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The angiotensin-converting enzyme inhibitor perindopril treatment alters cardiovascular and subjective effects of methamphetamine in humans

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ABSTRACT

A variety of medications have been assessed for their potential efficacy for the treatment of methamphetamine dependence. We conducted this study in an attempt to evaluate the potential of a novel class of medications, angiotensin-converting enzyme inhibitors, as treatments for methamphetamine dependence. All participants met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, third revision (DSM-IV-TR) criteria for methamphetamine abuse or dependence and were not seeking treatment at the time of study entry. The study was conducted using a double-blind design. Subjects received a baseline series of intravenous (IV) doses of methamphetamine (15 mg and 30 mg) and placebo. Subjects received a second identical series of methamphetamine doses 3 and 5 days after initiation of once-daily oral placebo or perindopril treatment. The dose of perindopril was 2 mg, 4 mg, or 8 mg administered in the morning. Perindopril treatment was tolerated well. There were no main effects of perindopril on methamphetamine-induced changes in cardiovascular or subjective effects. There were significant perindopril*methamphetamine interactions for diastolic blood pressure and for ratings of "Any Drug Effect", indicating inverted *U* dose-effect functions for these indices.
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1. Introduction

A variety of medications have been assessed for their potential efficacy for the treatment of methamphetamine (MA) dependence. We recently reported that bupropion, an antidepressant binding to dopamine (DA) and norepinephrine (NE) transporters, with additional activity at nicotinic acetylcholine receptors, reduced the euphoria associated with experimental administration of methamphetamine, and cue-induced craving for MA, in human volunteers (Newton et al., 2006). In a subsequent randomized clinical trial, bupropion treatment was more effective than placebo for reducing MA use in patients with modest pre-randomization use frequency (Elkashef et al., 2008; Shoptaw et al., 2008). Taken together, the available data suggest that medications that reduce the positive subjective effects of MA may be useful therapeutic agents in the treatment of MA dependence.

We conducted this study in an attempt to evaluate the potential of a novel class of medications, angiotensin-converting enzyme (ACE) inhibitors, as treatments for MA dependence. Preclinical data indicate that treatment with ACE inhibitors increases striatal DA content (Jenkins et al., 1997) and hastens recovery from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity (Kurosaki et al., 2005), suggesting previously unexpected links between the renin–angiotensin system and the striatal DA system. Clinical experience suggests that treatment with ACE inhibitors may improve functioning of patients with Parkinson's disease who are receiving L-DOPA (Reardon et al., 2000), leading others to suggest that ACE inhibitors may be beneficial treatments for stimulant use disorders (Margolin et al., 2000).

It is becoming increasingly clear that angiotensin II (AT-II), binding at central AT-1 receptors, alters drug-seeking behavior in preclinical models, though as yet studies have been limited to ethanol consumption in rats and mice (Grupp, 1992; Lingham et al., 1990). Transgenic mice expressing a rat angiotensinogen gene (thereby over-expressing angiotensinogen) demonstrated enhanced ethanol self-administration, and this is blocked in mice expressing an antisense angiotensinogen gene (Maul et al., 2001). Mice that over-expressed angiotensinogen, and therefore had increased levels of angiotensin II, consumed substantially *more* alcohol than wild-type mice. Treatment with the ACE inhibitor spirapril reduced alcohol consumption in both groups of mice. In a subsequent study that used transgenic rats expressing an antisense RNA against angiotensinogen (Maul et al., 2005), expression of the antisense RNA resulted in reduced angiotensin II levels exclusively in the central nervous system (CNS). Transgenic rats with reduced CNS angiotensin II consumed markedly less alcohol (but not sucrose solution) compared to their wild-type controls. Additional experiments in AT-1, angiotensin II, and bradykinin receptor knockout mice confirmed that the central effect of angiotensin II on alcohol consumption was mediated exclusively by the angiotensin II receptor AT-1.

Of the available ACE inhibitors, we selected perindopril because it is known that this drug alters central DA turnover when administered

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Table 1
Participant characteristics.

	Perindopril groups			
	0 mg	2 mg	4 mg	8 mg
	($N=5$)	($N=8$)	($N=8$)	($N=9$)
Gender				
Male	5	8	8	7
Female	0	0	0	2
Ethnicity				
White (not Hispanic)	4	4	5	4
Hispanic or Latino	0	3	1	4
African American	1	1	1	0
Native American	0	0	1	1
Age	30.4 ± 3.6	34.6 ± 2.4	37.5 ± 2.7	34.7 ± 3.9
Education	14.4 ± 0.7	12.6 ± 0.4	12.9 ± 0.7	13.2 ± 0.5
Substance use				
Years of MA use	4.0 ± 1.5	10.0 ± 2.5	13.1 ± 2.9	12.4 ± 2.9
MA use last 30 days	15.6 ± 2.2	21.0 ± 2.7	14.9 ± 2.9	21.9 ± 3.5
Nicotine use in last 30 days (%)	60	88	100	78
Route of MA use	60% Smoke 20% IV 20% Oral	63% Smoke 37% Multiple	25% Smoke 25% Nasal 25% IV 25% Multiple	63% Smoke 13% Oral 13% IV 26% Multiple
Alcohol use in last 30 days (%)	100	83	88	56
Marijuana use in last 30 days (%)	80	57	75	67
Cocaine use in last 30 days (%)	60	0	38	11
Heroin use in last 30 days (%)	0	0	0	0
Sedatives use in last 30 days (%)	20	0	13	0
PCP use in last 30 days (%)	20	14	0	0

peripherally (Jenkins et al., 1997). Other ACE inhibitors (e.g., captopril) have more modest effects on brain ACE activity (Cushman et al., 1989).

2. Methods

2.1. Subjects

Participants were recruited through advertisements and were paid for their participation. All met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, third revision (DSM-IV-TR) criteria for MA abuse or dependence and were not seeking treatment at the time of study entry. Other inclusion criteria included being between 18 and 45 years of age, a history of using MA by the smoked or intravenous (IV) route, and normal laboratory assessment and vital signs. Exclusion criteria included a history of seizure disorder, head trauma, dependence on other drugs aside from nicotine, prior adverse reaction to MA, or the presence of any other axis I psychiatric disorder. Serious medical conditions such as heart disease, acquired immune deficiency syndrome (AIDS), asthma, Parkinson's disease, and other serious medical conditions were also exclusionary. Concomitant use of psychotropic medications was not allowed. Thirty participants completed the study. This study was approved by the institutional review board at the University of California, Los Angeles (UCLA), and all participants gave informed consent after being fully appraised of potential risks of participation.

2.2. Study design

The study was conducted using a double-blind design. Following admission to the clinical research center (CRC), subjects received IV doses of MA (15 mg and 30 mg, in that order) on 2 subsequent days. The investigators (but not the participants) were unblended as to the order of the MA doses. Each MA infusion was preceded or followed by an IV infusion of saline in a random order in order to maintain the blind. Subjects received a second identical series of MA/saline doses beginning 3 days after initiation of once-daily oral placebo or perindopril treatment. MA and saline were administered using a syringe pump, ensuring that dosing procedures were consistent across doses of MA and across subjects. The dose of perindopril was 2 mg, 4 mg, or 8 mg administered in the morning. Dose assignment was random.

2.3. Data analysis

Analysis of variance (ANOVA) was used to determine effects of perindopril dose, MA dose, and the interaction term (perindopril – MA). Significant perindopril – MA interactions were followed with Bonferonni–Dunn *post hoc* tests to evaluate differences between perindopril dosages.

3. Results

3.1. Participants

Thirty participants completed the study (Table 1). The majority of participants were Caucasian and male, with an approximate age of 34 years, had received 13 years of education on average, had used MA for about 10 years, and used MA for 17 of the past 30 days. The majority of participants used MA by the smoked route, and also smoked cigarettes, used alcohol, and a majority also used marijuana on occasion.

3.2. Tolerability

MA-dependent volunteers generally tolerated perindopril treatment well. There were no differences across the treatment groups for total number of adverse events (reported complaints or abnormal

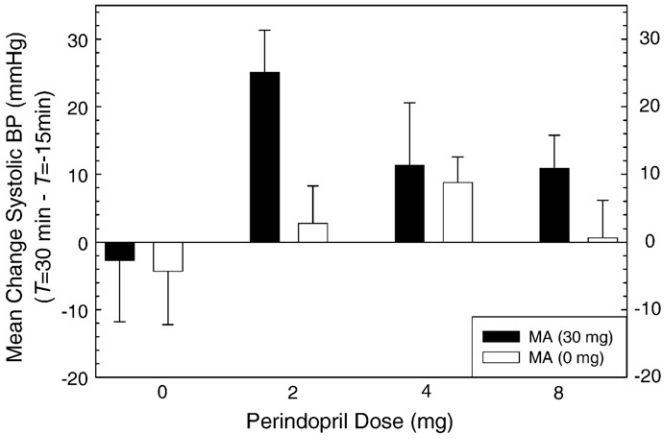

Fig. 1. Systolic Blood Preasure.

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