

# Human pharmacology of the methamphetamine stereoisomers

**Objective:** To help predict the consequences of precursor regulation, we compared the pharmacokinetics and pharmacodynamics of the methamphetamine (INN, metamfetamine) stereoisomers.

**Methods:** In this study 12 methamphetamine abusers received intravenous *d*-methamphetamine (0.25 and 0.5 mg/kg), *l*-methamphetamine (0.25 and 0.5 mg/kg), racemic methamphetamine (0.5 mg/kg), or placebo with the use of a 6-session, double-blind, placebo-controlled, balanced crossover design. Pharmacokinetic measures (including area under the plasma concentration–time curve [AUC], elimination half-life, systemic clearance, apparent volume of distribution during the elimination phase, and apparent bioavailability) and pharmacodynamic measures (including heart rate, blood pressure, respiratory rate, and visual analog scale ratings for “intoxication,” “good drug effect,” and “drug liking”) were obtained.

**Results:** Pharmacokinetic parameters for the individual enantiomers given separately were similar, with dose-proportional increases in AUC and maximum plasma concentration. After racemate administration, the AUC for *d*-methamphetamine was 30% smaller than that for *l*-methamphetamine ( $P = .0085$ ). The elimination half-lives were longer for *l*-methamphetamine (13.3–15.0 hours) than for *d*-methamphetamine (10.2–10.7 hours) ( $P < .0001$ ). Compared with placebo, *d*-methamphetamine (0.25 mg/kg, 0.5 mg/kg, and racemic) increased the heart rate ( $P < .0001$ ), blood pressure ( $P < .0001$ ), and respiratory rate ( $P < .05$ ), and this increase lasted for 6 hours. The peak heart rate changes after racemic methamphetamine and 0.5 mg/kg *d*- and *l*-methamphetamine were similar ( $18.7 \pm 23.4$  beats/min,  $13.5 \pm 18.5$  beats/min, and  $10.7 \pm 10.2$  beats/min, respectively), but racemic methamphetamine and 0.5 mg/kg *d*-methamphetamine increased systolic blood pressure more than 0.5 mg/kg *l*-methamphetamine ( $33.4 \pm 17.8$  beats/min and  $34.5 \pm 18.9$  beats/min, respectively, versus  $19.5 \pm 11.3$  beats/min;  $P < .01$ ). *l*-Methamphetamine, 0.5 mg/kg, was psychoactive, producing peak intoxication ( $46.0 \pm 35.3$  versus  $30.3 \pm 24.9$ ) and drug liking ( $47.7 \pm 35.1$  versus  $28.6 \pm 24.8$ ) ratings similar to 0.5 mg/kg *d*-methamphetamine, but the effects of *l*-methamphetamine dissipated more quickly (approximately 3 hours versus 6 hours). The effects of 0.25 mg/kg *l*-methamphetamine were similar to those of placebo. Racemic methamphetamine was similar to *d*-methamphetamine with regard to most pharmacodynamic measures.

**Conclusion:** The pharmacokinetics of the methamphetamine enantiomers are similar, but there are substantial pharmacodynamic differences between the isomers. At high doses, *l*-methamphetamine intoxication is similar to that of *d*-methamphetamine, but the psychodynamic effects are shorter-lived and less desired by abusers. Racemic and *d*-methamphetamine have similar effects and would be expected to have comparable abuse liabilities. (Clin Pharmacol Ther 2006;80:403–20.)

John Mendelson, MD, Naoto Uemura, MD, PhD, Debra Harris, MD,  
Rajneesh P. Nath, MD, Emilio Fernandez, MD, Peyton Jacob III, PhD,  
E. Thomas Everhart, PhD, and Reese T. Jones, MD *San Francisco and Palo Alto, Calif,  
Cincinnati, Ohio, and Oita, Japan*

From the Addiction Pharmacology Research Laboratory, California Pacific Medical Center Research Institute, and Drug Dependence Research Center, Langley Porter Psychiatric Institute, University of California, San Francisco, San Francisco; University of Cincinnati, Cincinnati; ALZA, Palo Alto; and Department of Pharmaceutical Medicine, Oita University Faculty of Medicine, Oita.

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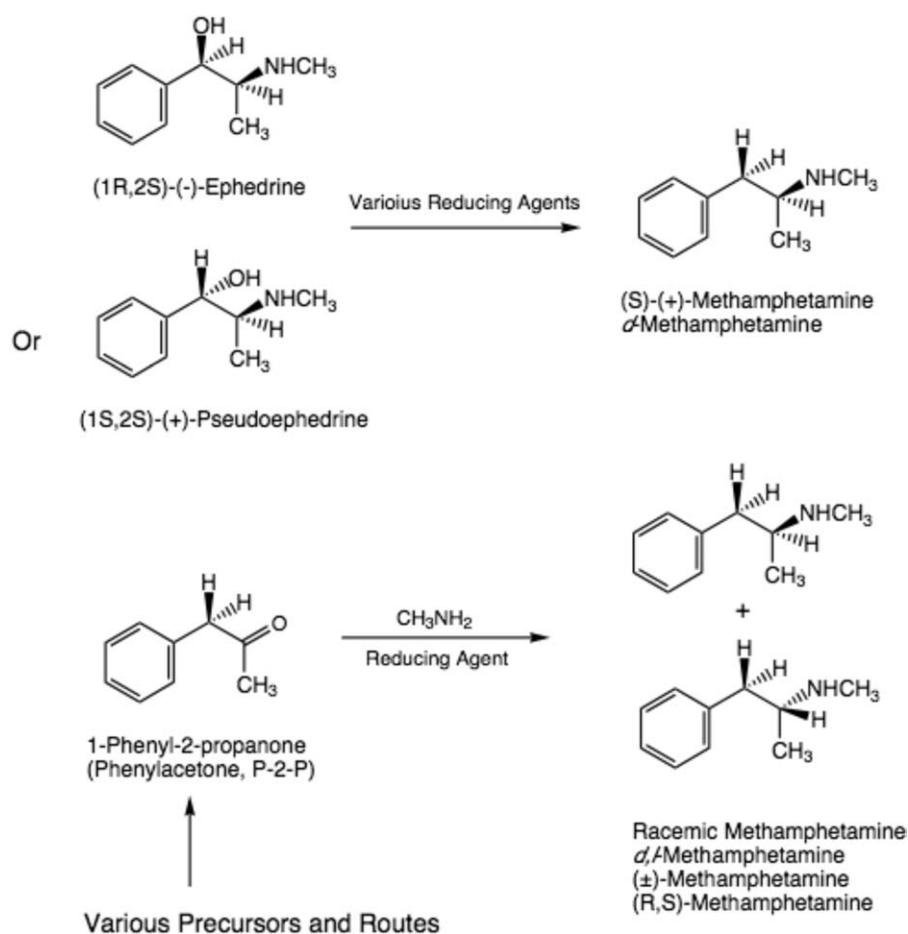
Reprint requests: John E. Mendelson, MD, Addiction Pharmacology Research Laboratory, 7th Floor, St Luke's Hospital, 3555 Cesar Chavez, San Francisco, CA 94110.

E-mail: [john.mendelson@cpmcni.org](mailto:john.mendelson@cpmcni.org)

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**Fig 1.** Various precursors and routes of synthesis for *d*-methamphetamine and racemic methamphetamine.

Methamphetamine (INN, metamfetamine) and amphetamine (INN, amfetamine) have a chiral center, and the drugs may be abused as single isomers or a mixture, depending on the drug product or source. To decrease methamphetamine abuse, many precursors are now controlled substances, including pseudoephedrine. Although *d*-methamphetamine is the isomer that is usually abused, other synthetic pathways via unregulated precursors can be used to make racemic and *l*-methamphetamine. In the United States illicit methamphetamine is predominately distributed as the *d*-isomer. Whether the pure isomer or a racemic mixture is encountered depends on the synthesis used by illicit manufacturers (usually referred to as clandestine laboratories). This, in turn, is controlled by the availability of precursors. Before 1980, most illicit methamphetamine was synthesized by reductive amination of phenylacetone (also called phenyl-2-propanone) with

methylamine, which yields a racemic mixture of methamphetamine isomers (Fig 1). In 1980 the US Drug Enforcement Administration made phenylacetone a Schedule II substance. Consequently, operators of clandestine laboratories began to use an alternate route to produce methamphetamine using ephedrine and, more recently, pseudoephedrine as the starting material. This route yields pure *d*-methamphetamine, and thus, today, most of the "street methamphetamine" in the United States is the *d*-isomer.<sup>1</sup>

The situation may be changing again because there are attempts to reduce the availability of ephedrine. In the United States ephedra is no longer available (because of adverse effects of the drug and its use as a methamphetamine precursor), and 20 states are considering or have enacted legislation restricting the availability of over-the-counter (OTC) cold medicines containing pseudoephedrine.<sup>2</sup> If these precursors become

less available, the phenylacetone route, which yields racemic methamphetamine, would likely be used, because there are many synthetic methods for the preparation of phenylacetone. There is evidence that this may be occurring,<sup>3,4</sup> and the availability of racemic methamphetamine may be increasing. If precursor regulation decreases the availability of *d*-methamphetamine but increases the manufacture of racemic methamphetamine, the toxic consequences of drug misuse may also change. Therefore it is important to understand the pharmacologic effects of racemic methamphetamine before policy changes produce unanticipated health outcomes. Although several studies have characterized the pharmacologic features of *d*-methamphetamine, the effects of racemic and *l*-methamphetamine in humans are relatively unexplored.<sup>5,6</sup> The levorotatory isomer of methamphetamine is present in the OTC Vicks Vapor Inhaler (Procter & Gamble, Cincinnati, Ohio) (containing 50 mg *l*-methamphetamine but called levmetamfetamine by the manufacturer). The dextrorotatory isomer of methamphetamine is marketed as Desoxyn (Abbott Laboratories, North Chicago, Ill) for the treatment of attention deficit disorder and narcolepsy.

Pharmacologic differences between the amphetamine enantiomers were recognized early in the 20th century.<sup>7</sup> In general, the *d*-isomers of amphetamine and methamphetamine are 2 to 10 times more potent in producing central nervous system (CNS) stimulation than the corresponding *l*-isomers.<sup>8-10</sup> However, in one study *l*-amphetamine produced relatively more cardiovascular activation than *d*-amphetamine.<sup>11</sup> If *l*-methamphetamine behaves like *l*-amphetamine, with relatively more cardiovascular stimulation and less CNS stimulation, then severe adverse events could actually increase if racemic methamphetamine becomes the dominant illicit form. In contrast, if *l*-methamphetamine attenuates CNS effects, the abuse potential of racemic methamphetamine may be less than that of *d*-methamphetamine. In rodents *d*-methamphetamine is more potent than *l*-methamphetamine in stimulating dopamine release,<sup>12,13</sup> suggesting a lower abuse potential of racemic or *l*-methamphetamine.

Data in humans on the pharmacokinetic differences between methamphetamine isomers are limited. Some evidence suggests that the metabolism of methamphetamine enantiomers is different in humans compared with animals. In humans the *l*-enantiomers of both amphetamine and methamphetamine are eliminated more slowly than the *d*-isomers. The half-life of *d*-amphetamine is  $7 \pm 1.2$  hours versus  $11 \pm 2.1$  hours for *l*-amphetamine,<sup>14</sup> and the values are approximately 5 hours and 6 hours for *d*- and *l*-methamphetamine,

respectively.<sup>15</sup> However, the latter study involved only 2 subjects. In contrast, the clearance of *l*-methamphetamine in rats is greater than that of *d*-methamphetamine.<sup>16</sup>

It has been suggested in the literature that *d*-methamphetamine is metabolized more extensively than *l*-methamphetamine in humans.<sup>17,18</sup> After the administration of racemic methamphetamine in 4 subjects, the urinary excretion of *d*-methamphetamine was lower and the urinary excretion of *d*-amphetamine was greater than that for the corresponding *l*-isomers.<sup>17</sup> One interpretation is that *d*-methamphetamine is metabolized more rapidly than the *l*-isomer. Taken together, these results suggest that the *l*-enantiomer might accumulate more rapidly with repeated dosing of the racemate, a possibility if abusers self-administer for the greater subjective effects of the *d*-isomer.<sup>1,19</sup>

Studies have not directly compared the pharmacokinetics of methamphetamine enantiomers using modern techniques, and the limited data that do exist are based on urinary excretion studies in a small number of subjects. In this study we characterize the plasma pharmacokinetics and pharmacodynamics of *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine in humans. We use these data to help predict the consequences of precursor regulation.

## METHODS

### Subjects

Twelve male intravenous methamphetamine users (mean age,  $32 \pm 7$  years) participated in the study. The subjects were not dependent on methamphetamine, alcohol, or other illicit drugs according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria; none was seeking treatment for methamphetamine-related problems. Inclusion criteria were as follows: aged 21 to 45 years; in good physical health as judged by medical examination, laboratory tests (including hematologic, hepatic, and renal serum chemical analysis), urinalysis, and electrocardiogram; within 15% of ideal body weight as defined by current health insurance table standards; and self-reported intravenous methamphetamine use from once weekly to once or twice every 6 weeks. Although not excluded, no women were recruited. Those subjects with significant medical or psychiatric illnesses; treatment of substance abuse in the last 12 months; current dependence on any drug (except caffeine or nicotine) according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria; use of any medication that could affect the ability to complete the study or alter drug kinetics; and a history of sensitivity to study

medications were excluded from the study. Serum hepatitis C status and human immunodeficiency virus status were not assessed. Written informed consent was obtained from all subjects. The Committee on Human Research, University of California, San Francisco, San Francisco, Calif, approved the study protocol. The study was carried out in accordance with the Declaration of Helsinki.

### Study design

A 6-session, double-blind, placebo-controlled, Latin-square, balanced crossover design was used. Single intravenous doses of *d*-methamphetamine, *l*-methamphetamine, racemic methamphetamine, or placebo were administered over a period of 1 minute via infusion pump control into a forearm vein. Intravenous doses were aseptically prepared by the UCSF School of Pharmacy investigational pharmacist from 10-mg/mL methamphetamine isomer stock solutions sterilized by use of Millipore filters (Millipore, Bedford, Mass) compounded by the School of Pharmacy, University of California, San Francisco. Investigational drugs were obtained from a commercial source (Sigma-Aldrich, St Louis, Mo) and recrystallized in our laboratories. The purity, chemical identity, and sterility were established before human use as outlined in Investigational New Drug 58,189. Each calculated aliquot was diluted with sterile 0.9% sodium chloride to a final volume of 10 mL to maintain the study blind. Saline solution alone served as the placebo.

The drugs and doses (all intravenous) were as follows: *d*-methamphetamine, 0.25 mg/kg; *d*-methamphetamine, 0.5 mg/kg; *l*-methamphetamine, 0.25 mg/kg; *l*-methamphetamine, 0.5 mg/kg; racemic methamphetamine, 0.5 mg/kg (0.25 mg/kg *d*-methamphetamine plus 0.25 mg/kg *l*-methamphetamine); and placebo (0.9% sodium chloride).

The subjects were admitted as inpatients to the General Clinical Research Center on the evening before the experimental session and remained there for 48 hours after methamphetamine administration. Experimental sessions were performed at the Drug Dependence Research Center laboratories (Langley Porter Psychiatric Institute, University of California, San Francisco). The subjects were asked to abstain from drug and alcohol use (except for caffeine and nicotine) for 48 hours before admission. They participated in all 6 experimental sessions approximately 1 week apart. On admission, they provided a blood sample for laboratory tests, as well as a urine sample for urinalysis and toxicology screening. Evidence of recent illicit drug use or short-term illness delayed the study session.

After baseline measurements were obtained, *d*-methamphetamine, *l*-methamphetamine, racemic methamphetamine, or placebo (normal saline solution) was administered intravenously. Pharmacodynamic measurements and plasma for analysis of pharmacokinetic parameters were obtained over the next 48 hours.

### Blood collection

A plastic catheter was inserted into an arm vein, and 7.5 mL of whole blood was collected before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours after dosing.

### Methamphetamine and amphetamine: Stereoselective assay

After administration of *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine, corresponding active metabolites were determined by use of an enantioselective assay. A chiral capillary gas chromatography column (beta-DEXcst; Restek, Bellefonte, Pa) resulted in good separation of the trifluoroacetyl derivatives of both enantiomers. We developed a gas chromatography-mass spectrometry method for the determination of methamphetamine and amphetamine enantiomers in plasma using this column. The analytes were extracted from plasma by a liquid-liquid extraction procedure (ethyl acetate/heptane [4:1]) and converted to the trifluoroacetyl derivatives with trifluoroacetylhydrazide. Methamphetamine- $d_{14}$  and amphetamine- $d_{11}$  were used as internal standards. Standard curves were linear over the range of 0.5 to 500 ng/mL in plasma. The limits of quantification for the assay method were 1 ng/mL for the methamphetamine and amphetamine enantiomers.

### Pharmacokinetic analysis

The plasma concentration-time profiles for *d*-methamphetamine, *l*-methamphetamine, and amphetamine were analyzed by use of the pharmacokinetic data analysis program WinNonlin Professional (version 3.1, Pharsight, Mountain View, Calif). The area under the plasma concentration-time curve up to the time of the last measurable plasma concentration ( $AUC_{0-t}$ ) of methamphetamine and amphetamine was calculated by use of the linear trapezoidal rule. The AUC to infinity was determined by extrapolation of  $AUC_{0-t}$  by use of the terminal rate constant ( $\lambda$ ), which was calculated by log-linear regression of the terminal linear phase of the plasma concentration-time curves. The elimination half-life ( $t_{1/2}$ ) was calculated by use of the following equation:  $t_{1/2} = \ln 2 / \lambda$ .



Systemic clearance (CL) and apparent volume of distribution during the elimination phase ( $V_d$ ) were calculated by use of the following formula:  $CL = \text{Dose}/AUC$  and  $V_d = CL/\lambda$ , respectively. AUC ratios were compared with estimates of the apparent "exposure" of the *d*- and *l*-enantiomers. This method is similar to that used for establishing the relative bioavailability of 2 formulations. The apparent relative exposure to *d*- and *l*-methamphetamine and amphetamine was defined as follows:

$$\text{Exposure (\%)} = \left( \frac{AUC \text{ d-enantiomer}}{AUC \text{ l-enantiomer}} \right) \times 100$$

The analyses were performed separately for both doses (0.25 and 0.5 mg/kg) of *d*-methamphetamine and *l*-methamphetamine and the racemate. The mean plasma AUC ratios were presented with 90% confidence intervals (CIs). On the basis of logic similar to that used previously, had this CI been contained entirely within the range from 80% to 125%, this would have been consistent with demonstrating "exposure bioequivalence" in terms of AUC.

### Pharmacodynamic measures

**Physiologic measures.** Heart rate and systolic and diastolic blood pressure were measured with an automated noninvasive electronic device (Escort II+, model 20301; Medical Data Electronics, Arleta, Calif). The rate-pressure product was calculated as systolic blood pressure multiplied by heart rate. The respiratory rate was counted manually. The skin temperature and tympanic (core) temperature were measured by use of thermocouples on an index finger and adjacent to the tympanic membrane (Mallinckrodt Mon-a-therm, model 6500; Mallinckrodt Medical, St Louis, Mo). All measures were obtained before dosing and at 0.08, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours after dosing. Blood and urine samples were collected for pharmacokinetic analysis and determination of methamphetamine and metabolite levels.

**Subjective measures.** Verbal ratings of global intoxication (on a scale ranging from 0 to 100) were obtained at the same time intervals as the physiologic measures, with 0 representing no drug effect and 100 representing the highest level of intoxication. Visual analog scales were used to rate other subjective effects from 0 ("none") to 100 ("most ever") for "any drug effect," "good drug effect," "drug liking," "bad drug effect," "intoxication," and "high" and were obtained before dosing and at 0.5, 1, 1.5, 3, 4, 5.5, 8, 12, and 24 hours after dosing. The Profile of Mood

States was used to assess subjective mood changes on specific subscales for tension-anxiety, depression-dejection, anger-hostility, vigor, confusion, and fatigue.<sup>20</sup> Subjects rated the presence and intensity of symptoms on a scale ranging from 0 to 4, where 0 indicates "no effect" and 4 indicates "extremely strong." Ratings were obtained before dosing and at 0.5, 1.5, 4, 12, 24, and 48 hours after dosing.

The Beck Depression Inventory and the State-Trait Anxiety Inventory were used to measure symptoms of anxiety and depression.<sup>21,22</sup> These were obtained before dosing and at 2 and 48 hours after dosing. The Buss Aggression Scale was used to evaluate anger, hostility, and verbal and physical aggression<sup>23</sup> and was obtained before dosing and at 3 and 24 hours after dosing. A monetary value was obtained for each dose at baseline and at 0.08, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours after dosing, and it ranged from \$0 to \$20. The monetary value was the value in dollars if the dose was purchased illicitly.

### Statistical analysis

For each pharmacokinetic parameter, the mean, SD, and 95% CI were calculated for both doses (0.25 mg/kg and 0.5 mg/kg) of *d*- and *l*-methamphetamine and the racemate. The effect of dosing conditions on the pharmacokinetics of *d*- and *l*-methamphetamine and the active metabolite (amphetamine) was analyzed by use of repeated-measures ANOVA. Dosing conditions were considered independent factors in the ANOVA model. The AUC, CL,  $t_{1/2}$ , and  $V_d$  for *d*- and *l*-methamphetamine and the AUC and  $t_{1/2}$  for *d*- and *l*-amphetamine, as well as the amphetamine/methamphetamine AUC ratios of both enantiomers, were the dependent factors.

Pharmacodynamic data across time were analyzed by repeated-measures ANOVA. Treatment conditions and observation times were considered within-subject factors. Change scores (postdose values minus predose values) were used in these analyses. Peak scores for all subjective and physiologic variables were also analyzed by repeated-measures ANOVA.

When a significant F test was observed, post hoc comparisons were conducted by use of the Fisher least significant difference or Scheffé test. Missing data, which accounted for less than 1% of the data, were replaced by the group mean at that specific time point. Effects were considered statistically significant at  $P \leq .05$ .

## RESULTS

### Subjects

Twelve male intravenous methamphetamine users (mean age,  $32.3 \pm 7.4$  years [range, 23-43 years]) completed the study. The mean weight and height were  $73.5 \pm 7.0$  kg (range, 68.2-90.9 kg) and  $177.6 \pm 6.1$  cm (range, 165-185 cm), respectively. On the basis of self-reported ethnicity, there were 9 white subjects and 3 black subjects.

### Tolerability of methamphetamine

No serious adverse events occurred during the study, and all doses of methamphetamine were well tolerated. No clinically significant changes in electrocardiography, physical examination, vital signs, biochemical tests, or hematologic parameters were evident.

### Pharmacokinetic results

The mean plasma concentration-time profiles are shown in Fig 2. Plasma levels of methamphetamine peaked immediately after administration and were detectable 36 to 48 hours after dosing. Estimated pharmacokinetic parameters are listed in Table I. No methamphetamine was detected just before drug administration.

The mean AUC values for methamphetamine after separate enantiomer doses were similar between *d*- and *l*-methamphetamine. The mean plasma AUC ratios of the *d*- and *l*-enantiomers were 0.910 (90% CI, 0.837-0.983) and 0.894 (90% CI, 0.821-0.967) for the 0.25-mg/kg dose and 0.5-mg/kg dose, respectively. This illustrates that the apparent "exposure" of *d*-methamphetamine to *l*-methamphetamine is almost 90% with regard to methamphetamine AUC. However, the AUC for *l*-methamphetamine was 30% greater ( $P = .0085$ ) than that for *d*-methamphetamine after the racemic dose of methamphetamine (Fig 2, B). The mean plasma AUC ratio of racemic methamphetamine was 0.679 (90% CI, 0.622-0.736), which did not meet the criteria for exposure bioequivalence.

Mean maximum plasma concentration ( $C_{\max}$ ) values were similar among *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine. The mean  $C_{\max}$  ratios of the *d*- and *l*-enantiomers were 1.215 (90% CI, 1.044-1.385), 1.086 (90% CI, 0.974-1.199), and 1.008 (90% CI, 0.970-1.047) for the 0.25-mg/kg, 0.5-mg/kg, and racemic doses, respectively. Both the AUC and  $C_{\max}$  for methamphetamine after the 0.5-mg/kg doses were approximately 2-fold higher than those for the corresponding 0.25-mg/kg doses, suggesting linear pharmacokinetics within our experimental dose range.

The clearance of *d*-methamphetamine was greater than that of *l*-methamphetamine after racemic methamphetamine ( $P < .0001$ ). However, the clearance values for both *d*- and *l*-enantiomers were similar across the 2 dose levels (0.25 and 0.5 mg/kg) when each isomer was given separately.

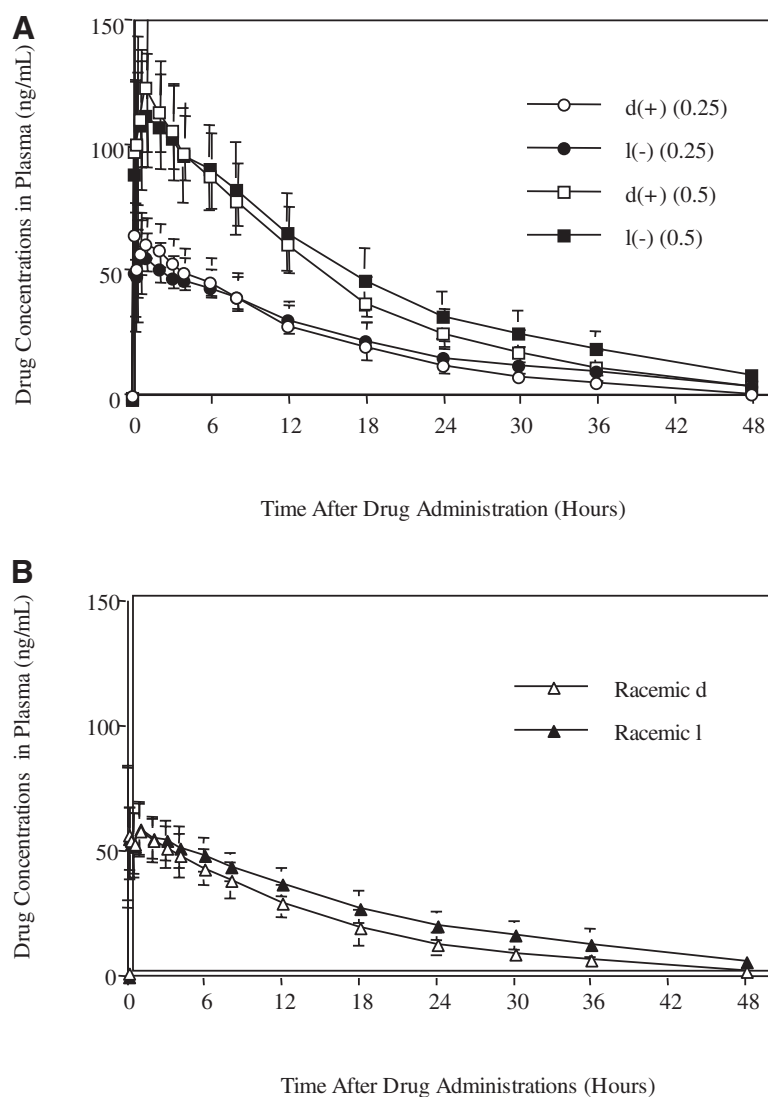
The mean  $V_d$  was 3.73 to 4.17 L/kg across all dosing conditions and was not significantly different between the 2 enantiomers ( $P = .2206$ ). The difference in clearance (*d*-isomer > *l*-isomer) found after administration of racemic methamphetamine can be explained by the difference in elimination half-lives of each enantiomer. In general, the half-lives for *d*-methamphetamine were shorter than those for *l*-methamphetamine ( $P < .0001$ ). After the 0.5-mg/kg dose of *d*- and *l*-methamphetamine, the half-lives were  $10.3 \pm 2.6$  and  $13.3 \pm 3.5$  hours, respectively ( $P = .0049$ ). The mean half-life of *l*-methamphetamine was slightly longer after racemic administration.

After intravenous dosing, the active metabolites of methamphetamine, *d*- and *l*-amphetamine, were detectable in plasma and peaked 12 to 18 hours after dosing. The elimination of *d*- and *l*-amphetamine was slower than that of methamphetamine (Fig 3). The AUC and  $C_{\max}$  values for *d*- and *l*-amphetamine were considerably smaller than those for the parent drug (Table I and Fig 3). The AUC ratios for amphetamine to methamphetamine were significantly higher for the *d*-enantiomer (0.16-0.17) than for the *l*-enantiomer (0.03-0.04). The AUC for *d*-amphetamine was 4- to 7-fold greater than that for *l*-amphetamine within the same dose levels; the *d*- and *l*-enantiomers did not show exposure bioequivalence in terms of the amphetamine AUCs. The  $t_{1/2}$  ranged between 33.0 and 65.0 hours but showed great variability.

### Pharmacodynamic measures

**Physiologic measures.** Compared with placebo, all doses containing *d*-methamphetamine (0.25 mg/kg, 0.5 mg/kg, and racemic) significantly increased systolic and diastolic blood pressure, heart rate, and rate-pressure product (all  $P < .0001$ ), as well as respiration rate ( $P < .05$ ), across time (Fig 4). The 0.25-mg/kg and 0.5-mg/kg doses of *l*-methamphetamine significantly increased heart rate and rate-pressure product ( $P < .01$ ), yet 0.25 mg/kg of *l*-methamphetamine had no effect on blood pressure ( $P = .32$ ).

Racemic methamphetamine produced increases in heart rate, blood pressure, and rate-pressure product similar to those of 0.5 mg/kg *d*-methamphetamine across time. Compared with corresponding doses of *l*-methamphetamine, all doses containing *d*-metham-



**Fig 2.** **A**, Mean plasma concentration–time curves for *d*- and *l*-methamphetamine after 0.25 and 0.5 mg/kg of the corresponding form of methamphetamine (intravenously). *Open circles*, 0.25 mg/kg of *d*-methamphetamine; *solid circles*, 0.25 mg/kg of *l*-methamphetamine; *open squares*, 0.5 mg/kg of *d*-methamphetamine; *solid squares*, 0.5 mg/kg of *l*-methamphetamine. Data are given as mean  $\pm$  SD ( $N = 12$ ). **B**, Mean plasma concentration–time curves for *d*- and *l*-methamphetamine after 0.5-mg/kg dose of racemic methamphetamine (*d*-methamphetamine/*l*-methamphetamine [1:1]). *Open triangles*, *d*-Methamphetamine; *solid triangles*, *l*-methamphetamine. Data are given as mean  $\pm$  SD ( $N = 12$ ).

phetamine produced greater and longer-lasting cardiovascular effects. For example, doses containing 0.25 mg/kg of *d*-methamphetamine produced larger and more sustained increases in cardiovascular activation than the 0.5-mg/kg *l*-methamphetamine dose. In all conditions blood pressure, heart rate, and rate-pressure product peaked at approximately 5 to 15 minutes after

dosing. However, the values of these measures returned to baseline between 2 and 4 hours after either dose of *l*-methamphetamine. In contrast, the effects of *d*-methamphetamine persisted for up to 6 hours (Fig 4).

Peak systolic and diastolic blood pressure and rate-pressure product were significantly greater than with placebo for all conditions except 0.25 mg/kg of

**Table I.** Pharmacokinetic parameters for *d*- and *l*-methamphetamine and its metabolite amphetamine

Parameter	Dose	
	<i>d</i> -Methamphetamine, 0.25 mg/kg	<i>l</i> -Methamphetamine, 0.25 mg/kg
Methamphetamine		
AUC <sub>0-t</sub> (48 h) (ng · h/mL)	965.2 ± 189.7 (844.7-1085.7)	1072.2 ± 207.6 (940.3-1204.1)
AUC <sub>0-∞</sub> (ng · h/mL)	1010.3 ± 210.2 (876.7-1143.8)	1190.7 ± 287.7 (1007.9-1373.5)
C <sub>max</sub> (ng/mL)	76.7 ± 25.3 (60.6-92.8)	65.4 ± 18.1 (53.9-76.9)
CL (L · h <sup>-1</sup> · kg <sup>-1</sup> )	0.257 ± 0.053 (0.224-0.291)	0.221 ± 0.05 (0.189-0.252)
t <sub>1/2</sub> (h)	10.2 ± 2.3 (8.8-11.7)	13.6 ± 3.8 (11.2-16.0)
V <sub>d</sub> (L/kg)	3.73 ± 0.94 (3.13-4.33)	4.15 ± 0.76 (3.66-4.63)
Amphetamine AUC <sub>0-t</sub> (ng · h/mL)	150.9 ± 75.4 (103.0-198.8)	32.1 ± 21.6 (13.4-45.8)
C <sub>max</sub> (ng/mL)	4.8 ± 2.1 (3.4-6.1)	1.2 ± 0.8 (0.7-1.6)
t <sub>1/2</sub> (h)	32.5 ± 21.1 (18.4-46.7)	64.6 ± 41.2 (26.5-102.7)
Amphetamine/methamphetamine AUC ratio	0.163 ± 0.079 (0.118-0.207)	0.029 ± 0.019 (0.019-0.040)

AUC<sub>0-t</sub>, Area under plasma concentration–time curve up to time of last measurable plasma concentration; AUC<sub>0-∞</sub>, area under plasma concentration–time curve extrapolated to infinity; C<sub>max</sub>, maximum plasma concentration; CL, systemic clearance; t<sub>1/2</sub>, elimination half-life; V<sub>d</sub>, apparent volume of distribution during elimination phase; AUC, area under plasma concentration–time curve; N/A, not applicable.

*l*-methamphetamine ( $P < .01$ ) (Fig 4 and Table II). Racemic methamphetamine and 0.5 mg/kg of *d*-methamphetamine increased mean peak systolic pressure values by  $33 \pm 18$  mm Hg and  $34 \pm 19$  mm Hg, respectively. In contrast, 0.25 and 0.5 mg/kg of *l*-methamphetamine only increased mean peak systolic blood pressure values by  $14 \pm 9$  mm Hg and  $19 \pm 11$  mm Hg, respectively ( $P < .05$ ). Differences in peak heart rate were less marked between conditions. All doses of *d*- and *l*-methamphetamine lowered skin temperature more than placebo ( $P < .05$ ). Core temperature was not significantly different between conditions.

**Subjective measures.** With regard to the visual analog scales, compared with placebo, the administration of 0.25 and 0.5 mg/kg of *d*-methamphetamine, 0.5 mg/kg of *l*-methamphetamine, and racemic methamphetamine significantly increased the verbal intoxication rating ( $P < .0001$ ), as well as visual analog scale ratings of “intoxication,” “any drug effect,” “drug liking,” “good drug effect,” “high,” and “bad drug effect” ( $P < .01$ ), across time (Fig 5). No significant difference was found between 0.25 mg/kg of *l*-methamphetamine and placebo.

Racemic methamphetamine was similar to 0.25 mg/kg of *d*-methamphetamine with regard to all subjective measures and 0.5 mg/kg with regard to “intoxication” (verbal rating) (Fig 5) and monetary value (Fig 6). For several of these measures (“intoxication,” “any drug effect,” and “drug liking”), the 0.5-mg/kg *l*-methamphetamine dose produced significantly smaller effects compared with 0.5 mg/kg of *d*-methamphetamine ( $P < .0001$ ) and racemic methamphetamine ( $P < .05$ ).

Its effect was also less than that of 0.25 mg/kg of *d*-methamphetamine for “drug liking” ( $P < .01$ ). The effects of *l*-methamphetamine approached baseline at approximately 3 hours after dosing (Fig 5), whereas doses containing *d*-methamphetamine remained intoxicating for up to 6 hours. Interestingly, despite less intoxication with *l*-methamphetamine, both enantiomers had similar monetary value (Fig 6).

The peak effects for all doses containing *d*-methamphetamine (0.5 mg/kg, 0.25 mg/kg, and racemic) and 0.5 mg/kg of *l*-methamphetamine on “any drug effect,” “drug liking,” “good drug effect,” and “high” were greater than those for placebo ( $P < .05$ ). However, with the exception of the placebo and 0.25-mg/kg *l*-methamphetamine doses, few significant differences were found among the peak effects of the other doses (Table II). Subjects found that all doses of *d*-methamphetamine and the high dose of *l*-methamphetamine had monetary value and were willing to pay a mean of \$10.70 to \$14.60 per dose. In contrast, low-dose *l*-methamphetamine was worth no more than placebo.

With regard to the Profile of Mood States, no significant differences were found between conditions on any of the subscales across time, although condition-by-time interactions were significant ( $P < .0001$ ) for the arousal, elation, fatigue, friendliness, positive mood, and vigor scales. After 0.25 and 0.5 mg/kg of *l*-methamphetamine, ratings on the majority of these scales reached a trough at approximately 1.5 hours after dosing, whereas ratings after 0.25 and 0.5 mg/kg of *d*-methamphetamine and racemic methamphetamine



Dose			
<i>d</i> -Methamphetamine, 0.5 mg/kg	<i>l</i> -Methamphetamine, 0.5 mg/kg	<i>d</i> -Methamphetamine, (racemic [1:1])	<i>l</i> -Methamphetamine (racemic [1:1])
1887.2 ± 335.1 (1674.3-2100.1)	2156.9 ± 452.0 (1869.7-2444.0)	937.6 ± 223.6 (795.5-1079.7)	1230.5 ± 239.0 (1078.6-1382.3)
1978.1 ± 374.7 (1740.0-2216.7)	2368.1 ± 524.1 (2035.0-2701.2)	990.7 ± 254.1 (829.3-1152.1)	1406.6 ± 350.3 (1184.1-1629.2)
131.9 ± 24.4 (116.3-147.4)	125.9 ± 30.7 (106.4-145.7)	68.9 ± 20.7 (55.8-82.0)	68.7 ± 21.6 (55.0-82.4)
0.259 ± 0.039 (0.234-0.284)	0.221 ± 0.048 (0.19-0.251)	0.266 ± 0.058 (0.229-0.302)	0.188 ± 0.046 (0.158-0.217)
10.3 ± 2.6 (8.7-11.9)	13.3 ± 3.5 (11.1-15.6)	10.7 ± 2.6 (9.0-12.4)	15.0 ± 4.6 (12.0-17.9)
3.80 ± 1.05 (3.14-4.47)	4.17 ± 1.25 (3.38-4.96)	3.97 ± 0.90 (3.40-4.54)	3.85 ± 0.86 (3.30-4.40)
295.8 ± 110.5 (225.6-366.0)	83.5 ± 40.1 (58.1-109.0)	162.4 ± 68.5 (118.9-205.9)	41.2 ± 26.5 (24.4-58.0)
9.2 ± 3.3 (7.1-11.4)	2.5 ± 1.1 (1.8-3.2)	4.9 ± 1.8 (4.9-7.6)	1.5 ± 0.8 (1.0-2.0)
33.5 ± 29.5 (14.8-52.3)	43.6 ± 24.9 (25.8-61.4)	40.6 ± 42.7 (11.9-69.3)	N/A
0.162 ± 0.067 (0.125-0.200)	0.038 ± 0.016 (0.029-0.047)	0.173 ± 0.066 (0.136-0.211)	0.032 ± 0.020 (0.021-0.044)

were still elevated and had scores above those of the other conditions.

Peak ratings of arousal, elation, positive mood, and vigor were significantly higher after 0.25 and 0.5 mg/kg of *d*-methamphetamine and racemic methamphetamine than after placebo ( $P < .01$ ). *d*-Methamphetamine, 0.25 mg/kg, and racemic methamphetamine also produced greater ratings on the friendliness scale compared with placebo ( $P < .05$ ). *l*-Methamphetamine, 0.5 mg/kg, produced greater ratings only on the arousal scale compared with placebo ( $P < .05$ ).

With regard to the State-Trait Anxiety Inventory, Beck Depression Inventory, and Buss Aggression Scale, no significant differences were found between experimental conditions.

## DISCUSSION

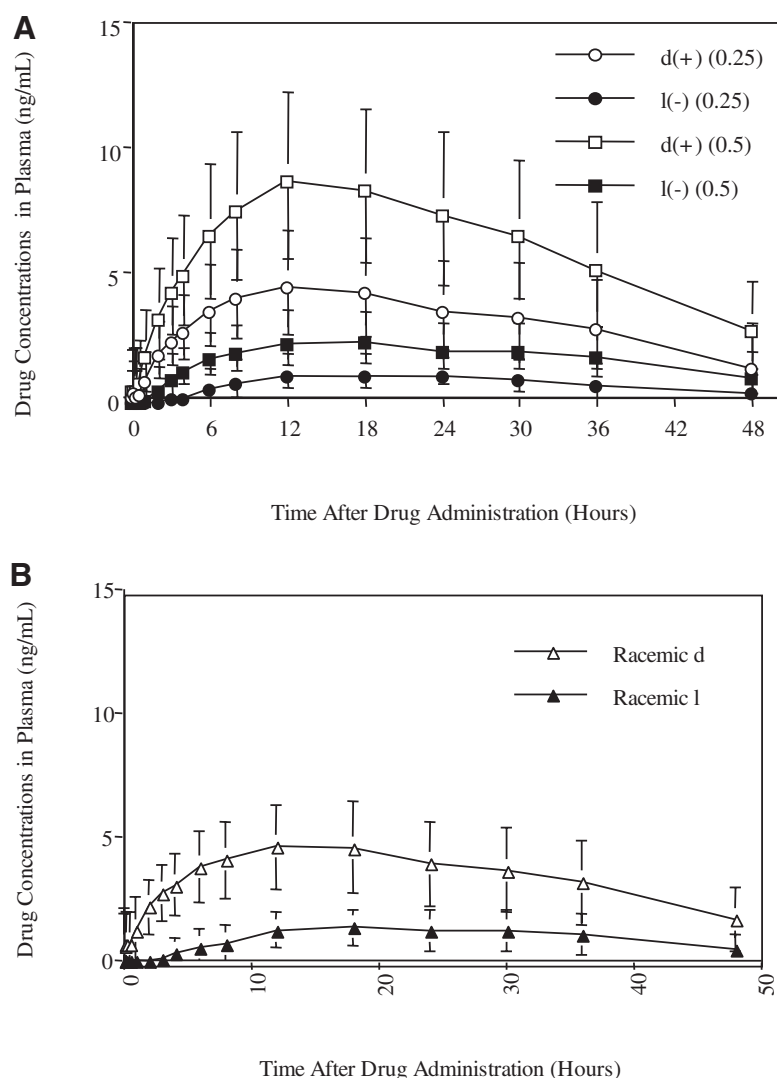
In this study we show that racemic methamphetamine has effects similar to those of pure *d*-methamphetamine, suggesting that this form of the drug has an abuse potential similar to that for *d*-methamphetamine. In contrast, although *l*-methamphetamine is psychoactive, this isomer alone generally produces less pleasurable effects than doses containing *d*-methamphetamine. Finally, we show that the differing pharmacodynamic profiles of the methamphetamine enantiomers are not a result of differences in biodisposition.

## Pharmacokinetics

This is the first experiment to establish the enantiomer-specific pharmacokinetic profile of *d*- and *l*-methamphetamine after racemic methamphetamine.

We found that the apparent exposure of the *d*- and *l*-enantiomers was bioequivalent (in terms of AUC in plasma as an exposure marker) after the administration of 0.25 mg/kg and 0.5 mg/kg of *d*- and *l*-methamphetamine; *d*-methamphetamine had a relative exposure close to 90% compared with *l*-methamphetamine. In contrast, after the racemate, *d*-methamphetamine had a relative exposure of 68%, which did not meet the criteria for bioequivalence.

The mechanism by which the AUC for *l*-methamphetamine was greater than that for *d*-methamphetamine after administration of the racemate is not clearly understood. The results of our study suggest that 1 enantiomer is inhibiting or inducing the metabolism of the other. For example, either *d*-methamphetamine or *d*-amphetamine may inhibit the conversion of *l*-methamphetamine to *l*-amphetamine or *l*-methamphetamine or *l*-amphetamine could induce the conversion from *d*-methamphetamine to *d*-amphetamine (or both). As shown in Table I, clearance for the *d*-isomer is similar for both doses and the racemate. For the *l*-isomer, clearance is the same at both doses but is less in the racemate, suggesting inhibition by the *d*-isomer. The AUCs of *d*- and *l*-amphetamine were proportional for all doses of *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine. We investigated only one metabolite (amphetamine). Other pathways that account for the observed pharmacokinetic differences after racemic administration may be involved (eg, *p*-hydroxylation). Whether the presence (or absence) of one enantiomer can alter the metabolism of the other needs to be examined further.

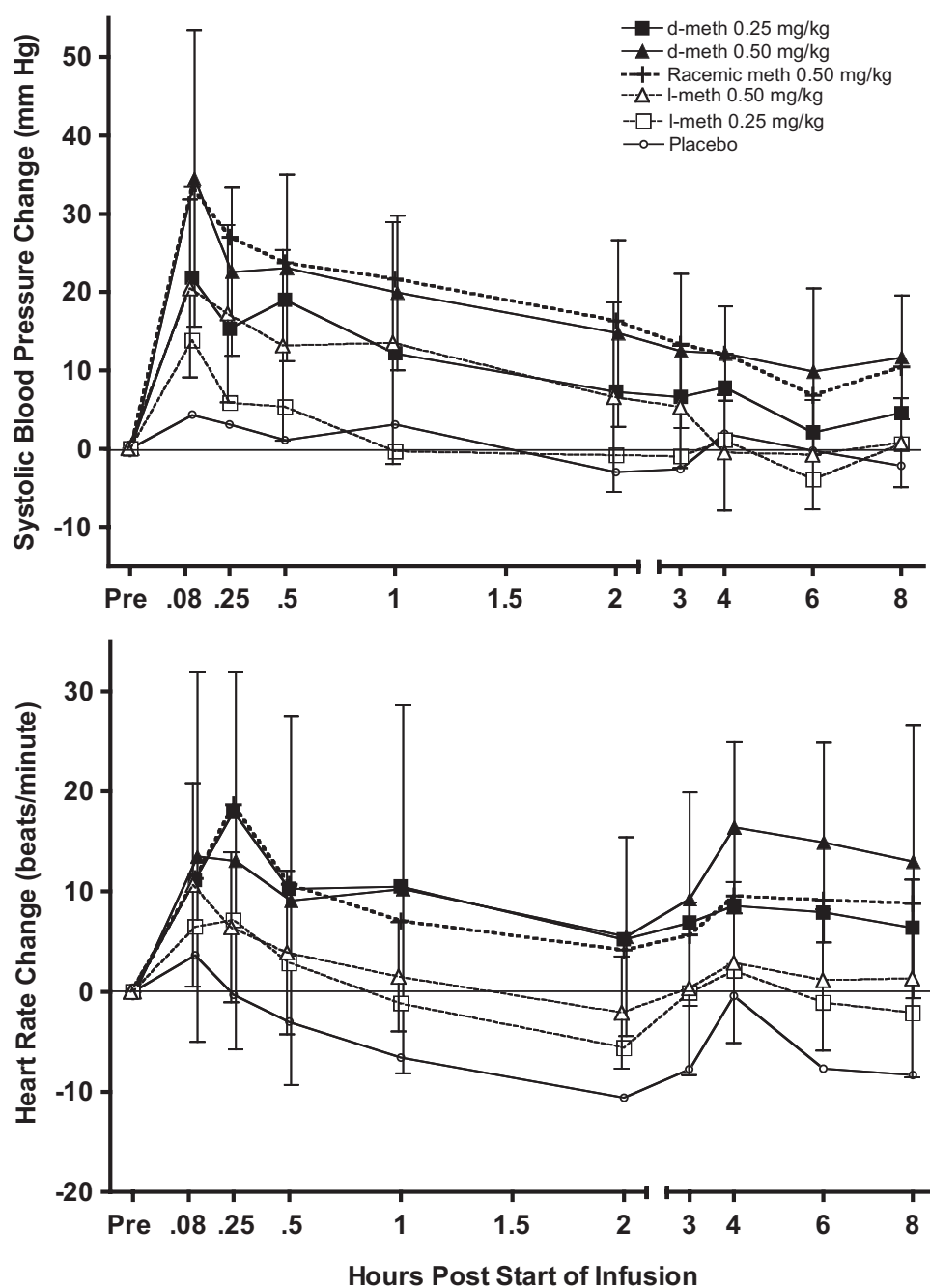


**Fig 3.** A, Mean plasma concentration–time curves for *d*- and *l*-amphetamine after 0.25 and 0.5 mg/kg of corresponding form of methamphetamine (intravenously). *Open circles*, 0.25 mg/kg of *d*-amphetamine; *solid circles*, 0.25 mg/kg of *l*-amphetamine; *open squares*, 0.5 mg/kg of *d*-amphetamine; *solid squares*, 0.5 mg/kg of *l*-amphetamine. Data are given as mean  $\pm$  SD (N = 12). B, Mean plasma concentration–time curves for *d*- and *l*-amphetamine after 0.5-mg/kg dose of racemic methamphetamine (*d*-methamphetamine/*l*-methamphetamine [1:1]). *Open triangles*, *d*-Amphetamine; *solid triangles*, *l*-amphetamine. Data are given as mean  $\pm$  SD (N = 12).

The reported half-life of *d*-methamphetamine is approximately 9 to 13 hours<sup>6,24-29</sup> and is similar to our data. Our data show that the  $t_{1/2}$  for *l*-methamphetamine is slightly longer than that for *d*-methamphetamine (approximately 13–15 hours versus 10–11 hours); this is the first comparison of the  $t_{1/2}$  between *d*- and *l*-methamphetamine. The longer half-life (elimination) of *l*-methamphetamine probably accounts for the difference in clearance of the enantiomers after the race-

mate because the volumes of distribution are similar and clearance was different only when the racemate was given.

Although the AUC and CL for each dose of *d*- and *l*-methamphetamine may be similar, a small difference in elimination could lead to an accumulation of *l*-methamphetamine in the plasma if the racemate were used repeatedly. Drug abusers often take several closely spaced doses of methamphetamine over rela-



**Fig 4.** Mean changes in systolic blood pressure and heart rate after *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine. *Solid squares*, 0.25 mg/kg of *d*-methamphetamine; *open squares*, 0.25 mg/kg of *l*-methamphetamine; *solid triangles*, 0.5 mg/kg of *d*-methamphetamine; *open triangles*, 0.5 mg/kg of *l*-methamphetamine; *dashed lines*, racemic methamphetamine; *circles*, placebo. Mean data are shown ( $N = 12$ ), except for 0.5 mg/kg of *d*- and *l*-methamphetamine, for which data are given as mean  $\pm$  SD. Pre, Predosing.

**Table II.** Mean peak changes in physiologic and subjective measures

Measure	Condition					
	Placebo	<i>l</i> -Methamphetamine		Racemic methamphetamine	<i>d</i> -Methamphetamine	
		0.25 mg/kg	0.5 mg/kg		0.25 mg/kg	0.5 mg/kg
Physiologic measures (SD)						
Heart rate (beats/min)	3.7 (9.8)	6.5 (8.6)	10.7 (10.2)*	18.7 (23.4)*†	18.0 (11.7)*†	13.5 (18.5)*
Systolic blood pressure (mm Hg)	4.3 (9.9)	13.8 (9.3)	19.5 (11.3)*	33.4 (17.8)*†‡§	21.8 (12.8)*	34.5 (18.9)*†‡§
Diastolic blood pressure (mm Hg)	3.9 (6.5)	6.9 (7.9)	12.8 (6.8)*	15.7 (11.7)*†	13.5 (8.0)*†	20.0 (10.1)*†‡§
Rate-pressure product (heart rate × systolic blood pressure)	911 (2164)	1862 (1387)	3219 (1580)*	4466 (3591)*†	3493 (1874)*†	4438 (2709)*†
Respiration rate (breaths/min)	0.5 (2.3)	−1.1 (3.1)	1.4 (2.3)†	1.8 (4.1)†	4.1 (1.6)*†‡	2.9 (2.7)*†
Skin temperature (°C)	−1.9 (2.4)	−3.9 (2.5)*	−4.2 (3.7)*	−4.4 (1.3)*	−5.7 (3.2)*	−5.2 (2.6)*
Subjective measures (SD)						
Intoxication (0-100 verbal rating)	3.1 (4.9)	14.7 (25.3)	40.4 (34.1)*†	39.2 (40.0)*	43.8 (32.3)*†	47.0 (37.8)*†
Monetary value (\$)	1.1 (2.4)	4.6 (6.1)	11.3 (8.8)*†	10.7 (9.2)*	11.6 (8.2)*†	14.6 (9.6)*†
Visual analog scales (0-100)						
Intoxication	1.7 (4.7)	14.6 (20.3)	30.3 (24.9)*	24.7 (27.4)*	36.7 (25.6)*†	46.0 (35.3)*†
Any drug effect	1.1 (4.0)	15.7 (21.0)	33.0 (27.7)*	29.6 (28.1)*	38.5 (28.6)*†	47.7 (34.1)*†
Drug liking	2.1 (3.9)	14.9 (19.6)	28.6 (24.8)*	33.3 (28.7)*	38.9 (29.1)*†	47.7 (35.1)*†
Good drug effect	0.9 (1.9)	15.3 (20.9)	33.1 (27.4)*	28.8 (29.1)*	37.9 (30.2)*†	48.2 (35.2)*†
High	1.5 (3.7)	13.8 (20.8)	31.0 (25.9)*	25.4 (28.4)*	38.3 (28.8)*†	46.5 (35.0)*†
Profile of Mood States						
Arousal (−64 to 68)	−0.2 (4.4)	2.4 (5.3)	4.8 (6.7)*	7.9 (9.1)*†	9.3 (7.8)*†	7.8 (7.4)*†
Elation (0-24)	−1.2 (2.1)	0.3 (3.2)	−0.1 (1.9)	2.5 (5.7)*	3.8 (4.6)*†‡	4.8 (4.7)*†‡
Friendliness (0-28)	−0.9 (2.5)	0.2 (5.2)	1.3 (4.1)	3.9 (6.1)*	4.2 (4.7)*†	2.8 (5.1)
Positive mood (−60 to 24)	−2.2 (3.8)	−1.0 (6.4)	−0.3 (3.7)	2.7 (5.6)*†	2.8 (3.8)*†	4.7 (4.1)*†‡
Vigor (0-32)	−0.8 (3.1)	0.5 (4.5)	1.8 (3.8)	4.2 (5.1)*†	4.9 (5.0)*†‡	4.3 (4.4)*†

\*Statistically significantly greater than placebo.

†Statistically significantly greater than *l*-methamphetamine, 0.25 mg/kg.‡Statistically significantly greater than *l*-methamphetamine, 0.5 mg/kg.§Statistically significantly greater than *d*-methamphetamine, 0.25 mg/kg.

||Statistically significantly greater than racemic methamphetamine.

tively short time periods. Enantiomer-specific pharmacokinetic data for repeated methamphetamine dosing are not yet available in humans. There may be a greater stereoselective accumulation of *l*-methamphetamine, and this may increase adverse effects. Because the clearance of the *l*-enantiomer was less after the racemic dose, these effects may be greater for racemic methamphetamine.

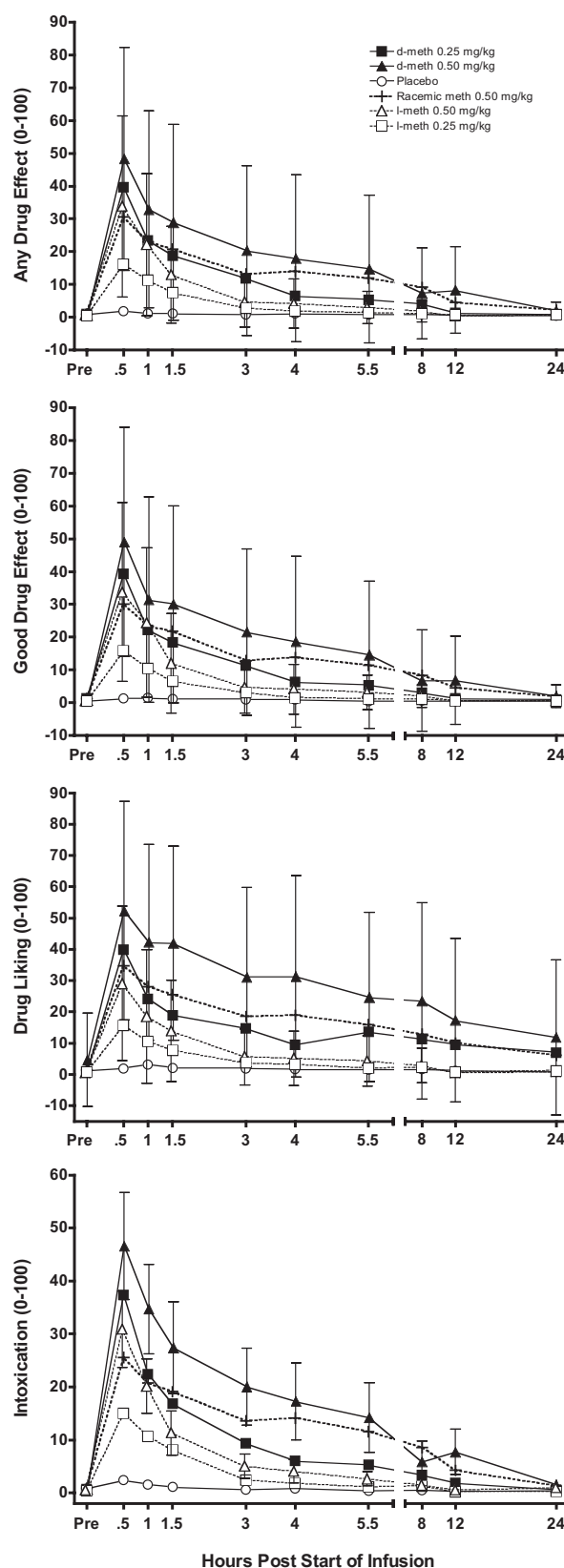
The pharmacokinetics of both *d*- and *l*-methamphetamine were dose-proportional in terms of AUC in plasma. Other stimulants have nonlinear pharmacokinetics in humans. For example, we found that 3,4-methylenedioxymethamphetamine (MDMA) (ec-

stasy) and its metabolite 3,4-methylenedioxymethamphetamine (MDA) show stereoselective and nonlinear pharmacokinetics over a range of doses from 0.5 to 1.5 mg/kg.<sup>30</sup> Another stimulant, methylphenidate, also has a chiral structure, and *d*-methylphenidate has a 40-fold higher plasma concentration than *l*-methylphenidate after controlled-release delivery.<sup>31</sup> Thus we initially speculated that methamphetamine might also have stereoselective nonlinear pharmacokinetics. However, our data show that this is not the case for methamphetamine, at least over the dose range studied. At these active and abused doses, methamphetamine follows linear pharmacoki-

netics when the plasma concentration–time profiles (AUC) are being analyzed.

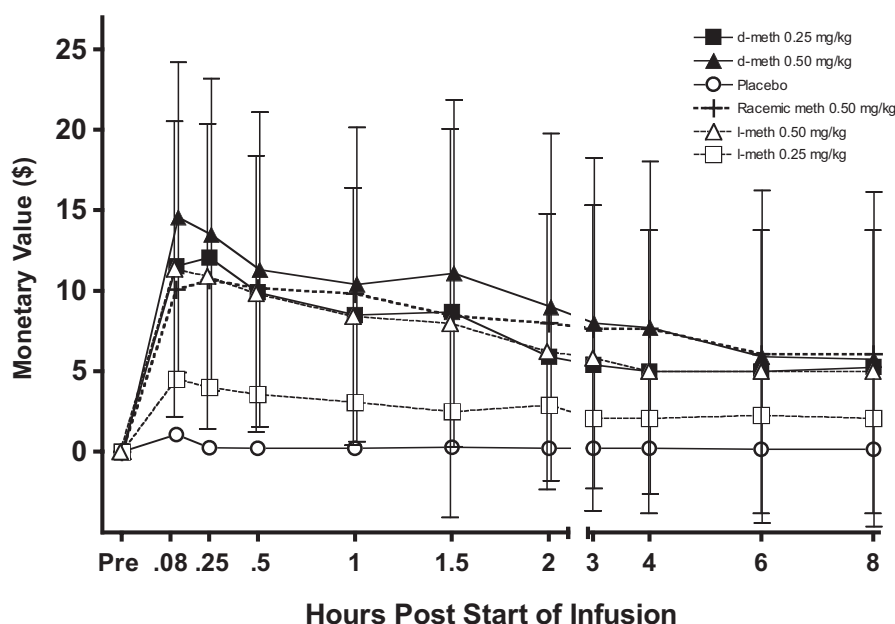
After intravenous dosing, the AUC for *d*-amphetamine is larger than that for *l*-amphetamine. The ratios of AUCs for *d*-amphetamine to *d*-methamphetamine were 0.163 to 0.173. These values are consistent with recent data from our laboratories; plasma AUC ratios for *d*-amphetamine to *d*-methamphetamine were 0.16 to 0.19 after intravenous doses of deuterated or nondeuterated *d*-methamphetamine.<sup>32</sup> However, these AUC ratios for *d*-amphetamine to *d*-methamphetamine after intravenous dosing appeared to be lower than those found after oral dosing of *d*-methamphetamine.<sup>28</sup> The AUC ratios for *d*-amphetamine to *d*-methamphetamine were  $0.21 \pm 0.25$  in plasma and  $0.24 \pm 0.11$  in oral fluid after oral dosing. The difference in the formation of amphetamine between the oral and intravenous routes suggests the existence of some first-pass effects. No published data are available on the pharmacokinetics of amphetamine after *l*-methamphetamine administration. The ratios of AUCs for *l*-amphetamine to *l*-methamphetamine were 0.029 to 0.038, which were markedly lower than those for *d*-amphetamine to *d*-methamphetamine.

The lower AUC values for *l*-amphetamine after *l*-methamphetamine administration suggest reduced metabolism of *l*-methamphetamine to *l*-amphetamine, resulting in lower levels. Higher *d*-methamphetamine levels compared with *l*-amphetamine levels have been observed in drug abusers, probably reflecting abuse of racemic methamphetamine.<sup>33</sup> Thus stereoselective differences in amphetamine metabolism must be considered before the toxicology data of amphetamine in drug abusers are interpreted. Nagai et al<sup>33</sup> analyzed urine from 30 Japanese methamphetamine addicts and classified the data into 5 groups: In the first group ( $n = 16$ ), only *d*-methamphetamine and *d*-amphetamine were found; in the second group ( $n = 1$ ), only *l*-methamphetamine and *l*-amphetamine were found; in the third group ( $n = 5$ ), *d*-methamphetamine and *d*-amphetamine were greater than *l*-methamphetamine and *l*-am-



**Fig 5.** Mean visual analog scale subjective responses after *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine. Solid squares, 0.25 mg/kg of *d*-methamphetamine; open squares, 0.25 mg/kg of *l*-methamphetamine; solid triangles, 0.5 mg/kg of *d*-methamphetamine; open triangles, 0.5 mg/kg of *l*-methamphetamine; dashed lines, racemic methamphetamine; circles, placebo. Mean data are shown ( $N = 12$ ), except for 0.5 mg/kg of *d*- and *l*-methamphetamine, for which data are given as mean  $\pm$  SD.





**Fig 6.** Mean visual analog scale subjective response for monetary value after *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine. *Solid squares*, 0.25 mg/kg of *d*-methamphetamine; *open squares*, 0.25 mg/kg of *l*-methamphetamine; *solid triangles*, 0.5 mg/kg of *d*-methamphetamine; *open triangles*, 0.5 mg/kg of *l*-methamphetamine; *dashed lines*, racemic methamphetamine; *circles*, placebo. Mean data are shown ( $N = 12$ ), except for 0.5 mg/kg of *d*- and *l*-methamphetamine, for which data are given as mean  $\pm$  SD.

phetamine; in the fourth group ( $n = 4$ ), *l*-methamphetamine and *l*-amphetamine were greater than *d*-methamphetamine and *d*-amphetamine; and in the fifth group ( $n = 4$ ), *l*-methamphetamine was greater than *d*-amphetamine and *l*-amphetamine was less than *d*-amphetamine. The metabolic profile found in the fifth group supports our finding that the AUC for amphetamine is much smaller for the *l*-enantiomer compared with the *d*-enantiomer after methamphetamine administration. Although the methamphetamine crystals analyzed by Nagai et al did not contain the racemic form (1:1), these findings show that methamphetamine can be abused as either *d*-methamphetamine or *l*-methamphetamine or as some combination of both enantiomers.

We found that amphetamine pharmacokinetics may depend on the dose of the parent drug, methamphetamine. Within the same enantiomers, the AUC ratios of amphetamine between the 2 doses (0.5 and 0.25 mg/kg) were 1.9 for the *d*-isomer and 2.6 for the *l*-isomer. A dose-proportional increase in the AUC for *d*-amphetamine occurred after *d*-methamphetamine administration. However, our data suggest that a higher dose of *l*-methamphetamine may produce a slight in-

crease in the AUC for *l*-amphetamine that is not dose-proportional. The underlying mechanism for this finding is not clear. It is possible that *d*-methamphetamine inhibits the metabolism of *d*-amphetamine or that the enzyme that mediates the conversion of *d*-methamphetamine to *d*-amphetamine may be limited or saturated.

### Pharmacodynamics

Differences in cardiovascular and subjective effects also occurred between enantiomers. In general, *d*-methamphetamine and racemic methamphetamine produced significantly longer-lasting cardiovascular and subjective effects than *l*-methamphetamine. Although the peak effects of 0.5 mg/kg of *l*-methamphetamine were similar to those with the doses containing *d*-methamphetamine, these effects dissipated rapidly (Figs 4 and 5). The 0.5-mg/kg *l*-methamphetamine dose produced significantly fewer subjective effects across time than the comparable dose of *d*-methamphetamine and racemic methamphetamine. The exception was monetary value, which remained similar to all doses containing *d*-methamphetamine across time (Fig 6). For those effects that were increased by the higher *l*-methamphetamine dose, the magnitude was similar to the

0.25-mg/kg *d*-methamphetamine dose. In contrast, the 0.25-mg/kg dose of *l*-methamphetamine produced few physiologic or subjective effects, often no greater than placebo. Both isomers produced a dose-response effect for the majority of subjective measures.

Our findings illustrate that the small enantiomer-specific differences in pharmacokinetics do not explain the differences between isomers with regard to the cardiovascular and subjective effects. The pharmacodynamic differences between isomers could be explained by the metabolite of *d*-methamphetamine, *d*-amphetamine (Fig 3). Although the AUC for the metabolite amphetamine was considerably smaller than that for the parent, methamphetamine, amphetamine by itself is a potent CNS stimulant. The distribution of *d*-amphetamine in the striatum is rapid after *d*-methamphetamine administration.<sup>34</sup> Therefore the enantiomer-specific difference in amphetamine disposition may increase brain levels of *d*-amphetamine, producing significant CNS effects.

Methamphetamine is thought to exert its behavioral effects by increasing midbrain synaptic concentrations of dopamine and norepinephrine by a combination of enhanced release and uptake inhibition.<sup>35-37</sup> However, dopamine release in the nucleus accumbens appears to be most involved in mediating the rewarding effects.<sup>38</sup> The amphetamines interact with several components of the monoamine synapse including the neuronal transporter (uptake transporter), vesicular storage system, and monoamine oxidase.<sup>39,40</sup> Reports indicate that these actions on the synapse are stereoselective, with the *d*-enantiomer being more potent than the *l*-enantiomer.<sup>12,13</sup>

The stereoisomers of methamphetamine produce markedly different dopamine, norepinephrine, and serotonin responses in various brain regions in rats.<sup>41,42</sup> *d*-Methamphetamine (2 mg/kg) is more potent in releasing caudate dopamine than *l*-methamphetamine (12 and 18 mg/kg). By use of in vitro uptake and release assays, *d*-methamphetamine (50% effective concentration [EC<sub>50</sub>], 24.5 ± 2.1 nmol/L) was 17 times more potent in releasing dopamine than *l*-methamphetamine (EC<sub>50</sub>, 416 ± 20 nmol/L) and significantly more potent in blocking dopamine uptake (inhibition constant [K<sub>i</sub>], 114 ± 11 nm versus 4840 ± 178 nm).<sup>12,13</sup>

These differences in dopamine release could explain the significantly greater subjective effects produced by *d*-methamphetamine (racemic and 0.5 mg/kg) compared with *l*-methamphetamine (0.5 mg/kg) on several measures (ie, "intoxication," "any drug effect," and "drug liking"). The effects of 0.5 mg/kg of *l*-methamphetamine were less than even a lower dose of *d*-meth-

amphetamine (0.25 mg/kg) for "drug liking." Furthermore, the subjective effects for *l*-methamphetamine dissipated relatively quickly, reaching baseline values at 3 hours after dosing compared with approximately 6 hours for *d*-methamphetamine. Peak ratings for arousal, elation, positive mood, and vigor were significantly higher for doses containing *d*-methamphetamine than for placebo and continued to increase over time, whereas *l*-methamphetamine (0.5 mg/kg) produced greater ratings only on arousal, which also dissipated rapidly (trough at 1.5 hours).

The report of Morgan<sup>11</sup> that the cardiovascular system is more affected by the *l*-isomer of amphetamine might lead us to expect a similar or greater cardiovascular response after *l*-methamphetamine. In contrast, all doses containing *d*-methamphetamine significantly increased systolic and diastolic blood pressure, heart rate, and rate-pressure product, whereas *l*-methamphetamine had significantly fewer cardiovascular effects. *d*-Methamphetamine may also activate  $\alpha$ -adrenergic receptors by releasing norepinephrine from peripheral sympathetic terminals via monoamine transport mechanisms. In vitro, *d*-methamphetamine's potency for norepinephrine release is twice that of *l*-methamphetamine, which may account for the greater cardiovascular effects that we observed in response to *d*-methamphetamine.<sup>13</sup> Previous reports in humans found that after *d*-methamphetamine administration, systolic blood pressure and diastolic blood pressure increase significantly.<sup>5</sup> We found that heart rate increases but only slightly and that rate-pressure product increases markedly as a result of the increased systolic blood pressure.<sup>5,6,43</sup>

In studies of a related stimulant-like drug, MDMA (ecstasy),<sup>44</sup> the ability of serotonergic antagonists to attenuate MDMA cardiovascular effects suggests that serotonin may play a role in this physiologic response.<sup>45,46</sup> The similar caudate serotonin levels for *d*-methamphetamine (2 mg/kg) and *l*-methamphetamine (12 mg/kg) found in rats could predict the relatively lower cardiovascular effect from *l*-methamphetamine found in our study.<sup>41</sup> In addition, increases in both behavioral and neurotransmitter response to *l*-methamphetamine are not dose-proportional,<sup>41</sup> so the relative effects of the *d*- and *l*-isomer may vary considerably with the doses administered.

Of interest, racemic methamphetamine had effects similar to those of the highest dose of *d*-methamphetamine. Because of the greater cardiovascular and subjective effects of the *d*-isomer, we would expect the racemic mixture (50:50) of *d*-methamphetamine/*l*-methamphetamine to be less rewarding as a psychostimu-

lant, yet our findings do not support this. There is no simple explanation of why racemic methamphetamine is often as potent as an equal quantity of *d*-methamphetamine. The AUC of *d*-methamphetamine or *l*-methamphetamine given as 0.25 mg/kg alone and the AUC of the same isomer when administered as 0.25 mg/kg in the racemic mixture were equivalent, suggesting similar pharmacologic effects between doses. However, racemic methamphetamine has more than an additive effect compared with the equivalent doses of *d*-methamphetamine/*l*-methamphetamine in the racemic mixture. One possible explanation is that differences may be a result of the metabolite *d*-amphetamine. Both subjective and cardiac effects of racemic methamphetamine were often similar to those of the dose containing more *d*-methamphetamine. In contrast, our lower dose of *d*-methamphetamine (0.25 mg/kg) was often similar to the high dose of *l*-methamphetamine (0.5 mg/kg) (Figs 4 and 5). This suggests that behavioral and cardiac activation by *l*-methamphetamine may be a result of differences in receptor dynamics or may be acting through different pathways or mechanisms than *d*-methamphetamine.

### Precursor regulation

Propelled by the methamphetamine epidemic, 20 states are considering legislation that would extend precursor regulation to pseudoephedrine, a drug used in many common OTC cold medicines. Although no one really knows exactly where illicit methamphetamine is produced, media reports suggest that most (80%) of the nation's methamphetamine is smuggled from Mexico or produced in large-scale laboratories. The rest is produced in small, often home-based laboratories that these new laws target.<sup>2,47</sup> Because large laboratories that probably do not rely on OTC cold medicines produce the majority of illicit methamphetamine, the proposed legislation may do little to reduce methamphetamine availability. For example, although seizures of small clandestine laboratories have decreased by 81% in Oklahoma, there are no reports indicating that the rate of illicit supply or abuse has fallen.<sup>2,47</sup> Furthermore, there are indications that pseudoephedrine is now being smuggled from Southeast Asia into the United States.<sup>48</sup> Before further attempts in precursor regulation are promulgated, we believe it is critical to understand the expected consequences of likely changes in precursors on methamphetamine pharmacologic and toxicologic characteristics. Most authorities believe that, in addition to decreasing supply through precursor regulation, treatment and prevention programs will be needed to reduce demand for methamphetamine.<sup>49</sup>

### Study limitations

There are limitations to our study. We investigated only the intravenous route of methamphetamine administration. Administration orally, nasally, or via smoking might result in other pharmacologic differences between the 2 enantiomers. We examined only 2 doses of *d*- and *l*-methamphetamine over a limited dose range; however, we achieved subjective and cardiovascular responses that were 25% to 50% of the maximum considered safe, and our low dose of *l*-methamphetamine had effects similar to those of placebo. Higher doses could be toxic and difficult to study safely, even under controlled laboratory conditions, and lower doses probably have minimal effects in partially tolerant abusers. We only investigated single intravenous doses. Because drug addicts often binge, the pharmacologic characteristics of repeated-dosing experiments may provide further insights. Finally, our primary interests were in methamphetamine and its active metabolite, amphetamine, in plasma. Other metabolic pathways such as *p*-hydroxylation and urinary excretion are also important but were not examined in this study.

### Conclusions

*d*-Methamphetamine, alone or as a racemate, produces more subjective and cardiovascular effects than equivalent doses of *l*-methamphetamine. Although a relatively large dose of *l*-methamphetamine produced similar peak subjective and cardiovascular effects, they dissipated more rapidly. The enantiomer-specific difference in *d*-amphetamine disposition and the greater dopamine and serotonin responses in animals with *d*-methamphetamine suggest pharmacologic mechanisms for the differences in response observed with the isomers.<sup>12,13,41</sup> On the basis of our data, we predict that racemic methamphetamine will have an abuse potential similar to that for *d*-methamphetamine. Fortunately, we would not predict a significant increase in behavioral or cardiovascular toxicity with abuse of racemic mixtures; *l*-methamphetamine does not appear to increase the toxic effects of *d*-methamphetamine. However, toxic effects may increase, especially under repeated-dosing conditions, because the stereoselective differences in the pharmacokinetics of *d*-methamphetamine, *l*-methamphetamine, and racemic methamphetamine may lead to an accumulation of *l*-methamphetamine. The health risks (if any) associated with this remain to be identified. With the assumption that illicit producers will switch precursors (as they have in the past) and racemic methamphetamine will become widely available, it is unlikely that this different form of the drug will increase the rates of abuse or toxic effects. Accordingly,

the potential benefits of precursor control need to be weighed against the burdens of regulation.

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