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Effects of topiramate on methamphetamine-induced changes in attentional and perceptual-motor skills of cognition in recently abstinent methamphetamine-dependent individuals

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Abstract

Methamphetamine-dependent individuals often cite the need to maintain enhanced cognitive performance and attention as a reason for continuing or relapsing to drug-taking. Further, methamphetamine addicts might not comply with taking a potentially therapeutic medication if it had a profound effect on these cognitive processes. Topiramate, a sulfamate-substituted fructopyranose derivative, has been suggested as a putative therapeutic medication for treating methamphetamine dependence. Examination of topiramate's effects on cognitive performance and attention is a clinically and scientifically important component of understanding its potential therapeutic profile. In 10 male and female individuals who met DSM-IV criteria for methamphetamine dependence, we examined the effects of low (50 mg b.i.d.)- and high (100 mg b.i.d.)-dose topiramate – in both the presence and absence of low (15 mg)- and high (30 mg)-dose intravenous methamphetamine – on cognitive performance, attention, and concentration on the rapid visual information processing task and the digit symbol substitution test. Intravenous methamphetamine enhanced cognitive performance, attention, and concentration among recently withdrawn methamphetamine addicts – an effect that hitherto had not been well characterized. Topiramate's cognitive effects were mixed and rather paradoxical, with a tendency to improve attention and concentration both alone and in the presence of methamphetamine while worsening psychomotor retardation. No deleterious interaction occurred between topiramate and methamphetamine on any of these cognitive processes. While clinical studies with topiramate should prepare participants for possible psychomotor retardation, the cognitive effects profile observed would not likely present an important obstacle to compliance in motivated patients. Topiramate's complicated cognitive effects among methamphetamine addicts need more comprehensive examination.
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1. Introduction

Concern about the dramatic rise of methamphetamine in the U.S., particularly on the Pacific Coast (Hunt, 1995; U.S. Department of Health and Human Services, 2001), has spurred renewed interest in the programmatic development of efficacious treatment medications. While the main approach toward medications development has been to identify compounds that reduce methamphetamine's reinforcing effects associated with its abuse liability, the cognitive effects of potential compounds and their interaction with methamphetamine need to be fully characterized. This is because the need to increase cognitive performance is often cited as a reason for initiating or maintaining methamphetamine use (Brecht et al., 2004; von Mayrhauser et al., 2002). Hence, it might be difficult to maintain clinical compliance, even with an efficacious compound, should

Abbreviations: AUC, area under the curve; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; DSST, digit symbol substitution test; RVIPT, rapid visual information processing task.

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it have profound effects on cognitive performance either alone or in combination with methamphetamine.

Human laboratory studies form a bridge between preclinical and clinical studies that would allow accurate characterization of the effects of a putative therapeutic medication both alone and in combination with methamphetamine. Yet, while ample studies have demonstrated that *d*-amphetamine enhances cognitive processing on computerized tasks that test performance and attention (Gunne, 1977; Harvey, 1987; Johnson et al., 1996; Spiegel, 1979; Weiss and Laties, 1962), presumably due to enhancement of catecholamine (Cole and Robbins, 1987, 1992) and particularly dopamine release (Drachman, 1977), only one study has reported on the effects of intravenously administered methamphetamine on cognitive performance in methamphetamine-dependent individuals (Johnson et al., 2005b). In that study, intravenous *d*-methamphetamine produced dose-dependent increases in attention, concentration, and psychomotor performance. These results suggest that methamphetamine-addicted individuals, like healthy human volunteers (Johnson et al., 2000), experience measurable increases in cognitive performance with experimentally administered intravenous methamphetamine. This is the case despite the expectation of deteriorated cognitive functioning (Salo et al., 2002) due to presumed fronto-striatal damage (Ernst et al., 2000; Volkow et al., 2001). Replication of these results would not only establish this human laboratory paradigm for testing cognitive performance and attention among methamphetamine-dependent individuals but also provide added support for the notion that addicted individuals might continue taking the drug to maintain or enhance cognitive performance.

Topiramate, a sulfamate-substituted fructopyranose derivative, has been shown to be efficacious in the treatment of both alcohol (Johnson et al., 2003) and cocaine (Kampman et al., 2004) dependence, and to promote smoking cessation among alcohol-dependent individuals who smoke (Johnson et al., 2005a). These therapeutic effects have been attributed to its hypothesized potential to reduce levels of cortico-mesolimbic dopamine, the primary neurochemical substrate for the acquisition and maintenance of drug-seeking behavior for the majority of abused drugs including alcohol, cocaine, tobacco, and amphetamines (Hemby et al., 1997; Wise, 1998). Naturally, therefore, there is both scientific and clinical interest in testing topiramate as a potential treatment for methamphetamine dependence. Clinical effectiveness of topiramate would, however, depend upon the demonstration not only that it can reduce methamphetamine-induced reinforcement but also that its use is not associated with a profound decrease in cognitive performance and attention.

Clinical studies with topiramate have, however, suggested that its administration is associated with decreases in executive functioning (Kockelmann et al., 2004), verbal fluency (Deutsch et al., 2003), and attention and concentration (Tatum et al., 2001). Importantly, these studies have been conducted in individuals with epilepsy, and there has been no formal testing, to date, of topiramate's effects on cognitive performance and attention in any addicted individuals, let alone the subpopulation of those dependent upon methamphetamine. Hence, the effects of topiramate on cognitive performance and attention among individuals dependent upon methamphetamine are not known. Since individuals with methamphetamine dependence and chronic seizure disorder or epilepsy are prone to fronto-striatal damage (Fujikawa et al., 2000; Morioka et al., 2002; Soffer et al., 1986), we would predict that topiramate administration in individuals with methamphetamine dependence also would be associated with impairment of cognitive performance and attention. Nevertheless, the effects of topiramate on methamphetamine-induced enhancement of cognitive performance and attention are not known. Obviously, if topiramate was shown to impair methamphetamine-induced cognitive enhancement, this could be an important obstacle in the pairing of skills or cognitive-based therapies – presently the mainstay of psychosocial treatment for methamphetamine dependence (Rawson et al., 2004) – with topiramate treatment. In such an eventuality, the practical recommendation might be for clinical trials to pair topiramate with behavioral or simple compliance-based psychosocial interventions.

Therefore, in the present study, we determined – in recently abstinent methamphetamine-dependent individuals – whether intravenously administered methamphetamine would be associated with dose-dependent increases in cognitive performance, whether topiramate would impair or augment cognitive performance and attention, and whether topiramate would impair or augment methamphetamine-induced increases in cognitive performance and attention.

2. Methods

2.1. Subjects

We studied 10 non-treatment-seeking, DSM-IV (American Psychiatric Association, 1994)-diagnosed methamphetamine-dependent individuals (7 males) between the ages of 31 years and 44 years (mean = 37 years) who had been recruited by local newspaper, radio, and television advertisement. All subjects were recently abstinent in that they had been using methamphetamine up to a few days prior to study enrollment. These subjects did not meet diagnostic criteria for any other axis 1 psychiatric disorder except nicotine dependence. See Table 1 for additional demographic data. All subjects gave informed consent prior to their inclusion in the study. The same group participated in a study of the effects of acute topiramate dosing on methamphetamine-induced subjective mood (Johnson et al., in press). Subjects were compensated for study participation.

2.2. Experimental design

This study was approved by the Institutional Review Board at The University of Texas Health Science Center at San Antonio and, therefore, was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. We conducted a double-blind, placebo-controlled, cross-over design, administering oral doses of topiramate (0 mg, 100 mg, and 200 mg) as a pretreatment before intravenous doses of methamphetamine (0 mg, 15 mg, and 30 mg). The 3 × 3 factorial