced discriminative signal (Fig. 3). Although it has been reported that microinjections of GR55562, another selective 5-HT$_{1B}$ receptor antagonist, into VTA decreased the cocaine-induced discriminative effects [11], there are some differences with our study: systemic administration versus microinjection into VTA of the 5-HT$_{1B}$ receptor antagonists, different 5-HT$_{1B}$ receptor antagonists and different training drug. However, as Filip et al. [11] suggested, higher concentration of the antagonist and greater activation of 5-HT$_{1B}$ receptors associated with intra-VTA administration than can be reached with systemic administration might be the critical factor.

The above behavioral results are consistent with previous reports which demonstrated that 5-HT$_{1B}$ agonists played a modulatory role in some behavioral effects of psychostimulants. For example, in drug discrimination studies, microinjections of CP93129 into VTA induced partial substitution for cocaine but combined administration of CP93129 with a low dose of cocaine produced an increase in the discriminative signal of cocaine [11]. Systemic administration of RU24969 also produced a partial substitution for cocaine; however, administration of a fixed dose of RU24969 in combination with different doses of co-

caine produced a leftward shift in the cocaine dose-response function [3]. It has also been reported that several 5-HT$_{1B}$ agonists increase AMPH-induced behavioral effects. For instance, Przegaliński et al. [30] reported that peripheral administration of CP94253 increased AMPH-induced locomotor hyperactivity. On the other hand, Papla et al. [24] demonstrated that microinjections of CP93129 into VTA did not affect basal locomotor activity, however, combinations of CP93129 and AMPH produced an increase in AMPH-induced locomotor activity, and this effect was reduced by pretreatment with 5-HT$_{1B}$ antagonist GR55562. Taken together, previous data and our results suggest that 5-HT$_{1B}$ receptors are able to modulate psychostimulant-induced behaviors including the discriminative effects of AMPH examined by the CTA procedure.

The activation of 5-HT$_{1B}$ receptors in VTA might be involved in the modulation of the discriminative signal of AMPH observed in the present study. This speculation is based on the following facts. First, the 5-HT$_{1B}$ receptors are located as autoreceptors on 5-HT neurons and as a heteroreceptors on non-5-HT neurons to control neurotransmitter release such a GABA [26]. Second, although the NAcc contains a high density of 5-HT$_{1B}$ receptors [2], a previous study has reported that microinjections of CP93129 and GR55562 into NAcc shell did not modify AMPH discrimination [9] suggesting that 5-HT$_{1B}$ receptors in the NAcc are not involved in the discriminative properties of AMPH. However, a number of studies have reported that activation of 5-HT$_{1B}$ receptors in NAcc increases other psychostimulant-induced behaviors such a locomotor activity [28], sensitization [31] and cocaine discrimination [12]. In contrast, it has been reported that microinjections of 5-HT$_{1B}$ agonist CP93129 into NAcc reduced the breaking points of AMPH self-administrations maintained in a progressive ratio schedule [13]. Third, evidence suggests that 5-HT$_{1B}$ receptors are also localized at moderate density in VTA and a large proportion of these receptors are located as heteroreceptors on presynaptic terminals of GABAergic interneurons that synapse with DAergic neurons [2] and on GABAergic projections from NAcc to VTA [33]. Activation of 5-HT$_{1B}$ heteroreceptors in the VTA reduces GABA release onto DAergic neurons in VTA resulting in their disinhibition and consequently increasing DA release in NAcc [15]. In support to this suggestion, it has been reported that administration of CP93129 or RU24969

inhibited GABA release from VTA slices. This effect was blocked by the pretreatment with SB216641, a selective 5-HT$_{1B}$ receptor antagonist [35]. Also, it has been reported that intra-VTA administration of CP93129 produced a potentiation of cocaine-induced increases in NAcc DA levels [23]. Further support for the involvement of VTA 5-HT$_{1B}$ receptors in the modulation of psychostimulant-induced effects come from behavioral studies. As it was mentioned above, direct administration of CP93129 into the VTA produced a partial substitution for cocaine, whereas intra-VTA administration of GR55562 decreased cocaine discrimination. In combination tests, CP93129 increased cocaine discrimination and GR55562 reduced the CP93129-induced increases in cocaine discrimination [11]. In addition, Papla et al. [24] reported that microinjections of CP93129 (0.003–0.03 μg/side) into VTA did not affect basal locomotor activity (although higher doses of CP93129 enhanced basal locomotion [29]), however, combinations of CP93129 and AMPH produced an increase of AMPH-induced locomotor activity, and this effect was reduced by pretreatment with 5-HT$_{1B}$ antagonist GR55562. Our results are in agreement with these data, since systemic administration of selective 5-HT$_{1B}$ agonist CP94253 did not substitute for AMPH but combined administration of CP94253 with 0.3 mg/kg dose of AMPH increased the discriminative signal of AMPH and this effect was blocked by systemic administration of a selective 5-HT$_{1B}$ antagonist GR127935.

In conclusion, the present results indicate that 5-HT$_{1B}$ receptor agonists RU24969 and CP94253 increased the discriminative signal of AMPH and that this effect was reversed by 5-HT$_{1B}$ antagonist GR-127935. These data provide further evidence that 5-HT$_{1B}$ receptor ligands may modulate psychostimulant-induced behavior, particularly the discriminative properties of AMPH.

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