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Short communication

Effects of 7-day repeated treatment with the 5-HT$_{2A}$ inverse agonist/antagonist pimavanserin on methamphetamine vs. food choice in male rhesus monkeys

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A B S T R A C T

Background: Preclinical drug vs. food choice is an emerging group of drug self-administration procedures that have shown predictive validity to clinical drug addiction. Emerging data suggest that serotonin (5-HT)$_{2A}$ receptors modulate mesolimbic dopamine function, such that 5-HT$_{2A}$ antagonists blunt the abuse-related neurochemical effects of monoamine transporter substrates, such as amphetamine or methamphetamine. Whether subchronic 5-HT$_{2A}$ antagonist treatment attenuates methamphetamine reinforcement in any preclinical drug self-administration procedure is unknown. The study aim was therefore to determine 7-day treatment effects with the 5-HT$_{2A}$ inverse agonist/antagonist pimavanserin on methamphetamine vs. food choice in monkeys.

Methods: Behavior was maintained under a concurrent schedule of food delivery (1 g pellets, fixed-ratio 100 schedule) and intravenous methamphetamine injections (0–0.32 mg/kg/injection, fixed-ratio 10 schedule) in male rhesus monkeys (n = 3). Methamphetamine choice dose-effect functions were determined daily before and during 7-day repeated pimavanserin (1.0–10 mg/kg/day, intramuscular) treatment periods.

Results: Under control conditions, increasing methamphetamine doses resulted in a corresponding increase in methamphetamine vs. food choice. Repeated pimavanserin administration failed to attenuate methamphetamine choice and produce a reciprocal increase in food choice in any monkey up to doses (3.2–10 mg/kg) that suppressed rates of operant responding primarily during components where behavior was maintained by food pellets.

Conclusions: Repeated 5-HT$_{2A}$ receptor inverse agonist/antagonist treatment did not attenuate methamphetamine reinforcement under a concurrent schedule of intravenous methamphetamine and food presentation in nonhuman primates. Overall, these results do not support the therapeutic potential of 5-HT$_{2A}$ inverse agonists/antagonists as candidate medications for methamphetamine addiction.

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1. Introduction

Methamphetamine addiction continues to be an insidious and global public health problem for which there are no efficacious pharmacological or behavioral treatment strategies (Brensiver et al., 2013; Carson and Taylor, 2014). Specifically, the United States Drug Enforcement Agency (DEA) reported that methamphetamine was the second most nationally identified illicit substance, only behind cannabis (DEA, 2015). Moreover, methamphetamine use disorder accounted for the majority of global persons entering treatment for drug use (UNODC, 2015). In summary, these epidemiological data support the need for preclinical research to improve our understanding of the neuropharmacological mechanisms involved in methamphetamine reinforcement. This improved mechanistic understanding should facilitate the development of clinically effective strategies to treat methamphetamine addiction.

Previous studies have implicated a role of serotonin (5-HT)$_{2A}$ receptors in the abuse-related neurochemical and behavioral effects of amphetamine or methamphetamine. For exam-
ple, pretreatment with the 5-HT$_{2A}$ antagonist SR46349-B or M100,907 attenuated amphetamine-induced increases in extracel-
lular dopamine (DA) levels in the striatum and nucleus accumbens of rodents (Auclair et al., 2004; Porras et al., 2002) and in the caudate
nucleus of nonhuman primates (Murnane et al., 2013a), respect-
ively. Consistent with these neurochemical results, pretreatment with the 5-HT$_{1A2C}$ agonist 5-dimethoxy-4-idoamphetamine
(DO1) enhanced methamphetamine discriminative stimulus effects
(Marona-Lewicka and Nichols, 1997; Munzar et al., 2002, 1999),
whereas the 5-HT$_{1A2C}$ antagonist ketanserin attenuated metham-
phetamine discriminative stimulus effects (Munzar et al., 1999).
Although these data implicate a potential role of 5-HT$_{2A}$ receptors in
methamphetamine abuse-related effects, there are no published
studies determining whether 5-HT$_{2A}$ receptors are necessary for
methamphetamine reinforcement.

The study aim was to determine repeated 5-HT$_{2A}$ inverse
agonist/antagonist pimavanserin treatment effects on metham-
phetamine reinforcement under a methamphetamine vs. food
choice procedure. A preclinical drug vs. food choice procedure was
utilized to investigate methamphetamine reinforcement mecha-
nisms for the following two reasons. First, preclinical drug vs.
food choice procedures have been predictive of human drug abuse
and addiction (Ahmed, 2010; Banks and Negus, 2012). Second,
preclinical drug vs. food choice procedures provide a dependent
measure of behavioral allocation that may be less sensitive to
reinforcement-independent rate-altering drug effects produced by
treatment drugs that may have potential as candidate medica-
tions (Banks et al., 2015). Pimavanserin was selected because it
is more selective for 5-HT$_{2A}$ vs. 5-HT$_{2C}$ receptors than M100,907
(Vanover et al., 2006) and has been recently approved by the Food
and Drug Administration for Parkinson’s disease-induced psychosis
treatment (Cummings et al., 2014; Walsh, 2016). If pimavanserin
attenuated methamphetamine choice and produced a correspond-
ing increase in food choice, these preclinical results would suggest
5-HT$_{2A}$ receptors were necessary for methamphetamine reinforce-
ment and support further research evaluating 5-HT$_{2A}$ receptor
inverse agonists/antagonists as candidate anti-methamphetamine
drug candidates.

2. Methods

2.1. Subjects

Studies were conducted in three adult male rhesus mon-
keys (Macaca mulatta) surgically implanted with a double-lumen
catheter (0.76 mm ID × 2.36 mm OD, STI Flow, Morrisville, NC)
inserted into a femoral or jugular vein and who had metham-
phetamine self-administration histories (Banks and Blough, 2015;
Schwientek and Banks, 2015). Monkeys were maintained on a
diet of fresh fruit and food biscuits (Lab Diet High Protein Monkey
Biscuits #5045, PMI Nutrition Inc., St. Louis, MO) delivered after
the behavioral session. Water was continuously available in the
housing chamber and a 12 h light-dark cycle was in effect. Mon-
keys had visual, auditory and olfactory contact with other monkeys
throughout the study. Operant procedures and foraging toys were
provided for environmental manipulation and enrichment. Videos
or music was also played daily in animal housing rooms to pro-
vide additional environmental enrichment. Animal research and
maintenance were conducted according to the Guide for the Care
and Use of Laboratory Animals (National Research Council, 2011).
Animal facilities were licensed by the United States Department of
Agriculture and accredited by the Association for Assessment and
Accreditation of Laboratory Animal Care. The Institutional Animal
Care and Use Committee approved both the research and environ-
mental enrichment protocols.

2.2. Apparatus

The housing chamber served as the experimental chamber
and was equipped with a custom operant panel, a pellet dis-
penser (Med Associates, Model ENV-203–1000, St. Albans, VT),
and two syringe pumps (Model PHM-108, Med Associates). One “self-
administration” pump delivered contingent methamphetamine
injections through one catheter lumen. The second “treatment”
pump delivered a 0.1 ml noncontingent saline infusion through the
second catheter lumen at a programmed rate of every 20 min from
1200 each day until 1100 the following morning. The intravenous
catheter was protected by a customized stainless steel tether and
jacket system (Lomir Biomedical, Malone, NY) that permitted mon-
keys to move freely within the home chamber. Catheter patency
was periodically evaluated by intravenous ketamine (5 mg/kg) ad-
ministration through one lumen of the double-lumen catheter.
The catheter was considered patent if intravenous ketamine admin-
istration produced muscle tone loss within 10 s.

2.3. Methamphetamine vs. food choice procedure

Daily experimental sessions were conducted from 0900 to
1100 h in each monkey’s home chamber as described previ-
ously (Banks and Blough, 2015). The terminal choice procedure
consisted of five 20 min components, with a different unit metham-
phetamine dose available during each successive component (0, 0.01,
0.032, 0.1, and 0.32 mg/kg/injection during components 1–5,
respectively). Manipulating the injection volume controlled the
methamphetamine dose (0, 0.03, 0.1, 0.3, and 1.0 ml/injection,
respectively). Components were separated by 5 min timeout
periods. During each component, the left, food-associated key
was transilluminated red, and completion of the FR require-
ment (FR100) resulted in 1 g food pellet delivery. The right,
methamphetamine-associated key was transilluminated green,
and completion of the FR requirement (FR10) resulted in delivery of
the intravenous unit methamphetamine dose available during that
component. Stimulus lights for the methamphetamine-associated
key were flashed on and off in 3 s cycles, and longer flashes
were associated with larger methamphetamine doses. Monkeys
could complete up to a total of 10 ratio requirements between
the food- and methamphetamine-associated keys. Responding on
either key reset the ratio requirement on the other key. Each ratio
requirement completion initiated a 30 s timeout, during which
all stimulus lights were turned off, and responding had no pro-
grammed consequences. Choice behavior was considered stable
when the lowest unit methamphetamine dose maintaining greater
than 80% methamphetamine vs. food choice varied by ≤0.5 log units
for 3 consecutive days.

Once methamphetamine vs. food choice was stable, test ses-
sions were conducted to determine 7-day repeated pimavanserin
(1–10 mg/kg, IM) treatment effects on methamphetamine vs. food
choice. Pimavanserin was administered between 0755 and 0805 h,
approximately 60 min before the 0900 h start of the behavioral ses-
tion. Pimavanserin treatment was tested up to doses that decreased
either methamphetamine choice or operant responding. The 3-
sky saline infusion period before each test drug treatment was
used as the “baseline.” At the conclusion of each 7-day treatment
period, intramuscular injections were terminated for at least 4 days
and until methamphetamine vs. food choice had returned to pre-
treatment levels. Pimavanserin doses were counterbalanced across
subjects.

2.4. Data analysis

The primary dependent measures were (1) percent metham-
phetamine choice, defined as (number of ratios completed on
the methamphetamine-associated key (*total number of ratios completed*)\(^{100}\) and (2) number of ratio requirements (hereafter referred to as “choices”) completed. The last 3-day mean of each experimental condition for each monkey for each dependent measure was then plotted as a function of unit methamphetamine dose during the behavioral session. Results were analyzed using a linear mixed-effects analysis with unit methamphetamine dose and pimavanserin dose as the fixed main effects and subjects as the random effect. Post-hoc comparisons against baseline conditions within a given methamphetamine dose were performed using the Dunnett’s test following a significant main effect of pimavanserin dose or methamphetamine dose \(\times\) pimavanserin dose interaction. The criterion for significance was set a priori at the 95% confidence level \((p < 0.05)\). All analyses were conducted using JMP Pro 12.2, SAS, Cary, NC.

2.5. Drugs

\((+)\)-Methamphetamine HCl and pimavanserin l-tartrate were provided by the National Institute on Drug Abuse Drug Supply Program (Bethesda, MD). All drug doses were expressed as the salt forms listed above and all drug solutions were passed through a sterile 0.2 \(\mu\)m filter (Millipore, Billerica, MA) before administration.

3. Results

3.1. Effects of pimavanserin on methamphetamine vs. food choice

Under control conditions during which saline was continuously infused through the treatment lumen “baseline”, increasing methamphetamine doses resulted in behavioral reallocation away from the food-associated key and towards the methamphetamine-associated key (Fig. 1). Repeated pimavanserin treatment failed to significantly alter methamphetamine vs. food choice or choices completed per component (Fig. 1). Due to individual subject sensitivity to pimavanserin potency to produce rate-altering effects, individual data are shown in Fig. 2. In monkey M1515, repeated pimavanserin treatment had no effect up to pimavanserin doses (10 mg/kg) that decreased rates of operant responding primarily during components maintained by food. Furthermore, repeated 10 mg/kg pimavanserin treatment also decreased body weight in this monkey by more than 1 kg. In both monkey M1516 and M1523, a pimavanserin dose of 3.2 mg/kg decreased rates of operant responding to such an extent that larger pimavanserin doses were not tested.

4. Discussion

The study aim was to determine whether repeated 5-HT\(_{2A}\) inverse agonist/antagonist pimavanserin administration decreased methamphetamine reinforcement in monkeys. The main finding was that pimavanserin did not attenuate methamphetamine choice and produce a corresponding increase in food choice in any monkey up to doses that decreased operant response rates and produced significant weight loss. Overall, the present results do not support the potential clinical utility of 5-HT\(_{2A}\) inverse agonists/antagonists as anti-methamphetamine addiction medications.

The present behavioral results were inconsistent with previous neurochemical (Auclair et al., 2004; Murnane et al., 2013a; Porras et al., 2002) and behavioral (Munzar et al., 1999) results demonstrating 5-HT\(_{2A}\) antagonists attenuated amphetamine or methamphetamine abuse-related effects. There are three potential reasons for these inconsistent results. First, potential species differences between rats and nonhuman primates in either 5-HT\(_{2A}\) or methamphetamine neuropharmacology could explain these inconsistent results. A second potential explanation could be related to differences in dosing regimens. For example, previous studies utilized acute dosing regimens whereas the present study determined 5-HT\(_{2A}\) inverse agonist/antagonist effects under a repeated subchronic dosing regimen. Examination of pimavanserin treatment days 1–3 did not reveal a rightward shift in the methamphetamine choice dose-effect function in any monkey (data not shown). A third potential explanation could be related to differences in experimental dependent measures. Previous studies determined 5-HT\(_{2A}\) antagonist effects on amphetamine-induced dopamine release in either nucleus accumbens (Auclair et al., 2004; Porras et al., 2002) or caudate nucleus (Murnane et al., 2013a) and methamphetamine discriminative stimulus effects (Munzar et al., 1999); whereas the present study determined 5-HT\(_{2A}\) inverse agonist/antagonist effects on methamphetamine reinforcement. However, repeated pimavanserin treatment effects on methamphetamine self-administration were consistent with previous studies evaluating ketanserin and M100,907 acute pre-treatments on cocaine self-administration (Fantegrossi et al., 2002; Murnane et al., 2013b). Overall, the present results and the previous literature highlight the importance of repeated pharmacological
pretreatments and determination of treatment effects on multiple dependent measures to characterize candidate medication treatment efficacy.

Conceptually, 5-HT$_{2A}$ receptor antagonists represent an “antagonist-like” pharmacotherapeutic approach for methamphetamine addiction with the neurobiological aim of blunting methamphetamine-induced nucleus accumbens dopamine release and corresponding reinforcing effects. The present behavioral results suggest this may not be a therapeutically advantageous treatment option for methamphetamine addiction. The present results are consistent with previous methamphetamine vs. food choice studies in nonhuman primates evaluating “antagonist-like” pharmacological treatments such as dopamine antagonists PG01037, buspirone, and risperidone or the dopamine D3 partial agonist PG619 (Banks and Blough, 2015; John et al., 2015a, 2015b). Furthermore, both the dopamine partial agonist aripiprazole and the dopamine antagonist risperidone have failed to reduce methamphetamine choice in the human laboratory (Stoops et al., 2013) or methamphetamine use in clinical trials (Coffin et al., 2013; Nejtek et al., 2008; Tiihonen et al., 2007). Moreover, “antagonist-like” approaches have not been successful pharmacotherapeutic strategies to treat amphetamine-type or cocaine addictions based on a recent meta-analysis (Kishi et al., 2013). In summary, we interpret this scientific literature to suggest methamphetamine addiction medications development might benefit from a paradigm shift to novel “agonist-like” therapies that
both decrease methamphetamine use and promote more adaptive behavior maintained by alternative non-drug reinforcers.

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Contributors

Banks designed the study, performed the data analysis, and drafted the manuscript.

Conflicts of interest

The author has no conflicts of interest to declare.

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