Published in final edited form as:

Pharmacol Biochem Behav. 2016 February ; 141: 58–65. doi:10.1016/j.pbb.2015.12.001.

Relationship between discriminative stimulus effects and plasma methamphetamine and amphetamine levels of intramuscular methamphetamine in male rhesus monkeys

Matthew L. Banks^{1,2}, Douglas A. Smith¹, David F. Kisor³, and Justin L. Poklis¹

¹Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA USA 23298

²Institute for Drug and Alcohol Studies, Virginia Commonwealth University, Richmond, VA

³Department of Pharmaceutical Sciences, Manchester University College of Pharmacy, North Manchester, IN USA 46962

Abstract

Methamphetamine is a globally abused drug that is metabolized to amphetamine, which also produces abuse-related behavioral effects. However, the contributing role of methamphetamine metabolism to amphetamine in methamphetamine's abuse-related subjective effects is unknown. This preclinical study was designed to determine 1) the relationship between plasma methamphetamine levels and methamphetamine discriminative stimulus effects and 2) the contribution of the methamphetamine metabolite amphetamine in the discriminative stimulus effects of methamphetamine in rhesus monkeys. Adult male rhesus monkeys (n=3) were trained to discriminate 0.18 mg/kg intramuscular (+)-methamphetamine from saline in a two-key food-reinforced discrimination procedure. Time course of saline, (+)-methamphetamine (0.032-0.32 mg/kg), and (+)-amphetamine (0.032-0.32 mg/kg) discriminative stimulus effects were determined. Parallel pharmacokinetic studies were conducted in the same monkeys to determine plasma methamphetamine and amphetamine levels after methamphetamine administration and amphetamine levels after amphetamine administration for correlation with behavior in the discrimination procedure. Both methamphetamine and amphetamine produced full, 90%, methamphetamine-like discriminative stimulus effects. Amphetamine displayed a slightly, but significantly, longer duration of action than methamphetamine in the discrimination procedure. Both methamphetamine and amphetamine behavioral effects were related to methamphetamine and amphetamine plasma levels by a clockwise hysteresis loop indicating acute tolerance had

Corresponding Author: Matthew L. Banks, PharmD, PhD, Department of Pharmacology and Toxicology, Virginia Commonwealth University, 410 N. 12th St. PO Box 980613, Richmond, VA 23298, Matthew.Banks@vcuhealth.org, Phone: 804-828-8466, Fax: 804-828-2117.

Authorship Contribution: Participated in research design: Banks

Conducted experiments: Smith, Poklis

Performed data analysis: Banks, Kisor

Wrote or contributed to the writing of the manuscript: Banks, Smith, Kisor, and Poklis

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

developed to the discriminative stimulus effects. Furthermore, amphetamine levels after methamphetamine administration were absent when methamphetamine stimulus effects were greatest and peaked when methamphetamine discriminative stimulus effects returned to saline-like levels. Overall, these results demonstrate the methamphetamine metabolite amphetamine does not contribute to methamphetamine's abuse-related subjective effects.

Graphical abstract

Keywords

methamphetamine; amphetamine; drug discrimination; rhesus monkey; pharmacokinetics; hysteresis

1.0 Introduction

According to the most recent 2014 World Drug Report published by the United Nations Office on Drugs and Crime, methamphetamine accounted for 80% of all amphetamine-type stimulant seizures (UNODC, 2014). Furthermore, the 2014 United States National Forensic Laboratory Information System midyear report estimates that methamphetamine ranks second behind cannabis/THC and above cocaine in both number and percentage of total drugs submitted for analysis (Drug Enforcement Administration, 2014). These epidemiological results support public health concerns regarding the prevalence and significance of methamphetamine abuse and addiction. Moreover, these epidemiological results suggest a need for preclinical studies to improve our mechanistic understanding of methamphetamine abuse-related effects.

Using positron emission tomography in humans, ^{11}C -(+)-methamphetamine uptake and clearance from the central nervous system was examined (Fowler *et al.*, 2008). Furthermore, this time course of radiolabeled methamphetamine correlated with the time course of verbal 'high' reports after methamphetamine administration suggesting that methamphetamine uptake into the central nervous system is responsible for the abuse-related subjective effects (Newton *et al.*, 2006). Consistent with these imaging results, plasma methamphetamine levels also correlate with methamphetamine subjective effects in humans (Cook *et al.*, 1993). Overall, these human results suggest that plasma methamphetamine levels are the

primary mediator of methamphetamine's abuse-related behavioral effects. However, methamphetamine is metabolized to amphetamine, another known abused drug, in humans (Cook *et al.*, 1993, Huestis and Cone, 2007) and the degree to which amphetamine levels might contribute to methamphetamine's abuse-related behavioral effects is unknown.

Preclinical drug discrimination procedures are hypothesized to model the subjective-like drug effects in humans (Fischman and Foltin, 1991, Schuster and Johanson, 1988). Although the use of preclinical drug discrimination procedures appears to be diminishing (McMahon, 2015), these procedures are particularly useful, compared to drug self-administration procedures, for understanding the relationship between abuse-related behavioral effects as a consequence of changing plasma drug levels (Banks *et al.*, 2013, Banks *et al.*, 2015, Lamas *et al.*, 1995). For example, a clockwise hysteresis loop related plasma cocaine levels and cocaine discriminative stimulus effects suggesting cocaine levels were the primary mediator of the behavioral effects (Lamas *et al.*, 1995). In contrast, a counter-clockwise hysteresis loop related plasma amphetamine levels and cocaine-like discriminative stimulus effects after lisdexamfetamine administration suggesting that amphetamine, and not lisdexamfetamine, levels were the primary mediator of the behavioral effects (Banks *et al.*, 2015). Given that methamphetamine is metabolized to amphetamine, the degree to which methamphetamine or amphetamine levels contribute to the methamphetamine discriminative stimulus effects remains to be empirically determined.

The present study was designed to address two main aims. The first aim was to ascertain, using a reverse translational approach, whether plasma methamphetamine levels correlated with methamphetamine discriminative stimulus effects in a preclinical model of human subjective-like effects. If preclinical discrimination procedures were predictive of human subjective drug effects, then we would predict a concordant behavioral and pharmacokinetic relationship. However, this hypothesis has not been directly tested for methamphetamine. A second aim was also to determine whether the methamphetamine metabolite amphetamine contributed to the methamphetamine discriminative stimulus effects. To the best of our knowledge, there are no human or preclinical studies that have determined the role of the methamphetamine metabolite amphetamine in methamphetamine-induced behavioral effects. If methamphetamine metabolism to amphetamine contributed to or mediated the discriminative stimulus effects of methamphetamine in rhesus monkeys, we would predict a counter-clockwise hysteresis loop (Louizos *et al.*, 2014) between methamphetamine-like discriminative stimulus effects and amphetamine plasma levels similar to a counter-clockwise hysteresis loop between cocaine-like discriminative stimulus effects and amphetamine plasma levels after lisdexamfetamine administration (Banks *et al.*, 2015).

2.0 Methods

2.1 Subjects

Three adult male rhesus monkeys (*Macaca mulatta*) weighing between 6-11 kg served as research subjects. Two monkeys (M1510 and M1511) were experimental naïve at the start of methamphetamine discrimination training and one monkey (M1479) had a previous history of responding under a two-key food-reinforced cocaine vs. saline discrimination procedure. However, this monkey had not participated in cocaine discrimination studies for

at least 3 months before initiating methamphetamine discrimination training. Although there are reports of retained drug discriminations following sequential training (Li and McMillan, 2003, McMillan *et al.*, 1996), the influence of this previous cocaine discrimination should be minimal for the proposed experiments given the shared pharmacological discriminative stimulus mechanisms between cocaine and methamphetamine or amphetamine (Kamien and Woolverton, 1989, Kleven *et al.*, 1990, Negus *et al.*, 2007). The monkeys diet consisted of food biscuits (Lab Diet® High Protein Monkey Biscuits, PMI Feeds, Inc. St. Louis, MO) supplemented with fresh fruit. Water was continuously available in the home chamber. Additionally, monkeys could earn 1-g banana-flavored food pellets (5TUR grain-based precision primate tablets, Test Diets, Richmond, IL) during daily experimental sessions (described below). A 12h light-dark cycle was in effect (lights on from 6AM to 6PM), and temperature and humidity levels were controlled and monitored daily. Environmental enrichment consisting of various puzzles, foraging devices in addition to videos or radio was provided during the week at the conclusion of the behavioral sessions. Animal research facilities were licensed by the United States Department of Agriculture and accredited the Association for Assessment and Accreditation of Laboratory Animal Care. The Institutional Animal Care and Use Committee approved both experimental and environmental enrichment protocols.

2.2 Methamphetamine Discrimination Procedure

Experimental behavioral sessions were conducted in each monkey's home chamber. On the front wall of each chamber was an operant response panel that included three square response keys arranged horizontally and only the left and right keys were used in the present studies. Attached to each panel was a pellet dispenser (Med Associates, ENV-203-1000, St. Albans, VT). Equipment operation and data collection were accomplished with a Windows-based computer and MED-PC IV software (Med Associates).

Monkeys were initially trained to discriminate 0.1 mg/kg intramuscular (IM) methamphetamine from saline in a two-key, food-reinforced drug discrimination procedure. However, none of the monkeys met accurate discrimination criterion after 136 training sessions and thus the methamphetamine-training dose was increased to 0.18 mg/kg. All monkeys met discrimination criterion within 73 sessions (range 63-73) after increasing the methamphetamine dose. Discrimination training was conducted 5 days per week during daily sessions composed of two components. Each component consisted of a 5-minute response period, during which the right and left response keys were transilluminated red and green, respectively, and monkeys could earn up to 10 pellets by responding under a fixed-ratio (FR) 30 schedule of food presentation. Training sessions were composed of two components presented at 3-h intervals, and either saline or (0.18 mg/kg methamphetamine) was administered IM approximately 15 min prior to the start of each component. Thus, on training days, monkeys would receive a sequence of saline (S) and methamphetamine (M) injections in the order SS, SM, MS, or MM. These training sequences were randomly presented. The goal of this training regimen was to engender daily experience with randomized sequences of saline- and methamphetamine-appropriate components. The 3h duration of inter-component intervals was selected to exceed the time course of discriminative stimulus effects produced by the methamphetamine-training dose in rhesus

monkeys (unpublished results) and to thereby minimize effects of methamphetamine administered in earlier trials on performance during later trials on the same day. Following administration of saline, only responding on the green key (the saline-appropriate key) produced food, whereas following administration of 0.18 mg/kg methamphetamine, only responding on the red key (the methamphetamine-appropriate key) produced food. Responses on the inappropriate key reset the FR requirement on the appropriate key. The criterion for accurate discrimination was 85% injection-appropriate responding before delivery of the first reinforcer, 90% injection-appropriate responding for the entire component, and response rates 0.1 responses/s (sufficient to earn at least one pellet) for all components during 7 of 8 consecutive sessions.

Time course test sessions were identical to training sessions except (1) completing the response requirement on either key produced food and (2) 5-min response components began 10, 30, 56, 100, 180, 300, and 560 min after injection to assess the time course of drug effects. Saline, (+)-methamphetamine (0.032-0.32 mg/kg) and (+)-amphetamine (0.032-0.32 mg/kg) were tested in a randomized order. Test sessions were separated by at least 3 days, and were usually conducted on Tuesdays and Fridays, with training sessions conducted on other weekdays. Test sessions were conducted only if performance during the previous two training sessions met the criteria for accurate discrimination described above.

On a separate day, a single 5-min behavioral test session was conducted to determine the discriminative-stimulus effects of methamphetamine and amphetamine following a 3 min pretreatment. This experiment was conducted to correlate behavioral effects with plasma methamphetamine and amphetamine levels at the 3-min time point.

2.3 Plasma methamphetamine and amphetamine analysis

Blood samples (2-3mLs) were collected from the same three discrimination monkeys trained to sit calmly in custom restraint chairs as previously described (Banks *et al*, 2013). Samples were immediately transferred to Vacutainer© tubes containing 3.0 mg of sodium fluoride and 6.0 mg Na₂EDTA before and 3, 10, 30, 56, 100, 180, and 300 min after 0.32 mg/kg (IM) methamphetamine or 0.32 mg/kg (IM) amphetamine administration. Samples were immediately centrifuged at 1000g for 10 min. The plasma supernatant was transferred into a labeled storage tube and frozen at -80°C until analyzed. Amphetamine and methamphetamine were isolated by liquid/liquid extraction and analyzed using liquid chromatography coupled to gas chromatography and mass spectrometry as previously described (Poklis and Moore, 1995). Plasma amphetamine and methamphetamine levels were determined by linear regression based on the standard curve.

2.4 Data Analysis

The primary dependent measures were (1) percent methamphetamine-appropriate responding (%MAR) {defined as (number of responses on the methamphetamine-associated key divided by the total number of responses on both the methamphetamine-and saline-associated keys)*100}, and (2) response rates during each component. These dependent measures were then plotted as a function of time after drug or saline administration.

Pharmacokinetic parameters after 0.32 mg/kg (+)-methamphetamine or (+)-amphetamine administration were estimated using a one-compartment extravascular model and assuming no lag time for which an intramuscular dose route could be applied (WinNonlin version 2.1, Pharmsight, Princeton, NJ). In addition, a hysteresis analysis was conducted by plotting %MAR as a function of plasma methamphetamine or amphetamine levels (ng/mL) after (+)-methamphetamine administration. Hysteresis analysis was also conducted examining the relationship between amphetamine levels and methamphetamine-like discriminative stimulus effects after (+)-amphetamine administration at all time points.

2.5 Drugs

(+)-Methamphetamine HCl was provided by the National Institute on Drug Abuse Drug Supply Program (Bethesda, MD). (+)-Amphetamine hemisulfate was purchased from commercial supplier (Sigma Aldrich, St. Louis, MO). All drug doses were dissolved in sterile water, passed through a 0.2 μ m sterile filter (Millipore, Billerica, MA) and are expressed as the salt forms listed above.

3.0 Results

3.1 Discriminative stimulus effects of methamphetamine and amphetamine

On all training days that preceded test days, monkeys responded exclusively on the methamphetamine-appropriate key during methamphetamine training components (mean $\pm$ SEM: 100 $\pm$ 0) and exclusively on the saline-appropriate key during saline training components (100 $\pm$ 0). Mean ($\pm$ SEM) response rates were 2.5 ($\pm$ 0.4) and 2.3 ($\pm$ 0.4) responses per second during methamphetamine and saline training components, respectively. Figures 1 and 2 show individual subject (Panels A-C) and group (Panel D) data for the time course of saline, methamphetamine (Figure 1), and amphetamine (Figure 2) to produce methamphetamine-appropriate responding. Saline administration produced 10% MAR at all time points and in all test sessions. 0.32 mg/kg was the lowest methamphetamine and amphetamine dose to produce full substitution, defined as 90% MAR, in all three monkeys and as a result, this was the dose chosen for the pharmacokinetic studies. There was no significant effect of methamphetamine or amphetamine on rates of operant responding (Supplemental Figure 1).

3.2 Plasma methamphetamine and amphetamine levels after methamphetamine administration

Figure 3 shows individual (Panels A-C) and group (Panel D) mean $\pm$ SEM plasma methamphetamine levels as a function time after 0.32 mg/kg IM methamphetamine administration. For comparison, individual (Panels A-C) and group (Panel D) mean $\pm$ SEM plasma amphetamine levels as a function of time after 0.32 mg/kg IM amphetamine administration are shown in Figure 4. Table 1 shows the mean estimated pharmacokinetic parameters of methamphetamine and amphetamine. Peak methamphetamine levels ranged from 38.7 to 67.5 ng/mL (mean $\pm$ SEM, 51.0 $\pm$ 8.5) and levels peaked at 10 min in two monkeys and 56 min in one monkey. In contrast, amphetamine levels after methamphetamine administration were below the lower limit of detection until 56 min and peaked at 180 min in one monkey and 300 min in two monkeys. Peak amphetamine levels

ranged from 31.3 to 42.9 ng/mL (mean $\pm$ SEM, 37.2 $\pm$ 3.3), and peaked at 10 min for one monkey and 30 min for the other two monkeys after amphetamine administration.

Figure 5 shows a clockwise hysteresis loop of methamphetamine discriminative stimulus effects after 0.32 mg/kg IM methamphetamine as a function of plasma methamphetamine levels for all three individual monkeys and the group means. Supplemental Figure 2 shows a clockwise hysteresis loop of methamphetamine-like discriminative stimulus effects after 0.32 mg/kg IM amphetamine as a function of plasma amphetamine levels.

4.0 Discussion

The aim of the present study was to determine the relationship between plasma methamphetamine levels and methamphetamine discriminative stimulus effects in rhesus monkeys. A secondary aim was to determine the role of the methamphetamine metabolite amphetamine in the discriminative stimulus effects of methamphetamine. There were two main findings. First, time course of methamphetamine plasma levels paralleled the time course of its discriminative stimulus effects and were characterized by a clockwise hysteresis loop. A similar clockwise hysteresis loop was also observed between plasma amphetamine levels and methamphetamine-like discriminative stimulus effects of amphetamine. Second, there was an inverse relationship between plasma amphetamine levels after methamphetamine administration and methamphetamine discriminative stimulus effects, such that when amphetamine levels were low or not detectable, monkeys were responding exclusively on the methamphetamine-associated key. When plasma amphetamine levels peaked at 300 min, responding was on the saline-associated key. Overall, these results do not support a significant role of the methamphetamine metabolite amphetamine in the discriminative stimulus effects of methamphetamine in rhesus monkeys.

The present study confirmed previous studies in pigeons (Sasaki *et al.*, 1995), rats (French and Witkin, 1993), squirrel monkeys (Tidey and Bergman, 1998), and humans (Sevak *et al.*, 2011) that methamphetamine functions as a discriminative stimulus and extended these previous findings to rhesus monkeys. Furthermore, the time course of methamphetamine discriminative stimulus effects was qualitatively similar to previous results reported in squirrel monkeys (Czoty *et al.*, 2004). Moreover, (+)-amphetamine and (+)-methamphetamine produced full methamphetamine-like discriminative stimulus effects at equipotent doses. The present results are also consistent with previous behavioral results demonstrating methamphetamine and amphetamine produce overlapping discriminative stimulus effects in humans (Lamb and Henningfield, 1994), monkeys (Woolverton and English, 1997), rats (Desai *et al.*, 2010), and pigeons (Li and McMillan, 2001) and consistent with a shared pharmacological mechanism between methamphetamine and amphetamine (Goodwin *et al.*, 2009).

Curiously, (+)-amphetamine displayed a slight, but significant, longer duration of action than (+)-methamphetamine in the discrimination procedure. One potential explanation for the longer amphetamine time course could be related to the apparent longer elimination half-life of amphetamine compared to methamphetamine. Previous human drug discrimination studies with amphetamine and methamphetamine have not reported time course of drug

effects (Lamb and Henningfield, 1994, Sevak *et al.*, 2009), thus precluding a direct comparison between previous human results and the present results. Previous rat studies comparing (+)-methamphetamine and (+)-amphetamine on both neurochemical and behavioral endpoints have demonstrated either similar (Bauer *et al.*, 2013, Melega *et al.*, 1995, Shoblock *et al.*, 2003) or prolonged (Shoblock *et al.*, 2003) pharmacodynamic effects of amphetamine compared to methamphetamine. Overall, the present results are consistent with and extend the scientific literature to drug discrimination studies in nonhuman primates suggesting potential pharmacodynamic differences between amphetamine and methamphetamine.

To the best of our knowledge, pharmacokinetic parameters have not been previously reported for either methamphetamine or amphetamine in rhesus monkeys and the individual variability in methamphetamine metabolism in monkeys parallels the individual variability in humans (Li *et al.*, 2010). Pharmacokinetic parameters for both methamphetamine and amphetamine were estimated using a one-compartment model consistent with previously published rat (Segal and Kuczenski, 2005) and human (Cook *et al.*, 1993) studies. Although other pharmacokinetic models have been utilized to describe methamphetamine pharmacokinetics (Li *et al.*, 2010, Newton *et al.*, 2005), a comparison of different models revealed the one-compartment model used in the present study provided the best fit. The methamphetamine half-life (195 min; 3.2 h) in the present study was in-between previously reported half-lives in adult rats (~1 h) (Hutchaleelaha and Mayersohn, 1996, Rivière *et al.*, 1999) and adult humans (9-12 h) (Cook *et al.*, 1993, Mendelson *et al.*, 1995, Newton *et al.*, 2005). Similar to methamphetamine, the amphetamine half-life (282 min; 4.7 h) in the present study was between the reported half-life of amphetamine in adult rats (~1 h) (Hutchaleelaha *et al.*, 1994, Rowley *et al.*, 2012) and adult humans (12 h) (Rowland, 1969, Wong *et al.*, 1998). However, in children (Brown *et al.*, 1979), amphetamine has a reported a half-life of 6.8 h. Thus, based on this one pharmacokinetic parameter, the present results may suggest that amphetamine and methamphetamine metabolism in the rhesus monkey approximates children more so than adults.

Unexpectedly, plasma amphetamine levels after methamphetamine administration were below the lower limit of detection until 56 min and peaked around 180-300 min post methamphetamine. The slow rise of amphetamine levels after methamphetamine administration in the present study is consistent with previous human pharmacokinetic studies with amphetamine levels peaking between 10 and 24 hours after methamphetamine and still detectable after 48 hours (Cook *et al.*, 1993). Although amphetamine is the primary methamphetamine metabolite in humans, other potential metabolites include *para*-hydroxymethamphetamine and *N*-hydroxymethamphetamine (Li *et al.*, 2010). Although these two other potential metabolites were not directly measured in the present study, *para*-hydroxymethamphetamine levels were approximately three-fold less than amphetamine levels in humans (Li *et al.*, 2010). Thus, given the non-detectable amphetamine levels reported in the present study when methamphetamine discriminative stimulus effects were greatest, the likelihood of one of these other metabolites contributing to the methamphetamine discriminative stimulus effects appears to be minimal, but remains to be empirically determined.

Plasma methamphetamine and amphetamine levels mostly paralleled the methamphetamine-like discriminative stimulus effects of both compounds. However, both plasma methamphetamine and amphetamine levels persisted longer than the discriminative stimulus effects. Furthermore, in the case of methamphetamine, plasma amphetamine levels peaked at 300 min post-methamphetamine administration when responding was predominantly on the saline-associated key. These findings, together with a clockwise hysteresis loop (Louizos *et al.*, 2014) suggest that acute tolerance may have developed to the methamphetamine-like discriminative stimulus effects after both methamphetamine and amphetamine administration. Acute tolerance to the behavioral and cardiovascular effects of methamphetamine and amphetamine has also been reported in humans (Angrist *et al.*, 1987, Brauer *et al.*, 1996, Kirkpatrick *et al.*, 2012) and dogs (Vidrio, 1982). Overall, the present results suggest that not only are absolute methamphetamine or amphetamine levels important for producing behavioral effects, but also the direction of changes in plasma levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We acknowledge the technical assistance of Crystal Reyns and Kevin Costa for coding the original version of the behavioral program.

Funding and Disclosures: Research reported in this publication was supported by the National Institute on Drug Abuse of the National Institutes of Health under Award Numbers R01DA031718 and P30DA033934. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

- Administration Drug Enforcement. National Forensic Laboratory Information System Special Report: Synthetic cannabinoids and synthetic cathinones reported in NFLIS, 2010-2013. Office of Diversion Control, Department of Justice; Springfield, VA: 2014.
- Angrist B, Corwin J, Bartlik B, Cooper T. Early pharmacokinetics and clinical effects of oral D-amphetamine in normal subjects. *Biol Psychiatry*. 1987; 22:1357–68. [PubMed: 3663788]
- Banks ML, Blough BE, Fennell TR, Snyder RW, Negus SS. Role of phenmetrazine as an active metabolite of phendimetrazine: Evidence from studies of drug discrimination and pharmacokinetics in rhesus monkeys. *Drug Alcohol Depend*. 2013; 130:158–66. [PubMed: 23211394]
- Banks ML, Hutsell BA, Blough BE, Poklis JL, Negus SS. Preclinical assessment of lisdexamfetamine as an agonist medication candidate for cocaine addiction: Effects in rhesus monkeys trained to discriminate cocaine or to self-administer cocaine in a cocaine versus food choice procedure. *Int J Neuropsychopharmacol*. 2015; 18 pii: pyv009.
- Bauer CT, Banks ML, Blough BE, Negus SS. Use of intracranial self-stimulation to evaluate abuse-related and abuse-limiting effects of monoamine releasers in rats. *Br J Pharmacol*. 2013; 168:850–62. [PubMed: 22978626]
- Brauer LH, Ambre J, De Wit H. Acute tolerance to subjective but not cardiovascular effects of d-amphetamine in normal, healthy men. *J Clin Psychopharmacol*. 1996; 16:72–6. [PubMed: 8834422]
- Brown G, Hunt R, Ebert M, Bunney W Jr, Kopin I. Plasma levels of d-amphetamine in hyperactive children. *Psychopharmacology*. 1979; 62:133–40. [PubMed: 111276]

- Cook CE, Jeffcoat AR, Hill JM, Pugh DE, Patetta PK, Sadler BM, et al. Pharmacokinetics of methamphetamine self-administered to human subjects by smoking S-(+)-methamphetamine hydrochloride. *Drug Metab Dispos.* 1993; 21:717–23. [PubMed: 8104133]
- Czoty PW, Makriyannis A, Bergman J. Methamphetamine discrimination and in vivo microdialysis in squirrel monkeys. *Psychopharmacology.* 2004; 175:170–8. [PubMed: 15064912]
- Desai RI, Paronis CA, Martin J, Desai R, Bergman J. Monoaminergic psychomotor stimulants: Discriminative stimulus effects and dopamine efflux. *J Pharmacol Exp Ther.* 2010; 333:834–43. [PubMed: 20190012]
- Fischman MW, Foltin RW. Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. *Br J Addict.* 1991; 86:1563–70. [PubMed: 1786488]
- Fowler JS, Volkow ND, Logan J, Alexoff D, Telang F, Wang GJ, et al. Fast uptake and long-lasting binding of methamphetamine in the human brain: Comparison with cocaine. *NeuroImage.* 2008; 43:756–63. [PubMed: 18708148]
- French D, Witkin JM. Effects of the dopamine release inhibitor, CGS 10746B, on the locomotor stimulant and discriminative stimulus effects of cocaine and methamphetamine. *Pharmacol Biochem Behav.* 1993; 46:989–93. [PubMed: 8309980]
- Goodwin JS, Larson GA, Swant J, Sen N, Javitch JA, Zahniser NR, et al. Amphetamine and methamphetamine differentially affect dopamine transporters in vitro and in vivo. *J Biol Chem.* 2009; 284:2978–89. [PubMed: 19047053]
- Huestis MA, Cone EJ. Methamphetamine disposition in oral fluid, plasma, and urine. *Ann N Y Acad Sci.* 2007; 1098:104–21. [PubMed: 17332086]
- Hutchaleelaha A, Mayersohn M. Influence of activated charcoal on the disposition kinetics of methamphetamine enantiomers in the rat following intravenous dosing. *J Pharm Sci.* 1996; 85:541–5. [PubMed: 8742948]
- Hutchaleelaha A, Sukbuntherng J, Chow HH, Mayersohn M. Disposition kinetics of d- and l-amphetamine following intravenous administration of racemic amphetamine to rats. *Drug Metab Dispos.* 1994; 22:406–11. [PubMed: 8070317]
- Kamien JB, Woolverton WL. A pharmacological analysis of the discriminative stimulus properties of d-amphetamine in rhesus monkeys. *J Pharmacol Exp Ther.* 1989; 248:938–46. [PubMed: 2649658]
- Kirkpatrick M, Gunderson E, Levin F, Foltin R, Hart C. Acute and residual interactive effects of repeated administrations of oral methamphetamine and alcohol in humans. *Psychopharmacology.* 2012; 219:191–204. [PubMed: 21748253]
- Kleven MS, Anthony EW, Woolverton WL. Pharmacological characterization of the discriminative stimulus effects of cocaine in rhesus monkeys. *J Pharmacol Exp Ther.* 1990; 254:312–7. [PubMed: 2195158]
- Lamas X, Negus SS, Hall E, Mello NK. Relationship between the discriminative stimulus effects and plasma concentrations of intramuscular cocaine in rhesus monkeys. *Psychopharmacology.* 1995; 121:331–8. [PubMed: 8584615]
- Lamb RJ, Henningfield JE. Human d-amphetamine drug discrimination: methamphetamine and hydromorphone. *J Exp Anal Behav.* 1994; 61:169–80. [PubMed: 7513346]
- Li L, Everhart T, Jacob Iii P, Jones R, Mendelson J. Stereoselectivity in the human metabolism of methamphetamine. *Br J Clin Pharmacol.* 2010; 69:187–92. [PubMed: 20233182]
- Li M, McMillan DE. Four-choice drug discrimination in pigeons. *Behav Pharmacol.* 2001; 12:621–8. [PubMed: 11856899]
- Li M, McMillan DE. Retention of sequential drug discriminations under fixed-interval schedules for long time periods without training. *Eur J Pharmacol.* 2003; 476:79–85. [PubMed: 12969752]
- Louizos C, Yanez JA, Forrest ML, Davies NM. Understanding the hysteresis loop conundrum in pharmacokinetic/pharmacodynamic relationships. *J Pharm Pharm Sci.* 2014; 17:34–91. [PubMed: 24735761]
- McMahon L. The rise (and fall?) of drug discrimination research. *Drug Alcohol Depend.* 2015; 151:284–8. [PubMed: 26207268]
- McMillan DE, Sun WL, Hardwick WC. Effects of drug discrimination history on the generalization of pentobarbital to other drugs. *J Pharmacol Exp Ther.* 1996; 278:50–61. [PubMed: 8764335]

- Melega WP, Williams AE, Schmitz DA, DiStefano EW, Cho AK. Pharmacokinetic and pharmacodynamic analysis of the actions of D-amphetamine and D-methamphetamine on the dopamine terminal. *J Pharmacol Exp Ther*. 1995; 274:90–6. [PubMed: 7616454]
- Mendelson J, Jones RT, Upton R, Jacob P. Methamphetamine and ethanol interactions in humans. *Clin Pharmacol Ther*. 1995; 57:559–68. [PubMed: 7768079]
- Negus SS, Mello NK, Blough BE, Baumann MH, Rothman RB. Monoamine releasers with varying selectivity for dopamine/norepinephrine versus serotonin release as candidate “agonist” medications for cocaine dependence: Studies in assays of cocaine discrimination and cocaine self-administration in rhesus monkeys. *J Pharmacol Exp Ther*. 2007; 320:627–36. [PubMed: 17071819]
- Newton T, Roache J, De La Garza R, Fong T, Wallace C, Li SH, et al. Safety of intravenous methamphetamine administration during treatment with bupropion. *Psychopharmacology*. 2005; 182:426–35. [PubMed: 16163531]
- Newton TF, Roache JD, De La Garza R II, Fong T, Wallace CL, Li SH, et al. Bupropion Reduces Methamphetamine-induced subjective effects and cue-induced craving. *Neuropsychopharmacology*. 2006; 31:1537–44. [PubMed: 16319910]
- Poklis A, Moore KA. Stereoselectivity of the TDxADx/FLx Amphetamine/Methamphetamine II amphetamine/methamphetamine immunoassay—response of urine specimens following nasal inhaler use. *J Toxicol Clin Toxicol*. 1995; 33:35–41. [PubMed: 7837311]
- Rivière GJ, Byrnes KA, Gentry WB, Owens SM. Spontaneous locomotor activity and pharmacokinetics of intravenous methamphetamine and its metabolite amphetamine in the rat. *J Pharmacol Exp Ther*. 1999; 291:1220–6. [PubMed: 10565845]
- Rowland M. Amphetamine blood and urine levels in man. *J Pharm Sci*. 1969; 58:508–9. [PubMed: 5787465]
- Rowley HL, Kulkarni R, Gosden J, Brammer R, Hackett D, Heal DJ. Lisdexamfetamine and immediate release d-amphetamine – Differences in pharmacokinetic/pharmacodynamic relationships revealed by striatal microdialysis in freely-moving rats with simultaneous determination of plasma drug concentrations and locomotor activity. *Neuropharmacology*. 2012; 63:1064–74. [PubMed: 22796358]
- Sasaki JE, Tatham TA, Barrett JE. The discriminative stimulus effects of methamphetamine in pigeons. *Psychopharmacology*. 1995; 120:303–10. [PubMed: 8524978]
- Schuster CR, Johanson CE. Relationship between the discriminative stimulus properties and subjective effects of drugs. *Psychopharmacol Ser*. 1988; 4:161–75. [PubMed: 3293041]
- Segal DS, Kuczenski R. Human Methamphetamine pharmacokinetics simulated in the rat: Single daily intravenous administration reveals elements of sensitization and tolerance. *Neuropsychopharmacology*. 2005; 31:941–55. [PubMed: 16123749]
- Sevak RJ, Stoops WW, Hays LR, Rush CR. Discriminative stimulus and subject-rated effects of methamphetamine, d-amphetamine, methylphenidate, and triazolam in methamphetamine-trained humans. *J Pharmacol Exp Ther*. 2009; 328:1007–18. [PubMed: 19104030]
- Sevak RJ, Vansickel AR, Stoops WW, Glaser PE, Hays LR, Rush CR. Discriminative-stimulus, subject-rated, and physiological effects of methamphetamine in humans pretreated with aripiprazole. *J Clin Psychopharmacol*. 2011; 31:470–80. [PubMed: 21694622]
- Shoblock J, Sullivan E, Maisonneuve I, Glick S. Neurochemical and behavioral differences between d-methamphetamine and d-amphetamine in rats. *Psychopharmacology*. 2003; 165:359–69. [PubMed: 12491026]
- Tidey JW, Bergman J. Drug Discrimination in methamphetamine-trained monkeys: Agonist and antagonist effects of dopaminergic drugs. *J Pharmacol Exp Ther*. 1998; 285:1163–74. [PubMed: 9618419]
- UNODC. World Drug Report 2013. Vienna: UNODC; 2014.
- Vidrio H. Cardiovascular effects of methamphetamine in dogs treated chronically with the amine. *J Cardiovasc Pharmacol*. 1982; 4:326–9. [PubMed: 6175818]
- Wong YN, Wang L, Hartman L, Simcoe D, Chen Y, Laughton W, et al. Comparison of the single-dose pharmacokinetics and tolerability of modafinil and dextroamphetamine administered alone or in combination in healthy male volunteers. *J Clin Pharmacol*. 1998; 38:971–8. [PubMed: 9807980]

Woolverton WL, English JA. Effects of some phenylethylamines in rhesus monkeys trained to discriminate (+)-amphetamine from saline. *Drug Alcohol Depend.* 1997; 44:79–85. [PubMed: 9088779]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Highlights

- METH and AMPH produced dose- and time-dependent discriminative stimulus effects
- A clockwise hysteresis loop related METH levels and METH stimulus effects
- METH metabolism to AMPH does not contribute to stimulus effects

Figure 1.

Potency and time course of the discriminative stimulus effects of (+)-methamphetamine (0.032-0.32 mg/kg, IM) in rhesus monkeys ($n=3$) trained to discrimination methamphetamine (0.18 mg/kg, IM) from saline. Top ordinates: percent methamphetamine-appropriate responding. Bottom ordinates: rates of responding in responses per second. Abscissae: time in min after injection (log scale). Symbols above "S" and "M" represent the averages for all training sessions preceding test sessions when the saline- and methamphetamine-associated keys were correct, respectively.

Figure 2.

Potency and time course of the discriminative stimulus effects of (+)-amphetamine (0.032-0.32 mg/kg, IM) in rhesus monkeys (n=3) trained to discrimination methamphetamine (0.18 mg/kg, IM) from saline. Top ordinates: percent methamphetamine-appropriate responding. Bottom ordinates: rates of responding in responses per second. Abscissae: time in min after injection (log scale). Symbols above "S" and "M" represent the averages for all training sessions preceding test sessions when the saline- and methamphetamine-associated keys were correct, respectively.

Figure 3.

Plasma methamphetamine levels (ng/mL) of as a function of time after administration of (+)-methamphetamine (0.32 mg/kg, IM; triangles) in rhesus monkeys (n=3). Ordinate: plasma levels in ng/mL. Abscissae: time in min after drug administration (log scale).

Figure 4.

Plasma amphetamine levels (ng/mL) of as a function of time after administration of (+)-methamphetamine (0.32 mg/kg, IM; triangles) or (+)-amphetamine (0.32 mg/kg, IM; squares) in rhesus monkeys (n=3). Ordinate: plasma levels in ng/mL. Abscissae: time in min after drug administration (log scale).

Figure 5.

Hysteresis plots of methamphetamine-appropriate responding in the discrimination procedure as a function of plasma methamphetamine levels after 0.32 mg/kg (+)-methamphetamine in rhesus monkeys (n=3). Symbols in Panel D represent group means and error bars are omitted for graphical clarity. The arrow direction indicates the relationship between plasma drug levels and methamphetamine-appropriate responding as a function of time.

Table 1

Estimated mean ($\pm$ SEM) pharmacokinetic parameters for (+)-methamphetamine and (+)-amphetamine after a single intramuscular dose (0.32 mg/kg) in rhesus monkeys (n=3). C_{max} maximum concentration, T_{max} time to reach maximum concentration, $AUC_{(0-\infty)}$ area under the curve extrapolated to infinity, $t_{1/2}$ elimination half-life, Vd apparent volume of distribution, Cl clearance. Experimental data were fitted to a one-compartment extravascular model. Data are the average for parameter values in individual monkeys.

	C_{max} (ng/mL)	T_{max} (min)	$AUC_{(0-\infty)}$ (ng/mL $\times$ min)	$t_{1/2}$ (min)	Vd (mL/kg)	Cl (mL/min)
Methamphetamine	51.0 ($\pm$ 8.5)	15.3 ($\pm$ 2.0)	13,634.9 ($\pm$ 3188.0)	195.2 ($\pm$ 75.6)	6.2 ($\pm$ 1.1)	0.026 ($\pm$ 0.005)
Amphetamine	37.2 ($\pm$ 3.3)	23.8 ($\pm$ 4.9)	14,889.6 ($\pm$ 5702.9)	282.2 ($\pm$ 144.7)	8.0 ($\pm$ 1.1)	0.027 ($\pm$ 0.008)