Published in final edited form as:

Pharmacol Biochem Behav. 2013 November ; 112: . doi:10.1016/j.pbb.2013.09.006.

Oral administration of GZ-793A, a VMAT2 inhibitor, decreases methamphetamine self-administration in rats

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Abstract

Despite the high prevalence of use of methamphetamine (METH), there is no FDA-approved pharmacological treatment available currently for METH addiction. The vesicular monoamine transporter (VMAT2) has been proposed as a novel target to treat METH abuse. GZ-793A, a lobelane analog and selective VMAT2 inhibitor, has been shown previously to decrease METH self-administration specifically when administered via the subcutaneous route in rats. Since oral administration is the preferred clinical route, the present experiments determined if oral administration of GZ-793A would decrease specifically METH self-administration. Experiments 1 and 2 assessed the dose-effect functions of oral administration of GZ-793A (30-240 mg/kg) on intravenous METH self-administration and food-maintained responding, respectively. Experiments 3 and 4 assessed the time-course (20-180 min pretreatment) of oral administration of GZ-793A on METH self-administration and food-maintained responding, respectively. Oral administration of GZ-793A dose-dependently decreased METH self-administration, with the highest dose (240 mg/kg) producing a 85% decrease compared to control baseline. The decrease in METH self-administration produced by GZ-793A (120 mg/kg) lasted at least 180 min. In contrast, GZ-793A failed to alter food-maintained responding at any of the doses or pretreatment intervals tested. The oral effectiveness and the specificity of GZ-793A to decrease methamphetamine self-administration supports the feasibility of developing VMAT2 inhibitors as treatments for METH abuse.

Keywords

methamphetamine; VMAT2; dopamine; self-administration

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DISCLOSURE/CONFLICTS OF INTEREST

The University of Kentucky holds patents on GZ-793A. A potential royalty stream to Dwoskin, Crooks and Zheng may occur consistent with University of Kentucky policy.

INTRODUCTION

Methamphetamine (METH) is a highly addictive stimulant, which in recent years has reached nearly epidemic levels of use worldwide (Maxwell and Rutkowski, 2008; McKetin et al., 2008). METH use is associated with a number of health consequences, including cognitive dysfunction, aggression and hyperthermia (Albertson et al., 1999; Barr et al., 2006; Lynch and House, 1992; Murray, 1998; Scott et al., 2007), while chronic use is thought to contribute to anxiety, depression, psychosis and psychomotor dysfunction (Darke et al., 2008; Homer et al., 2008; Scott et al., 2007). Despite the prevalence and negative consequences of METH abuse, there is no FDA-approved pharmacotherapy available currently for treating METH abuse.

While METH is known to affect serotonin and norepinephrine systems (Kogan et al., 1976), its rewarding properties relate primarily to its effects on dopamine (DA) systems. METH releases DA in reward-relevant brain regions, including nucleus accumbens and medial prefrontal cortex (Wise and Rompre, 1989). Multiple mechanisms of action underlie the METH-induced activation of DA systems, including: (1) reversal of the DA transporter (DAT; Guillot, 2009); (2) enhanced DA synthesis by facilitation of tyrosine hydroxylase activity (Guillot, 2009); (3) inhibition of DA metabolism by monoamine oxidase (Kitanaka et al., 2003; Larsen et al., 2002); and (4) enhanced transport of DA from the vesicles into the cytosol via a substrate action at the vesicular monoamine transporter-2 (VMAT2; Guillot, 2009).

VMAT2 has been proposed as a target for treating METH abuse (Dwoskin and Crooks, 2002; Zheng et al., 2006). Lobeline, a VMAT2 inhibitor derived from the plant *Lobelia inflata* (Teng et al., 1997), attenuates both METH-induced DA release from striatal slices (Miller et al., 2001; Nickell et al., 2010) and METH self-administration in rats (Harrod et al., 2001). However, lobeline also acts at nicotinic acetylcholine receptors (nAChRs), such that it does not selectively interact with VMAT2 (Dwoskin and Crooks, 2002). Lobelane is a defunctionalized lobeline analog that retains affinity for VMAT2, while having negligible affinity for nAChRs (Miller et al., 2004; Nickell et al., 2010). Unfortunately, while lobelane attenuates METH self-administration acutely, tolerance develops with repeated administration (Neugebauer et al., 2007). Thus, neither lobeline nor lobelane have an ideal profile as a pharmacotherapy due to either lack of selectivity or a lack of efficacy across repeated treatments.

Recent work has identified an *N*-dihydroxyl lobelane analog, *N*-(1,2*R*-dihydroxylpropyl)-2,6-*cis*-di-(4-methoxyphenethyl) piperidine hydrochloride (GZ-793A; for chemical structure, see Horton et al., 2011), as a promising candidate to treat METH abuse. GZ-793A exhibits greater potency and selectivity for inhibiting VMAT2 function compared to lobelane, and it inhibits METH-induced DA release from rat striatal slices (Horton et al., 2011). Also, GZ-793A reduces METH self-administration and blocks METH conditioned place preference (CPP; Beckmann et al., 2012). Within the same dose range (10-30 mg/kg, s.c.) that decreases METH self-administration and CPP, GZ-793A does not reduce cocaine self-administration or food-maintained responding (Beckmann et al., 2012), revealing its selectivity for diminishing the behavioral effects of METH. In addition, unlike lobelane, tolerance does not develop to the decrease in METH self-administration produced by GZ-793A across repeated daily treatments. Moreover, GZ-793A is not self-administered and does not produce CPP (Beckmann et al., 2012), indicative of low abuse liability.

Although these preclinical findings suggest that GZ-793A is a promising lead toward the development of VMAT2 inhibitors to treat METH abuse, the behavioral results obtained thus far have been limited to the s.c. route of administration. However, the oral route of

administration is preferred for clinical applications (Ranade, 1991; Shahiwala, 2011). Thus, the present experiments evaluated the dose-related efficacy and specificity of GZ-793A following oral administration on METH self-administration in rats to further evaluate this novel compound as a lead for the treatment of METH abuse.

MATERIALS AND METHODS

Subjects

Adult male Sprague-Dawley rats (Harlan Inc., Indianapolis, IN) were housed individually upon arrival and allowed to acclimate to the colony for 7 days with *ad libitum* access to food (Teklad Global Rodent Diet 2018, Harlan Laboratories). The colony was maintained in a temperature- and humidity-controlled environment, under a 12:12 hr light/dark cycle. All experiments were conducted during the light phase of the cycle. All experimental protocols were in accordance with the 2011 NIH *Guide for the Care and Use of Laboratory Animals* and approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

Apparatus

Operant conditioning chambers (ENV-008, MED Associates, St. Albans, VT), enclosed within sound-attenuating compartments (ENV-018M, MED Associates) were used for each experiment. Chambers were connected to a PC interface (SG-502, MED Associates) and were operated using MED-PC™ software. Each operant chamber had a 5 × 4.2 cm recessed food tray and 2 retractable levers mounted on either side of the food tray. A 28 V, 3-cm diameter, white cue light was mounted 6 cm above each lever. METH infusions were administered intravenously through a silastic catheter implanted into the jugular vein and exiting the animal through a metal cannula embedded in a dental acrylic head-mount. Drug infusions were delivered by an automated syringe pump (PHM-100, MED Associates).

Drugs

d-Methamphetamine HCl (METH) was obtained from Sigma-Aldrich (St. Louis, MO). *N*-(1,2*R*-Dihydroxypropyl)-2,6-*cis*-di-(4-methoxyphenethyl)piperidine HCl (GZ-793A) was synthesized according to methods described previously (Horton et al., 2011). Each drug was prepared in sterile saline (0.9% NaCl) and doses were expressed as salt weight.

METH Self-administration Procedure

METH self-administration training was based on methods reported previously (Beckmann et al., 2012; Neugebauer et al., 2007). All rats were trained initially to press one lever to receive food reinforcement (45 mg pellet, BIO-SERV, #F0021, Frenchtown, NJ). Responding on one lever (active lever) delivered the food pellet, while responding on the second lever (inactive lever) had no programmed consequence. Training continued until all rats reached stable criterion for responding on a fixed ratio 5 (FR5) schedule of reinforcement for food, defined as: (1) less than 20% variability in number of pellets earned across 3 consecutive daily sessions; (2) 10 or more pellets earned per session; and (3) a minimum of a 2:1 ratio of active:inactive lever presses. Rats were then anesthetized (100 mg/kg ketamine and 5 mg/kg diazepam, i.p.) and implanted with an indwelling catheter into the right jugular vein. Following a one-week recovery period, rats were trained to self-administer METH (0.05 mg/kg/infusion, delivered in a volume of 0.1 ml over 5.9 sec) in daily 60-min FR5 sessions, with a 20-sec time out following each infusion; the time out was signaled by illumination of both lever lights. Testing with GZ-793A began when responding for METH stabilized, defined as: (1) less than 20% variability in the number of infusions earned across 3 consecutive daily sessions; (2) 10 or more infusions per session; and (3) a

minimum of a 2:1 ratio of active:inactive lever presses. All GZ-793A test sessions were identical to the training sessions and at least two maintenance sessions (i.e., no GZ-793A treatment) were conducted between each GZ-793A test session in order to maintain METH self-administration. The effect of GZ-793A was defined by the percent change in METH self-administration compared to the control baseline, which was defined as the number of infusions on the maintenance session immediately prior to the test session.

Food-maintained Responding Procedure

Food-maintained responding was tested using methods similar to those used for METH self-administration, with the exception that rats did not undergo catheter surgery and they were maintained on an FR 5 schedule for food reinforcement rather than METH reinforcement throughout the entire experiment.

Oral Gavage Procedure

Food was removed from each home cage 2 h prior to each oral gavage with GZ-793A or saline. Prior to administering GZ-793A, rats were habituated first to the gavage procedure on 4 consecutive days. On these habituation days, rats received an oral gavage of saline (1 ml) 20 min prior to the session. A gavage of saline (1 ml) also was given prior to the two maintenance sessions intervening between each GZ-793A test session. On test sessions, GZ-793A was mixed in a concentration of 15 mg/ml and was administered by oral gavage with the volume adjusted to provide the dose based on body weight; e.g. for a rat weighing 350 mg, 30 mg/kg was administered in 0.7 ml, 60 mg/kg was administered in 1.4 ml, 120 mg/kg was administered in 2.8 ml and 240 mg/kg was administered in 5.6 ml. When a dose required more than 3 ml of solution to be administered, the dose was divided into two equal volumes and administered in a divided dose separated by 10 min. Saline gavage was given in a volume of 1 ml.

Dose-effects of oral GZ-793A

Experiment 1 determined the dose-effect function for oral administration of GZ-793A on METH self-administration. Rats were given GZ-793A (30, 60, 120 or 240 mg/kg, p.o.) 20 min prior to the operant session. The dose order was randomized according to a semi-random Latin square design. Percent baseline responding was calculated as follows: (number of active responses on test session) / (number of active responses on baseline session) $\times$ 100.

Experiment 2 determined the dose-effect function for oral administration of GZ-793A on food-maintained responding. Rats were given GZ-793A (30, 60, 120 or 240 mg/kg, p.o.) 20 min prior to the operant session. The dose order was randomized according to a semi-random Latin square design and percent baseline responding was calculated as described previously.

Time-course effects of oral administration of GZ-793A

Experiments 3 and 4 determined the time-course effects for oral administration of GZ-793A (120 mg/kg) on METH self-administration (Experiment 3) and food-maintained responding (Experiment 4); the test dose of GZ-793A used in these experiments was shown to be the lowest effective dose when administered 20 min prior to the METH self-administration session (Experiment 1). GZ-793A was administered at 3 different pretreatment times (20, 60 or 180 min) prior to the session. Saline gavage (1 ml) also was administered 20 min prior to the session. Pretreatment interval was randomized according to a semi-random Latin square design and percent baseline responding was calculated as described previously.

Statistical Analyses

Separate one-factor repeated-measures ANOVAs for each experiment were used to determine the effects of oral administration of GZ-793A on responding for METH or food reinforcement. All post-hoc analyses were conducted using Bonferroni's corrected pair-wise comparisons, with statistical significance declared at $p < 0.05$.

RESULTS

Baseline Responding

For METH self-administration, the mean ($\pm$ S.E.M.) number of responses on the active and inactive levers during stable baseline (no treatment) sessions was 91.2 ± 15.2 and 7.0 ± 4.0 , respectively (averaged across both Experiments 1 and 3). For food-maintained responding, the mean ($\pm$ S.E.M.) number of responses on the active and inactive levers during stable baseline (no treatment) sessions was 256.7 ± 49.1 and 3.3 ± 1.6 , respectively (averaged across both Experiments 2 and 4).

Dose-effect of oral administration of GZ-793A

Oral administration of GZ-793A decreased the number of METH infusions self-administered in a dose-dependent manner (Figure 1A). ANOVA revealed a main effect of dose [$F(4, 20) = 12.5$, $p < 0.01$], with post-hoc analyses indicating that the two highest doses of GZ-793A (120 and 240 mg/kg) decreased the number of METH infusions compared to saline control, $p < 0.05$. In contrast, ANOVA on inactive lever presses during METH self-administration sessions revealed no significant effect of dose (results not shown).

Oral administration of GZ-793A did not alter the number of pellets earned (Figure 1B). ANOVA revealed no significant effect of dose. ANOVA on inactive lever presses during food-maintained responding sessions also revealed no significant effect of dose (results not shown).

Time-course effects of oral administration of GZ-793A

Oral administration of GZ-793A decreased the number of METH infusions across each time interval evaluated (Figure 2A). ANOVA revealed no significant differences in the effect of GZ 793A across the 3 time intervals [$F(2, 10) = 0.7$, $p > 0.05$], with post-hoc comparisons against the control baseline indicating that GZ-793A significantly decreased the number of METH infusions at each of the time intervals tested (20, 60 and 180 min). In contrast, saline given 20 min prior to the session had no significant effect compared to the control baseline. A separate ANOVA revealed no significant effect on inactive presses.

Oral administration of GZ-793A did not alter food-maintained responding at any of the time intervals tested (Figure 2B). ANOVA revealed no effect of pretreatment time on active lever presses. In addition, ANOVA on inactive lever presses during food-maintained responding sessions also revealed no significant effect of pretreatment interval (results not shown).

Discussion

The current experiments determined the effect of oral administration of GZ-793A on the reinforcing properties of METH and food. In Experiment 1, oral administration of GZ-793A (120 and 240 mg/kg) decreased responding for METH, with ~85% reduction at the highest dose (240 mg/kg) of GZ-793A tested compared to baseline responding. In Experiment 3, oral administration of GZ-793A (120 mg/kg) decreased responding for METH across all pretreatment intervals (up to 180 min). In contrast, in Experiments 2 and 4, there were no effects of GZ-793A on food-maintained responding at any dose or time interval tested,

indicating that the effectiveness of oral administration of GZ-793A was specific for METH reinforcement.

While the procedures used in the present experiments are similar to those used previously to assess the effect of GZ-793A administered by the s.c. route (Beckmann et al., 2012), the unit dose of METH employed for self-administration was higher in the present study (0.05 vs. 0.03 mg/kg/infusion). Despite the differences in unit dose, baseline responding for METH was similar across studies, with ~18 infusions at 0.05 mg/kg/infusion dose and ~20 infusions at 0.03 mg/kg/infusion dose. However, since total METH intake across the session was higher in the current study relative to that reported previously (Beckmann et al. 2012; ~0.9 vs. 0.6 mg/kg across the session), some caution is needed making direct comparisons between previous results using the s.c. route and the current results employing the oral route of administration. Despite this caveat, the current results using oral administration of GZ-793A extend these previous findings. The current study evaluated the dose effect of GZ-793A administered 20 min prior to METH self-administration sessions. As expected, the lowest effective oral dose (120 mg/kg) in the current study was greater than the lowest effective s.c. dose (10 mg/kg; Beckmann et al., 2012). Moreover, the current study showed that the decrease in METH self-administration following oral administration of GZ-793A persisted for at least 180 min, which is 3-times longer (180 vs 60 min) than observed following the s.c. route of administration (Beckmann et al., 2012). The prolonged duration of action for GZ-793A administered via the oral route suggests a potential clinical benefit because patients would be required to take the medication less frequently.

When comparing the METH self-administration and food-maintained responding results in the current study, it should be noted that the baseline rates of lever pressing for these reinforcers varied, with the rate of responding for food higher than the rate of responding for METH. While differential rates of responding can influence drug effects (Dews, 1958; Kelleher and Morse, 1968), drugs tend to disrupt high rates of responding more readily than low rates of responding. Since this was not the case, it is unlikely that a rate dependency interpretation explains the observation that oral administration of GZ-793A reduced METH self-administration while food-maintained behavior was unchanged.

As mentioned previously, oral administration is the preferred route of administration due to its general ease, extended effect, and patient compliance (Ranade, 1991; Shahiwala, 2011). Demonstrating oral efficacy is a major objective in the development of GZ-793A or other related VMAT2 inhibitors for clinical use. Although a relatively high oral dose of GZ-793A (120 mg/kg) was needed to decrease METH self-administration, there are a number of reasons why a drug may have low bioavailability when given orally, including physicochemical properties and pharmacokinetic profile (Martinez and Amidon, 2002). Unfortunately, the lack of information about absorption, bioavailability or metabolic half-life of oral GZ-793A represents a limitation of the current study. Nonetheless, taken together with previous results, the current study provides support for the development of VMAT2 inhibitors as a novel class of orally active drugs for the treatment of METH abuse.

Acknowledgments

We thank Emily Denehy and William McCuddy for technical assistance. This work was supported by NIH grants U01 DA13519 and T32 DA01617.

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Highlights

- We examined the effects of oral administration of GZ-793A, a VMAT2 inhibitor, on methamphetamine self-administration.
- Rats showed a dose-dependent decrease in methamphetamine self-administration.
- Within the same dose range, food-maintained responding was not altered.
- The effect of GZ-793A lasted for at least 180 min.
- These results support the development of orally available VMAT2 inhibitors for the treatment of methamphetamine abuse.

Figure 1. Dose-effect functions for oral administration of GZ-793A on METH self-administration and food-maintained responding

Panel A: Relative to saline control, oral administration of GZ-793A dose-dependently decreased METH self-administration; $n=6$. Infusions earned are expressed as a percent of baseline (no treatment) represented by the dashed line. Asterisk (*) denotes significant difference from saline control, $p<0.05$. **Panel B:** Relative to saline control, oral administration of GZ-793A did not alter food-maintained responding; $n=6$. Food pellets earned are expressed as a percent of baseline (no treatment) represented by the dashed line.

Figure 2. Time-course effects of oral administration of GZ-793A on METH self-administration and food-maintained responding

Panel A: Relative to the control baseline, oral administration of GZ-793A (120 mg/kg) decreased METH self-administration across all time intervals tested (20, 60 and 180 min); there was no effect of saline administered at the 20 min time interval; $n=6$. Infusions earned are expressed as a percent of baseline (no treatment) represented by the dashed line. Asterisk (*) denotes significant difference from baseline control, $p < 0.05$. **Panel B:** Relative to baseline control, oral administration of GZ-793A (120 mg/kg) did not alter food-maintained responding; $n=6$. Food pellets earned are expressed as a percent of baseline (no treatment) represented by the dashed line.