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Role of phenmetrazine as an active metabolite of phendimetrazine: Evidence from studies of drug discrimination and pharmacokinetics in rhesus monkeys☆

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ABSTRACT

Background: Monoamine releasers such as *d*-amphetamine that selectively promote release of dopamine/norepinephrine versus serotonin are one class of candidate medications for treating cocaine dependence; however, their clinical utility is limited by undesirable effects such as abuse liability. Clinical utility of these compounds may be increased by development of prodrugs to reduce abuse potential by slowing onset of drug effects. This study examined the behavioral and pharmacokinetic profile of the Schedule III compound phendimetrazine, which may serve as a prodrug for the N-demethylated metabolite and potent dopamine/norepinephrine releaser phenmetrazine.
Methods: Monkeys ($n = 5$) were trained in a two-key food-reinforced discrimination procedure to discriminate cocaine (0.32 mg/kg, IM) from saline, and the potency and time course of cocaine-like discriminative stimulus effects were determined for (+)-phenmetrazine, (−)-phenmetrazine, (+)-phendimetrazine, (−)-phendimetrazine, and (±)-phendimetrazine. Parallel pharmacokinetic studies in the same monkeys examined plasma phenmetrazine and phendimetrazine levels for correlation with cocaine-like discriminative stimulus effects.
Results: Both isomers of phenmetrazine, and the racemate and both isomers of phendimetrazine, produced dose- and time-dependent substitution for the discriminative stimulus effects of cocaine, with greater potency residing in the (+) isomers. In general, plasma phenmetrazine levels increased to similar levels after administration of behaviorally active doses of either phenmetrazine or phendimetrazine.
Conclusions: These results support the hypothesis that phenmetrazine is an active metabolite that contributes to the effects of phendimetrazine. However, behavioral effects of phendimetrazine had a more rapid onset than would have been predicted by phenmetrazine levels alone, suggesting that other mechanisms may also contribute.

1. Introduction

Despite decades of research, there is currently no Food and Drug Administration-approved pharmacological treatment strategy for cocaine dependence (Kampman, 2010; Vocci and Ling, 2005). For other drugs of abuse, such as heroin, agonist-substitution therapy has been successful as a maintenance strategy for addiction treatment (Kreek et al., 2002; Nyswander, 1956). The goal of agonist-based pharmacotherapy is to use a medication that has pharmacological effects similar to those of the abused drug, slow onset to reduce abuse liability, and long duration of action to assist in compliance (Grabowski et al., 2004b). Research over the last decade has suggested that this agonist-based strategy may also have utility in treating cocaine dependence (Herin et al., 2010; Rothman et al., 2005).

One example of this medication approach for treatment of cocaine dependence is *d*-amphetamine, a monoamine releaser that selectively promotes release of dopamine and norepinephrine versus serotonin. Chronic *d*-amphetamine treatment has been shown to decrease cocaine self-administration by rodents, nonhuman primates and humans (Chiodo et al., 2008; Czoty et al., 2011; Greenwald et al., 2010; Negus, 2003) and to decrease cocaine use in clinical trials (Grabowski et al., 2001, 2004a; Shearer et al., 2003). One manifestation of the shared pharmacological effects of *d*-amphetamine and cocaine is their similar discriminative stimulus effects in nonhuman primates and other species (Beardsley et al., 2001; de la Garza and Johanson, 1985; Gold and Balster, 1996; Negus et al., 2009; Oliveto et al., 1998). *d*-Amphetamine also has a

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long duration of action in nonhuman primates and humans, which is another desirable attribute of an agonist-based pharmacotherapy (Chait et al., 1986; Negus et al., 2009). However, *d*-amphetamine is a Schedule II psychostimulant with a rapid onset of action that contributes to its high abuse liability, and it also produces undesirable cardiovascular effects that ultimately limit its clinical utility as a pharmacotherapy for cocaine dependence.

One strategy for improving the clinical utility of dopamine/norepinephrine-selective monoamine releasers might be development of a prodrug to slow the rate of onset of drug effects in an attempt to reduce abuse potential (Balster and Schuster, 1973; Huttunen et al., 2011; Schindler et al., 2009). We have previously shown that (+)-phenmetrazine is another dopamine/norepinephrine-selective monoamine releaser that produces cocaine-like discriminative stimulus effects and decreases cocaine self-administration in rhesus monkeys (Banks et al., 2012, 2011; Negus et al., 2009); however, like *d*-amphetamine, phenmetrazine has a relatively rapid onset and high potential for abuse (Chait et al., 1987; Corwin et al., 1987; de la Garza and Johanson, 1987; Griffiths et al., 1976), and it was withdrawn from the market in the United States. Phendimetrazine in an N-methyl analog of phenmetrazine that itself has low potency to affect monoamine release or uptake, but that may serve as a prodrug for phenmetrazine in vivo (Rothman et al., 2002). Consistent with this characterization, previous studies have demonstrated that phendimetrazine shares *d*-amphetamine discriminative stimulus effects in monkeys (de la Garza and Johanson, 1987; Evans and Johanson, 1987). More importantly, phendimetrazine appears to have reduced abuse potential compared to phenmetrazine in some drug self-administration assays (Corwin et al., 1987), and phendimetrazine is currently available clinically as a Schedule III agent for treatment of obesity. Taken together, these results support further research of phendimetrazine as a candidate "agonist" pharmacotherapy for treating cocaine dependence (Banks et al., 2011; Negus et al., 2009; Rothman et al., 2002).

Although existing data suggest that phendimetrazine may be an inactive parent drug that serves as a prodrug for the active metabolite phenmetrazine, this issue has not been directly addressed in pharmacokinetic studies. Accordingly, the aim of the present study was to correlate cocaine-like discriminative stimulus effects of phenmetrazine and phendimetrazine with plasma phenmetrazine levels in rhesus monkeys. Phendimetrazine is clinically available as a racemate of the more potent (+) and less potent (−) isomers, and this study assessed effects of both isomers of phenmetrazine and phendimetrazine as well as of racemic phendimetrazine. We hypothesized that, in accordance with the relative potencies of phenmetrazine isomers to promote dopamine release (Rothman et al., 2002), the (+)-isomers of phenmetrazine and phendimetrazine would be more potent than the (−) isomers in producing cocaine-like discriminative stimulus effects. Furthermore, we hypothesized that phendimetrazine would yield behaviorally active levels of phenmetrazine as an active metabolite, and that the potency and time course of cocaine-like discriminative stimulus effects of phendimetrazine would correlate with generation of the phenmetrazine metabolite. Overall, these expected results would provide a basis for further studies with phendimetrazine as a prodrug for phenmetrazine and a candidate "agonist" pharmacotherapy for cocaine dependence.

2. Methods

2.1. Animals

Studies were conducted in 5 adult male rhesus monkeys (*Macaca mulatta*). Monkeys were maintained on a diet of fresh fruit and food biscuits (Lab Diet High Protein Monkey Biscuits, PMI Feeds, Inc., St. Louis, MO) provided in the afternoon after the operant session. In addition, monkeys could earn up to 70 1-g banana-flavored pellets (Grain-based Precision Primate Pellets, Test Diets, Richmond, IL) during daily experimental sessions (see below). Water was continuously available. A 12 h light–dark cycle was in effect (lights on from 7 AM to 7 PM). Environmental enrichment consisting of foraging boards, novel treats, videos or radio were also provided in the afternoons after behavioral sessions. All monkeys had prior exposure to monoaminergic and opioidergic compounds (unpublished results) before training in the two-key food-reinforced cocaine vs. saline discrimination procedure. The facility was licensed by both the United States Department of Agriculture and the Association for Assessment and Accreditation of Laboratory Animal Care, and protocols were approved by the Institutional Animal Care and Use Committee.

2.2. Drug discrimination procedures

2.2.1. Apparatus. Experimental sessions were conducted in each monkey's home cage. The front wall was equipped with an operant response panel that included three square response keys arranged horizontally. Each housing chamber was also equipped with a pellet dispenser (Med Associates, ENV-203-1000, St. Albans, VT). Operation of the operant panels and data collection were accomplished with computers and software purchased from Med Associates.

2.2.2. Discrimination training. Monkeys were trained to discriminate 0.32 mg/kg cocaine intramuscularly (IM) from saline in a two-key, food-reinforced drug discrimination procedure. Discrimination training was conducted 5 days/week during daily sessions composed of multiple components. Each component consisted of a 5-min response period, during which the right and left response keys were transilluminated red and green, respectively, and monkeys could earn up to 10 food pellets by responding under a fixed-ratio (FR) 30 schedule of food presentation. Training sessions were composed of three components presented at 2-h intervals, and either saline or 0.32 mg/kg cocaine was administered IM 15 min prior to the start of each component. Thus, on training days, monkeys would receive a sequence of saline (S) and cocaine (C) injections in the order SSS, SSC, SCS, CSS, SCC, CSC, CCS, or CCC, and training sequences were randomly presented. The goal of this training regimen was to engender daily experience with randomized sequences of saline- and cocaine-appropriate components. The 2hr duration of inter-component intervals was selected to exceed the time course of discriminative stimulus effects produced by the training dose of cocaine in rhesus monkeys (Lamas et al., 1995) and to thereby minimize effects of cocaine 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 0.32 mg/kg cocaine, only responding on the red key (the cocaine-appropriate key) produced food. Responses on the inappropriate key reset the FR requirement on the appropriate key. The criterion for accurate discrimination was >80% injection-appropriate responding before delivery of the first reinforcer, >90% injection-appropriate responding for the entire component, and response rates >0.1 responses/sec (sufficient to earn at least one pellet) for all components during 7 of 8 consecutive sessions.

2.2.3. Discrimination testing. Test sessions were identical to training sessions except that (a) responding on either key produced food, (b) monkeys received only one injection of vehicle or a dose of the test drug at the start of the session, and (c) 5-min response components began 10, 30, 56, 100, 180, 300 and 560 min after the injection to assess the time course of drug effects. The