Pharmacology, Biochemistry and Behavior 99 (2011) 423–427

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Low dose, short-term rivastigmine administration does not affect neurocognition in methamphetamine dependent individuals

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ARTICLE INFO

Article history:
Received 19 January 2011
Received in revised form 28 April 2011
Accepted 15 May 2011
Available online 23 May 2011

Keywords:
Methamphetamine
Cognition
Neurocognition
Neuropsychological impairment
Rivastigmine
Acetylcholine

ABSTRACT

Neurocognitive impairment is a well-documented consequence of methamphetamine addiction. Not surprising, methamphetamine-associated neurocognitive impairment has been identified as an important target of treatment. Thus, this study sought to determine whether rivastigmine, an acetylcholinesterase inhibitor and cognition enhancing agent, could improve neurocognitive performance in a sample of long-term, high-dose methamphetamine addicts who were not seeking treatment at the time of enrollment in the study. This double-blind, placebo-controlled study evaluated whether a daily dose 0, 3, or 6 mg of rivastigmine, administered over six consecutive days, would enhance performance on measures of attention/information processing speed, episodic memory, and executive/frontal lobe functioning relative to test performance at baseline. The results revealed that rivastigmine did not alter neurocognition in this cohort. There are a number of factors that may have mitigated the effects of rivastigmine in this particular study, including especially the short-term, low-dose treatment regimen utilized. The negative findings notwithstanding, the study serves as a springboard for future investigations that will examine whether other medications can alter neurocognition in methamphetamine dependent study participants.

1. Introduction

Long-term, high-dose methamphetamine use is a risk factor for the onset of neurocognitive impairment in humans (Kalechstein and Newton, 2007). A review of the extant literature on methamphetamine use and neurocognition revealed that 24 of 25 studies showed that methamphetamine dependence is associated with poorer performance on measures of attention/information processing speed, learning and memory, and/or executive/frontal systems functioning (Kalechstein and Newton, 2007). Two of these studies reported that 22 to 57% of participants were impaired, depending on the domain assessed (e.g., Cherner et al., 2009; Kalechstein et al., 2003). Moreover, methamphetamine-associated neurocognitive impairment is durable, i.e., unlikely to resolve with protracted abstinence (Volkow et al., 2001; Cherner et al., 2009). For example, the results of Cherner et al. showed that 5 of 11 participants continued to demonstrate global neurocognitive impairment after 6 months of continuous abstinence. In the one study that failed to detect differences between methamphetamine users and matched controls (Johanson et al., 2006), the lack of significant findings was at least partially attributable to the fact that the study relied on a test battery, the CANTAB, which demonstrated variable sensitivity in another study that examined the association between amphetamine use and neurocognition (Ornstein et al., 2000).

As a result of an accretion of articles on this topic, some researchers have identified methamphetamine-associated neurocognitive impairment as a neglected area of critical concern (Kalechstein et al., 2010; Sofuoglu, 2010). Sofuoglu (2010) highlighted the association between neurocognitive impairment and adverse functional outcomes, such as poor treatment retention in studies of cocaine-dependent and alcohol-dependent individuals, and also emphasized the need to identify and test candidate medications that potentially can ameliorate this condition.

It is noteworthy that stimulant-associated neurocognitive impairment can be ameliorated; for example, administration of 400 mg of modafinil for 3 days resulted in significantly improved response accuracy on measures of working memory in those study participants who demonstrated relatively poor performance at baseline (Kalechstein et al., 2010). A recent study by Ghahremani et al. (2011) showed that acute modafinil exposure improved performance on a reversal learning task in methamphetamine users. For the current study, rivastigmine was being evaluated for its safety and potential efficacy in a phase I clinical study in long-term, high-dose methamphetamine using volunteers. The effect of rivastigmine on neurocognitive impairment was identified as a secondary outcome.

Several reasons underlay the decision to focus on the remediation of neurocognitive impairment using rivastigmine. Namely, rivastigmine is classified as a cognition-enhancing agent (Hasselmo and Sarter, 2011)

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doi:10.1016/j.pbb.2011.05.013

and, in some double-blind, placebo-controlled studies, administration of rivastigmine was associated with improved performance on tests of attention, memory in individuals diagnosed with Alzheimer's disease (Feldman et al., 2007; Frankfort et al., 2007) and traumatic brain injury (Silver et al., 2009; Tenovuo et al., 2009). In these studies, the efficacy of rivastigmine was greatest in studies that utilized higher doses, e.g., 7.9 mg per day for much longer period of times, e.g., 39 weeks (Silver et al., 2009); however, because the efficacy of rivastigmine has not been evaluated in samples of long-term, high-dose methamphetamine using individuals, we sought to determine whether relatively low-dose, short-term administration of rivastigmine would be associated with improved performance on measures of attention/information processing speed, episodic memory, and working memory.

2. Materials and method

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 (American Psychiatric Association, 2000) criteria for methamphetamine dependence, have a breathalyzer test indicating an undetectable blood alcohol level upon admission, had a medical history and brief physical examination demonstrating no clinically significant contraindications for study participation, and had a negative urine drug screen, with the exception of methamphetamine or marijuana. Exclusion criteria included having neurological or psychiatric disorders, as assessed by MINI (Sheehan et al., 1998), such as episode of major depression within the past 2 years, lifetime history of schizophrenia, other psychotic illness, or bipolar illness, current organic brain disease or dementia assessed by clinical interview, history of or any current psychiatric disorder which would require ongoing treatment or which would make study compliance difficult, history of suicide attempts within the past 3 months and/or current suicidal ideation/plan, or history of psychosis occurring in the absence of current methamphetamine use, meet DSM-IV-TR criteria for dependence on alcohol or other drugs, except for nicotine or marijuana. Data regarding demographic profile and substance use history are included in Table 1.

Table 1
Demographics and drug use.

Category	Total N = 17
Gender	
Male	14
Female	3
Ethnicity	
Caucasian	13
Hispanic	3
African–American	1
Age	34.4 ± 2.0
Education (in years)	13.2 ± 0.5
Estimated premorbid IQ	110.9 ± 2.2
Methamphetamine	
Years of use	10.2 ± 1.5
Recent use (last 30 days)	17.4 ± 2.4
Amount used per day (in grams)	0.8 ± 0.1
Nicotine (n = 14)	
Years of use	12.5 ± 2.0
Recent use (last 30 days)	26.7 ± 1.8
Number of cigarettes per day	16.7 ± 2.6
Alcohol (n = 14)	
Years of use	13.5 ± 2.6
Recent use (last 30 days)	2.2 ± 1.0
Marijuana (n = 11)	
Years of use	12.5 ± 2.9
Recent use (last 30 days)	8.0 ± 2.9

2.2. Procedure

The primary objective of the parent protocol was to characterize the effects of treatment with rivastigmine (0, 1.5, and 3 mg, twice per day) on the subjective and reinforcing effects produced by experimental administration of methamphetamine (0, 15 and 30 mg, IV) in the laboratory (data to be presented in a separate publication). A secondary objective, and the focus of this manuscript, was to determine the effects of rivastigmine treatment on cognitive functioning in long-term, high-dose methamphetamine using individuals. Participant reimbursement was not contingent upon performance on the neurocognitive tests.

This was a double-blind, placebo-controlled, within-subjects study. Participants resided in the Michael DeBakey VA Medical Center. Upon admission, study participants provided a negative urine toxicology screen, which reveals that they had not used methamphetamine for at least 3 to 5 days prior to that day. They completed neurocognitive battery assessments at 10:30 am on Days 1 (admission/pre-randomization) and 9 (discharge/post-randomization). On the dates of the neurocognitive assessments, participants were not allowed to smoke cigarettes during the 60 min prior to the test administration, during the assessment, or during the 60 min following the test administration.

On Days 2 and 6 participants received 3 double-blind methamphetamine infusion sessions in which the dose (0, 15 and 30 mg, IV) was randomized and separated by 3 h. They were randomly assigned to placebo or rivastigmine for days 3–8. On day 7, participants completed two sessions in which they received either placebo or 5 mg of IV methamphetamine. Infusions were separated by 15 min and the methamphetamine and placebo sessions were randomized in a double-blind manner. Additionally, each session was associated with a specific color (red or blue) and participants were informed to remember the color, as that color would be associated with the same dose of drug (placebo vs 5 mg of IV methamphetamine) for the sessions on the following day. On day 8, participants participated in a similar session to that of day 7, but they could now choose whether or not to self-administer each of the 10 infusions. On day 9, after completing the cognitive battery, they were discharged from the study and returned for enrollment and randomization to alternate rivastigmine dosing conditions after at least 1 week had passed.

2.3. Tests administered

The following tests were administered during the baseline and post-treatment phase of each study arm. Participants were provided with standardized instructions, both oral and written, prior to the administration of each task. Additionally, participants were always reminded to respond as quickly and as accurately as possible. The tests were selected based on studies demonstrating that these and or similar measures were shown to be valid and reliable with respect to differentiating between long-term, high-dose methamphetamine using individuals and matched controls (Cherner et al., 2009; Levine et al., 2006; Newton et al., 2003).

2.3.1. Wechsler Adult Intelligence Scale—III (WAIS-III; Wechsler, 2007)

The Vocabulary and Matrix Reasoning subtests of the WAIS-III were administered. These raw scores from these subtests were included in an algorithm, the Oklahoma Premorbid Intelligence Estimation algorithm (Schoenberg et al., 2002), which estimates level of intellectual function prior to the onset of drug use.

2.3.2. Continuous Performance Test—II (CPT-II; Conners, 2002)

The CPT-II measures sustained attention. Participants were instructed to press the space bar whenever any letter, except for 'X,' appeared on the computer screen. The letters were presented for 250 ms, and new letters appeared at intervals of 1, 2, or 4 s. The inter-stimuli time intervals varied pseudo-randomly. The variables of interest