Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 1827–1830

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Evaluation of the effects of rivastigmine on cigarette smoking by methamphetamine-dependent volunteers

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ARTICLE INFO

Article history:
Received 22 December 2010
Received in revised form 8 July 2011
Accepted 15 July 2011
Available online 22 July 2011

Keywords:
Acetylcholine
Addiction
Methamphetamine
Nicotine-dependence
Rivastigmine
Smoking

ABSTRACT

Compared to smokers alone, smokers with co-morbid substance use disorders are at greater risk of suffering from smoking-related death. Despite this, relatively few studies have examined smoking cessation treatments for those with stimulant dependence. In the current study, we sought to evaluate the effects produced by short-term exposure to the cholinesterase inhibitor rivastigmine (0, 3 or 6 mg) on cigarette smoking in non-treatment-seeking, methamphetamine-dependent volunteers. This was a double-blind, placebo-controlled, crossover study that took place over 9 days. The data indicate that rivastigmine treatment did not alter Fagerström Test for Nicotine Dependence scores, carbon monoxide readings, or cigarettes smoked per day, but a trend toward reduced urges to smoke ($p<0.09$) was detected during treatment with rivastigmine 3 mg. These data, while preliminary, indicate that cholinesterase inhibitors warrant consideration as treatments for nicotine dependence, including use in stimulant-dependent individuals who exhibit significantly higher rates of smoking than the general population.

1. Introduction

Cigarette smoking is the leading cause of death and morbidity in the US (Centers for Disease Control and Prevention, 2008). Among those with substance use disorders, rates of smoking are almost 70%, approximately 3- to 4-fold greater than the general population (Kalman et al., 2005). Even higher rates of smoking, 87–92%, are reported among those with methamphetamine-dependence (Weinberger and Sofuoglu, 2009). In our own research, we have routinely shown similarly high rates of smoking among methamphetamine-dependent individuals (De La Garza et al., 2008, 2009; De La Garza et al. ; Newton et al. ; Zorick et al., 2009). Compared to smokers alone, smokers with co-morbid substance use disorders are at greater risk of suffering from smoking-related death (Hser et al., 1994; Hurt et al., 1996). While the cause of increased negative health outcomes is unknown, likely reasons are that co-morbid smokers are a more treatment-resistant population (using more drug more frequently, earlier initiation, etc.) and there may be additive effects of combining two drugs with known negative health effects (Weinberger and Sofuoglu, 2009). The U.S. Department of Health and Human Services Clinical Practice Guidelines explicitly recommends addressing cigarette smoking in treatments for substance dependence (Fiore et al., 2008). However, relatively few studies have examined smoking cessation treatments for those with stimulant dependence (Morisano et al., 2009; Weinberger and Sofuoglu, 2009). In many addiction treatment settings, smoking is actually endorsed in the form of regular smoke breaks (Knapp et al., 1993); a strategy apparently adopted by treatment providers concerned that reducing smoking may impede successful treatment outcomes. However, a meta-analysis of smoking interventions in addiction treatment settings suggests smoking cessation treatments may actually enhance longer-term addiction outcomes (Prochaska et al., 2004).

Among the general population of smokers, millions attempt to quit smoking each year, but the majority of those who attempt to quit on their own fail within 8 days of the initial quit attempt (Hughes et al., 2004). Currently, first-line pharmacotherapies for smoking cessation include nicotine replacement therapy, bupropion, and varenicline. These medications consistently improve smoking cessation rates relative to placebo in randomized control trials, however rates of abstinence are only 20–33% at 6-months after the initial quit attempt (Fiore et al., 2008). Therefore, it is important to continue the search for new pharmacotherapies to mitigate withdrawal symptoms and prevent relapse during smoking cessation.

Substantial evidence points to nicotine as the primary agent in tobacco leading to abuse and dependence (Dwoskin et al., 2009; Govind et al., 2009; Livingstone and Wonnacott, 2009). Nicotine binds to nicotinic acetylcholine receptors (nAChRs) in brain and activates the mesocorticolimbic dopamine system (Grenhoff et al., 1986; Zhang

Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; ANOVA, analysis of variance; BuChE, butyrylcholinesterase; CO, carbon monoxide; DSM, diagnostic and statistical manual; FTND, Fagerström Test for Nicotine Dependence; METH, methamphetamine; nAChRs, nicotinic acetylcholine receptors; SRNU, Self-Report of Nicotine Use; UTS, Urge to Smoke.

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doi:10.1016/j.pnpbp.2011.07.006

et al., 2009) in the same manner as other drugs of abuse (Pierce and Kumaresan, 2006) and rewarding stimuli (Hyland et al., 2002). Chronic nicotine administration results in upregulation of high affinity nicotine binding sites in neuronal nAChRs, which has been suggested as the neurobiological basis of nicotine dependence (Govind et al., 2009). Based on nicotine's effects on the brain, compounds that inhibit the breakdown of ACh warrant consideration as possible smoking cessation pharmacotherapies. In fact, the acetylcholinesterase (AChE) inhibitor galantamine reduced smoking and craving for cigarettes in alcohol-dependent participants (Diehl et al., 2006), although similar effects were not observed in smokers with schizophrenia (Kelly et al., 2008). More recently, 4 weeks of the AChE and butyrylcholinesterase (BuChE) inhibitor rivastigmine (6 mg/day) produced significant decreases in both smoking and craving relative to placebo in alcohol-dependent participants (Diehl et al., 2009). To our knowledge there are no data on the effects of AChE inhibitors on smoking behaviors in healthy, non-drug-dependent individuals.

The purpose of the current study was to evaluate the effects produced by short-term exposure to rivastigmine on smoking behavior in non-treatment seeking methamphetamine (METH)-dependent volunteers.

2. Methods

This double-blind, placebo-controlled, crossover study was funded by the National Institute on Drug Abuse, and approved by the Baylor College of Medicine and Michael E. DeBakey VA Medical Center 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 for cigarette smoking or METH use at the time of the study, between 18 and 55 years of age, met DSM-IV-TR (DSM-IV-TR 2000) criteria for METH dependence, had 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 METH 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, 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 METH use, or meet current or past DSM criteria for dependence on alcohol or other drugs, except for nicotine.

2.2. Procedure

Participants resided for 9 days on the Research Commons of the Michael E. DeBakey VA Medical Center. During the 9-day stay, participants were exposed to low doses of methamphetamine (study days 2, 6, 7, and 8) to measure physiological, subjective and reinforcing effects (*those data and outcomes have been submitted for publication elsewhere*). In this manuscript, we focus on changes in nicotine smoking behavior that occurred during the protocol. The participants were not only non-treatment seeking methamphetamine users, but they were also non-treatment seeking nicotine-dependent individuals. Participants were randomized to one of 3 rivastigmine dosing conditions (0, 3 and 6 mg) from days 1 to 8, and on day 9 they were discharged from the study then returned for enrollment and randomization to alternate rivastigmine dosing conditions. The period between study enrollments was >7 days but <28 days.

During screening, all participants tested METH-positive (via urine toxicology) indicating that they were active METH users. Upon enrollment, however, all participants were required to report to the hospital METH-negative, which necessitated cessation of use for at least 4–6 days. No participants exhibited signs of withdrawal at enrollment or during the study as assessed by daily mood questionnaires or adverse events reporting (data not shown).

2.3. Assessment of nicotine dependence

The Fagerström Test for Nicotine Dependence (FTND) is a 5-item questionnaire that has been previously demonstrated to be reliable and valid and is widely used to characterize nicotine dependence (Heatherton et al., 1991). The FTND score was assessed once daily every morning at 7 AM.

2.4. Self-reported cravings for cigarettes

The Urge to Smoke Questionnaire (UTS) has been previously demonstrated to be positively associated with nicotine withdrawal (Jarvik et al., 2000). The UTS consists of 10 items, with each item scored on a 7-pt scale. Participants were administered the UTS once daily every morning at 7 AM. The mean score was calculated for all 10 questions for each day and this value was used in the final data analyses.

2.5. Assessment of cigarette smoking

Cigarette smoking was assessed via daily breath carbon monoxide (CO; Vitalograph® Inc, Lenexa, KS) and the Self-Report of Nicotine Use (SRNU) questionnaire. The key question from the SRNU was "in the past 24 h how many cigarettes have you smoked?" Available answers were 1) 1–3 cigarettes, 2) 3–10 cigarettes, 3) 10–20 cigarettes, and 4) greater than 1 pack (i.e., 20 cigarettes).

2.6. Rivastigmine

Rivastigmine inhibits both AChE and BuChE with equal potency and has selectivity for central activity. Following oral dosing, the plasma half-lives of rivastigmine and its primary metabolite are roughly 1 h and 2 h, respectively; however, cholinesterase inhibition lasts much longer (~10 h). Commercially available rivastigmine tablets (3 mg) were encapsulated in gelatin capsules by the VA Medical Center research pharmacy, and placebo was prepared in a similar manner. Two rivastigmine or matched placebo pills were administered orally at 7:00 AM and 7:00 PM (i.e., 0 + 0 mg, 3 + 0 mg, or 3 + 3 mg) beginning on day 1 (in the PM) and continuing through day 8 (in the AM) of the protocol.

2.7. Data analyses

Data were analyzed using StatView 5.0 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were compiled for demographic and drug use variables. All primary measures, including FTND scores, breath CO, UTS scores, and SRNU scores were analyzed individually using repeated measures analysis of variance (ANOVA) as a function of rivastigmine dose (0, 3 and 6 mg) and Time (days 1–8). All data, except time, were analyzed as between-subjects factors. For all measures, statistical significance was set at $p<0.05$. All data are presented as mean ± standard error of the mean (S.E.M.).