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Short communication

Effects of acute treatments with the serotonin 2A antagonist M100907 alone or in combination with the serotonin 2C agonist WAY163909 on methamphetamine self-administration in rhesus monkeys

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ABSTRACT

Background: Serotonin 5-HT_{2A} receptor antagonists and 5-HT_{2C} receptor agonists have been proposed as important candidates for the development of pharmacotherapies for psychostimulant abuse, with evidence suggesting that those receptors may act together to control behavior. However, the role of 5-HT_{2A} receptors on the reinforcing effects of psychostimulant drugs has not been fully elucidated.
Methods: In the present study, we investigated the effects of the selective 5HT_{2A} receptor antagonist M100907 alone or in combination with the selective 5HT_{2C} agonist WAY 163909 on intravenous methamphetamine self-administration in rhesus macaques (N = 3). Methamphetamine self-administration (0.01-0.03 mg/kg/inf) was evaluated under a fixed-ratio 20-schedule of reinforcement, and acute pretreatments were conducted 1 h (M100907) or 45 min (WAY 163,909) prior to the beginning of self-administration sessions at the EDMax dose of methamphetamine once stability criteria were met.
Results: Pretreatment with M100907 (0.03–0.3 mg/kg, i.m.) dose-dependently attenuated methamphetamine self-administration, with the highest dose significantly decreasing response rates compared to vehicle. Combined administration of ineffective doses of M100907 and WAY 163,909 had no effects on methamphetamine self-administration.
Conclusions: Our study indicates that acute selective 5-HT_{2A} receptor blockade decreases peak methamphetamine intake in nonhuman primates. Combination approaches with sub-threshold doses of 5-HT_{2A} receptor antagonists and 5-HT_{2C} receptor agonists, on the other hand, do not seem to be effective in decreasing methamphetamine reinforcement. Further studies are needed in order to investigate the effects of chronic treatments with M100 on complete METH SA dose-response curves.

1. Introduction

Drug addiction is a worldwide public health concern. Amphetamine-type stimulants are some of the most commonly used and abused drugs in the world (United Nations Office on Drugs and Crime, 2016). In particular, methamphetamine (METH) is a stimulant with a high potential for abuse, and its use has been increasing across the globe (United Nations Office on Drugs and Crime, 2016). METH blocks monoamine transporters and dopamine (DA) metabolism, also acting as a monoamine releaser, increasing DA concentration in the synapse of the nucleus accumbens (NAcc) (Ciccarone, 2011).

Increased extracellular DA levels in the NAcc is a common factor among drugs of abuse, leading scientists to investigate medications that directly target DA neurotransmission (Minozzi et al., 2015). However, despite decades of extensive research, there is no effective FDA-approved DA-based medication to date. As a result, the focus has been shifted towards other neurotransmission systems that also exert modulatory effects on the DA system, such as the serotonergic system (Howell and Cunningham, 2015). The serotonin 5-HT_{2A} and 5-HT_{2C} receptors are the two serotonin receptors that seem to play a significant

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role in drug abuse (Howell and Cunningham, 2015). Due to their regional distribution in the brain, antagonism of 5-$HT_{2A,}$ as well as, activation of 5-HT_{2C} receptors have been proposed as potential treatments for drug addiction and relapse (Manvich et al., 2012; Murnane et al., 2013; Howell and Cunningham, 2015; Berro et al., 2017).

Recent studies in rats have shown that, in addition to exerting effects separately, a combination of subthreshold doses of the selective $5HT_{2A}$ receptor antagonist M100907 (M100) and the selective $5HT_{2C}$ receptor agonist WAY163909 (WAY) decreased cocaine self-administration (SA) and cocaine-induced reinstatement (Cunningham et al., 2013). In rhesus monkeys, although WAY has been shown to decrease cocaine and METH SA (Berro et al., 2017), M100 has shown no effects on cocaine SA (Murnane et al., 2013).

These studies provide further evidence of the oppositional control of $5HT_{2A}$ and $5HT_{2C}$ receptor ligands over the abuse-related effects of psychostimulants. However, in light of equivocal results obtained with serotonin 5-HT_{2A} antagonists on drug SA, this area needs additional investigation. No study to date has evaluated the effects of $5HT_{2A}$ receptor antagonists or of a combination of a $5HT_{2A}$ receptor antagonist and a $5HT_{2C}$ receptor agonist on METH SA. Therefore, the aim of the present study was to investigate the effects of the selective $5HT_{2A}$ receptor antagonist M100 alone or in combination with the selective $5HT_{2C}$ agonist WAY on METH SA in rhesus monkeys.

2. Materials and methods

2.1. Subjects

Subjects were two male (ROf8 and RJl8) and one female (RZs9) adult rhesus macaques (*Macaca mulatta*) weighing between 9–15 kg. All subjects were individually housed, had constant access to water and were fed monkey chow, fruits and vegetables daily. Ambient conditions within the colony are maintained at a temperature of 22 ± 2 °C and at 45–50% humidity. The room lighting is set to a 12 h light/dark cycle (lights on at 7:00 A.M.). All subjects have a pharmacology history of exposure to psychostimulants. All protocols and animal care and handling strictly follow the National Institutes of Health Guide for the Care and Use of Laboratory Animals (8th edition, revised 2011) and the recommendations of the American Association for Accreditation of Laboratory Animal Care, and were approved by the Emory University Animal Care and Use Committee (protocol #2003465).

2.2. Drugs

(±) Methamphetamine (METH) hydrochloride (National Institute on Drug Abuse, Bethesda, MD, USA) was dissolved in 0.9% sterile saline and administered intravenously. WAY163909 (WAY) hydrochloride (provided as a generous gift from Pfizer Inc®, New York, NY, USA), was dissolved in 10 mg/mL beta-cyclodextrin and administered intramuscularly. M100907 (M100) was synthesized at the Chemical Biology Research Branch, National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism at the National Institutes of Health (Bethesda, MD, USA), and was dissolved in sterile water and 0.1 N hydrochloric acid and administered intramuscularly. The doses of each drug were calculated and expressed as the salt form.

2.3. Surgery

Animals were initially anesthetized with Telazol (tiletamine HCl and zolazepam HCl, 2.0 mg i.m.) and ketamine HCl (20 mg i.m.), and anesthesia was maintained throughout the procedure with inhaled isoflurane (0.5–1.5%). A major vein (femoral or jugular) was implanted with a chronic indwelling catheter attached to a subcutaneous vascular access port, as previously described (Howell and Wilcox, 2001). All surgeries were conducted under aseptic conditions.

2.4. Self-administration protocol

Subjects self-administered METH under a fixed ratio 20-schedule of reinforcement on 60-minute sessions, three to four days a week, as previously described (Berro et al., 2017). Briefly, for the duration of the self-administration (SA) sessions, the animals were positioned in a primate chair (Primate Products) and placed in a sound-attenuating experimental chamber. At the beginning of the session, the chamber was illuminated with a white light that served as a discriminative stimulus. Once the animal completed the FR 20 response requirement, the stimulus light changed from white to red (CS) for 15 s followed by a METH infusion (0.5 ml infused over 3 s) and subsequently a 60-s timeout period. At the end of the timeout, the white light was presented again to signal the opportunity to complete another FR. Response rates were calculated as the total number of lever presses during the active period divided by the active time throughout the session.

Before the beginning of pretreatment studies, the unit dose of METH (0.001, 0.003, 0.01 or 0.03 mg/kg/infusion) was altered until the maximally effective behavioral-stimulant dose of METH (EDMax) was identified for each individual subject. The EDMax dose was 0.03 mg/kg/infusion in one subject and 0.01 mg/kg/infusion in the remaining subjects.

Once the EDMax was determined, the pretreatment studies began. After meeting stability criteria during METH SA maintenance (response rates that varied by < 30% over 3-days), animals received vehicle or M100 (0.03, 0.1 or 0.3 mg/kg) pretreatments at their EDMa x 1 h before SA sessions began. Second, once stable, subjects received a pretreatment with the highest ineffective dose of M100 1 h before SA sessions began and/or a pretreatment with the highest ineffective dose of WAY, established during previous studies from our group (Berro et al., 2017), 45-minutes prior to the onset of SA sessions. The highest ineffective dose of M100 was 0.03 mg/kg in two subjects and 0.1 mg/kg in the remaining subject. The highest ineffective dose of WAY was 0.1 mg/kg in all subjects. The order of treatments and doses was randomized across subjects.

3. Results

3.1. Effects of pretreatment with M100 on METH SA

The mean response rate and drug intake (± S.E.M.) during METH SA maintenance were 0.61 ± 0.19 responses/s and 0.53 ± 0.16 mg/kg/session, respectively, for the EDMax dose of METH. One-way RM ANOVA corrected for multiple comparisons using Dunnett's post hoc test revealed a significant difference between treatment conditions for both response rates [$F(2,4) = 10$, $p < 0.05$] and drug intake [$F(2,4) = 3.73$, $p < 0.05$]. Pretreatment with M100 dose-dependently decreased response rates and drug intake during METH SA, with the high ($p < 0.05$) dose significantly decreasing response rates (Fig. 1A) and METH intake (Fig. 1B) compared to vehicle. No next-day effects were observed on drug intake following M100 pretreatment sessions (data not shown).

Individual subject data show that, regardless of sex, M100 dose-dependently decreased response rates during METH SA (Figs. 1C, 1D and 1E). Although we were not able to include full dose-effect functions on the effects of M100 on rates of METH SA, we were able to conduct experiments evaluating the effects of the medium (0.1 mg/kg) and high (0.3 mg/kg) doses of M100 on METH SAT at the -0.5ED_{Max} dose for one of our subjects (RJl8). Our preliminary data show that regardless of the METH dose, 0.3 mg/kg M100 decreased response rates (and consequently drug intake) for this particular subject (Fig. 1E).

3.2. Effects of pretreatment with a combination of ineffective doses of M100 and WAY on METH SA

Two-way RM ANOVA showed no significant effect of M100 [F

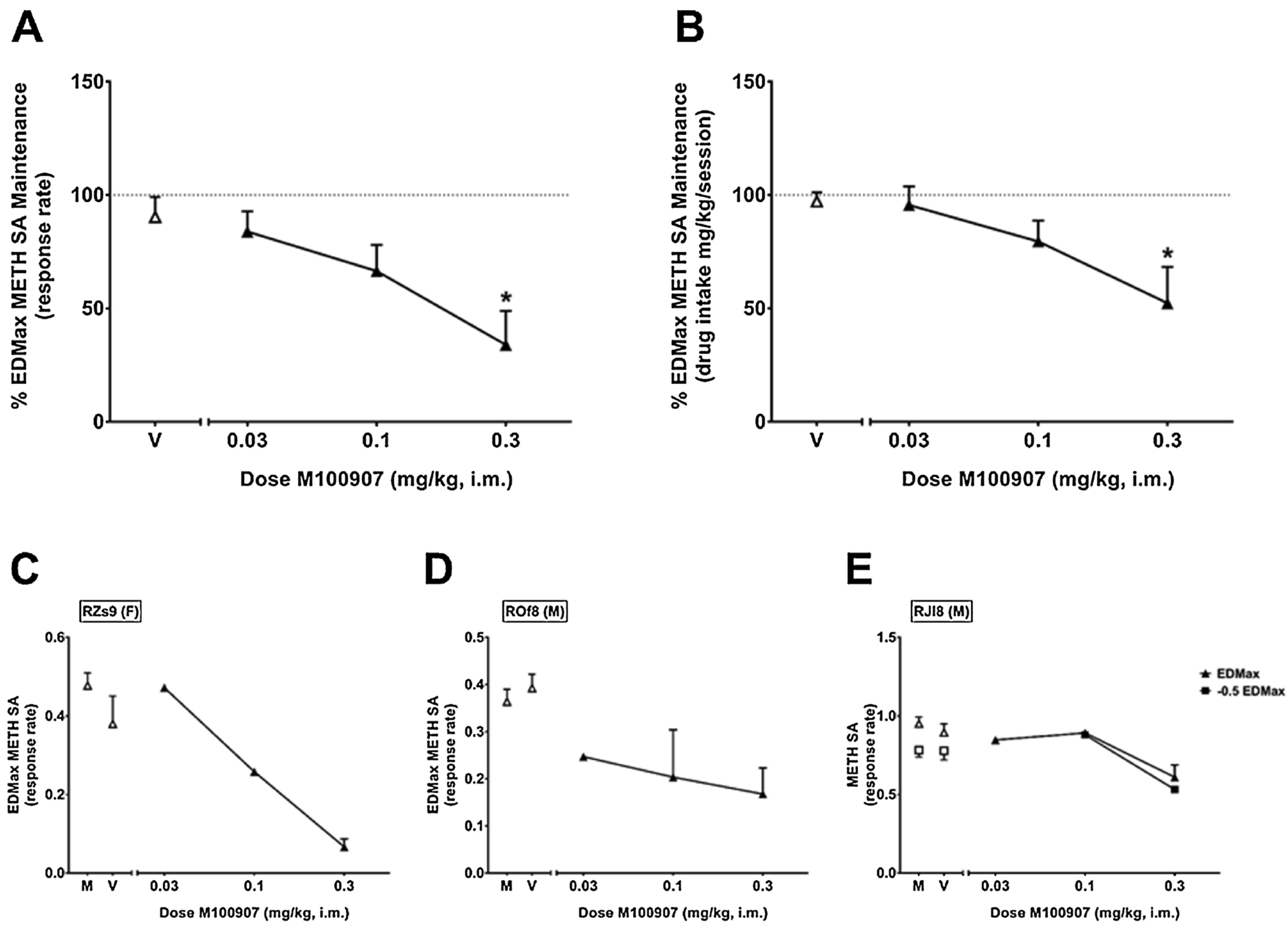

Fig. 1. Effects of pretreatment with the serotonin 5-HT_{2A} receptor antagonist M100907 on methamphetamine (METH, N = 3) self-administration (SA). (A) Response rates (responses/s) and (B) methamphetamine intake (mg/kg/session) during self-administration at the maximally effective behavioral-stimulant dose (EDMax) of methamphetamine (FR 20 schedule, 0.01-0.03 mg/kg/infusion, i.v.) after pretreatment with vehicle (Veh) or M100907 (0.03, 0.1 or 0.3 mg/kg, i.m.). Data are presented as normalized data (percentage of average response rates during self-administration maintenance). Dotted lines represent response rates during self-administration maintenance (100%). (C, D, E) Individual subject data (responses/s) during self-administration at the EDMax or one-half log-step unit dose below the EDMax dose (−0.5 EDMax) of methamphetamine. Data are expressed as mean ± SEM. $^{*}p < 0.05$ compared with vehicle pretreatment.

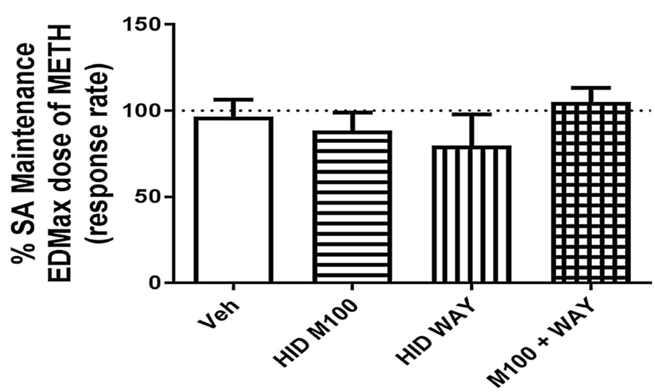

Fig. 2. Effects of pretreatment with the highest ineffective dose (HID) of the serotonin 5-HT_{2A} receptor antagonist M100907 (M100), the serotonin 5-HT_{2C} receptor agonist WAY 163,909 (WAY) or a combination of both on methamphetamine (METH, N = 3) self-administration (SA). Response rates (responses/s) during self-administration at the maximally effective behavioral-stimulant dose (EDMax) of methamphetamine (FR 20 schedule, 0.01-0.03 mg/kg/infusion, i.v.) after pretreatment with vehicle (Veh), M100907 (0.03-0.01 mg/kg, i.m.), WAY 163,909 (0.1 mg/kg, i.m.) or the drug combo. Data are presented as normalized data (percentage of average response rates during self-administration maintenance). Dotted lines represent response rates during self-administration maintenance (100%). Data are expressed as mean ± SEM. $^{*}p < 0.05$ compared with vehicle pretreatment.

$(1,2) = 0.28$, $p > 0.05$] or WAY [$F(1,2) = 0.006$, $p > 0.05$] pretreatments, as well as no significant interaction effect between the two pretreatments [$F(1,2) = 1.47$, $p > 0.05$] (Fig. 2).

4. Discussion

In the present study, we examined the effects of the 5-HT_{2A} receptor antagonist M100 on METH SA alone, and in combination with the 5-HT_{2C} receptor agonist WAY at subthreshold doses. Our results demonstrated that M100 pretreatments dose-dependently decreased METH SA in all subjects, with the highest dose significantly decreasing response rates compared to vehicle. Combined administration of ineffective doses of M100 and WAY, on the other hand, had no effects on METH SA.

Our findings support the current theory that the antagonism of 5-HT_{2A} receptors would decrease the reinforcing effects of psychostimulants. Serotonin 5-HT_{2A} receptors are highly expressed on glutamate, and DA excitatory neurons in the prefrontal cortex and ventral tegmental area, respectively, and activation of these receptors is expected to increase DA neurotransmission in the mesoaccumbens pathway (Howell and Cunningham, 2015). Conceptually, antagonism of these receptors would be expected to decrease mesoaccumbens DA transmission, and therefore decrease the reinforcing effects of psychostimulant drugs.

Based on these assumptions, M100 would be expected to decrease psychostimulant SA. However, previous findings had shown that M100 did not attenuate cocaine SA or decrease cocaine-induced NAcc DA overflow in rhesus monkeys (Murnane et al., 2013). Studies in rodents had also shown no effects of M100 on cocaine SA (Fletcher et al., 2002; Nic Dhonnchadha et al., 2009; Pockros et al., 2011). Importantly, while both cocaine and METH lead to increased DA levels in the NAcc by blocking DA transporters (DAT), METH also acts as a DA releaser (Ciccarone, 2011), inducing higher levels of extracellular DA compared to cocaine. Thus, it is possible that the effectiveness of 5-HT_{2A} receptor antagonism in blocking psychostimulant-induced DA overflow in the NAcc is dependent on direct DA release in the synaptic cleft, which would explain why it attenuated METH, but not cocaine, SA. Although we do not have data on the effects of M100 on METH-induced extracellular DA levels in rhesus monkeys, microdialysis studies in rodents have shown that pretreatment with 5-HT_{2A} receptor antagonists attenuated the increase in extracellular DA levels in the striatum and NAcc induced by amphetamine-type stimulants (Auclair et al., 2004; Porras et al., 2002). Alternatively, other functions of the 5-HT_{2A} receptor might also be involved in the ability of M100 to decrease METH SA that is not directly related to a decrease in mesolimbic DA neurotransmission.

Importantly, although we were not able to include full dose-effect functions on the effects of M100 on rates of METH SA, preliminary findings from one of the subjects included in the present study show that regardless of the METH dose, 0.3 mg/kg M100 decreased response rates (and consequently drug intake) for this particular subject (Fig. 1E). Further studies investigating repeated M100 treatments on complete METH SA dose-response curves are needed in order to conclusively state whether M100 attenuated METH reinforcement or the potency of METH to function as a reinforcer. However, our preliminary data suggest that M100 has not enhanced the potency of METH to function as a reinforcer.

To the best of our knowledge, the present study is the first to provide evidence for a role of 5-HT_{2A} receptors on METH reinforcement in nonhuman primates. Recent studies have shown that chronic administration of pimavanserin, a 5-HT_{2A} receptor inverse agonist/antagonist, did not decrease METH or cocaine reinforcement under drug vs. food choice procedures in rhesus monkey (Banks, 2016; Banks and Negus, 2017). Of note, differences in treatment regimens might explain the contradictory findings obtained in the present vs. previous studies. While Banks (2016) and Banks and Negus (2017) used repeated subchronic treatments, in the present study animals were acutely treated with M100. In addition, the present study did not investigate the behavioral selectivity of the effects of M100 on METH reinforcement compared to schedule-controlled responding maintained by a non-drug reinforcer, such as food-maintained responding. We have, however, previously demonstrated that M100 does not affect general daytime home-cage activity at the doses used in the present study (Perez Diaz et al., 2017), suggesting that the effects of M100 on METH SA were not due to a decrease in motor activity. Thus, the limitations of the present study emphasize the importance of further studies investigating the effects of chronic treatments with M100 on METH SA as well as on food-maintained responding in the future.

Based on previous studies showing that a combination of ineffective doses of M100 and WAY was able to suppress impulsive action, cocaine intake, and cue reactivity in rats (Cunningham et al., 2013) and METH-induced sleep impairment in rhesus monkeys (Perez Diaz et al., 2017), we tested the effects of a combination of the highest ineffective doses of M100 and WAY on METH SA. Serotonin 5-HT_{2A} and 5-HT_{2C} receptors modulate mesoaccumbens DA neurotransmission in oppositional ways, as activation of 5-HT_{2A} increases, whereas 5-HT_{2C} activation decreases, the activity of DA neurons located in the ventral tegmental area (Howell and Cunningham, 2015). Our results showed no significant differences in METH SA after pretreatment with the combination of WAY and M100 as compared to either WAY or M100 alone or vehicle. Although no studies to date have investigated the effects of combined subthreshold doses of M100 and WAY on METH-induced NAcc DA overflow in rhesus monkeys, our findings suggest that this approach is not effective in blocking the neurochemical effects of METH associated with its abuse. Thus, combination approaches do not seem to be effective in decreasing METH reinforcement.

In summary, our findings show that acute treatment with M100, but not a combination of subthreshold doses of M100 and WAY, decreased METH SA, suggesting that serotonin 5-HT_{2A} receptors play an important role in the reinforcing properties of METH. Further investigation of the effects of 5-HT_{2A} receptor antagonism on psychostimulant abuse and reinforcement will provide a better understanding of the direct mechanisms underlying the present findings, and might help present a promising avenue for future addiction therapies.

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Contributors

LFB and LLH were responsible for the study concept and design. MOG, HS, LFB and KCR contributed to the acquisition of data. All authors assisted with data analysis and interpretation of findings. MOG, HS and LFB drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content and approved the final version for publication.

Conflicts of interest

No conflict declared.

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