Preclinical Evidence That 5-HT$_{1B}$ Receptor Agonists Show Promise as Medications for Psychostimulant Use Disorders

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Abstract

**Background:** 5-HT$_{1B}$ receptor agonists enhance cocaine intake during daily self-administration sessions but decrease cocaine intake when tested after prolonged abstinence. We examined if 5-HT$_{1B}$ receptor agonists produce similar abstinence-dependent effects on methamphetamine intake.

**Methods:** Male rats were trained to self-administer methamphetamine (0.1 mg/kg, i.v.) on low (fixed ratio 5 and variable ratio 5) and high (progressive ratio) effort schedules of reinforcement until intake was stable. Rats were then tested for the effects of the selective 5-HT$_{1B}$ receptor agonist, CP 94,253 (5.6 or 10 mg/kg), or the less selective but clinically available 5-HT$_{1B/1D}$ receptor agonist, zolmitriptan (10 mg/kg), on methamphetamine self-administration both before and after a 21-day forced abstinence period during which the rats remained in their home cages.

**Results:** The inverted U-shaped, methamphetamine dose-response function for intake on the fixed ratio 5 schedule was shifted downward by CP 94,253 both before and after abstinence. The CP 94,253-induced decrease in methamphetamine intake was replicated in rats tested on a variable ratio 5 schedule, and the 5-HT$_{1B}$ receptor antagonist SB 224,289 (10 mg/kg) reversed this effect. CP 94,253 also attenuated methamphetamine intake on a progressive ratio schedule both pre- and postabstinence. Similarly, zolmitriptan attenuated methamphetamine intake on a variable ratio 5 schedule both pre- and postabstinence, and the latter effect was sustained after each of 2 more treatments given every 2 to 3 days prior to daily sessions.

**Conclusions:** Unlike the abstinence-dependent effect of 5-HT$_{1B}$ receptor agonists on cocaine intake reported previously, both CP 94,253 and zolmitriptan decreased methamphetamine intake regardless of abstinence. These findings suggest that 5-HT$_{1B}$ receptor agonists may have clinical efficacy for psychostimulant use disorders.

Keywords: methamphetamine, addiction, CP 94,253, zolmitriptan, rodent

Introduction

Psychostimulant addiction remains a prevalent problem worldwide (NDIC, 2011; NIDA, 2015), and yet there are still no FDA-approved, effective pharmacological treatments for psychostimulant use disorders. We and others have suggested that the serotonin$_{1B}$ receptor (5-HT$_{1B}$R) may be a useful target for medication development for these disorders (Callahan and Cunningham, 1995; Rocha et al., 1997; Miszkiel et al., 2011; Neisewander et al., 2014). Advances in medicinal chemistry...
have discovered drugs with high selectivity for 5-HT₁BRs (Koe et al., 1992; Selkirk et al., 1998; Murray and Rees, 2009; Rodriguez et al., 2014). The agonist 5-propoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-pyrrolo[3,2-b]pyridine (CP 94,253) and the antagonist 1′-methyl-5-[(2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl]-4-yl]carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3′,4′-piperidine (SB 224,289) have high affinities (Kᵢ = 2 and 8.2 nM, respectively) for 5-HT₁BRs (Koe et al., 1992; Selkirk et al., 1998). The selectivity profiles of CP 94,253 and SB 224,289 have established these drugs as useful tools for studying the role of 5-HT₁BRs in psychostimulant addiction. Another group of 5-HT₁BR agonists are tryptamine based, including zolmitriptan (Zomig), which is an FDA-approved drug used to treat migraine headaches. Although zolmitriptan is not as selective for 5-HT₁BRs as CP 94,253, it has a high affinity (Kᵢ = 5.01 nM) for 5-HT₁BRs.

Initial experiments examining the effects of 5-HT₁BR agonists found that these drugs facilitated cocaine self-administration (Parsons et al., 1998). However, we found that the effects of 5-HT₁BR agonists vary depending on whether or not animals have undergone abstinence. Specifically, CP 94,253 shifts the cocaine self-administration dose-response curve leftward when given as a pretreatment prior to a daily self-administration session (preabstinence) but produces a downward shift when given as a pretreatment prior to resumption of self-administration after prolonged (i.e., 21 days) abstinence (Pentkowski et al., 2009; Pentkowski et al., 2014). In addition, CP 94,253 pretreatment increases breakpoints and cocaine intake on a progressive ratio (PR) schedule compared with vehicle pretreatment when tested during daily maintenance sessions. In contrast, following a 21-day period of forced abstinence (postabstinence), CP 94,253 decreases cocaine intake and response rates on the PR schedule. Furthermore, CP 94,253 attenuates cocaine-seeking behavior in tests of both cue-induced and cocaine-primed reinstatement following a few weeks of extinction training during which the rats were abstinence (Pentkowski et al., 2009). Cocaine-seeking behavior under these conditions reflects incentive motivational effects produced by the cues and cocaine priming injections (Markou et al., 1993). Therefore, these results suggest that preabstinence administration of 5-HT₁BR agonists facilitates the reinforcing and motivational properties of cocaine while postabstinence 5-HT₁BR agonists attenuate these effects.

This study examined if CP 94,253 produces a similar abstinence-dependent decrease in methamphetamine intake. First, we examined CP 94,253 pretreatment effects on the methamphetamine self-administration dose-response function using low ratio schedules of reinforcement (i.e., fixed and variable ratio 5; FR5 and VR5). Second, we examined CP 94,253 pretreatment effects on a PR schedule of methamphetamine reinforcement as this more demanding schedule is particularly sensitive to changes in motivation for a drug. Third, we examined if the effects of CP 94,253 pretreatment on methamphetamine intake were 5-HT₁BR mediated by administering the 5-HT₁BR antagonist SB 224,289 to reverse the agonist effects. Fourth, we examined if CP 94,253 and SB 224,289 affected locomotor activity. Finally, we examined if acute and intermittent repeated treatment with zolmitriptan affected methamphetamine intake. Since both methamphetamine and cocaine enhance monoaminergic neurotransmission by an action at monoamine transporters, we hypothesized that CP 94,253 would increase methamphetamine intake preabstinence and decrease methamphetamine intake postabstinence similar to that observed with cocaine intake.

## Methods

### Animals

Male Sprague Dawley rats (Charles River) weighing 225 to 250 g were single-housed in a climate-controlled environment on a 14:10 reverse light/dark cycle (lights off at 6:00 AM). Rats had ad libitum access to food except for initial self-administration training when they were food restricted to 90% of their ad libitum weights. The experiments proceeded in accordance with a protocol approved by the Arizona State University Institutional Animal Care and Use Committee.

### Drugs

Methamphetamine hydrochloride (Sigma-Aldrich) was dissolved in bacteriostatic saline (Hospira Inc.) and filtered with 0.2-µm membrane Acrodisc syringe filters (PALL Corporation). CP 94,253 hydrochloride (Tocris Bioscience) was dissolved in saline, and SB 224,289 hydrochloride (Tocris Biosciences) was dissolved in 10% (2-hydroxypropyl)-β-cyclodextrin (Sigma-Aldrich) in saline and sonicated for 2 minutes. Zolmitriptan (Sigma-Aldrich) was dissolved in 10% dimethyl sulfoxide in saline and sonicated for 5 minutes. CP 94,253, SB 224,289, and zolmitriptan were prepared fresh daily. Vehicle refers to the respective solvent. All drug injections, with the exception of self-administered methamphetamine, were injected at a volume of 1 mL/kg body weight.

### Surgery

Rats underwent surgery for implantation of chronic indwelling catheters into the jugular vein as detailed previously (Pockros et al., 2011). Rats had 6 to 7 days of recovery before commencing self-administration training. Catheters were flushed daily with 0.1 mL of either timentin (experiment 1; 66.67 mg/mL; GlaxoSmithKline) or cefazolin (experiment 2; 3, 4, and 5; 10 mg/mL; WG Critical Care, LLC) mixed with heparin/saline (70 U/mL; APP Pharmaceuticals). In addition, catheter patency was tested periodically by administering 0.05 mL of methohexital sodium (16.7 mg/mL; Jones Pharma Inc.), a dose that produces brief loss of muscle tone when administered i.v.

### Apparatus

The operant conditioning chambers (Med Associates) contained an active and inactive lever, a cue light, and a tone generator as
Experiment 1: Effects of CP 94,253 on Methamphetamine Self-Administration on a Progressive Ratio Schedule Pre- and Postabstinence

The timeline for this experiment is outlined in Figure 1. A new cohort of experimentally naive rats was food restricted and trained to self-administer methamphetamine, progressing from a FR1 to a VR5 schedule during 2-hour sessions (11–13 sessions) using the same procedure as the previous experiment, with the exception that food restriction was gradually discontinued once rats were on the VR5 schedule. After meeting the stability criterion on the VR5 schedule, rats were trained on the PR schedule of methamphetamine reinforcement during 4-hour sessions until again meeting the stability criterion (10–18 sessions). We capped session length to 4 hours to ensure that CP 94,253 would remain effective throughout the test (Parsons et al., 1998). We also reduced the methamphetamine dose to one-half the training dose (0.05 mg/kg, i.v.) with the intention that more rats would reach break point during the 4-hour session. Breakpoint was defined as the last schedule of reinforcement completed prior to a 1-hour period during which the next required ratio failed to be completed, or 4 hours had elapsed, whichever came first. After rats met the stability criterion on the PR schedule, they were randomly assigned to either a CRF 94,253 (10 mg/kg, s.c.; n = 8) or a vehicle group (n = 7), counterbalanced for similar number of total drug infusions during training. The dose of CP 94,253 was selected based on our previous research demonstrating that it selectively reduces cocaine intake without affecting sucrose intake (Pentkowski et al., 2009). These groups received their respective treatments 15 minutes before testing on the PR schedule. After testing, both groups of rats were placed into abstinence for 21 days as described in experiment 1. Postabstinence, both groups received their injections, which were identical to those given preabstinence, 15 minutes prior to a test for resumption of methamphetamine self-administration on the PR schedule.
Experiment 3: Reversing the Attenuating Effects of CP 94,253 on Methamphetamine Self-Administration with SB 224,289

The timeline for this experiment is outlined in Figure 3. A new cohort of experimentally naïve rats was trained to self-administer methamphetamine, progressing from a FR1 to a VR5 schedule (~12–17 sessions) of methamphetamine (0.1 mg/kg, i.v.) reinforcement. Rats were food restricted only during acquisition of self-administration and all sessions lasted for 2 hours. Once reinforcement rates stabilized under free feeding conditions (~4–12 sessions), rats were randomly assigned to 1 of 2 groups (n = 14 and 17, respectively); Group 1 received an i.p. injection of either vehicle or SB 224,289 (10 mg/kg, i.p.) 30 minutes prior...
to the first test and the opposite treatment injection 30 minutes prior to the second test (i.e., rats that received vehicle on test 1 received SB 224,289 on test 2 and vice versa). Group 1 also received a vehicle injection 15 minutes prior to both tests. For Group 2, identical procedures were followed except that rats received vehicle followed by CP 94,253 (5.6 mg/kg, s.c.) on one test day and SB 224,289 (10 mg/kg, i.p.) followed by CP 94,253 (5.6 mg/kg, s.c.) on the other test day.

In addition to testing whether the antagonist would reverse the effects of the agonist in this experiment, we also verified that these rats showed a CP 94,253-induced decrease in methamphetamine intake postabstinence (not included on timeline). A subset of rats, randomly selected from both Group 1 and Group 2, underwent 21 days of abstinence as described above. They were then assigned to 2 groups, counterbalanced for the number of infusions obtained during training. One group (n=11) received an injection of CP 94,253 (5.6 mg/kg, s.c.) while the other group (n=11) received an injection of vehicle 15 minutes prior to a test for resumption of methamphetamine self-administration (0.1 mg/kg, i.v.).

Experiment 4: Effects of 5-HT1B Drugs on Spontaneous Locomotion

The timeline for this experiment is outlined in Figure 4. Rats from experiment 2 were used and they had a history of methamphetamine self-administration (38 sessions) and had undergone an abstinence period (23 days). On abstinence day 24, rats were placed into locomotor test chambers for a 60-minute habituation period. The test chambers (45.72 x 25.4 x 20.32 cm) were similar to the home cages and had a camera mounted above to record horizontal movement with Topscan software (Clever Systems). The rats were then tested twice for locomotor activity with 3 rest days intervening the 2 test days. They remained in their home cages during rest days. Thirty minutes prior to the first test, rats were pretreated with either vehicle or SB 224,289 (10 mg/kg, i.p.) and 30 minutes prior to the second test the rats received the opposite treatment as that given on the first test (i.e., rats that received vehicle on test 1 received SB 224,289 on test 2 and vice versa). They were also randomly assigned to 1 of 2 groups. Group 1 (n=7) received a vehicle injection 15 minutes prior to both tests, and Group 2 (n=7) received CP 94,253 (10 mg/kg, s.c.) 15 minutes prior to both tests. The tests began by placing the rat into the test chamber, and distance traveled was measured for 2 hours.

Experiment 5: Effects of Zolmitriptan on Methamphetamine Self-Administration Pre- and Postabstinence

The timeline for this experiment is outlined in Figure 5. Rats that were used in experiment 3 were tested for the effects of zolmitriptan on methamphetamine after achieving stable SA rates on a VR5 schedule (~3–11 sessions) of methamphetamine reinforcement (0.1 mg/kg, i.v.) across 2-hour training sessions. Rats were then randomly assigned to either a zolmitriptan (10 mg/kg, s.c.; n=9) or a vehicle treatment group (n=6), counterbalanced for similar number of total drug infusions. Rats received their assigned treatment 15 minutes prior to the start of a self-administration session. Then rats underwent a period of abstinence for 29 to 36 days followed by a test phase. During the test phase, the rats again received their assigned treatment of either
Data Analysis

Statistical analyses were conducted with IBM SPSS Statistics v. 23. Descriptive statistics are reported as the mean ± SEM. Self-administration data, including active and inactive lever responses, and infusions obtained were analyzed by either repeated-measures ANOVA or a mixed-design ANOVA with drug pretreatment(s) and dose of methamphetamine as between-subject or within-subject factors depending on the experimental design. In addition, breakpoint and total distance travelled were analyzed as described above for experiments 2 and 4, respectively. All sources of significant effects were further analyzed by Tukey’s posthoc tests. There was some attrition in each experiment due to catheter failure or failure to acquire SA.

Results

Experiment 1

Methamphetamine produced an inverted U-shaped dose-effect function, and CP 94,253 decreased methamphetamine infusions and active lever responses both pre- and postabstinence (Figure 1). For the preabstinence tests, there were main effects of methamphetamine dose for both infusions [F (4, 36) = 17.67, P < .05] and active lever responses [F (4, 36) = 8.40, P < .05]. Posthoc tests indicated that the 0.01- and 0.03-mg/kg doses produced higher values than the lowest dose (0.003 mg/kg) and the highest dose (0.30 mg/kg) produced lower values than all doses except 0.10 mg/kg (Tukey’s comparisons, P < .05) (Figure 1AB). There were also main effects of treatment, which indicated that averaged across methamphetamine dose, rats exhibited lower infusion and active lever response rates when pretreated with CP 94,253 than when pretreated with vehicle (Figure 1A,B, insets). There were no significant effects for inactive lever responses during preabstinence tests (Figure 1C).

Analysis of postabstinence infusions showed main effects of treatment [F (1, 9) = 30.74, P < .05] and methamphetamine dose [F (4, 36) = 35.27, P < .05], as well as a treatment by methamphetamine dose interaction [F (4, 36) = 2.87, P < .05]. CP 94,253 pretreatment decreased infusions at the 3 lowest doses of methamphetamine compared with vehicle pretreatment (Tukey’s comparisons, P < .05) (Figure 1D). The analysis of postabstinence active lever responses also revealed main effects for treatment [F (1, 9) = 10.38, P < .05] and methamphetamine dose [F (4, 36) = 22.20, P < .05], but no treatment by methamphetamine dose interaction. The main effect of methamphetamine dose was due to the inverted U-shaped dose-response function similar to preabstinence. The main effect of treatment shows that averaged across methamphetamine doses, rats exhibited lower infusion and active lever response rates when pretreated with CP 94,253 than when pretreated with vehicle (Figure 1D,E, insets).
The rats in this experiment underwent 21 days of abstinence and were then tested for the effects of CP 94,253 (5.6 mg/kg, s.c.) on resumption of methamphetamine self-administration (0.1 mg/kg, i.v.). Similar to the results from experiment 1, pretreatment with a 5.6-mg/kg dose of CP 94,253 decreased the number of infusions and active lever responses compared with pretreatment with vehicle during the postabstinence tests (data not shown). The mean number of methamphetamine infusions obtained in the vehicle vs CP 94,253 pretreatment groups was 12.40 ± 0.88 and 8.90 ± 0.71, respectively [t(9) = 7.72, P < .05]. The mean number of active lever responses in the vehicle vs CP 94,253 pretreatment groups was 70.30 ± 20.81 and 49.20 ± 17.89, respectively [t(9) = 2.62, P < .05]. There was no group difference for inactive lever responses.

Experiment 4

Neither CP 94,253 or SB 224,289 pretreatment altered locomotor activity (Figure 4). There were no main or interaction effects between treatment and the total distance traveled by rats.

Experiment 5

Acute zolmitriptan treatment decreased methamphetamine infusions and active lever responses during preabstinence tests (Figure 5A,B). Comparisons between vehicle and zolmitriptan showed a difference in infusions [t(10) = 3.50, P < .05] and active lever responses [t(10) = 2.90, P < .05]. There were no effects on inactive lever responses after vehicle or zolmitriptan treatment with means of 39.18 ± 16.37 and 16.55 ± 6.41, respectively.

Zolmitriptan pretreatment given intermittently across 3 postabstinence tests consistently decreased infusions and active lever responses (Figure 5C,D). The ANOVA showed a main effect of treatment group for infusions [F(1, 11) = 21.92, P < .05] but no effect of treatment day or treatment group by treatment day interaction. For active lever responses, there were significant main effects of treatment group [F(1, 10) = 21.17, P < .05] and treatment day [F(2, 20) = 6.08, P < .05], but no treatment group by treatment day interaction. Posthoc tests for treatment day showed that zolmitriptan treatment produced lower active lever response rates on day 2 compared with treatment days 1 and 3. There were no effects on inactive lever responses after vehicle or zolmitriptan treatment with means of 7.89 ± 3.68 and 3.56 ± 0.68, respectively.

Discussion

Unlike the abstinence-dependent modulatory role of 5-HT1B agonists on cocaine intake that we observed previously (Pentkowski et al., 2012, 2014), this study found that 5-HT1B agonists attenuated methamphetamine intake when given either pre- or postabstinence. Specifically, a moderate dose of CP 94,253 (5.6 mg/kg, s.c.) decreased methamphetamine intake and active lever response averaged across methamphetamine dose available both when administered during maintenance of daily self-administration sessions and following a period of abstinence (main effect of pretreatment, Figure 1, insets). After abstinence, the effect of CP 94,253 was more pronounced at lower doses of methamphetamine, primarily because intake appeared higher under the vehicle pretreatment condition postabstinence compared with preabstinence. This enhancement of cocaine intake postabstinence is consistent with sensitized cocaine self-administration reported previously (Schenk and Partridge, 1997). Thus, the findings suggest that CP 94,253 attenuates expression of the
abstinence-induced, enhanced sensitivity to methamphetamine observed with vehicle pretreatment. CP 94,253 (10 mg/kg, s.c.) also decreased methamphetamine intake (0.05 mg/kg, i.v.) under a PR schedule of reinforcement both pre- and post-abstinence (Figure 2), further suggesting attenuation of methamphetamine reinforcing and/or motivational effects. Importantly, administration of the 5-HT_{1B}R antagonist, SB 224,289 (10 mg/kg, i.p.), blocked the attenuating effects of CP 94,253 (5.6 mg/kg, s.c.) on methamphetamine intake in rats tested during maintenance of self-administration on a VRS schedule (Figure 3), suggesting that the effects of the agonist are mediated by 5-HT_{1B}Rs. Finally, we report that zolmitriptan (10 mg/kg, s.c.) also attenuated methamphetamine intake on a VRS schedule. Zolmitriptan treatment given acutely during maintenance, as well as given intermittently following abstinence, decreased methamphetamine intake and active lever responses (Figure 5).

There are a number of possible reasons for the 5-HT_{1B}R agonist-induced decreases in methamphetamine self-administration, including an effect on methamphetamine reinforcement value and/or incentive motivation, an effect on anxiety, or an effect on motor capability. The decrease in methamphetamine intake is unlikely due to impairments in motor capability, as treatment with the 5-HT_{1B}R ligands did not alter spontaneous locomotion (Figure 4) or inactive lever responses at the doses used in the present study. Furthermore, previous research from our laboratory has shown that CP 94,253 (0.3–10.0 mg/kg, s.c.) has no effect on sucrose reinforcement (Pentkowski et al., 2009). Although the antagonist SB 224,289 decreases cocaine-induced locomotion in drug naive rats (Hoplight et al., 2005), it has no effect on locomotion in rats with a history of cocaine self-administration (Pentkowski et al., 2009, 2014). Thus, it seems unlikely that CP 94,253 or SB 224,289 altered methamphetamine intake by impairing motor capability.

We cannot rule out the possibility that CP 94,253 may have influenced methamphetamine intake nonspecifically by increasing anxiety-like behaviors rather than attenuating reinforcement per se. Indeed, previous studies have found that either 5-HT_{1B}R agonists or antagonists can increase baseline and cocaine-induced anxiety-like behaviors (Lin and Parsons, 2002; Hoplight et al., 2005; Pentkowski et al., 2009). It is important to note that the rats in these previous studies were naïve to the experimental procedures used to assess anxiety-like behaviors, which would likely maximize any potential drug effect. In contrast, rats tested for CP 94,253 effects on methamphetamine self-administration in the present study were well habituated to the testing environment, which would likely minimize potential anxiogenic effects. Furthermore, animals with increased exposure to stress, such as foot-shock, often increase rather than decrease drug intake (Goeders and Guerin, 1994; Ahmed and Koob, 1997; Piazza and Le Moal, 1998; Logrip et al., 2012), mitigating the idea that CP 94,253 may have induced anxiety-like states that interfered with responding. Finally, it seems that potential anxiogenic effects of CP 94,253 on reinforcement would manifest as a decrease in both sucrose and psychostimulant intake, yet CP 94,253 has been shown to selectively decrease cocaine intake (Pentkowski et al., 2009).

We suggest that the most likely explanation for the agonist-induced decreases in methamphetamine intake in the present study is that 5-HT_{1B}R agonists modulate psychostimulant reinforcement and/or incentive motivation (Pentkowski et al., 2012, 2014). The decrease of methamphetamine intake in response to 5-HT_{1B}R stimulation following abstinence may result from an attenuation of the expression of enhanced sensitivity to the reinforcing effects of methamphetamine. This explanation is consistent with our previous findings that 5-HT_{1B}R agonists or 5-HT_{1B}R overexpression by viral gene transfer attenuate cocaine self-administration following a period of abstinence, as well as reduce cocaine-seeking behavior (Pentkowski et al., 2009, 2012, 2014). Furthermore, these agonist effects are reversed by 5-HT_{1B}R antagonists, including SB 224,289, supporting a 5-HT_{1B}R mechanism.

We were surprised that CP 94,253 attenuated methamphetamine intake prior to any abstinence given that this same treatment enhances cocaine intake prior to abstinence (Pentkowski et al., 2009, 2014). However, others have shown that 5-HT_{1B}R agonists attenuate d-amphetamine intake without prolonged abstinence, as well as attenuate d-amphetamine-induced responding for conditioned reward (Fletcher and Korth, 1999; Fletcher et al., 2002; Miszkiel et al., 2012; Miszkiel and Przegalinski, 2013). Therefore, the 5-HT_{1B}R agonist enhancement of cocaine intake prior to abstinence may be due to differences in the pharmacological actions of cocaine vs amphetamines. While both amphetamines and cocaine inhibit and down-regulate 5-HT, dopamine, and noradrenergic transporters (Arazzo and Rutledge, 1973; Ritz, Cone, and Kuhar, 1990), they interact differently with the transporters. Amphetamines, including methamphetamine, not only inhibit monoamine transport, but also redistribute intracellular monoamines by acting at the vesicular monoamine transporter causing release of monoamines into the cytosol while at the same time reversing monoamine transport across the plasma membrane, resulting in monoamine release (Sulzer et al., 1995; Sager and Torres, 2011; Panenka et al., 2013). Cocaine and amphetamines also interact at different sites on the dopamine transporter and produce differential effects on the releasable vesicular pool and on regulation of vesicular monoamine transporter (Thomsen et al., 2009). The latter effects may result in differences in the releasable pool of dopamine after cocaine vs methamphetamine following acute or subchronic administration (Brown et al., 2001).

Although the specific mechanisms responsible for the attenuating effect of 5-HT_{1B}R agonists on cocaine and methamphetamine self-administration are unclear, we hypothesize that such mechanisms may involve a dysregulation of 5-HT_{1B}R functions (Neiswander et al., 2014). 5-HT_{1B}R are widely distributed in the brain (Bruinvels et al., 1994; Lanfumey and Hamon, 2004; Varnas et al., 2005; Clark et al., 2006) and are expressed as either 5-HT terminal autoreceptors or heteroreceptors on terminals of non-5-HTergic cells. In both cases, these receptors negatively couple to adenylyl cyclase activity via G-proteins and function to inhibit neurotransmitter release (Hen 1992; Sari, 2004; McDevitt and Neumaier, 2011; Barnes and Neumaier, 2011). Several manipulations in the mesolimbic system have provided evidence for a modulatory role of 5-HT_{1B}Rs in psychostimulant addiction; specifically, overexpression of 5-HT_{1B}Rs in the nucleus accumbens of rats facilitates the rewarding and reinforcing effects of cocaine (Neumaier et al., 2002; Pentkowski et al., 2012). Furthermore, local activation of 5-HT_{1B}Rs in the ventral tegmental area alters cocaine-induced increases in dopamine levels in the nucleus accumbens and cocaine-induced decreases in gamma-aminobutyric acid levels (Parsons et al., 1999; O’Dell and Parsons, 2004). Similarly, activation of 5-HT_{1B}Rs in the nucleus accumbens dose-dependently decreases the rewarding and reinforcing effects of amphetamine (Fletcher and Korth, 1999; Fletcher, 2002).

The present findings suggest that 5-HT_{1B}R agonists are potential targets for developing pharmacotherapies for psychostimulant addiction. Here we show that the clinically available anti-migraine medication zolmitriptan, which is a 5-HT_{1B}R agonist, attenuated methamphetamine intake. The attenuation
of methamphetamine intake was likely mediated, at least in part, by stimulation of 5-HT₁Rs, although it is possible that 5-HT₁Rs may have also contributed to the attenuation effect. Zolmitriptan, unlike CP 94,253, has a higher affinity for 5-HT₁Rs (Kᵢ = 0.63 nM) than for 5-HT₁Rs (Kᵢ = 5.01 nM; Murray et al., 2011). CP 94,253 also has affinity for 5-HT₁Rs (Kᵢ = 49 nM; Koe et al., 1992), and therefore 5-HT₁Rs may also contribute to its effects on methamphetamine self-administration. The effects of zolmitriptan on methamphetamine self-administration were not likely due to a decrease in general activity, as we did not observe any differences in inactive lever responses in our treatment groups. Furthermore, previous research found that zolmitriptan (1–30 mg/kg, i.p.) attenuates alcohol-induced aggression in mice but has no effect on locomotion (de Almeida et al., 2001).

In conclusion, this study provides evidence that the selective 5-HT₁₆ agonist, CP 94,253, attenuates methamphetamine self-administration pre- and postabstinence under several schedules of reinforcement and in an antagonist-reversible manner. These findings build upon previous research demonstrating similar effects of 5-HT₁₆ agonists on d-amphetamine self-administration (Fletcher and Korth, 1999; Fletcher et al., 2002; Miszkiel et al., 2012; Miszkiel and Przegalinski, 2013), and together the effect of the agonists on self-administration of amphetamines contrasts with the enhanced cocaine self-administration that has been observed prior to any abstinence (Pentkowski et al., 2009, 2014). These results suggest that 5-HT₁₆ agonists may differentially modulate cocaine and methamphetamine self-administration initially, but that after a period of abstinence, the agonists inhibit the reinforcing effects of both psychostimulants. The latter findings suggest that 5-HT₁₆ agonists may have potential therapeutic effects for psychostimulant abuse. In addition, we have provided evidence that the FDA-approved CP 94,253 also attenuates methamphetamine self-administration both pre- and postabstinence. Our findings suggest that 5-HT₁₂ agonists warrant further investigation as putative treatments of psychostimulant use disorders. Important future directions include determining the neural circuitry involved in the agonist effects, whether the effects are also observed in female rats, and whether the effects are observed in rats given more extensive access to the stimulants and more extensive abstinence.

Acknowledgments

We thank Nathan Pentkowski for his input on this study and Juliette Venault, Allegra Campagna, Katelin Ennis, Thomas Benson, Jennifer Taylor, and JP Bonadonna for their technical assistance.

This work was supported by the National Institute on Drug Abuse (DA01164 to J.L.N. and DA025606 to M.F.O.), and the National Institutes of General Medical Sciences for ASU Post-baccalaureate Research Education Program for Biomedical Research and Initiative to Maximize Student Development (GM071798 and GM099650 to R.G.).

Statement of Interest

None.

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