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Influence of aripiprazole pretreatment on the reinforcing effects of methamphetamine in humans

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ABSTRACT

Methamphetamine use disorders remain a significant public health concern. Methamphetamine produces its behavioral effects by facilitating release of monoamines like dopamine (DA) and serotonin (5-HT). Results from animal studies show that acute pretreatment with DA and 5-HT antagonists attenuates the effects of methamphetamine, but this area remains largely unexplored in humans. This study sought to assess whether aripiprazole, a partial agonist at D_2/5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors, would attenuate the reinforcing and subject-rated effects of oral methamphetamine. Seven subjects with histories of recreational stimulant use completed a placebo-controlled, crossover, double-blind protocol in which they first sampled doses of oral methamphetamine (0, 4, 8 or 16 mg) following acute pretreatment with aripiprazole (0 and 15 mg). During each Sampling Session, subjects also completed a battery of subject-rated, cardiovascular, and other performance measures. In subsequent Self-Administration Sessions, subjects were provided the opportunity to earn the previously sampled methamphetamine dose on a progressive-ratio procedure. Methamphetamine functioned as a reinforcer, and produced prototypical stimulant-like subject-rated and cardiovascular effects (*e.g.*, increased ratings of Stimulated; elevated blood pressure). Aripiprazole reduced methamphetamine self-administration and attenuated some of the positive subject-rated effects of methamphetamine (*e.g.*, ratings of Like Drug). These results indicate that acute aripiprazole pretreatment attenuates the abuse-related effects of methamphetamine.

1. Introduction

Methamphetamine use remains a persistent public health concern. Data from the National Survey on Drug Use and Health (NSDUH) suggest that 439,000 Americans reported past-month methamphetamine use and 133,000 individuals indicated past-year initiation of methamphetamine use in 2011 (Substance Abuse and Mental Health Services Administration, 2012). Methamphetamine use is commonly associated with comorbid psychiatric problems and disorders, as well as needle sharing and risky sexual behaviors, which can lead to increased risk of contracting HIV (see Semple et al., 2004; Shoptaw et al., 2005, 2006; Zweben et al., 2004). These risks highlight the need for a better understanding of methamphetamine abuse in humans.

Several *in vitro* and *in vivo* studies have demonstrated that dopamine (DA) and serotonin (5-HT) contribute to the behavioral effects of amphetamine in animals. A seminal preclinical study showed that dose-dependent enhancements in synaptic levels of DA and 5-HT were related to locomotor, sniffing, and stereotyped behavioral responses to amphetamine in rats (Kuczenski and Segal, 1989). Additionally, Wee et al. (2007) found that acute pretreatment with aripiprazole, a partial agonist at D_2/5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors, reduced methamphetamine self-administration in rats. A number of preclinical drug-discrimination studies have implicated both central DA and 5-HT systems in mediating the behavioral effects of methamphetamine (Bergman, 2008; Czoty et al., 2004; Munzar and Goldberg, 2000; Munzar et al., 1999; Tidey and Bergman, 1998). For example, in one of these previous studies, 10 squirrel monkeys were trained to discriminate methamphetamine (0.3 mg/kg) from saline (Tidey and Bergman, 1998). A D_2 receptor agonist, (+)-PHNO, dose-dependently increased methamphetamine-appropriate responding,

Abbreviations: 5-HT, serotonin; ANOVA, analysis of variance; DA, dopamine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; DSST, digit symbol substitution task; hr, hours; kg, kilograms; LHBP, Laboratory of Human Behavioral Pharmacology; MDMA, 3,4-methylenedioxymethamphetamine (ecstasy); methamphetamine HCL, methamphetamine hydrochloride; mg, milligrams; min, minute; NSDUH, National Survey on Drug Use and Health; SEM, standard error of the mean; SAMHSA, Substance Abuse and Mental Health Services Administration; THC, tetrahydrocannabinol.

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whereas pretreatment with remoxipride, a D_2 antagonist, attenuated the discriminative-stimulus effect of methamphetamine. The results of two other studies suggest that 5-HT receptors also contribute to the discriminative-stimulus effects of methamphetamine in animals (Munzar et al., 1999; Sasaki et al., 1995).

These preclinical data indicate that DA and 5-HT antagonists might be viable pharmacotherapies for managing methamphetamine use disorders through extinction processes. Clinical data testing the effects of chronic DA and 5-HT antagonists have not revealed promising results, however. For example, in one study, maintenance on 15 mg aripiprazole increased ratings of methamphetamine-induced euphoria while reducing negative subject-rated effects relative to placebo maintenance (Newton et al., 2008). Clinical trials have demonstrated that aripiprazole either does not change amphetamine use (Coffin et al., 2013; Sulaiman et al., 2012) or increases it (Tiihonen et al., 2007). Most clinical research has examined the effects of chronic DA/5-HT antagonist dosing on the effects of methamphetamine or methamphetamine use, but no studies have translated preclinical research to determine how acute administration of a DA/5-HT antagonist changes methamphetamine self-administration.

Thus, the present study sought to examine the effects of acute aripiprazole administration on the reinforcing effects of methamphetamine in humans. A progressive-ratio procedure was used, as this procedure has consistently proven to be a sensitive measure of drug reinforcement (*e.g.*, Comer et al., 1997, 1998; Rush et al., 2001; Stoops et al., 2004). A battery of subject-rated, performance, and cardiovascular measures was included to complement the self-administration data. We hypothesized that, when administered concurrently with methamphetamine, 15 mg aripiprazole would act as an antagonist and reduce methamphetamine self-administration as evidenced by a decrease in break points. In addition, we hypothesized that aripiprazole would reduce the stimulant-like subject-rated effects of methamphetamine.

2. Method

2.1. Subjects

Seven non-treatment-seeking adult subjects (5 males, 2 females; 6 White [1 Hispanic], 1 Black) completed the protocol. All subjects reported recreational stimulant use in the past year (*i.e.*, mixed salt amphetamine [Adderall], 3,4-methylededioxymethamphetamine [MDMA; ecstasy], methylphenidate or cocaine). On average (±SEM), subjects were 23 (±2) years of age and weighed 74 (±4) kg. One of the seven subjects reported daily use of cigarettes (15 cigarettes/day) and all reported weekly alcohol use (12 ± 3 drinks/week). In addition to daily cigarette and weekly alcohol use, subjects reported recent recreational use of other drugs. In the month prior to screening, two subjects used marijuana, one subject used opioids, and one subject used benzodiazepines. One subject met Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for alcohol abuse, but a study physician determined that this diagnosis would not interfere with his ability to complete the study.

The Institutional Review Board of the University of Kentucky Medical Center approved this experiment and all subjects gave their written informed consent prior to participating. Subjects were paid $40 per session and earned an additional $40 per session completion bonus if they finished the study. Subjects underwent extensive screening prior to enrollment (*e.g.*, Sevak et al., 2010). To meet inclusion criteria, subjects had to (1) report past-year recreational use of stimulant drugs (*e.g.*, amphetamine, ecstasy, methylphenidate, cocaine) and (2) be in good health with no contraindications to stimulant or antipsychotic medications.

2.2. General procedures

Subjects reported to the University of Kentucky Laboratory of Human Behavioral Pharmacology (LHBP) at the University of Kentucky Chandler Medical Center for a total of 18 sessions (2 Practice and 16 Experimental). Subjects were informed that during their participation they would receive aripiprazole, methamphetamine and placebo. Other than receiving this general information, subjects were blind to the doses of aripiprazole and methamphetamine to be administered during each session. Subjects were told that the purpose of the study was to determine (1) how different drugs affect mood and behavior, (2) the effects of drugs on physiology (cardiovascular measures), and (3) whether subjects like the drug and are willing to take it again. Other than this general explanation of purpose, subjects were not given any information regarding what outcomes might be expected.

2.2.1. Practice Sessions

Subjects completed two Practice Sessions to familiarize them with the subject-rated questionnaires, the performance task, and the progressive-ratio procedure. The first Practice Session followed the Sampling Session timeline and the second Practice Session followed the Self-Administration Session timeline, as described below, with the exception that no drug was administered. Subject-rated questionnaires, the performance task, and the progressive-ratio procedure were administered on a Macintosh iMac computer (Apple Computer Inc., Cupertino, CA).

2.2.2. Sampling Sessions

A total of eight Sampling Sessions (*i.e.*, one for each aripiprazole and methamphetamine dose combination) were conducted to familiarize subjects with the doses of drug they could choose to work for in subsequent sessions. Sampling Sessions for each dose combination always preceded a Self-Administration Session in which that same dose combination was available, similar to previous studies conducted in our laboratory (*e.g.*, Rush et al., 2001; Stoops et al., 2005, 2007).

For all sessions, subjects arrived daily at approximately 0800 to the LHBP. Sessions lasted 7 hr. Immediately after arriving urine and expired breath samples were collected to confirm drug and alcohol abstinence, respectively. Female subjects also received urine pregnancy tests prior to each session, which were negative throughout their participation. If subjects tested positive for alcohol or other drugs they were sent home and their session rescheduled. Exceptions included THC, due to the long elimination time, and methamphetamine positive results that corresponded to experimental administration. To ensure that subjects were not acutely intoxicated, subjects had to pass a field sobriety test prior to beginning each session. To further enhance safety, neither aripiprazole nor methamphetamine was administered until at least 1.5 and 2 hr, respectively, after subjects arrived at the laboratory. Vital signs were recorded at 30 min intervals between 0830 and 0930 and subjects were provided a standard breakfast (*i.e.*, a juice box, and 2 Nutri-grain® bars or 1 standard single-serving cereal with skim milk).

At 0830, subject-rated and performance measures were completed. At 0930, subjects received a single red capsule containing aripiprazole or placebo. At 1000, subjects received eight blue and white capsules (each containing 1/8th of the total methamphetamine dose [0, 4, 8, or 16 mg]) to acquaint them with the effects of the drug dose that could be earned during the following Self-Administration Sessions. Subjects were instructed to pay attention to and make notes about the effects of the drug, as they would later be given the opportunity to work for the capsules again.

For all sessions, subject vitals were recorded and subject-rated measures and performance measures were administered at 1 hr intervals after the second drug (*i.e.*, methamphetamine or placebo) administration (*i.e.*, from 1100 to 1500). Between these measures, subjects were allowed to engage in sedentary, quiet recreational activities (*e.g.*, read newspapers or magazines, complete puzzles, watch television). At 1300, subjects were allowed to eat lunch, which was provided by the LHBP. If no drug effects (cardiovascular or behavioral) were detected at 5 hr post-administration, subjects were released from the laboratory.