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Effects of *l*-methamphetamine treatment on cocaine- and food-maintained behavior in rhesus monkeys

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Abstract

Rationale—Monoamine releasers with prominent dopaminergic actions, e.g., d-methamphetamine (d-MA), significantly reduce cocaine use and craving in clinical and preclinical laboratory studies. However, d-MA and related drugs also display high abuse potential, which limits their acceptability as agonist replacement medications for the management of Cocaine Use Disorder.

Objectives—The l-isomer of methamphetamine (l-MA), unlike d-MA, has preferential noradrenergic actions and is used medicinally with low, if any, abuse liability. The present study was conducted to determine whether l-MA could serve as an agonist replacement medication by both mimicking interoceptive effects of cocaine and decreasing intravenous (IV) cocaine self-administration.

Methods—Separate groups (N=4-5) of rhesus monkeys were studied to determine whether l-MA could (1) substitute for cocaine in subjects that discriminated intramuscular (IM) cocaine (0.4 mg/kg) from saline and, (2) decrease IV cocaine self-administration under a second-order FR2(VR16:S) schedule of reinforcement.

Results—l-MA, like d-MA but with approximately 5-fold lesser potency, substituted for cocaine in drug discrimination experiments in a dose-dependent manner. In IV self-administration studies, 5-10 day treatments with continuously infused l-MA (0.032-0.32 mg/kg/hr, IV) dose-dependently decreased cocaine-maintained responding; the highest dosage reduced cocaine intake to levels of saline self-administration without appreciable effects on food-maintained responding.

Conclusions—These results indicate that l-MA both shares discriminative-stimulus effects with cocaine and reduces cocaine self-administration in a behaviorally selective manner. l-MA and other compounds with a similar pharmacological profile deserve further evaluation for the management of Cocaine Use Disorder.

Keywords

cocaine; self-administration; drug discrimination; dopamine; norepinephrine; agonist therapy

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Introduction

Cocaine abuse leading to addiction (i.e., Cocaine Use Disorder) is a significant public health problem (SAMHSA, 2011) for which no effective medications have been identified. Among medication treatment strategies, the approach of ‘agonist replacement’, which is employed in the management of opioid and nicotine addiction, has shown the most promise to date (Grabowski et al. 2004; Stoops and Rush 2013). This strategy is predicated on the idea that drug intake will be decreased by treatment with a pharmacologically similar drug. From the perspective of drug discovery and development, then, the goal of this strategy is to identify a candidate medication that shares pharmacological properties with the illicit drug but with lesser abuse-related and other adverse effects.

The search for such a medication for Cocaine Use Disorder has led to the close evaluation of indirect monoamine agonists. Relatively non-selective releasers of dopamine (DA) and norepinephrine (NE), such as d-amphetamine or d-methamphetamine (d-MA) have been especially promising in both preclinical and clinical studies (reviewed in Herin et al. 2010); however, their own abuse liability (reflected in Schedule II/III under the Controlled Substances Act) and other unwanted effects (e.g., increased cardiovascular response, disruptions to circadian rhythm) likely preclude their clinical application. A lack of behavioral selectivity also has been observed in laboratory studies in nonhuman primates: doses of nonselective DA/NE releasers that decreased cocaine self-administration, e.g., d-amphetamine, typically produced nonspecific and disruptive behavioral effects early in treatment and have well-recognized abuse liability (Negus and Mello 2003; Negus et al. 2007; Negus et al. 2009; Czoty et al. 2010b; Czoty et al. 2010a; Kohut et al. 2013a). Habituation to some but not all the disruptive effects of these drugs (and not to their abuse liability) occurs over the course of prolonged exposure. Thus, the long-term biological impact (i.e., altered receptor systems, changes in sensitivity to other drugs, etc.) of such treatment remains unclear, underscoring the need for medications with fewer nonspecific behavioral effects. It is interesting to note that, in this regard, preclinical and clinical data suggest that one of the most widely abused DA/NE releasers, d-MA, may have lesser nonspecific effects than d-amphetamine when evaluated as a treatment medication (Negus et al. 2009; Mooney et al. 2011).

The issue of abuse liability of indirect monoamine agonists with therapeutic utility (e.g., attention deficit hyperactivity disorder [ADHD]) has been addressed through formulation of pro-drugs and extended or sustained release preparations. However, even for such formulations, regulatory concerns regarding drugs with prominent dopaminergic actions are likely to remain a major obstacle to FDA approval for the treatment of Cocaine Use Disorder; see Henningfield perspective in (Negus and Henningfield 2014). This consideration highlights the strong practical advantage of candidate medications without d-amphetamine-like abuse potential.

The methamphetamine molecule consists of a chiral center that yields two isomers; d-MA and l-methamphetamine (l-MA). The d-isomer, the predominant isomer in illicit methamphetamine, is a Schedule II drug that is prescribed infrequently for the treatment of

ADHD and is associated with intense psychomotor stimulant and cardiovascular effects (Cunningham et al. 2013; Kirkpatrick et al. 2012). In contrast, the l-isomer, often referred to as the inactive isomer, is available over-the-counter as the active ingredient in the non-prescription nasal decongestant, Vick's VapoInhaler®. In keeping with such pharmaceutical distinctions, the two isomers have similar pharmacokinetic (Mendelson et al. 2006; Fowler et al. 2007; Li et al. 2010) but different pharmacodynamic profiles. Thus, the two isomers are relatively equipotent in releasing NE *in vitro*, whereas d-MA is approximately 15-fold more potent than l-MA in releasing DA (Rothman et al. 2001). Similarly, d-MA is about 20-fold more potent than l-MA in increasing DA efflux in striatum and hippocampus in *in vivo* microdialysis studies in rodents (Kuczenski et al. 1995; Melega et al. 1999).

In view of the purportedly greater safety (i.e., lesser stimulant action and abuse liability) of l-MA than d-MA, the present studies were conducted to investigate its potential utility as an agonist replacement medication for the management of Cocaine Use Disorder. First, cocaine drug discrimination studies were conducted to compare the relative potency of d- and l-MA for producing cocaine-like discriminative-stimulus effects. Subsequently, the effects of l-MA on cocaine- and food-maintained responding were examined by administering each of several doses on a continuous basis (23-hr daily infusion) for 5-10 days. This regimen was used to model a possible clinical requirement for chronic medication and to evaluate the stability of l-MA's effects during prolonged treatment.

Methods

Subjects

Adult male and female rhesus macaques (*Macaca mulatta*; 5-10 kg) had continuous access to water and were fed Lab Diet Jumbo Monkey Chow (PMI Feeds Inc., St. Louis, MO), fresh fruit, and vegetables daily. Monkeys also earned banana-flavored food pellets during daily experimental sessions (Formula 4TUR banana flavor, Purina Mills Test Diet, Richmond, IN). A 12 hr light-dark cycle was in effect (lights on 0800–2000 hr) throughout the study, except during experimental sessions (see below).

Animal maintenance and research procedures were conducted following guidelines provided by the Institute of Laboratory Animal Resources (ILAR-NRC, 2011) and the NIH Office of Laboratory Animal Welfare (OLAW). The facility is licensed by the U.S. Department of Agriculture and all protocols were approved by the McLean Hospital Institutional Animal Care and Use Committee. Physical health and well-being were monitored daily by trained staff and by the attending veterinarian. Monkeys had visual, auditory and olfactory contact with other members of the vivarium throughout the study. Enrichment was provided through play objects in the home-cage, frequent interactions with staff, and the opportunity to engage in consequential behavior during daily experimental sessions.

Drug Discrimination Procedures

Apparatus—All monkeys were housed in stainless steel chambers (56 × 71 × 69 cm) equipped with custom operant response panels (28 × 28 cm) mounted on the front wall. Operant panels contained three square translucent response keys (5.1 × 5.1 cm) arranged 3.5

cm apart in a horizontal row 9 cm from the top of the operant panel. Each key could be transilluminated with red or green stimulus lights (SuperBright LEDs; Fairchild Semiconductor, San Jose, CA). An externally mounted pellet dispenser (model G5210; Gerbrands, Arlington, MA) delivered 1 g banana-flavored food pellets to a food receptacle mounted on the front of the chamber beneath the operant response panel. All experimental events were controlled through custom programmed software (Med-PC) on a Hewlett-Packard (model 8100 Elite CMT PC) desktop PC located in a separate room and connected to the chambers via a Med Associates Interface (Georgia, VT).

Discrimination Training and Testing—Five adult male rhesus macaques were trained to discriminate intramuscular (IM) injections of cocaine (0.4 mg/kg) from saline (see Kohut et al. 2013a). Briefly, training sessions consisted of 1 to 3 cycles, and each cycle consisted of a 15 min time-out period followed by a 5 min response period. All injections were administered 10 min prior to the response period. During each response period, the right and left response keys were transilluminated red or green, and monkeys could earn up to 10 food pellets under a 30-response fixed ratio (FR30) schedule of reinforcement. Pressing the injection-inappropriate key prior to completing the fixed-ratio reset the count to zero. Fulfillment of the following criteria for at least four consecutive sessions was required before testing could begin: (1) 80% responses on the injection-appropriate key prior to completion of the first FR30; (2) 90% responses in each cycle on the injection-appropriate key, and (3) response rates ≥ 0.5 responses/sec.

Testing began when monkeys met criterion levels of performance. Test sessions were identical to training sessions except that 1) completing the FR requirement on either key produced food, and 2) doses of the test drug were administered using a cumulative dosing procedure under which graded doses were administered in sequential cycles of the test session. Pretreatment times were based on preliminary time-course studies (Kohut, unpublished) and previously published PET data showing similar distribution of d- and l-MA in baboon brain (Fowler et al, 2007). Although negative control data is not shown in the present study, subjects also had a history of testing with compounds from several drug classes; some of which produce cocaine-like responding, and some that do not.

Data Analysis—The principle dependent variables were percent injection-appropriate responses and response rate in responses/sec. The percentage of total responding that occurred on the cocaine-associated key was calculated for each cumulative dose. ED₅₀ values, defined as the dose of the test compound that engendered 50% responding on the cocaine-associated lever, were determined using log-linear interpolation with individual subject dose-effect curves. Log ED₅₀ values and corresponding confidence limits (CLs) were converted to linear values for data presentation. Full generalization was defined as 80% responding on the cocaine-associated key. Conversely, 20% responding on the cocaine-associated key defined the absence of cocaine-like discriminative stimulus effects. Response rates were calculated by dividing the total responses on both keys when the cue lights were illuminated by the total session time (in sec) and are expressed as responses per second.

Drug Self-Administration Procedures

Apparatus—Five cocaine-experienced adult rhesus macaques (2 males, 3 females) were housed in stainless steel chambers (64 × 64 × 79 cm) equipped with a custom-designed operant response panel described above for drug discrimination studies. A pellet dispenser (Gerbrands Model G5210, Arlington, MA) and two syringe pumps (Model 981210, Harvard Apparatus, Inc., South Natick, MA), one for each lumen of the double-lumen catheter, were mounted on shelving above the chamber. A food cup for food pellets, chow, and fruit/vegetables was attached to the lower left front of the chamber.

Self-Administration Training and Testing—The procedures used to study the effects of *l*-methamphetamine on cocaine- and food-maintained responding were identical to those used previously with other monoamine releasers (Negus and Mello 2003; Negus et al. 2007; Negus et al. 2009; Kohut et al. 2013a). After initial training to respond for food pellets, subjects were surgically prepared with chronic indwelling double-lumen catheters as described previously (Negus and Mello 2003). During daily sessions, subjects could earn a maximum of 100 food pellets and 80 cocaine or saline injections per day in four food and cocaine self-administration sessions. Each 2 hr session consisted of 1 hr of food and 1 hr of cocaine access. Food was available at 1100, 1500, 1900, and 0600 hr the following morning, and cocaine was available at 1200, 1600, 2000, and 0700 hr the next morning. During food components, a red light illuminating the center response key signaled the availability of 1-g banana-flavored food pellets under a Fixed Ratio 2; Variable Ratio 16 (FR2; VR16:S) second order schedule of reinforcement. Under this schedule, completion of the VR16 schedule produced a stimulus change by turning off the illuminated key light and turning on a cue-light below the response key of the corresponding color for 1-sec (stimulus flash), and the second stimulus flash was accompanied by food delivery. During cocaine self-administration components, a green light signaled cocaine availability, and completion of the response requirement on the center response key resulted in delivery of a cocaine solution computer-controlled variations in pump infusion duration (Kohut et al 2013a). A 10-sec TO period during which stimulus lights were turned off followed delivery of each food pellet or drug injection. If 25 food pellets or 20 cocaine injections were delivered before the end of the 1-hr session, all stimulus lights were turned off, and responding had no consequences for the remainder of that session.

Training continued until monkeys met the following criteria for stable food and cocaine responding: 1) three consecutive days during which the number of drug injections/day varied by no more than 20% of the three-day mean with no upward or downward trend in performance, and 2) the mean number of food pellets and injections delivered per day equaled or was greater than 60. Once responding was stable, self-administration of saline and several doses of cocaine (0.003 - 0.1 mg/kg/inj) were studied in a randomized order in each monkey. Each dose was substituted for 5-10 days until responding was stable (i.e., the number of drug injections/day across three consecutive days varied by no more than 20% of the three-day mean with no upward or downward trend in performance). Initial dose-ranging experiments usually were conducted for 7-10 days to permit an assessment of the stability of decreases in cocaine- or food-maintained responding over time and, also, an evaluation of possible tolerance to the effects of *l*-MA treatment. Following each substitution test,

monkeys were returned to the maintenance dose of cocaine, 0.01 mg/kg/inj, for at least three days or until responding was stable to ensure reliable baseline responding before the next substitution test.

When baseline values for IV cocaine self-administration were established for a full range of unit doses of cocaine, subjects were returned to the maintenance dose of cocaine, and l-MA treatment studies began. During this phase of study, saline or l-MA was infused IV every 20 minutes for 23-hr each day (1030 – 0930 hr). Each treatment dose of l-MA was studied for 5 – 10 days or until periods of continuous saline treatment that continued daily until drug- and food-maintained responding returned to stable baseline levels as described above for training criteria. Initially, the effects of a range of l-MA doses (0.032 – 0.32 mg/kg/hr) on IV self-administration of 0.01 mg/kg cocaine were studied. Next, two doses of l-MA (0.1 and 0.32 mg/kg/hr) were further evaluated during the self-administration of a range of IV cocaine doses in each monkey.

Data Analysis—The primary dependent variable was the total number of drug or saline injections and food pellets earned per session. In cocaine dose-effect studies, the number of injections self-administered and food pellets earned during the last three days of each treatment condition were averaged for individual subjects. Each data point in grouped results reflects data from 4 of the 5 subjects (one subject exhausted all catheter sites, necessitating its replacement in the remaining l-MA experiments). l-MA-induced changes in drug-maintained responding from values obtained during saline treatment were evaluated at each dose of cocaine using a two-way repeated measures analysis of variance (ANOVA) with factors of Cocaine Dose (0 – 0.1 mg/kg) and Treatment (saline and 0.1 or 0.32 mg/kg/hr) and Bonferroni multiple comparison post-hoc tests, where appropriate. The lowest dose of cocaine (0.0032 mg/kg) was not tested during treatment with the 0.32 mg/kg/hr treatment dose of l-MA and consequently, two separate ANOVAs were conducted. One-way ANOVAs with Dunnett's post -hoc test were also used to determine which doses of cocaine (0.003-0.1 mg/kg/inj) produced responding greater than saline self-administration during treatment with saline, 0.1, and 0.32 mg/kg/hr l-MA. Separate two-way ANOVAs with factors of Time (days 1-5) and Treatment (saline and 0.1 or 0.32 mg/kg/hr) were also conducted for food and cocaine self-administration to determine which day of treatment with either 0.1 or 0.32 mg/kg/hr l-MA differed from saline treatment. Significant ANOVAs were followed by Bonferroni multiple comparison post-hoc tests. All figures and statistical analyses were generated with GraphPad Prism for Macintosh (GraphPad Software Inc., USA).

Drugs—Cocaine HCl was provided by the National Institute on Drug Abuse, NIH (Rockville, MD, USA), d-MA hydrochloride was purchased from Sigma-Aldrich (St. Louis, MO), and Dr. B. Blough (RTI International) provided l-MA hydrochloride for these studies. All drugs were dissolved in saline vehicle. Cocaine and l-MA solutions used for self-administration studies were filtered with a 0.22-micron syringe-driven filter (Millipore Corporation, Billerica, MA). All drug doses are expressed as the salt.

Results

Drug Discrimination

Figure 1 shows substitution data for tests with cumulatively administered cocaine, d-MA, and l-MA in monkeys trained to discriminate 0.4 mg/kg cocaine from saline. During training sessions immediately preceding dose-effect determinations, monkeys responded almost exclusively on the saline-associated key when saline was administered ($99.38 \pm 0.45\%$ saline-like responding) and almost exclusively on the cocaine-associated key when the training dose of cocaine (0.4 mg/kg) was administered ($99.92 \pm 0.08\%$ cocaine-like responding). Mean response rates ($\pm$ S.E.M.) were 2.79 ± 0.25 and 2.79 ± 0.29 responses/sec during saline and cocaine training cycles, respectively. Each drug dose-dependently increased the percentage of responses on the cocaine-associated key. Cocaine and d-MA were equipotent and approximately 5-fold more potent than l-MA in substituting for the training dose of cocaine (ED_{50} values, respectively: 0.09 [95% CLs: 0.06 - 0.14] mg/kg, 0.08 [95% CLs: 0.05 - 0.14] mg/kg, and 0.45 [95% CLs: 0.35 - 0.58] mg/kg). Cocaine, d-, and l-MA did not alter response rates at doses that engendered full substitution for the training dose of cocaine.

Drug Self-Administration

Initial studies were conducted to establish control values for the self-administration of IV saline and several doses of IV cocaine during continuous saline treatment. When saline was available for IV self-administration, an average of 15.33 ± 4.07 saline injections were delivered throughout the four sessions of the day. When cocaine was available for IV self-administration, the number of injections increased in a dose-dependent manner, and the cocaine dose-effect curve described an inverted-U shaped function in all monkeys. Approximately 25% of the maximal number of available injections were taken (22.20 ± 7.59) when a low unit dose of cocaine (0.0032 mg/kg/inj) was available, whereas nearly all available injections of cocaine were self-administered when unit doses of 0.01 and 0.032 mg/kg/inj were available (78.67 ± 1.17 and 75.53 ± 2.28 injections, respectively). Approximately 65% of the maximal number of possible injections (53.67 ± 3.49) were self-administered during availability of the highest unit dose of cocaine (0.1 mg/kg/inj). A repeated measures one-way ANOVA ($F(4,16)=55.22$; $p<0.0001$) with Dunnet's post-hoc test confirmed that unit doses of 0.01, 0.032, and 0.1 mg/kg cocaine were self-administered at significantly greater levels than saline (all p 's <0.0001). Food-maintained responding under the second-order schedule remained at or near maximal levels throughout IV cocaine dose-effect determinations.

Mean data for the first 5 days of treatment with saline and the effects of several dosages of l-MA on cocaine- (0.01 mg/kg/inj) and food-maintained responding are shown in Figure 2. As shown, cocaine- and food-maintained responding remained at maximal levels on each day of treatment with saline and 0.032 mg/kg/hr l-MA. However, cocaine self-administration declined significantly during treatment with 0.1 mg/kg/hr l-MA, as revealed by a two-way ANOVA showing a significant main effect of Time ($F(4,12)=9.632$; $p=0.001$) and a significant Time $\times$ Treatment interaction ($F(4,12)= 6.104$; $p=0.006$). Bonferroni post-hoc tests confirmed that cocaine self-administration was significantly reduced from control

values on days 2-5 of treatment with 0.1 mg/kg/hr of l-MA (all p 's < 0.01). Similarly, a two-way ANOVA comparing cocaine self-administration during control conditions (saline treatment) and 5-day continuous treatment with 0.32 mg/kg/hr of l-MA found significant main effects of Time ($F(4,12)=11.30$; $p=0.0005$), Treatment ($F(1,3)=99.51$; $p=0.0021$), and a significant Time $\times$ Treatment Interaction ($F(4,12)=7.865$; $p=0.0024$). Bonferroni post-hoc tests again showed that cocaine self-administration was significantly reduced from control values on days 2-5 of treatment with 0.32 mg/kg/hr of l-methamphetamine (all p 's < 0.0001). Food-maintained responding was not affected by continuous treatment with any dose of l-MA throughout these experiments (all p 's > 0.05).

A final set of experiments were conducted to examine the effects of treatment with the two effective dosages of l-MA (0.1 and 0.32 mg/kg/hr) on self-administration of a range of IV cocaine doses. Figure 3 shows mean cocaine- and food-maintained responding data for treatment with l-MA (0.1 and 0.32 mg/kg/hr) and saline. Continuous treatment with 0.1 mg/kg/hr l-MA had little effect on self-administration of the lowest and highest unit doses of cocaine, 0.0032 and 0.1 mg/kg/inj, but produced an approximately 40-60% decrease in self-administration of 0.01 and 0.032 mg/kg/inj cocaine. Two-way ANOVA revealed a significant main effect of Cocaine Dose ($F(4,12)=26.05$; $p<0.0001$) and a significant Cocaine Dose $\times$ Treatment Interaction ($F(4,12)=4.066$; $p=0.026$). Bonferroni post-hoc tests further indicated that 0.1 mg/kg/hr l-MA significantly decreased the self-administration of unit doses of 0.01 and 0.032 mg/kg cocaine. Continuous treatment with the higher dosage of 0.32 mg/kg/hr l-MA markedly decreased IV self-administration of all unit doses of cocaine studied, flattening the cocaine dose-effect curve. Two-way ANOVA showed significant main effects of Cocaine Dose ($F(3,9)=10.82$; $p=0.0024$) and Treatment ($F(1,3)=78.48$; $p=0.003$) as well as a significant Cocaine Dose $\times$ Treatment Interaction ($F(3,9)=6.68$; $p=0.012$); Bonferroni post-hoc tests confirmed that treatment with 0.32 mg/kg/hr l-MA decreased self-administration of each unit dose of cocaine studied (0.01-0.1 mg/kg/inj; all p 's < 0.001). Moreover, repeated measures one-way ANOVA found that, during treatment with either dose of l-MA, no dose of cocaine was self-administered to an extent greater than saline. Of importance, food-maintained responding was not affected by 5-day continuous treatment with either 0.1 or 0.32 mg/kg/hr l-MA throughout these experiments.

Discussion

The present studies indicate that l-MA can both produce cocaine-like discriminative stimulus effects and decrease IV cocaine self-administration in nonhuman primates. These are behavioral effects common to other monoamine releasers that previously have been proposed as candidate medications for the management of Cocaine Use Disorder (e.g., d-amphetamine, d-MA, phenmetrazine; see Rothman and Baumann 2003). However, unlike those releasers, l-MA is not considered to have a prominent stimulant-like behavioral profile, suggesting a lesser propensity for producing other unwanted behavioral effects.

The present finding that l-MA is less potent than d-MA in producing dose-related cocaine-like discriminative stimulus effects is in agreement with data from previous drug discrimination studies. For example, l-MA has been shown to be about 5-fold less potent than d-MA in rats trained to discriminate d-MA (Desai and Bergman 2010), which is similar

to the difference in potency observed here in cocaine-trained rhesus monkeys. A pharmacokinetic explanation for potency differences between d- and l-MA is unlikely, as both compounds show similar distribution and biodisposition (Melega et al. 1999; Fowler et al. 2007; Li et al. 2010). Rather, these findings are consistent with neuropharmacological data showing l-MA to be 15-20 fold less potent than d-MA in stimulating DA release *in vitro* (Rothman and Baumann 2003) and *in vivo* (Kuczenski et al. 1995; Melega et al. 1999) and similarly potent in stimulating norepinephrine release *in vitro* (Rothman et al. 2001). Notwithstanding such differences in relative potency, the cocaine-like discriminative stimulus effects of varying relative potency for releasing DA and NE and that the ability of l-MA, like other monoaminergic stimulants, to mimic the discriminative-stimulus effects of cocaine resides primarily in its dopaminergic actions (Spealman 1995; Czoty et al. 2004a; Czoty et al. 2004b; Kohut et al. 2013b). Nevertheless, differences in the relative potency with which l-MA and d-MA release monoamines may contribute to other aspects of their behavioral and pharmaceutical profiles that contribute to their dissimilar DEA scheduling (see Rothman et al. 2001).

The present studies show that chronic treatment with l-MA, like d-MA, significantly decreases IV self-administration of cocaine by rhesus monkeys. The procedure used, in which l-MA was continuously administered 23-hr/day, was designed to ensure that steady-state levels of the treatment medication and its metabolites were present during the four drug and food sessions each day as might be expected with extended release formulations (Mello et al. 2013). The effects of l-MA were dosage-dependent and occurred across a range of self-administered unit doses of cocaine, resulting in a downward shift in the cocaine dose-effect curve. Consistent with data from the present cocaine-discrimination experiments and previous studies, l-MA was approximately 3-5 fold less potent than d-MA (Negus et al. 2007) but equally effective in reducing cocaine self-administration, notwithstanding differences in relative potency for releasing DA and NE. These results with l-MA add to considerable evidence that monoamine releasers can decrease—and, at sufficiently high dosage, nearly eliminate—cocaine self-administration (Negus and Mello 2003; Negus et al. 2007; 2009).

Decreases in cocaine self-administration in the present studies occurred during treatment with dosages of l-MA that did not affect food-maintained responding. Indeed, anecdotal evidence from daily observation of subjects in these experiments suggests that there were few, if any, overt behavioral data showing that non-selective DA/NE releasers that decrease cocaine self-administration usually also decrease food-maintained responding early in treatment (Negus et al. 2007; 2009). The relative contribution of NE release to the medication efficacy and safety of monoamine releasers is not well understood, and such different effects on food-maintained behavior perhaps can be attributed to the NE selectivity of l-MA which, in turn, may be beneficial in medications for managing cocaine use disorders. However, l-MA, like many monoamine releasers under study as candidate medications, also increases extracellular levels of serotonin (Kuczenski et al. 1995; see also Banks et al. 2014; Rothman and Baumann 2006; Baumann et al. 2011a; Baumann et al. 2011b; Negus et al. 2007; 2009). Consequently, this idea must be considered with caution and, in the absence of additional evidence with compounds that differ in relative potency for

releasing DA and NE but do not greatly alter levels of extracellular serotonin, remains speculative.

One of the major impediments to the use of currently available monoamine releasers as agonist therapy for Cocaine Use Disorder is their psychomotor stimulant action, which likely is closely linked to their high abuse liability. Formulations of d-amphetamine, d-MA, and other prescription stimulants intended for oral use are often diverted for recreational or nonmedical use (Upadhyaya et al. 2005; McCabe et al. 2006; Rabiner et al. 2009). In this regard, epidemiological and clinical data indicates that, notwithstanding the availability of l-MA as an over-the-counter medication, it is not subject to significant diversion or abuse liability (Mendelson et al. 2006) and is considered to be a relatively safe drug with limited cardiovascular risk (Dufka et al. 2009; Mendelson et al. 2008). This contrasts with data indicating that IV l-MA can maintain self-administration behavior in rhesus monkeys (Winger et al, 1994) and produces an array of positive subjective effects (e.g., Good Drug Effect, Drug Liking) in experienced stimulant users (Mendelson et al. 2008). However, the latter studies in human subjects also suggest that such effects of l-MA are fewer and shorter-acting than those of d-MA and that, in contrast to d-MA, acute inhalation of a range of l-MA dosages (16 - 64 inhalations) produces aversive (i.e., Dizziness and Headache) as well as positive subjective effects (Mendelson et al. 2006; Mendelson et al. 2008). Possibly, such unpleasant effects of l-MA serve to limit overall intake and reduce its abuse liability (see Kohut and Riley, 2013; Riley, 2011). Additional studies are needed to determine how such factors may contribute to l-MA's potential clinical utility for the management of Cocaine Use Disorder.

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Fig 1.

Discriminative stimulus effects of cocaine, d-methamphetamine (d-MA), and l-methamphetamine (l-MA) in rhesus monkeys trained to discriminate cocaine (0.4 mg/kg, IM) from saline. Abscissae: cumulative dose of drug in mg/kg. Top ordinates: percentage of cocaine-lever responding during the entire cumulative dosing session. Bottom ordinates: rate of responding expressed as responses per second (r/s). ED₅₀ values for each drug are shown in text.

Fig 2.

Time course of treatment effects of saline or increasing doses of l-methamphetamine (l-MA) on responding maintained by 0.01 mg/kg/inj cocaine and food. Abscissae: consecutive day of treatment. Left ordinates: cocaine injections earned per day (maximum 80), filled circles. Right ordinates: food pellets earned per day (maximum 100), open squares. ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ vs. + saline treatment

Fig 3.

Effects of treatment with l-methamphetamine (l-MA) on cocaine- and food-maintained responding. Abscissae: dose of cocaine in mg/kg/inj. Left ordinate: total cocaine injections earned per day (out of 80 possible). Right panel ordinates: total food pellets earned per day (out of 100 possible). All data points show the mean $\pm$ SEM of the final 3 days of 5-10 day treatments in rhesus monkeys (n=4-5). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs + saline treatment