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Rivastigmine reduces "likely to use methamphetamine" in methamphetamine-dependent volunteers

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ABSTRACT

We previously reported that treatment with the cholinesterase inhibitor rivastigmine (3 mg, PO for 5 days) significantly attenuated "Desire for METH". Given that higher dosages of rivastigmine produce greater increases in synaptic ACh, we predicted that 6 mg should have more pronounced effects on craving and other subjective measures. In the current study, we sought to characterize the effects of short-term exposure to rivastigmine (0, 3 or 6 mg) on the subjective and reinforcing effects produced by administration of methamphetamine (METH) in non-treatment-seeking, METH-dependent volunteers. This was a double-blind, placebo-controlled, crossover study. Participants received METH on day 1, and were then randomized to placebo or rivastigmine on day 2 in the morning and treatment continued through day 8. METH dosing was repeated on day 6. The data indicate that METH (15 and 30 mg), but not saline, increased several positive subjective effects, including "Any Drug Effect", "High", "Stimulated", "Desire METH", and "Likely to Use METH" (all p's<0.0001). In addition, during self-administration sessions, participants were significantly more likely to choose METH over saline ($p<0.0001$). Evaluating outcomes as peak effects, there was a trend for rivastigmine to reduce "Desire METH" ($p=0.27$), and rivastigmine significantly attenuated "Likely to Use METH" ($p=0.01$). These effects were most prominent for rivastigmine 6 mg when participants were exposed to the low dose (15 mg, IV), but not high dose (30 mg, IV), of METH. The self-administration data reveal that rivastigmine did not alter total choices for METH (5 mg, IV/choice). Overall, the results indicate some efficacy for rivastigmine in attenuating key subjective effects produced by METH, though additional research using higher doses and longer treatment periods is likely needed. These data extend previous findings and indicate that cholinesterase inhibitors, and other drugs that target acetylcholine systems, warrant continued consideration as treatments for METH dependence.

1. Introduction

Methamphetamine (METH) is a highly addictive stimulant. According to the 2010 United States National Survey on Drug Use and Health (http://oas.samhsa.gov/nsduh.htm), the number of past month METH users was 353,000, and the number of recent new users of METH among persons aged 12 or older was 105,000. This latter value is disconcerting since it reflects ~29 new users of METH each day! Our research group and others have completed several safety and preliminary efficacy trials of potential medications for treating METH dependence. Despite these efforts, much work remains in identifying an effective pharmacotherapy. Recent review articles provide summaries of laboratory-based and outpatient trials conducted to date, and include lists of novel medications on the horizon (Elkashef et al., 2008; Haile et al., 2009; Kampman, 2008; Karila et al., 2010; Moeller et al., 2008; Rose and Grant, 2008; Vocci and Appel, 2007), as well as more recent efforts to develop a vaccine for METH dependence (Shen et al., 2012).

Although changes in the dopamine (DA) system have been most extensively studied, cholinergic transmission is also altered by drugs of abuse and both DA and acetylcholine (ACh) may contribute to psychostimulant reinforcement (Hurd et al., 1990; Mark et al., 1999a, 1999b). DA neurons express multiple types of muscarinic and nicotinic ACh receptors and an interplay of dopaminergic and cholinergic neurons in the nucleus accumbens allows coordinated functioning of these neurotransmitter systems. The role of nucleus accumbens cholinergic interneurons in the effects produced by cocaine was elucidated by recent optogenetic studies in rats (Witten et al., 2010), and the importance of ACh systems in the effects produced by cocaine has been thoroughly summarized by Adinoff and colleagues (Adinoff et al., 2010; Williams and Adinoff, 2008).

Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; ANOVA, analysis of variance; BCM, Baylor College of Medicine; BID, twice daily dosing; DA, dopamine; DSM, Diagnostic and Statistical Manual; IV, intravenous; MEDVAMC, Michael E. DeBakey Veteran Affairs Medical Center; METH, methamphetamine; NIDA, National Institute on Drug Abuse; PO, oral administration; S.E.M., standard error of the mean; VAS, visual analog scale.

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Postmortem data indicate that METH users exhibit reduced levels of the ACh synthetic enzyme choline acetyltransferase (Kish et al., 1999; Siegal et al., 2004), but normal or increased expression of the vesicular ACh transporter (Siegal et al., 2004). This may indicate compensatory neuroadaptive changes of the cholinergic system, and suggest that METH users in particular may benefit from treatment with ACh enhancing agents. Pharmacological interactions between nicotine and METH have been demonstrated by several investigators. In rats, nicotine acutely reduced METH self-administration and during reinstatement nicotine exposure significantly increased METH-seeking behavior (Neugebauer et al., 2010). Of interest, both nicotine and donepezil, but not the noncompetitive nicotinic receptor antagonist mecamylamine, reduced reinstatement induced by exposure to conditioned cues and by administration of priming doses of METH (Hiranita et al., 2006). Reinstatement of drug-seeking behavior is a preclinical model for craving in human subjects (Shaham et al., 2003), so these data suggest that enhancing ACh activity may reduce METH craving in humans. Additional data in rodents indicate that nicotine and nicotine agonists fully substitute for METH in a drug discrimination task, and that mecamylamine reduced the discriminative stimulus effects of the training dose of METH (Desai and Bergman, 2010; Gatch et al., 2008). These data indicate that compounds that increase ACh, including cholinesterase inhibitors, may attenuate subjective effects produced by METH in humans.

Given the above evidence, our research group completed a double-blind, placebo-controlled study to determine the effects of the cholinesterase inhibitor rivastigmine on the acute subjective effects produced by METH in METH-dependent human volunteers (De La Garza et al., 2008a, 2008b). We showed that METH (30 mg, IV) administration significantly increased self-reported "Desire for METH", and treatment with rivastigmine (3 mg, PO for 5 days) significantly attenuated this response. Knowing that higher dosages of rivastigmine produce greater increases in synaptic ACh, it is reasonable to predict that 6 mg will have more pronounced effects on craving and other subjective measures. As such, we sought to characterize the effects of short-term treatment with a higher dose of rivastigmine (6 mg) on the cardiovascular, subjective and reinforcing effects produced by a broader range of METH doses in non-treatment-seeking, METH-dependent volunteers. This human laboratory study is a critical next step in the evaluation of rivastigmine as a potential treatment for METH dependence.

2. Methods

This double-blind, placebo-controlled, crossover study was sponsored by the National Institute on Drug Abuse, and approved by the Baylor College of Medicine (BCM) and Michael E. DeBakey Veteran Affairs Medical Center (MEDVAMC) Institutional Review Boards. All volunteers provided written informed consent after being apprised of potential risks of study participation.

2.1. Sample

Participants were English-speaking volunteers who were not seeking abstinence-focused treatment at the time of the study, between 18 and 55 years of age, met DSM-IV-TR criteria for METH dependence, had a breathalyzer test indicating undetectable blood alcohol upon admission, a medical history and brief physical examination demonstrating no clinically significant contraindications for study participation, and a negative urine drug screen, with the exception of METH or marijuana. Participants were not-seeking treatment at the time of enrollment, and were not seeking to remain abstinent either since they all tested positive for recent METH use during screening and also agreed (during the informed consent process) to participate in a study in which METH would be administered as part of the protocol. Exclusion criteria included having neurological or psychiatric disorders, as assessed by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998), such as an episode of major depression within the past 2 years, lifetime history of schizophrenia, other psychotic illness, bipolar illness, current organic brain disease or dementia assessed by clinical interview, history of or any current psychiatric disorder that would require ongoing treatment or which would make study compliance difficult, history of suicide attempts within the past three months and/or current suicidal ideation/plan, history of psychosis occurring in the absence of current METH use, or meet DSM-IV TR criteria for dependence on alcohol or other drugs, other than nicotine or marijuana.

2.2. Procedure

Participants resided for 9 days on the Research Commons of the MEDVAMC (Table 1). On Day 1 (pre-randomization), participants received 3 infusions in which placebo was single-blind (administered at 9 AM), and 15 and 30 mg METH doses were double-blind and randomized (administered at either 10 AM or 2 PM). Saline and METH infusions were administered IV by a study physician over 2 min. All participants were randomly assigned to placebo or rivastigmine for days 2–8. METH dosing was repeated on day 6 (post-randomization). On days 7 and 8, participants completed sample and self-administration sessions. On day 9, participants were discharged from the study and returned for enrollment and randomization to alternate rivastigmine dosing conditions (crossover study design; i.e., all participants were exposed to all doses of rivastigmine).

2.3. Cardiovascular and safety measures

All adverse events, mood, heart rate and blood pressure data have been submitted for publication elsewhere.

2.4. Subjective effects

On days 1 and 6, visual analog scale (VAS) forms were completed at baseline (T = −15 min) and several time points following infusions of 15 and 30 mg METH and saline. VAS adjectives included ratings of 'Any drug effect', 'High', 'Desire METH', 'Stimulated', and 'Likely to Use METH if Given Access'. VAS effects were recorded on a continuous scale digitized between 0 (not at all) to 100 (strongest ever).

2.5. Reinforcing effects

Self-administration sessions were conducted on days 7 and 8. On day 7 (at 10 AM and 2 PM), participants were provided with 10 consecutive non-contingent *sample* doses of METH (0 or 5 mg, IV). This session served to inform participants of what was in the syringe and should be expected during choice sessions held on the subsequent day. Participants were told to take notes on the subjective effects (positive and/or negative) associated with each session which was randomly assigned the color RED or BLUE. On day 8, participants made a series of 10 choices between receiving the infusion of METH (0 or 5 mg) versus receiving no-infusion. Participants made these decisions on the basis of the RED or BLUE color coding provided on the previous day.

Table 1
Study overview.

Randomize to Rivastigmine	Day 1	Pre-Rand METH (0, 15 and 30 mg, IV)
(0, 1.5, or 3 mg, BID)	Day 6	Post-Rand METH (0, 15 and 30 mg, IV)
Day 2 (AM) through Day 8 (AM)	Day 7–8	Self-administration sessions
	Day 9	Discharge