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## KINETIC AND CARDIOVASCULAR EFFECTS OF ACUTE TOPIRAMATE DOSING AMONG NON-TREATMENT-SEEKING, METHAMPHETAMINE-DEPENDENT INDIVIDUALS

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### Abstract

Previously, we have shown that orally administered topiramate, a sulfamate-substituted fructopyranose derivative, appears to accentuate rather than diminish some aspects of methamphetamine-induced positive subjective mood and cognitive performance. One possible mechanism by which this might occur would be for topiramate to increase plasma methamphetamine level. Such an effect also would be expected to enhance methamphetamine-induced hemodynamic response. We, therefore, studied — in the same experiment from which the previous findings originated — the effects of topiramate on the kinetic profile and hemodynamic response to methamphetamine. In a 27-day inpatient study, 10 methamphetamine-dependent individuals participated in a double-blind, placebo-controlled, cross-over design, with oral doses of topiramate (0, 100, and 200 mg) administered as a pretreatment before intravenous doses of methamphetamine (0, 15, and 30 mg). The 3 × 3 factorial combination of topiramate and methamphetamine resulted in a sequence of the nine treatments administered to each subject in an order determined by a 9 × 9 Latin Square design. Methamphetamine alone was associated with prototypical increases in hemodynamic response that were not altered in the presence of topiramate. While there was no significant kinetic interaction between topiramate and methamphetamine, there was a non-significant trend for topiramate to increase plasma methamphetamine level. No significant adverse events were reported. The combination of topiramate and methamphetamine at pharmacologically relevant doses

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appears to be safe. Larger laboratory studies with chronic dosing regimens are needed to establish whether or not there is a kinetic interaction between topiramate and methamphetamine.

## Keywords

Blood pressure; Heart rate; Hemodynamic; Humans; Kinetic; Methamphetamine; Topiramate

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## INTRODUCTION

Previously, we have shown that topiramate, a sulfamate-substituted fructopyranose derivative, appears to accentuate some aspects of methamphetamine-induced positive subjective mood (Johnson et al., in press-A) and cognitive performance (Johnson et al., in press-B). Topiramate's enhancement of methamphetamine's positive subjective effects was the converse of the expected findings. While topiramate's primary pharmacological effects — facilitation of gamma-aminobutyric acid (GABA) and inhibition of kainate and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid-type glutamate pathways — should decrease cortico-mesolimbic dopamine activity (Johnson, 2005;Schiffer et al., 2001), leading us to hypothesize that topiramate would decrease positive subjective mood, topiramate enhanced it instead. Also, topiramate's anti-glutamnergic effect was expected to antagonize methamphetamine-induced increases in accuracy of responding in a sequential attentional task; instead, topiramate improved it.

One possible mechanism by which orally administered topiramate might enhance some aspects of intravenous methamphetamine-induced subjective mood and cognitive performance would be for it to increase plasma methamphetamine level through an alteration of metabolism, excretion, or both. Therefore, elucidation of the pharmacological effects of oral topiramate on the effects of intravenous methamphetamine requires an examination not only of their pharmacodynamic effects, both alone and combined, but also of their independent and combined kinetic profiles.

It would be reasonable to expect an enhancement of plasma methamphetamine level by topiramate to manifest physiologically as an increase in hemodynamic response as this has been shown to be dose-dependent (Johnson et al., 2005). Thus, examination of methamphetamine-induced hemodynamic response, in both the presence and absence of topiramate, would enable physiological validation of the impact of any observed kinetic effect.

Methamphetamine addiction can be associated with deleterious cardiovascular sequelae such as increased arterial pressure and tachycardia (Johnson et al., 2000;Perez-Reyes et al., 1991) and arrhythmias; for a review, see Frishman et al. (2003). Hence, careful examination under controlled conditions in the human laboratory for any marked potentiation of methamphetamine's cardiovascular effects by topiramate, which has been hypothesized to be a putative therapeutic agent for treating methamphetamine dependence, is of critical importance prior to embarking on clinical trials.

In the present study, we examined the effects of acute dosing with oral topiramate (100 mg and 200 mg) on the kinetic profile and hemodynamic response to acute intravenous methamphetamine (15 mg and 30 mg) among 10 non-treatment-seeking, methamphetamine-dependent individuals. These same individuals were subjects in our two recent studies (Johnson et al., in press-A, in press-B), which presented data pertaining to subjective and cognitive effects in the same experiment.

## METHODS

### Subjects

We studied 10 DSM-IV (American Psychiatric Association, 1994)-diagnosed methamphetamine-dependent subjects (7 males) between the ages of 31 and 44 years (mean, 37 years). Subjects were recruited by local newspaper, radio, and television advertisements. These subjects did not meet diagnostic criteria for any other axis 1 psychiatric disorder except nicotine dependence. All enrolled subjects had a history of prior intravenous drug use. See Table 1 for additional demographic data. All subjects gave informed consent prior to inclusion in the study.

### 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, 100, and 200 mg) as a pretreatment before intravenous doses of methamphetamine (0, 15, and 30 mg). The 3 × 3 factorial combination of topiramate and methamphetamine resulted in a sequence of the nine treatments administered to each subject in an order determined by a 9 × 9 Latin Square design. The designated topiramate dose (100 or 200 mg) was administered in two divided doses. The first dose (50 or 100 mg, respectively) was given at 2000 hours on the evening before the session, and the second dose was given at 0830 hours on the morning of the session. Treatment sessions were conducted on a Monday-Wednesday-Friday schedule so that there was a 2- to 3-day interval between sessions. All subjects were hospitalized for the entire study (27 days) in the University Clinical Psychopharmacology Laboratory, a residential research unit at the University Hospital, the main teaching hospital of The University of Texas Health Science Center at San Antonio.

### Choice of Medication Dose and Its Preparation

The maximum topiramate dose was chosen to represent the putative minimal effect dose observed in clinical trials for alcohol dependence (Johnson et al., 2003) and cocaine dependence (Ait-Daoud and Johnson, 2004;Kampman et al., 2004). The lower topiramate dose was half of the maximum dose. The maximum methamphetamine dose has previously been shown to produce marked positive subjective effects (Johnson et al., 1999); the lower dose was half of the maximum dose.

Topiramate tablets (25 mg), purchased from Ortho-McNeil Pharmaceutical, Inc. (Raritan, NJ, USA), were over-encapsulated in royal blue size 0 capsules (Shionogi Qualicaps, Inc., Whitsett, NC, USA) and filled with cornstarch. Placebo topiramate capsules were identical in both color and size and contained only cornstarch. The intravenous methamphetamine doses chosen were in accordance with National Institute on Drug Abuse guidelines for methamphetamine administration. Methamphetamine-HCl as 20-mg/ml ampoules suitable for human intravenous administration was obtained from the National Institute on Drug Abuse. For injection, methamphetamine solution was mixed with sterile 0.9% w/v normal saline to produce 0-, 15-, and 30-mg/3-ml injection volumes. Placebo methamphetamine was 3 ml of 0.9% w/v saline without methamphetamine.

### Laboratory Conditions

The experiment was done at the University Clinical Psychopharmacology Laboratory. Infusion procedures were performed in a testing room of approximately 18 × 11 feet. After insertion of

a venous catheter with a three-way stopcock adapter into a non-dominant arm or hand vein, subjects were seated in a comfortable chair and instructed not to rise or talk during the experiment. Methamphetamine or placebo was infused through polyethylene tubing with an automated syringe pump. Cardiovascular function was monitored continuously under close medical supervision. Timed recordings of hemodynamic response and blood draws for kinetic analysis were taken as described below.

### General Procedures

All subjects were caffeine abstinent while residing on the research unit, and cigarette smokers were limited to smoke breaks several times throughout the day but never within 1 hour of the methamphetamine infusion. Generally, the limited smoke breaks resulted in the smoking of only 5 to 10 cigarettes/day. On a separate experimental day before double-blind testing, all subjects were familiarized with the study procedures and conditions. During that session, a single-blind dose of methamphetamine (15 mg intravenously) was administered to ensure that the subjects had clinical tolerance to the methamphetamine infusion procedures. This initial injection also ensured that subjects were able to tolerate the lower dose of methamphetamine, in case their first experimental dose during double-blind testing was the higher dose of methamphetamine.

All women were stabilized on the oral contraceptive pill before testing to control for menstrual cycle effects (Di Paolo, 1994; King et al., 1986) and to prevent pregnancy.

### Test Day Procedures

In the evening before the session day, subjects were administered the first half of their topiramate or matching placebo dose at 2000 hours and instructed to retire to bed at 2300 hours. On the morning of each test session, subjects provided a urine sample at 0700 hours before receiving a standard hospital breakfast. Using an OnTrak TesTcup<sup>®</sup> (Varian Inc., Palo Alto, CA, USA), we tested each subject's urine for the presence of opiates, amphetamines, cocaine, benzodiazepines, or barbiturates and took a breath alcohol concentration. The urine drug screen and breath alcohol concentration had to be negative and zero, respectively, for further testing to proceed.

At 0800 hours, we placed a venous catheter in each subject's non-dominant arm or hand. Thirty minutes later, subjects took the second half of their topiramate dose. Then, at 0945 hours, we attached electrodes (including chest leads) to each subject to perform a 12-lead electrocardiogram and to monitor the electrocardiogram and heart rate continuously. Additionally, we attached a blood pressure cuff to each subject's dominant arm to permit frequent automated measurements of blood pressure. All of these cardiovascular parameters were collected electronically through a Spacelabs Ultraview<sup>®</sup> 1050, Module 90496 cardiac monitor (Spacelabs Medical Inc., Issaquah, WA, USA). At 1030 hours, the attending physician used a 2.2-ml length of polyethylene tubing to attach the venous catheter to an automated infusion pump (Baxter International Inc., Deerfield, IL, USA). Then, the attending physician commenced the intravenous infusion of 3 ml of methamphetamine or matching placebo for 60 sec by activating the syringe pump. Timed recordings of heart rate and blood pressure (i.e., hemodynamic response) were made every 2 min beginning at 15 min before intravenous methamphetamine infusion and continuing until 60 min after infusion (i.e., from -15 min through +59 min, with infusion given at t=0). Thereafter, hemodynamic response was measured every 15 min until +2 hours (i.e., at +75, +90, +105, and +120 min) and then again every hour until +6 hours post-infusion. Blood draws for the kinetic study of topiramate and methamphetamine levels were taken 15 min before and at 30, 60, 120, 180, 240, and 300 min

after the intravenous methamphetamine infusion. Behavioral measurements taken during this experiment have been reported elsewhere (Johnson et al., in press-A).

### Determination of Plasma Methamphetamine and Topiramate Levels

Blood was collected from participants, in accordance with standard aseptic phlebotomy procedures, into two 10-ml lavender-top ethylenediaminetetraacetic acid Vacutainer® tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) at various times after the administration of topiramate and methamphetamine (see schedule above). The blood collection tubes were centrifuged at  $1200 \times g$  for 10 min to separate the plasma from blood cells. Plasma was aspirated from the supernatant fraction and stored as 1-ml aliquots in properly labeled, capped polypropylene tubes at  $-80^{\circ}\text{C}$  until the day of analysis for topiramate or methamphetamine.

Topiramate was quantified using the Innofluor® Topiramate Assay System (Seradyn, Inc., Indianapolis, IN, USA) and a TDxFLx® analytical system (Abbott Laboratories, Abbott Park, IL, USA). The assay was performed according to the procedure provided with the assay kit. The limit of detectability was  $0.3 \mu\text{g/ml}$ , and the assay required  $75 \mu\text{l}$  of sample. Calibrators and control samples were analyzed with each batch of samples according to standard quality control procedures. Between- and within-day variability was less than 10%.

Methamphetamine was quantified using the Methamphetamine Direct Enzyme-Linked Immunosorbent Assay Kit (Bio-Quant, Inc., San Diego, CA, USA). The assay was performed according to the procedure provided with the assay kit. The limit of detectability was  $1 \text{ ng/ml}$ , and the assay required  $10 \mu\text{l}$  of sample. Calibrators and control samples were analyzed with each batch of collected samples according to standard quality control procedures. Intra-assay variability was less than 12.2%.

### Statistical Analysis

For hemodynamic response, measurements were taken at the time points specified above for each of the different combinations of methamphetamine and topiramate. Systolic and diastolic blood pressure recordings were used to calculate pulse pressure (systolic – diastolic) and mean arterial pressure ( $[(2 \times \text{diastolic}) + \text{systolic}]/3$ ). Recordings of abnormal arrhythmias were tabulated.

For kinetic studies, plasma methamphetamine and topiramate levels were measured 7 times during each testing day as specified above.

To reduce the dimensionality for all hemodynamic and kinetic measures, we used the area under the curve (AUC) and peak values on each day to summarize the observations. The AUC for each measure was determined by the trapezoidal rule. The peak value was taken to be the maximum value during the day. Log transformation was necessary to normalize plasma methamphetamine level. A mixed-model approach (SAS PROC MIXED) was used to compare the AUC and peak values from different combinations of methamphetamine and topiramate, with adjustment for the day effect. The correlation structure among repeated measures (i.e., for the nine different sessions) was taken to be AR(1). All statistical analyses were carried out using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

On AUC measures, methamphetamine significantly increased systolic, diastolic, and mean arterial pressures as well as heart rate ( $p < 0.0001$  for all). Pretreatment with the highest topiramate dose increased heart rate ( $p = 0.02$ ). On peak measures, methamphetamine

significantly increased systolic blood pressure ( $p<0.0001$ ), pulse pressure ( $p=0.002$ ), mean arterial pressure ( $p=0.0009$ ), and heart rate ( $p=0.0004$ ). For both the AUC and peak measures, there was no significant interaction between methamphetamine and topiramate on hemodynamic response (Table 2). No subject reported any serious or significant adverse event during the study (Table 3). Three subjects reported having cardiovascular-related adverse events. For subject #1, there were three episodes: 1) at a dose of 30 mg of methamphetamine with the 100-mg daily dose of topiramate, there was one isolated atrial premature contraction, slight ST-segment changes, elevated blood pressure, and self-reported palpitations; 2) at a dose of 30 mg of methamphetamine with the 200-mg daily dose of topiramate, there was a slight change in P waves and an associated change in the RR interval, and 3) at a dose of 15 mg of methamphetamine and 0 mg of topiramate, there was an isolated premature atrial contraction. For subject #2, there was an episode of mild sinus arrhythmia. For subject #3, there was a report of skin discomfort around the precordial leads. The recorded arrhythmias all followed methamphetamine infusion. No arrhythmia required specialized intervention or medication. All resolved spontaneously. None of these adverse events were considered to be of clinical significance.

For both the AUC and peak measures, topiramate dose had a significant effect ( $p<0.0001$ ) to increase plasma topiramate level. All the pairwise comparisons among the three different topiramate doses (i.e., 200 mg vs. 0 mg, 100 mg vs. 0 mg, and 200 mg vs. 100 mg) were significant at  $p<0.0001$ . Methamphetamine dose had no significant effect on topiramate level. There was no significant statistical interaction between methamphetamine and topiramate level. Using log AUC and log peak methamphetamine levels in the model to study the association between methamphetamine level and topiramate level, we found no correlation between the two. For the AUC and peak measures, methamphetamine dose had a significant effect ( $p<0.0001$ ) to increase plasma methamphetamine level. All the pairwise comparisons among the three different methamphetamine doses (i.e., 30 mg vs. 0 mg, 15 mg vs. 0 mg, and 30 mg vs. 15 mg) were significant. Methamphetamine had no statistically significant effect on plasma topiramate level (Figure 1). Nevertheless, there was a non-significant trend for topiramate to increase plasma methamphetamine level (Figure 2). Using AUC/peak topiramate level in the model to study the association between topiramate level and methamphetamine level, we found no correlation between the two.

## DISCUSSION

Despite decades of research on the pharmacology of psychostimulants, methamphetamine's hemodynamic and cardiotoxic effects are not well characterized in humans (Varner et al., 2002). Even less is known about these effects with the intravenous formulation of methamphetamine administered in the human laboratory. The present study establishes the hemodynamic and cardiovascular effects and safety of experimenter-administered intravenous methamphetamine, thereby building upon other human laboratory data (Newton et al., 2005a, 2005b). Notably, the administration of intravenous methamphetamine doses of up to 30 mg under controlled human laboratory conditions to methamphetamine addicts appears to be safe and only associated with prototypical increases in hemodynamic response. This is important because methamphetamine addiction has been associated with massive hypertensive crises that lead to cerebrovascular accidents and cardiovascular dysfunction.

Topiramate, in the doses that we tested, does not appear to have any significant hemodynamic effects of its own or in combination with methamphetamine, despite our expectation that topiramate's anti-dopaminergic effects would reduce methamphetamine-induced increases in hemodynamic response. There are at least four possible explanations for this finding.

First, it is possible that the doses of acute topiramate that we used were insufficient to produce the level of dopamine suppression needed to decrease methamphetamine-induced hemodynamic response. We do, however, consider this to be unlikely because the maximum dose of topiramate that we used (i.e., 200 mg/day) does appear sufficient to antagonize the central dopamine-mediated reinforcing effects of drugs of abuse such as alcohol (Johnson et al., 2003) and cocaine (Johnson, 2005;Kampman et al., 2004) in clinical settings and is, therefore, a pharmacologically relevant dose.

Second, unlike the case of alcohol and cocaine, it is tempting to speculate that topiramate's anti-dopaminergic effects might have been offset by a kinetic interaction with methamphetamine. While we did not observe a statistically significant kinetic interaction between topiramate and methamphetamine, perhaps due to the small study sample, it is evident from Figure 2 that there is a trend for topiramate to increase plasma methamphetamine level. Indeed, it is tempting to speculate that with a larger subject sample, the strength of this interaction would be expected to yield an effect of topiramate to increase methamphetamine level. Nevertheless, this trend for topiramate to increase methamphetamine level might have been sufficient to offset our hypothesized anti-dopaminergic effect for topiramate to decrease methamphetamine-induced hemodynamic response. Indeed, support for the idea that this kinetic interaction is meaningful clinically comes from other data in the same experiment where topiramate accentuated some methamphetamine-induced increases in positive subjective effects, reinforcing value, and attention and concentration (Johnson et al., in press-A, in press-B). Possible explanations for a potential kinetic interaction between topiramate and methamphetamine are elaborated upon below.

Third, hemodynamic response is controlled by complex central and peripheral mechanisms, both aminergic and non-aminergic. Even within the aminergic system, which is the principal pharmacological route through which methamphetamine exerts its hemodynamic effects, dopamine exerts only partial control because norepinephrine and serotonin, as well as the counter-regulatory effects of the parasympathetic system, also have a role; none of these non-dopaminergic pathways are affected by topiramate. Obviously, topiramate cannot be expected to have any effects on the wide variety of non-aminergic processes that control blood pressure, including the nitrergic, renin-angiotensin, and kallikrein-kinin systems, sodium-retaining hormones, peptides, calcium influx, and disease states that alter the tone of the microvasculature; for a review, see Oparil et al. (2003). Hence, only profound reductions in dopaminergic function might be expected to result in marked decreases in methamphetamine-induced hemodynamic response. Since this might not be achieved by an acute dosing paradigm, chronic or sustained dosing would be required to establish whether or not topiramate can produce such an effect.

Fourth, limbic system regulation of blood pressure through the baroreceptor reflex (Saha, 2005) is controlled by the balance between GABA/N-methyl-D-aspartate (NMDA) and non-NMDA glutamate neuronal excitation (Hatam and Nasimi, 2005;Nasimi and Hatam, 2005). It would, therefore, be reasonable to predict that topiramate would decrease methamphetamine-induced hemodynamic response through GABA facilitation and glutamate inhibition. Nevertheless, topiramate's anti-hypertensive effect is probably more likely to be seen with chronic administration, due to the decreased potential for counter-regulatory mechanisms to sustain hemodynamic response.

Importantly, topiramate administration was not associated with marked adverse events or clinically relevant adverse or cardiovascular events. Hence, clinical testing with topiramate as a potential treatment for methamphetamine dependence would appear to be safe.

The present study details the kinetic profiles of topiramate and methamphetamine, both alone and combined, in the human laboratory at pharmacologically relevant doses. Notably, the non-statistically significant trend for topiramate to increase plasma methamphetamine level was, at first, puzzling as these agents were administered through different routes; i.e., topiramate was given orally and methamphetamine was administered intravenously. Perhaps the most likely explanation for this is that topiramate might be impeding the excretion of methamphetamine. Topiramate tends to alkalinize the urine, an effect that has been associated with increased propensity for nephrolithiasis (Kuo et al., 2002; Lamb et al., 2004). Since the urinary excretion of amphetamines is enhanced by acidification, topiramate might have impeded the renal elimination of methamphetamine, which led to a slightly higher plasma level (Davis et al., 1971; Poklis et al., 1998). Obviously, a larger study with chronic dosing that is designed for a more complete exploration of pharmacokinetic parameters will be needed to establish whether or not topiramate has any significant effect on the excretion of methamphetamine.

## CONCLUSION

The administration of topiramate and methamphetamine under controlled conditions in the human laboratory was safe. There were no hemodynamic interactions between topiramate and methamphetamine. Although there was no significant kinetic interaction between topiramate and methamphetamine, there was a trend for topiramate to increase plasma methamphetamine level. Larger human laboratory studies would be needed to establish whether or not topiramate has a significant effect on methamphetamine excretion. While our data suggest that the clinical testing of topiramate for the treatment of methamphetamine dependence will be safe, a larger human laboratory study with chronic dosing is needed to confirm this notion.

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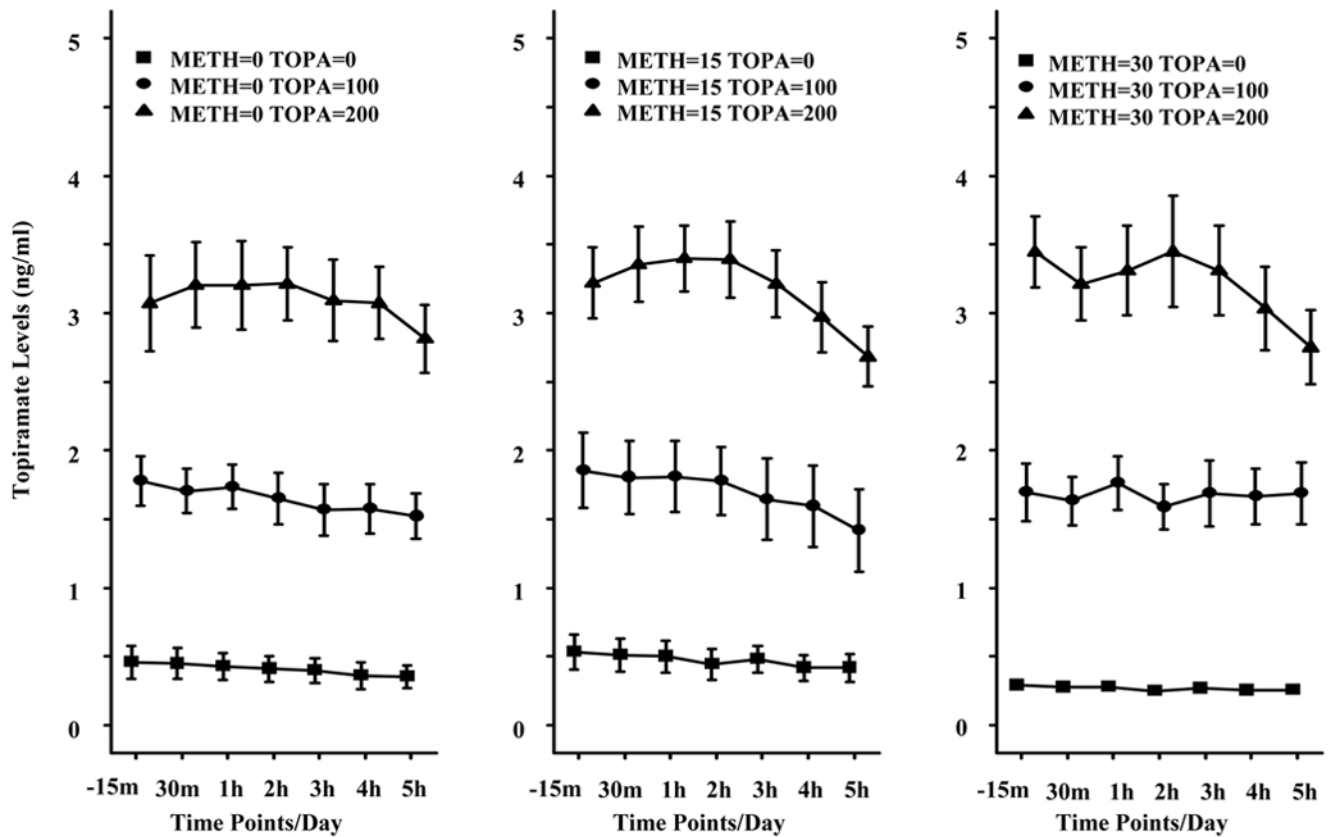
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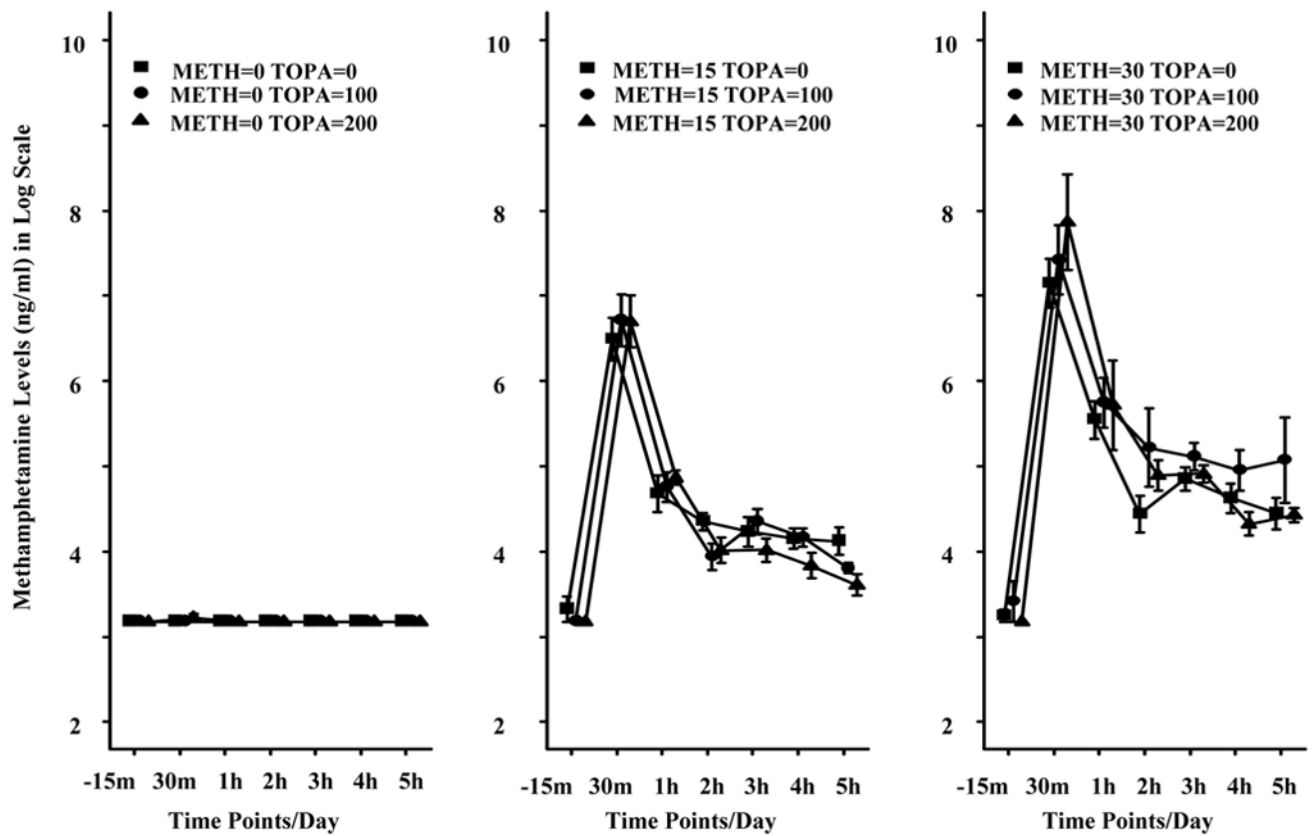
## Abbreviations

<b>AUC</b>	area under the curve
<b>DSM-IV</b>	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
<b>GABA</b>	gamma-aminobutyric acid
<b>NMDA</b>	N-methyl-D-aspartate



**Figure 1.**

Effects of various doses of methamphetamine (METH) and topiramate (TOPA) on plasma topiramate level. The points plotted are mean  $\pm$  standard error. Numbers shown after "METH=" and "TOPA=" are doses in milligrams.



**Figure 2.**

Effects of various doses of methamphetamine (METH) and topiramate (TOPA) on plasma methamphetamine level. The points plotted are mean  $\pm$  standard error. Numbers shown after "METH=" and "TOPA=" are doses in milligrams.

**Table 1**  
Demographics and Drug Use of 10 Non-Treatment-Seeking, Methamphetamine-Dependent Subjects at Intake

Age (years)*	37 (6.50)
Sex†	
Male	7 (70)
Female	3 (30)
Ethnicity†	
Hispanic	6 (60)
White	3 (30)
Black	1 (10)
Marital status†	
Single	5 (50)
Divorced	5 (50)
Married	0 (0)
Educational level†	
Partial college	5 (50)
High school	3 (30)
General equivalency diploma	2 (20)
Education years*	12 (1.49)
Employment status†	
Skilled worker	8 (80)
Unemployed	2 (20)
Days of methamphetamine use in last 30 days*	13.30 (7.86)
Days of alcohol use in last 30 days*	11.60 (10.55)
Cigarettes/day*	9.61 (7.02)

\* Values are expressed as mean (SD).

† Values are expressed as number (%).

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**Table 2**

Hemodynamic Effects of Various Doses of Methamphetamine and Topiramate

Measurement	Dose								Analysis of Variance
	0	0	0	15	15	15	30	30	
Methamphetamine infusion dose (mg)	0	0	0	15	15	15	30	30	<sup>a</sup> Main effect of methamphetamine
Topiramate daily dose (mg)	0	100	200	0	100	200	0	100	<sup>b</sup> Main effect of topiramate
<b>Measurement</b>	<b>Least-Squares Mean (95% Confidence Interval)</b>								<b>p-Value</b>
Systolic blood pressure	134 (125–143)	137 (128–147)	132 (123–142)	147 (137–156)	146 (137–155)	147 (138–156)	153 (144–163)	158 (148–167)	0.0001 <sup>a</sup>
Diastolic blood pressure	95 (88–103)	99 (92–106)	101 (94–108)	101 (94–108)	99 (91–106)	99 (91–106)	102 (95–109)	101 (94–109)	0.45 <sup>b</sup>
Pulse pressure	58 (52–64)	60 (54–66)	57 (52–63)	62 (57–68)	61 (56–67)	63 (57–69)	66 (60–71)	69 (63–75)	0.99 <sup>b</sup>
Mean arterial pressure	105 (97–112)	108 (101–116)	108 (100–115)	111 (104–119)	112 (104–119)	111 (103–119)	115 (108–123)	117 (110–125)	0.0015 <sup>a</sup>
Heart rate	106 (97–116)	98 (89–108)	98 (88–107)	106 (97–116)	112 (103–122)	108 (99–118)	110 (101–120)	117 (107–127)	0.0009 <sup>a</sup>
									0.66 <sup>b</sup>
									0.0004 <sup>a</sup>
									0.86 <sup>b</sup>

**Table 3** Adverse Events Following the Administration of Various Doses of Methamphetamine and Topiramate

	Dose													
	0	0	0	100	200	0	15	15	15	15	30	30	30	200
<b>Methamphetamine infusion dose (mg)</b>	0	0	0	100	200	0	15	15	15	15	30	30	30	200
<b>Topiramate daily dose (mg)</b>	0	0	0	100	200	0	0	0	0	0	0	0	100	200
<b>Adverse Event</b>	<b>Number of Subjects</b>													
Elevated blood pressure	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Elevated heart rate	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ST-segment changes	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Arrhythmia	0	0	0	0	0	1	0	0	0	0	0	0	1	2
Palpitations	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Skin discomfort around electrocardiogram leads	0	0	0	0	0	0	0	0	0	0	0	0	0	1
<b>Total</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>4</b>	<b>3</b>