0022-3565/03/3061-195–204$7.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
JPET 306:195–204, 2003

Vol. 306, No. 1
48439/1073497
Printed in U.S.A.

Risperidone Attenuates the Discriminative-Stimulus Effects of *d*-Amphetamine in Humans

CRAIG R. RUSH, WILLIAM W. STOOPS, LON R. HAYS, PAUL E. A. GLASER, and LON S. HAYS

Departments of Behavioral Science (C.R.R., W.W.S., L.S.H.), Psychiatry (C.R.R., L.R.H., P.E.A.G.), and Anatomy and Neurobiology (P.E.A.G.), College of Medicine; Department of Psychology (C.R.R., W.W.S.), College of Arts and Sciences, University of Kentucky, Lexington, Kentucky

Received December 20, 2002; accepted March 25, 2003

ABSTRACT

Studies conducted with nonhuman laboratory animals have consistently shown that atypical antipsychotics that are mixed dopamine and serotonin antagonists attenuate the discriminative-stimulus effects of amphetamine. In the present experiment, eight healthy humans learned to discriminate 15 mg of oral *d*-amphetamine. After acquiring the discrimination (i.e., ≥80% correct responding on four consecutive days), the effects of a range of doses of *d*-amphetamine (0, 2.5, 5, 10, and 15 mg), alone and after pretreatment with risperidone (0 and 1 mg), a D_2 dopamine and 5-hydroxytryptamine $(5\text{-HT})_2$ serotonin antagonist, were assessed. *d*-Amphetamine alone functioned as a discriminative stimulus and produced stimulant-like self-reported drug effects (e.g., increased ratings of "like drug"). These effects were generally a function of dose. Risperidone alone did not occasion *d*-amphetamine-appropriate responding, but impaired performance. Risperidone pretreatment significantly attenuated the discriminative-stimulus effects of *d*-amphetamine, and some of the self-reported drug effects. The results of the present experiment suggest that combining drug-discrimination and self-reported drug-effect questionnaires may be an effective strategy for assessing the behavioral effects of agonist-antagonist interactions. Future studies should compare the behavioral effects of *d*-amphetamine after pretreatment with a selective D_2 dopamine (e.g., haloperidol) or 5-HT_2 serotonin (e.g., ritanserin) antagonist to determine the relative contribution of dopamine and serotonin systems in mediating the behavioral effects of stimulants in humans. The results of these studies might guide the development of a pharmacotherapy for the treatment of amphetamine abuse/dependence.

Stimulant abuse/dependence is a significant public health concern. In 2001, approximately 1.6 million Americans had used a stimulant in the past month (Substance Abuse and Mental Health Services Administration, National Household Survey on Drug Abuse, http://www.samhsa.gov). The number of persons that used a stimulant for the first time increased steadily between 1991 and 2000 (Substance Abuse and Mental Health Services Administration, Drug Abuse Warning Network, http://www.samhsa.gov). The number of mentions in emergency departments involving amphetamine increased by more than 20% between 1997 and 2001 (Substance Abuse and Mental Health Services Administration, National Household Survey on Drug Abuse, http://www.samhsa.gov). The number of methamphetamine/amphetamine admissions to treatment programs increased by 62% between 1994 and 1999 (Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set, http://www.samhsa.gov). Because of public health concerns, identifying an effective pharmacotherapy for the management of amphetamine abuse and dependence is a research priority. An effective pharmacotherapy for amphetamine abuse or dependence has not yet been identified despite intense scientific efforts.

The results of preclinical behavioral pharmacology experiments suggest that atypical antipsychotics such as risperidone, olanzapine, and clozapine consistently attenuate the discriminative-stimulus effects of amphetamine (Kilbey and Ellinwood, 1979; Nielsen and Jepsen, 1985; Meert, 1991, 1996; Arnt, 1992, 1996; Mechanic et al., 2002). The discriminative-stimulus effects of drugs in animals are thought to be a model of the self-reported effects of drugs in humans. In one experiment, the discriminative-stimulus effects of *d*-amphetamine (1.0 mg/kg) were tested alone and after pretreatment with risperidone (0.04–2.5 mg/kg), olanzapine (0.0025–2.5 mg/kg), and clozapine (0.08–2.5 mg/kg) in rats trained to discriminate 1.0 mg/kg *d*-amphetamine (Arnt, 1996). Risperidone, olanzapine, and clozapine dose dependently decreased

This study was supported by National Institute on Drug Abuse Grant DA 10325 (to C.R.R.).
Article, publication date, and citation information can be found at http://jpet.aspetjournals.org.
DOI: 10.1124/jpet.102.048439.

ABBREVIATIONS: 5-HT, 5-hydroxytryptamine; MBG, morphine-benzedrine group; THC, tetrahydrocannibinol; ARCI, addiction research center inventory; PCAG, pentobarbital, chlorpromazine, alcohol group; LSD, lysergic acid diethylamide; BG, benzedrine group; A, amphetamine scale; DSST, digit-symbol-substitution test; AUC, area under the time-action curve; ANOVA, analysis of variance.

percentage of drug-appropriate responding. The results of these experiments suggest that these antipsychotics, which are mixed D_2 and 5-HT_2 antagonists (for reviews, see Fitton and Heel, 1990; Grant and Fitton, 1994; Fulton and Goa, 1997), block some of the behavioral effects of *d*-amphetamine that may contribute to its abuse.

Despite these provocative preclinical data, we know of only one human laboratory experiment in which the effects of amphetamine were examined after pretreatment with an atypical antipsychotic (Wachtel et al., 2002). In this experiment, the acute self-reported effects of methamphetamine (0 or 20 mg) were examined alone and after pretreatment with risperidone (0 or 0.75 mg). Methamphetamine alone produced prototypical stimulant-like self-reported drug effects (e.g., increased MBG scores on the Addiction Research Center Inventory). Risperidone pretreatment did not alter the self-reported effects of methamphetamine.

The reason for the discrepancy between experiments conducted with animals and humans is unknown, but may be attributable to the use of different methods. As noted above, the experiments conducted with animals assessed the discriminative-stimulus effects of amphetamine after pretreatment with risperidone, olanzapine, or clozapine. The only available study conducted with humans assessed the self-reported effects of amphetamine after pretreatment with risperidone. Although the discriminative-stimulus effects of drugs and their self-reported effects overlap, they are not isomorphic and can be dissociated (Rush et al., 1998, 2002).

Drug-discrimination procedures commonly used with laboratory animals have been adapted for use with humans (Kamien et al., 1993). Although the discriminative-stimulus effects of amphetamine after pretreatment with atypical antipsychotics have been studied in laboratory animals, comparable studies in humans do not exist. The present experiment was designed to assess the discriminative-stimulus effects of *d*-amphetamine (0–15 mg), alone and after pretreatment with risperidone (0 and 1 mg), in humans that had learned to discriminate 15 mg of *d*-amphetamine. *d*-Amphetamine is reliably discriminated by humans (Chait et al., 1986a,b; Chait and Johanson, 1988; Heishman and Henningfield, 1991; Rush et al., 1998; Kollins and Rush, 1999). The dose of risperidone studied, 1 mg, was chosen because it is the recommend initial acute dose (Physician's Desk Reference, 2003). We examined the discriminative-stimulus effects of *d*-amphetamine, alone and after pretreatment with risperidone, because drug discrimination involves extensive training before novel doses or drug combinations are tested. Because of the extensive training, all participants in a drug-discrimination experiment have similar recent behavioral and pharmacological histories. The extensive training that provides similar recent behavioral and pharmacological histories may reduce between-subject variability. However, to characterize more fully the effects of *d*-amphetamine, alone and after pretreatment with risperidone, a battery of self-reported drug-effect questionnaires previously shown to be sensitive to the acute effects of *d*-amphetamine was included (Rush et al., 1998). A performance task and physiological indices were also included. We predicted that risperidone pretreatment would attenuate the behavioral effects of *d*-amphetamine.

Materials and Methods

Participants

Ten healthy adults were recruited via newspaper ads, flyers, and word-of-mouth to participate in this experiment. Participants were paid $40/session to participate in this experiment and received performance-based payment as outlined below. One participant was unable to accurately discriminate 15 mg of *d*-amphetamine, whereas another participant was discharged for medical reasons unrelated to the study medications. Data from these participants were not included in the analyses. Eight participants (four males, four females) completed this experiment. These participants ranged in age from 18 to 28 years (mean = 23) and in weight from 57 to 95 kg (mean = 71). These participants reported consuming 9 to 508 mg caffeine/day (mean = 157) and had completed 14 to 18 years of education (mean = 16). One participant reported smoking 12 tobacco cigarettes per day. This participant was allowed to have one cigarette approximately midway through the experimental session. Participants completed questionnaires assessing drug use, medical and psychiatric histories, and provided written informed consent before participating. Individuals with current or past histories of serious psychiatric disorder, including substance abuse/dependence disorders, were excluded from participating. All participants were in good health with no contraindications to stimulant or antipsychotic medications. Drug urine screens conducted during screening were negative for amphetamine, benzodiazepines, barbiturates, cocaine, and opioids (Abuscreen ONTRAK; Roche Diagnostic Systems, Nutley, NJ). One participant tested positive for tetrahydrocannibinol (THC). In the female participants, urine pregnancy tests before and periodically during study participation were negative. The Institutional Review Board of the University of Kentucky Medical Center approved this study and the informed consent document.

General Procedures

Participants enrolled as outpatients at the Laboratory of Human Behavioral Pharmacology (University of Kentucky Medical Center) Monday through Friday for 20 to 27 (mean = 23) experimental sessions. Participants were informed that during their participation they would receive various drugs and that these could include placebo, various sedatives, muscle relaxants, and anxiolytics, stimulants and weight loss medications, antidepressants, antihistamines, and antipsychotics. Participants were told that the purpose of the study was to see whether they could tell the difference between various drugs, and how these drugs affect mood and behavior. Other than receiving this general information, participants were blind to the type of drug administered and were given no instructions regarding what they were "supposed" to do or what outcomes might be expected.

Before initiating medication testing, participants completed two "practice" sessions. These practice sessions were used to familiarize participants with the drug-discrimination task, self-reported drug-effect questionnaires, performance measure, and daily laboratory routine. No medications were administered on these days.

Throughout the study, participants were requested to refrain from using all illicit psychoactive drugs, caffeine, and solid food for 4 h before a scheduled experimental session, and alcohol for 12 h before a scheduled experimental session. On each experimental session day, participants arrived at the laboratory and provided a urine sample each session before drug administration, which was screened for the presence of amphetamine, barbiturates, benzodiazepines, cocaine, opioids, and THC. These urine samples were occasionally positive for amphetamine, which was likely due to the administration of the experimental medications. One participants' urine specimen was positive for THC five times during the conduct of this experiment, whereas another participants' urine specimen was positive for THC on one occasion. Yet another participant's urine specimen was positive for opioids one time. Experimental sessions were

canceled for this participant until an opioid-free urine specimen was obtained. Participants also provided an expired air specimen, which was assayed for the presence of alcohol using a hand-held breathalyzer (Intoximeters, Inc., St. Louis, MO). All expired air specimens were negative.

On experimental session days, participants completed the self-reported drug-effect questionnaires and performance task approximately 30 min before drug administration and then completed the drug-discrimination task, self-reported drug-effect questionnaires, and performance task 1, 2, 3, 4, and 5 h after drug administration. When not completing the drug-discrimination task, self-reported questionnaires, and performance task, participants were allowed to engage in recreational activities (e.g., watch television, play cards, or read) or socialize with each other.

Drug Discrimination Procedures

This experiment consisted of three phases, which were completed in a fixed order: 1) sampling phase, 2) acquisition phase, and 3) test phase.

Sampling Phase. All participants completed two sampling sessions to acquaint them with the drug effects. Participants reported to the laboratory and completed the self-reported drug-effect questionnaires and performance task (described below). During each sampling session, participants ingested four capsules that contained a total of 15 mg of *d*-amphetamine. *d*-Amphetamine was identified by letter code (e.g., drug A), but the participants were not explicitly informed of the capsules' contents. Below are the instructions given to each participant during the sampling phase. These instructions were printed on a piece of paper, and participants were instructed to carefully read them before each sampling session. A research assistant also read these instructions aloud. *d*-Amphetamine (15 mg) is identified as drug A for illustrative purposes only. A unique letter code was used for each participant.

Instructions (sampling sessions). This is drug A. When you think you received drug A, and in fact you did receive drug A, you can earn extra money by responding on the button labeled drug A. During this session, you should pay close attention to how drug A makes you feel, because in the future we will not tell you if you received drug A. Instead, you will have to decide whether you received drug A. In these future sessions, if you think you received drug A, and in fact you did receive drug A, you can earn extra money by responding on the button labeled drug A.

Whenever you do not think you received drug A, and in fact you did not receive drug A, you can earn extra money by responding on the button labeled not drug A.

Acquisition Phase. After the sampling phase, an acquisition phase was conducted to determine whether participants could discriminate 15 mg of *d*-amphetamine. During this phase, participants ingested capsules under double-blind conditions, but they were not told whether the capsules contained 15 mg of *d*-amphetamine (e.g., drug A) or placebo (e.g., not drug A). Participants were not explicitly instructed that they would be attempting to acquire a drug versus placebo discrimination. After capsule administration, participants completed the drug-discrimination task, self-reported drug-effect questionnaires, and performance measure periodically for 5 h. Participants were instructed that they could change their responses on the drug-discrimination task between hours 1, 2, 3, 4, and 5 based on what they believed at the time. After completing the drug-discrimination task, self-reported drug-effect questionnaires and performance task at the 5-h observation, participants opened a sealed envelope that informed the participant and the research assistant of the identity of the drug administered (i.e., drug A or not drug A). The criterion for having acquired the discrimination was ≥80% correct responding on four consecutive sessions on the drug-discrimination task described below. The order of drug administration was random except that each participant received each training condition, 15 mg of *d*-amphetamine and placebo, at least twice.

Below are the instructions given to each participant during the test-of-acquisition phase. These instructions were printed on a piece of paper, and participants were told to carefully read them prior to each experimental session. A research assistant also read these instructions aloud. These instructions were also used during the test phase described below.

Instructions (acquisition phase). Today, we will not tell you whether you received drug A or not drug A. Instead, you will have to decide whether you received drug A or not drug A. If you think you received drug A, and in fact you did receive drug A, you can earn extra money by responding on the button labeled drug A. If you do not think you received drug A, and in fact you did not receive drug A, you can earn extra money by responding on the button labeled not drug A. For example, if you feel that you did not receive any drug today, you should respond on the button labeled not drug A. Similarly, if you think that you received a drug, but it feels different than drug A, you should respond on the button labeled not drug A. You can change your drug identifications throughout today's session based on what you think at the time.

At the end of today's session, you will be given an envelope that will tell you whether you received drug A or not drug A. The number of points that you accumulated on the correct button will then be converted to money and you will be told how much bonus money you earned during today's session. At the end of some sessions, we may not be able to tell you whether you received drug A or not drug A. On the days that we cannot tell whether you received drug A or not drug A, your bonus earnings will be the greatest amount of money that you earned on either the drug A or the not drug A button.

Test Phase. After the acquisition phase, participants entered a test phase. The test phase consisted of test days interspersed with acquisition days. Approximately 60% of these sessions were test days, and the remainder were acquisition days. As noted above, participants were instructed that there would be days on which they would not be given any feedback concerning the accuracy of their drug-discrimination performance and that on these days they would be credited with the greater number of points allocated to the drug A or not drug A option. Thus, these days were similar to the acquisition days except that participants did not receive any feedback concerning their drug-discrimination performance, and they earned the bonus money allocated to drug A or not drug A, whichever was greater. Participants were not told the purpose of these "test" days, nor did they know when they were scheduled until after they opened the sealed envelope.

To ensure that participants continued to reliably discriminate 15 mg of *d*-amphetamine throughout the test phase, acquisition days were intermixed among the test days. These test-of-acquisition days were identical to those in the acquisition phase (i.e., participants received 15 mg of *d*-amphetamine or placebo), completed the drug-discrimination task periodically for 5 h after drug administration, were informed whether they had received drug A or not drug A, and they received bonus money contingent on the accuracy of their drug-discrimination performance. If a participant responded incorrectly on a test-of-acquisition day (i.e., ≤80% correct), additional test-of-acquisition days were scheduled. These additional test-of-acquisition days continued until the participant correctly identified both conditions once (i.e., 15 mg of *d*-amphetamine and placebo).

Ten *d*-amphetamine-risperidone conditions were studied during the test phase of the present experiment: 1) *d*-amphetamine (0 mg) plus risperidone (0 mg); 2) *d*-amphetamine (2.5 mg) plus risperidone (0 mg); 3) *d*-amphetamine (5 mg) plus risperidone (0 mg); 4) *d*-amphetamine (10 mg) plus risperidone (0 mg); 5) *d*-amphetamine (15 mg) plus risperidone (0 mg); 6) *d*-amphetamine (0 mg) plus risperidone (1 mg); 7) *d*-amphetamine (2.5 mg) plus risperidone (1 mg); 8) *d*-amphetamine (5 mg) plus risperidone (1 mg); 9) *d*-amphetamine (10 mg) plus risperidone (1 mg); and 10) *d*-amphetamine (15 mg) plus risperidone (1 mg). The order of drug administration during this phase of the experiment was random except that an active drug dose was never administered on more than three consecutive sessions.

Drug-Discrimination Measure

A point-distribution drug-discrimination task was completed 1, 2, 3, 4, and 5 h after oral drug administration on an Apple Macintosh microcomputer (Apple Computer, Inc., Cupertino, CA). In this procedure, the participant distributed 100 points between two options (i.e., drug A or not drug A) (Rush and Baker, 2001; Rush et al., 2002). Points accumulated on the correct option were exchangeable for money at a rate of $0.08/point. Thus, participants were able to earn a maximum of $40.00/session on this task. The dependent measure in this procedure was percentage of *d*-amphetamine-appropriate responding.

Self-Reported Questionnaires, Performance Task, and Physiological Measures

Self-reported drug-effect questionnaires were administered on an Apple Macintosh microcomputer. The self-reported drug-effect questionnaires were completed in fixed order. These questionnaires were completed approximately 30 min before drug administration, and 1, 2, 3, 4, and 5 h after drug administration.

Stimulant-Sensitive Adjective-Rating Scale. The stimulant-sensitive adjective-rating scale consisted of 21 items that have previously been shown to be sensitive to acute oral administrations of commonly abused stimulants (Di Marino et al., 1998; Rush and Baker, 2001; Rush et al., 2002). Participants rated each item using the computer mouse to point to and select among one of five response options: not at all, a little bit, moderately, quite a bit, and very much (scored numerically from 0 to 4, respectively). Responses to individual items were summed to produce a total score, so the maximum possible score was 84.

Adjective-Rating Scale. The adjective rating scale consisted of 32 items and contained two subscales: sedative and stimulant (Oliveto et al., 1992). Participants rated each of the items using a 5-point scale similar to the one described above. The stimulant subscale consisted of 16 adjectives (i.e., active, alert, irregular heartbeat, good mood, muscles twitching, agitated, energetic, excited, euphoric, irritable, nervous, restless, shaky, sweaty, talkative, and heart racing). The sedative subscale also consisted of 16 adjectives (i.e., clumsy, dizzy, confused, dazed, sleepy, depressed, difficulty walking, drowsy, nausea, drunk, fatigued, lazy, relaxed, tired, sluggish, and spaced out). Responses to individual items were summed to produce a composite score for each subscale. The maximum possible score on each subscale was 64.

Addiction Research Center Inventory (ARCI). The short form of the ARCI consisted of 49 true/false questions and contained five major subscales: morphine-benzedrine group (MBG) (a measure of euphoria); pentobarbital, chlorpromazine, alcohol group (PCAG) (a measure of sedation); lysergic acid diethylamide (LSD) (a measure of dysphoria); and benzedrine group (BG) and amphetamine (A) scales (empirically derived amphetamine-sensitive scales) (Martin et al., 1971; Jasinski, 1977).

Drug-Effect Questionnaire. This questionnaire consisted of 20 items that were presented on the video screen, one at a time. Participants rated each of the items using a 5-point scale similar to the one described above. The items rated were as follows: any effect, bad effects, good effects, high, rush, like drug, stimulated, impairing your performance, improving your performance, take this drug again, pay for this drug, active/alert/energetic, shaky/jittery, euphoric, irregular/racing heartbeat, talkative/friendly, nauseated/queasy/sick to stomach, nervous/anxious, restless, and sluggish/fatigued/lazy.

Digit-Symbol-Substitution Test (DSST). A computerized version of the DSST, which has been described previously, was used in this experiment (McLeod et al., 1982). Briefly, participants used a numeric keypad to enter a geometric pattern associated with one of nine digits displayed on a video screen. Participants had 90 s to enter as many geometric patterns as possible. The dependent measure was the number of patterns the participant entered correctly (i.e., trials correct).

Heart Rate and Blood Pressure. Heart rate and blood pressure were recorded using an automated blood pressure monitor (DINAMAP XL; Johnson and Johnson, Alexandria, TX). Heart rate and blood pressure were monitored for approximately 30 min before drug administration and at hourly intervals for 5 h afterwards. Heart rate and blood pressure were recorded immediately before participants completed the drug-discrimination, self-reported drug-effect questionnaires, and performance task.

Drug Administration

d-Amphetamine doses were prepared by overencapsulating 2.5 or 5 mg of commercially available drug (Dexedrine; SmithKline Beecham, Philadelphia, PA) in a size 00 capsule. Risperidone doses were prepared by overencapsulating 1 mg of commercially available drug (Risperdal; Janssen Pharmaceutica, Titusville, NJ) in a size 00 capsule. Lactose was used to fill the remainder of all the capsules. Placebo capsules contained only lactose.

During each experimental session participants ingested four capsules (i.e., three *d*-amphetamine- or placebo-containing capsules, and one risperidone- or placebo-containing capsule). Administering the appropriate number of drug- or placebo-containing capsules varied dose. Capsules were taken orally with approximately 150 ml of water. Drug administration procedures were designed to ensure that participants swallowed the capsules. To accomplish this, the research assistant 1) watched the participant to ensure that he/she swallowed the capsules and did not remove them from his/her mouth, 2) conducted a brief oral examination to ensure that the participant was not hiding the capsules under his/her tongue, and 3) spoke with the participant to determine whether he/she had anything in his/her mouth.

The behavioral effects of *d*-amphetamine peak approximately 2 to 3 h after oral administration (Chait et al., 1985, 1986a,b; Rush et al., 1998). Peak risperidone plasma concentrations occur approximately 1 h after oral administration (Grant and Fitton, 1994; Gupta et al., 1994; Keegan, 1994). Peak 9-hydroxyrisperidone concentrations occur approximately 3 h after oral administration (Gupta et al., 1994). The antipsychotic effects likely result from the combined concentrations of risperidone and 9-hydroxyrisperidone (Grant and Fitton, 1994; Gupta et al., 1994; Keegan, 1994). Based on these pharmacokinetic data, *d*-amphetamine and risperidone were administered simultaneously to assess behavioral effects across peak plasma levels of both drugs.

References below to placebo pertain to sessions in which placebo doses of both *d*-amphetamine and risperidone were administered. References to *d*-amphetamine alone pertain to sessions in which an active dose of *d*-amphetamine was administered in combination with 0 mg of risperidone. References to risperidone alone pertain to sessions in which the active dose of risperidone was administered in combination with 0 mg of *d*-amphetamine .

Data Analysis

Statistical analyses of group data were conducted to examine drug effects on the drug-discrimination task, self-reported drug-effect questionnaires, and performance measure. Data were analyzed statistically as raw scores. To correct for multiple comparisons and maintain consistency across measures, effects were considered significant for $p \leq 0.01$. For the 15 mg of *d*-amphetamine alone and placebo conditions, data were averaged across the four sessions of the acquisition phase in which the participant met the discrimination criterion as well as all exposures to these conditions in the test phase. Drug-discrimination data were analyzed statistically as the total percentage of points allocated to the drug option across the 5-h session (i.e., percentage of drug-appropriate responding). Self-reported drug-effect questionnaire and performance data were analyzed statistically as area under the time-action curve (AUC), which was calculated using the trapezoidal method. Data were then analyzed by two-factor repeated measure analysis of variance (ANOVA)

with *d*-amphetamine (0, 2.5, 5, 10, and 15 mg) and risperidone (0 and 1 mg) as factors (StatView 5.0.1; SAS Institute Inc., Cary, NC). Planned comparisons (i.e., Fisher's least significant difference) were conducted if a significant effect of *d*-amphetamine or risperidone was detected. These planned comparisons were used to make appropriate pairwise comparisons between means. Planned comparisons were first conducted to compare each of the nine active drug conditions with placebo. If a dose of *d*-amphetamine alone increased responding significantly above placebo, planned comparisons were conducted to compare the effects of these doses of *d*-amphetamine alone and after pretreatment with 1 mg of risperidone. Finally, if risperidone alone increased responding significantly above placebo, planned comparisons were conducted to compare this condition with each of the *d*-amphetamine-risperidone conditions.

Results

Drug-Discrimination Performance. The eight participants met the discrimination criterion in an average of 6.4 sessions (range = 4–11). ANOVA revealed a significant effect of *d*-amphetamine ($F_{4,28}$ = 6.8, p = 0.0006). Planned comparisons revealed that *d*-amphetamine (5, 10, and 15 mg) alone increased drug-appropriate responding significantly above placebo levels (Fig. 1). Only the combination of 10 mg of *d*-amphetamine and 1 mg of risperidone increased drug-appropriate responding significantly above placebo levels. Planned comparisons further revealed that percentage of drug-appropriate responding was significantly lower after the administration of 15 mg of *d*-amphetamine and 1 mg of risperidone relative to 15 mg of *d*-amphetamine alone.

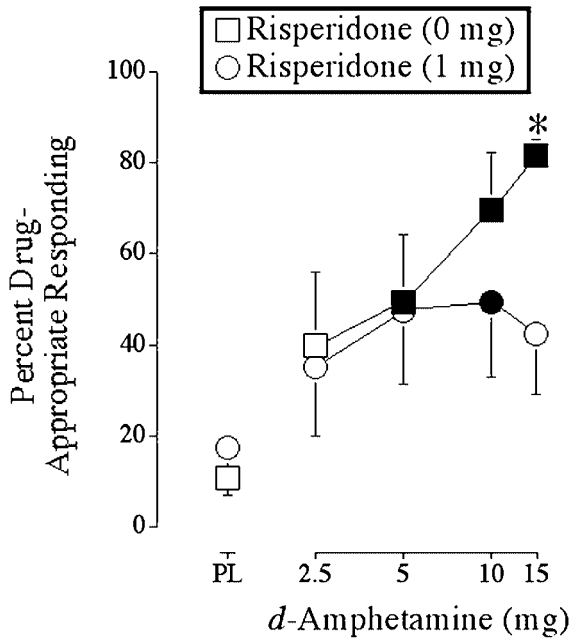

Fig. 1. Percentage of drug-appropriate appropriate responding for *d*-amphetamine alone, risperidone alone, *d*-amphetamine-risperidone combinations, and placebo. *x*-axes, *d*-amphetamine dose. Data points above placebo (PL) represent values when the doses of risperidone were administered in combination with 0 mg of *d*-amphetamine. Connected data points above 2.5, 5, 10, and 15 represent the effects of the *d*-amphetamine dose administered in combination with 0 mg (squares) or 1 mg (circles) of risperidone. Data points show means of eight participants. Brackets indicate one S.E.M. Filled symbols indicate those values that are significantly different from the placebo-placebo condition (i.e., square above PL). An asterisk indicates a significant difference between the 0 and 1 mg of risperidone conditions at the indicated *d*-amphetamine dose.

Stimulant-Sensitive Adjective-Rating Scale. ANOVA revealed a significant effect of *d*-amphetamine on scores on the Stimulant-Sensitive Adjective-Rating Scale ($F_{4,28}$ = 8.9, $p < 0.0001$). Planned comparisons revealed that 10 and 15 mg of *d*-amphetamine alone increased these ratings significantly above placebo levels (Fig. 2). The combination of 15 mg of *d*-amphetamine and 1 mg of risperidone also increased scores on the stimulant-sensitive adjective-rating scale significantly above placebo levels. Planned comparisons further revealed that these scores were significantly lower after the administration of 15 mg of *d*-amphetamine and 1 mg of risperidone relative to this dose of *d*-amphetamine alone.

Adjective-Rating Scale. ANOVA revealed a significant effect of *d*-amphetamine on scores on the Stimulant Scale of the Adjective-Rating Scale ($F_{4,28}$ = 8.8, $p < 0.0001$). Planned comparisons revealed that only 10 and 15 mg of *d*-amphetamine alone increased these scores significantly above placebo levels (Fig. 2). Planned comparisons also revealed that these ratings were significantly lower after the administration of these doses of *d*-amphetamine in combination with 1 mg of risperidone. There were no statistically significant effects on the Sedative Scale of the Adjective-Rating Scale.

ARCI. ANOVA revealed a significant effect of *d*-amphetamine on the A ($F_{4,28}$ = 7.3, p = 0.0004) and MBG ($F_{4,28}$ = 4.5, p = 0.006) scales of the ARCI, and a significant effect of risperidone on the A ($F_{1,7}$ = 11.4, p = 0.01), BG ($F_{1,7}$ = 10.4, p = 0.01), and PCAG ($F_{1,7}$ = 10.7, p = 0.01) scales. Planned comparisons revealed that 10 and 15 mg to *d*-amphetamine alone increased scores on the A and MBG scales significantly above placebo levels (Fig. 2). Risperidone pretreatment did not alter these effects of these doses of *d*-amphetamine to a statistically significant degree. Even though, as noted above, ANOVA revealed a significant effect of risperidone on the BG and PCAG scales, planned comparisons revealed that none of the dose conditions differed significantly from placebo.

Drug-Effect Questionnaire. ANOVA revealed a significant effect of *d*-amphetamine on seven items on the drug-effect questionnaire: willing to take again ($F_{4,28}$ = 5.5, p = 0.002), like drug ($F_{4,28}$ = 5.3, p = 0.003), good effects ($F_{4,28}$ = 5.9, p = 0.001), stimulated ($F_{4,28}$ = 5.0, p = 0.004), active/alert/energetic ($F_{4,28}$ = 4.5, p = 0.006), any effect ($F_{4,28}$ = 4.6, p = 0.006), and irregular/racing heart ($F_{4,28}$ = 4.5, p = 0.006). Figure 3 shows the effects of *d*-amphetamine, alone and after risperidone pretreatment for five of these items: willing to take again, like drug, good effects, stimulated and active/alert/energetic, along with ratings of talkative/friendly, which are described below. This figure shows that 10 and 15 mg of *d*-amphetamine alone increased these ratings significantly above placebo. Planned comparisons revealed that ratings of willing to take again were significantly lower after the administration of these doses of *d*-amphetamine in combination with 1 mg of risperidone. Planned comparisons revealed that ratings of like drug, good effects, stimulated, and active/alert/energetic were significantly lower after the administration of 15 mg of *d*-amphetamine in combination with 1 mg of risperidone relative to this dose of *d*-amphetamine alone.

Planned comparisons revealed that 10 and 15 mg of *d*-amphetamine alone increased ratings of any effects significantly above placebo levels, whereas only the highest dose of *d*-amphetamine alone increased ratings of irregular/racing

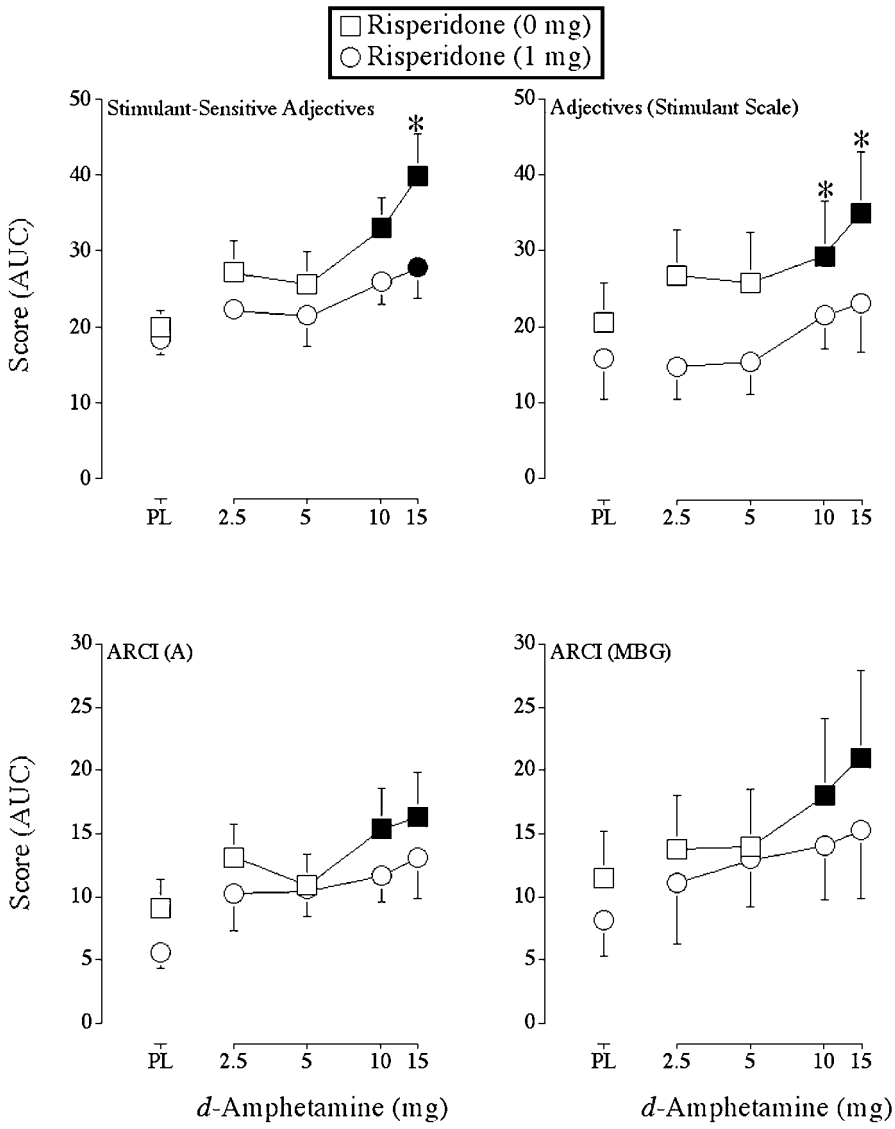

Fig. 2. Effects of *d*-amphetamine alone, risperidone alone, *d*-amphetamine-risperidone combinations, and placebo on the Stimulant-Sensitive Adjective-Rating Scale; the stimulant scale of the Adjective-Rating Scale; and the A and MBG scales of the ARCI. Data are expressed as AUC. *x*-axes: *d*-amphetamine dose. Data points above placebo (PL) represent values when the doses of risperidone were administered in combination with 0 mg of *d*-amphetamine. Connected data points above 2.5, 5, 10, and 15 represent the effects of the *d*-amphetamine dose administered in combination with 0 mg (squares) or 1 mg (circles) of risperidone. Data points show means of eight participants. Brackets indicate one S.E.M. Filled symbols indicate those values that are significantly different from the placebo-placebo condition (i.e., square above PL). An asterisk indicates a significant difference between the 0 and 1 mg of risperidone conditions at the indicated *d*-amphetamine dose.

heart (data not shown). These effects were not altered to a significant degree by risperidone pretreatment.

ANOVA revealed a significant interaction of *d*-amphetamine and risperidone on ratings of talkative/friendly ($F_{4,28}$ = 5.4, p = 0.002) and bad effects ($F_{4,28}$ = 4.7, p = 0.005). Planned comparisons revealed that 10 and 15 mg of *d*-amphetamine alone increased ratings of talkative/friendly significantly above placebo levels (Fig. 3). Planned comparisons further revealed that relative to these doses of *d*-amphetamine alone ratings of talkative/friendly were significantly lower after the administration of 10 and 15 mg of *d*-amphetamine in combination with 1 mg of risperidone. Planned comparisons revealed that only the combination of 2.5 mg of *d*-amphetamine and 1 mg of risperidone increased ratings of bad effects significantly above placebo levels (data not shown).

DSST. ANOVA revealed a significant effect of risperidone on trials correct on the DSST ($F_{1,7}$ = 17.2, p = 0.004). Planned comparisons revealed that 10 mg of *d*-amphetamine alone increased trials correct on the DSST, whereas 1 mg of risperidone alone decreased the number of trials correct significantly below placebo levels (data not shown). Combining 10 mg of *d*-amphetamine and 1 mg of risperidone resulted in a mutual antagonism of these effects.

Heart Rate and Blood Pressure. ANOVA revealed a significant effect of *d*-amphetamine ($F_{4,28}$ = 5.3, p = 0.003) and risperdone ($F_{1,7}$ = 11.3, p = 0.01) on heart rate. Planned comparisons revealed that *d*-amphetamine (5, 10, and 15 mg) in combination with 1 mg of risperidone, but not alone, increased heart rate significantly above placebo levels (Fig. 4).

ANOVA revealed a significant effect of *d*-amphetamine on mean arterial pressure ($F_{4,28}$ = 6.4, p = 0.0009). Planned comparisons revealed that the two higher doses of *d*-amphetamine alone, and the combination 15 mg of *d*-amphetamine and 1 mg of risperidone, increased mean arterial pressure significantly above levels observed with placebo (Fig. 4). Combining *d*-amphetamine and risperidone did not significantly alter the blood pressure effects relative to those observed with *d*-amphetamine alone.

Discussion

In the present experiment, the discriminative-stimulus and self-reported effects of *d*-amphetamine were assessed

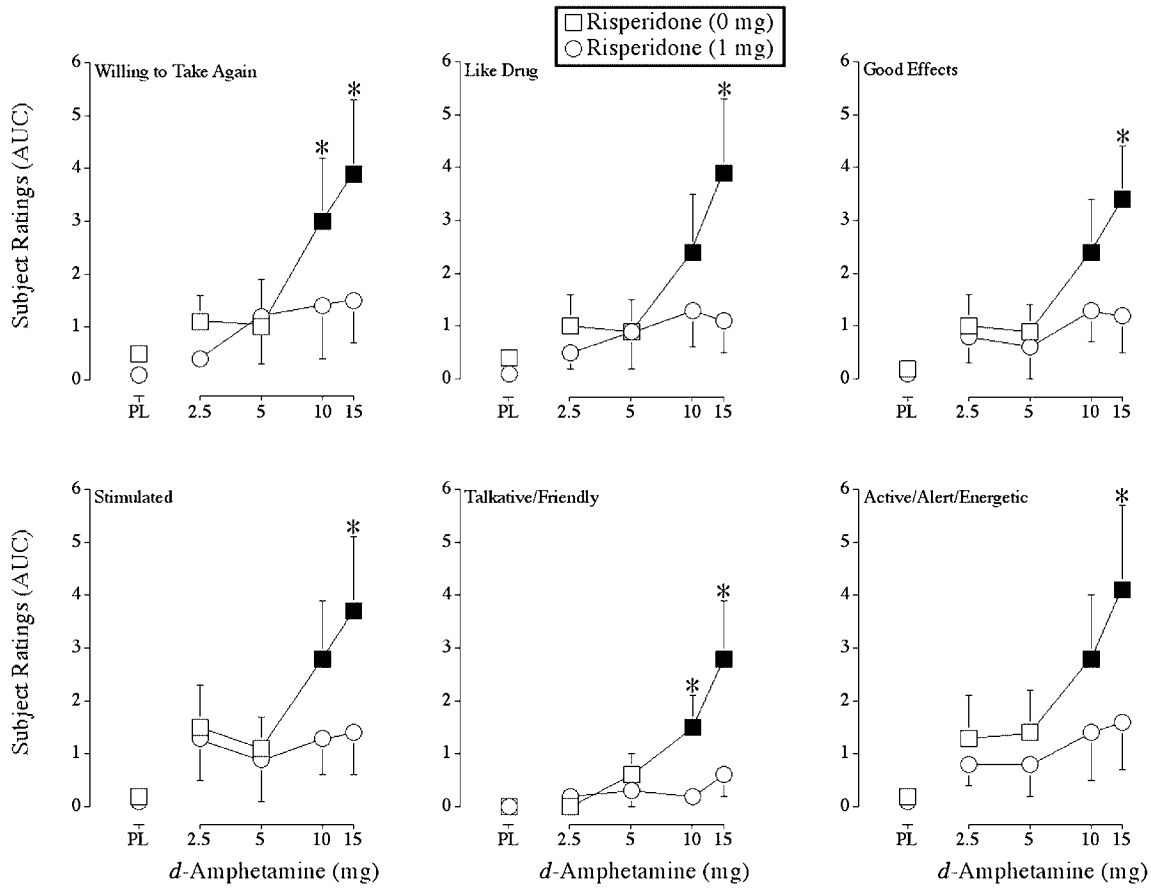

Fig. 3. Effects of *d*-amphetamine alone, risperidone alone, *d*-amphetamine-risperidone combinations, and placebo on ratings of willing to take again, like drug, good effects, stimulated, talkative/friendly, and active/alert/energetic from the drug-effect questionnaire. Data are expressed as AUC. *x*-axes, *d*-amphetamine dose. Data points above placebo (PL) represent values when the doses of risperidone were administered in combination with 0 mg of *d*-amphetamine. Connected data points above 2.5, 5, 10, and 15 represent the effects of the *d*-amphetamine dose administered in combination with 0 mg (squares) or 1 mg (circles) of risperidone. Data points show means of eight participants. Brackets indicate one S.E.M. Filled symbols indicate those values that are significantly different from the placebo-placebo condition (i.e., square above PL). An asterisk indicates a significant difference between the 0 and 1 mg of risperidone conditions at the indicated *d*-amphetamine dose.

alone and after pretreatment with risperidone in *d*-amphetamine-trained humans. *d*-Amphetamine alone functioned as a discriminative stimulus and dose dependently increased drug-appropriate responding. *d*-Amphetamine alone also produced stimulant-like self-reported drug effects (e.g., increased ratings of like drug) that were generally dose-dependent. These findings are concordant with the results of several previous reports in which the discriminative-stimulus and self-reported effects of *d*-amphetamine were assessed in humans (Chait et al., 1984, 1985, 1986a,b; Chait and Johanson, 1988; Heishman and Henningfield, 1991; Lamb and Henningfield, 1994; Rush et al., 1998; Kollins and Rush, 1999).

Risperidone alone did not occasion *d*-amphetamine-appropriate responding, nor did it produce significant increases on self-reported indices thought to measure sedation (e.g., PCAG scores of the ARCI). The results of the present experiment are concordant with those from a previous study in which 0.75 mg of risperidone alone did not significantly increase PCAG scores (Wachtel et al., 2002). Risperidone alone significantly impaired performance on a computerized version of the DSST, which is concordant with the results of a previous study in which 0.75 mg of risperidone impaired performance on a paper-and-pencil version of the DSST (Wachtel et al., 2002).

Risperidone pretreatment significantly attenuated the discriminative-stimulus effects of *d*-amphetamine. Although the discriminative-stimulus effects of *d*-amphetamine after pretreatment with various atypical antipsychotics have been widely studied in laboratory animals (Kilbey and Ellinwood, 1979; Nielsen and Jepsen, 1985; Meert, 1991, 1996; Arnt, 1992, 1996; Mechanic et al., 2002), we are unaware of any published studies in which a similar strategy was used with humans. The results of the present human laboratory experiment are concordant with those from previous studies in which the discriminative-stimulus effects of *d*-amphetamine were assessed alone and after risperidone pretreatment in amphetamine-trained rats (Meert, 1991, 1996). In these experiments, rats were trained to discriminate 1.25 mg/kg *d*-amphetamine. As expected, *d*-amphetamine (0.08–0.63 mg/kg) dose dependently increased the number of rats selecting the drug lever. Risperidone (0.05–1.25 mg/kg) dose dependently decreased the number of rats selecting the drug lever after administration of 1.25 mg/kg *d*-amphetamine. Worth noting is that the highest dose of risperidone tested completely blocked the discriminative-stimulus effects of 1.25 mg/kg *d*-amphetamine. We are not aware of any published reports in which the discriminative-stimulus effects of *d*-amphetamine were assessed alone and after pretreatment with risperidone in primates.

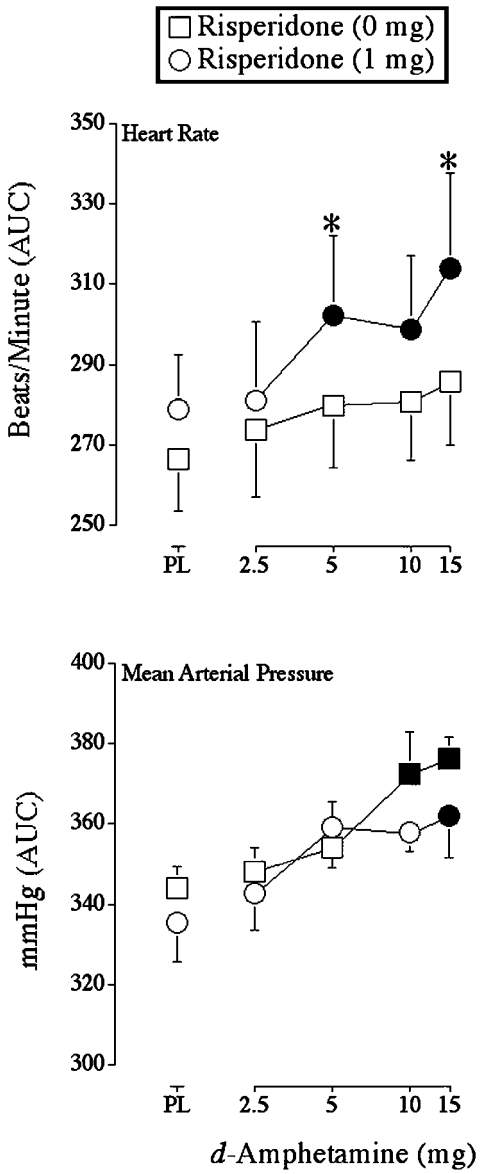

Fig. 4. Effects of *d*-amphetamine alone, risperidone alone, *d*-amphetamine-risperidone combinations, and placebo on heart rate and mean arterial pressure. Data are expressed as AUC. *x*-axes, *d*-amphetamine dose. Data points above placebo (PL) represent values when the doses of risperidone were administered in combination with 0 mg of *d*-amphetamine. Connected data points above 2.5, 5, 10, and 15 represent the effects of the *d*-amphetamine dose administered in combination with 0 mg (squares) or 1 mg (circles) of risperidone. Data points show means of eight participants. Brackets indicate one S.E.M. Filled symbols indicate those values that are significantly different from the placebo-placebo condition (i.e., square above PL). An asterisk indicates a significant difference between the 0 and 1 mg of risperidone conditions at the indicated *d*-amphetamine dose.

As mentioned above, risperidone is an antagonist at the D_2 dopamine and 5-HT_2 serotonin receptors (for reviews, see Grant and Fitton, 1994; Gupta et al., 1994; Keegan, 1994). Future studies with humans should compare the discriminative-stimulus effects of *d*-amphetamine after pretreatment with a more selective D_2 dopamine (e.g., haloperidol) and 5-HT_2 serotonin (e.g., ritanserin) antagonist to discern the relative contribution of dopamine or serotonin. Such experiments would more clearly determine the neuropharmacological factors that mediate the behavioral effects of stimulants in humans and might guide the development of a pharmacotherapy for the treatment of stimulant abuse/dependence.

Risperidone pretreatment also significantly attenuated some of the self-reported effects of *d*-amphetamine (e.g., ratings willing to take again and like drug on the drug-effect questionnaire). The present findings are discordant with the results from a previously published study in which the effects of methamphetamine (0 and 20 mg) were assessed after pretreatment with risperidone (0 and 0.75 mg) (Wachtel et al., 2002). In this previous study, risperidone pretreatment did not alter the self-reported effects of methamphetamine to a statistically significant degree. The reason for the discrepancy between the results of this previous report and the present experiment is unknown, but may be due to the use of different methods. First, and perhaps most notably, participants in the present experiment were trained to discriminate 15 mg of *d*-amphetamine before testing the effects of the *d*-amphetamine-risperidone combinations. Participants received money for correctly discriminating 15 mg of *d*-amphetamine as part of this training. This training continued during the test phase when the effects of the *d*-amphetamine-risperidone conditions were determined. What impact, if any, the training and monetary contingencies had on subsequent self-reported responses to the *d*-amphetamine-risperidone combinations is unknown. Second, in the present experiment a higher risperidone dose (i.e., 1 mg) was tested than was used in the previous study (i.e., 0.75 mg). Future experiments should determine whether lower risperidone doses might also attenuate the self-reported effects of *d*-amphetamine under conditions similar to those used in the present experiment (i.e., *d*-amphetamine-trained participants). Third, we tested a lower dose of *d*-amphetamine (i.e., 15 mg) relative to the dose of methamphetamine (i.e., 20 mg) that was used in the previous study. *d*-Amphetamine and methamphetamine are approximately equipotent (Lamb and Henningfield, 1994). Future studies should also determine whether risperidone attenuates the self-reported effects of higher *d*-amphetamine doses under conditions similar to those used in the present experiment. Ideally, a future study should assess the self-reported effects of a wide range of doses of *d*-amphetamine alone and after pretreatment with several doses of risperidone under experimental conditions similar to those used in the present experiment. However, the conduct of such a study with humans would present both ethical (i.e., increased number of drug exposures) and practical problems (i.e., participant attrition) (Fischman and Johanson, 1998).

Although pretreating participants with risperidone significantly attenuated some of the self-reported effects of *d*-amphetamine, this effect was not observed on other self-reported drug-effect measures (e.g., A and MBG scores on the ARCI). The A and MBG scales of the ARCI are widely used instruments that are sensitive to the acute effects of stimulants (Heishman and Henningfield, 1991; Lamb and Henningfield, 1994; Rush and Baker, 2001; Wachtel et al., 2002). The failure of risperidone to significantly attenuate the effects of *d*-amphetamine on the A and MBG scales of the ARCI in the present experiment is concordant with the results of a previous study in which the effects of methamphetamine-risperidone combinations were examined (Wachtel et al., 2002). The results of the present experiment along with those from this previous study suggest that the ARCI may have

limited utility for examining the combined effects of an agonist and antagonist.

We are aware of only two published studies in which the discriminative-stimulus and self-reported effects of a stimulant drug were assessed after pretreatment with an antagonist (Oliveto et al., 1997; Perkins et al., 1999). In the first study, six participants were trained to discriminate between caffeine (320 mg/70 kg) and placebo (Oliveto et al., 1997). A range of doses of caffeine (56–560 mg/70 kg) was then tested. The discriminative-stimulus effects of 320 mg/70 kg caffeine were assessed after pretreatment with a range of doses of triazolam (0.1–0.032 mg/70 kg) and buspirone (1–18 mg/kg). The discriminative-stimulus effects of a range of doses of caffeine (56–560 mg/70 kg) were also assessed alone and after pretreatment with a single dose of triazolam (0.18, 0.24, or 0.56 mg/70 kg, determined individually). Caffeine alone dose dependently increased drug-appropriate responding. Triazolam, but not buspirone, dose dependently attenuated the discriminative-stimulus effects of the training dose of caffeine. Triazolam pretreatment shifted the caffeine dose-response rightward. Caffeine alone dose dependently increased ratings of high and anxious. Triazolam did not significantly attenuate these self-reported effects of caffeine. In the second study, six smokers were trained to discriminate between 20 μg/kg intranasal nicotine and placebo (Perkins et al., 1999). A range of doses of nicotine (0, 3, 6, 12, and 20 μg/kg) was then tested alone and after pretreatment with mecamylamine (10 mg p.o.), a central and peripheral nicotine antagonist, and trimethaphan (10–40 μg/kg/min i.v.), a peripheral nicotine antagonist. Nicotine alone produced a significant dose-dependent increase in nicotine-appropriate responding and ratings of stimulated and buzzed. Mecamylamine, but not trimethaphan, attenuated the discriminative-stimulus and self-reported effects of nicotine. These results along with those from the present experiment suggest that combining drug-discrimination and self-reported drug-effect questionnaires may be an effective strategy for assessing the behavioral effects of agonist-antagonist interactions.

d-Amphetamine alone improved performance on the DSST, whereas risperidone alone impaired performance. Combining *d*-amphetamine and risperidone also resulted in a mutual antagonism of effects on the DSST relative to those observed with the constituent drugs. The results of the present experiment must therefore be viewed cautiously because the antagonism observed when *d*-amphetamine and risperidone were combined might be functional in nature rather than receptor-mediated. Future studies should test the discriminative-stimulus and self-reported effects of *d*-amphetamine alone and after pretreatment with a dose of risperidone that is devoid of behavioral effects when administered alone (e.g., 0.5 mg).

Future studies should use other drug-discrimination tasks such as the novel-response procedure because combining *d*-amphetamine and risperidone may have produced a unique stimulus complex (Bickel et al., 1993). The novel-response procedure provides an alternative for drug effects that are unlike those of the training drugs (e.g., *d*-amphetamine and placebo), and may be more sensitive for detecting differences between the discriminative-stimulus effects of agonist-antagonists combinations.

Finally, the results of the present experiment suggest that risperidone might be an effective pharmacotherapy for the treatment of stimulant abuse/dependence. However, the results of a rigorous clinical trial suggest that risperidone (2, 4, and 8 mg once daily in the evening) was not effective in reducing drug use or improving retention in treatment in cocaine-dependent patients relative to placebo (Grabowski et al., 2000). In fact, 4 and 8 mg of risperidone reduced treatment retention below levels observed with placebo, and the trial was terminated after conducting an interim analysis. The risperidone-treated patients often mentioned side effects as the reason for discontinuing their participation in the trial. Whether the lower dose of risperidone tested in the present experiment, 1 mg, might be acceptable to patients and reduce drug use is unknown, but certainly warrants scientific attention given the lack of an effective pharmacotherapy for the management of stimulant abuse/dependence.

Acknowledgments

We thank Frances Wagner, Jamie L. Haga, Allison Weber, Michelle Gray, Abigail Osborne, and Joe Kingery for expert medical and technical assistance.

References

Arnt J (1992) Sertindole and several antipsychotic drugs differentially inhibit the discriminative stimulus effects of amphetamine, LSD and St 587 in rats. *Behav Pharmacol* **3:**11–18.

Arnt J (1996) Inhibitory effects on the discriminative stimulus properties of D-amphetamine by classical and newer antipsychotics do not correlate with antipsychotic activity. Relation to effects on the reward system? *Psychopharmacology (Berl)* **124:**117–125.

Bickel WK, Oliveto AH, Kamien JB, Higgins ST, and Hughes JR (1993) A novel-response procedure enhances the selectivity and sensitivity of a triazolam discrimination in humans. *J Pharmacol Exp Ther* **264:**360–367.

Chait LD and Johanson CE (1988) Discriminative stimulus effects of caffeine and benzphetamine in amphetamine-trained volunteers. *Psychopharmacology (Berl)* **96:**302–308.

Chait LD, Uhlenhuth EH, and Johanson CE (1984) An experimental paradigm for studying the discriminative stimulus properties of drugs in humans. *Psychopharmacology (Berl)* **82:**272–274.

Chait LD, Uhlenhuth EH, and Johanson CE (1985) The discriminative stimulus and subjective effects of d-amphetamine in humans. *Psychopharmacology (Berl)* **86:** 307–312.

Chait LD, Uhlenhuth EH, and Johanson CE (1986a) Human drug discrimination: *d*-amphetamine and other anorectics. *NIDA Res Monogr* **67:**161–167.

Chait LD, Uhlenhuth EH, and Johanson CE (1986b) The discriminative stimulus and subjective effects of phenylpropanolamine, mazindol and d-amphetamine in humans. *Pharmacol Biochem Behav* **24:**1665–1672.

Di Marino ME, Haberny KA, Felch LJ, Walsh SL, Preston KL, and Bigelow GE (1998) Development of a subjective rating scale sensitive to acute cocaine administration. *National Institute on Drug Abuse Research Monograph Series, Problems of Drug Dependence, 1997: Proceedings of the 59th Annual Scientific Meeting* **178:**139.

Fischman MW and Johanson CE (1998) Ethical and practical issues involved in behavioral pharmacology research that administers drugs of abuse to human volunteers. *Behav Pharmacol* **9:**479–498.

Fitton A and Heel RC (1990) Clozapine. A review of its pharmacological properties and therapeutic use in schizophrenia. *Drugs* **40:**722–747.

Fulton B and Goa KL (1997) Olanzapine. A review of its pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. *Drugs* **53:**281–298.

Grabowski J, Rhoades H, Silverman P, Schmitz JM, Stotts A, Creson D, and Bailey R (2000) Risperidone for the treatment of cocaine dependence: randomized, double-blind trial. *J Clin Psychopharmacol* **20:**305–310.

Grant S and Fitton A (1994) Risperidone. A review of its pharmacology and therapeutic potential in the treatment of schizophrenia. *Drugs* **48:**253–273.

Gupta S, Black DW, and Smith DA (1994) Risperidone: review of its pharmacology and therapeutic use in schizophrenia. *Ann Clin Psychiatry* **6:**173–180.

Heishman SJ and Henningfield JE (1991) Discriminative stimulus effects of d-amphetamine, methylphenidate and diazepam in humans. *Psychopharmacology (Berl)* **103:**436–442.

Jasinski D (1977) Assessment of the abuse potentiality of morphine-like drugs (methods used in man), in *Drug Addiction I* (Martin WR ed) pp 197–258, Springer-Verlag New York Inc., New York.

Kamien JB, Bickel WK, Hughes JR, Higgins ST, and Smith BJ (1993) Drug discrimination by humans compared to nonhumans: current status and future directions. *Psychopharmacology (Berl)* **111:**259–270.

Keegan D (1994) Risperidone: neurochemical, pharmacologic and clinical properties of a new antipsychotic drug. *Can J Psychiatry* **39:**S46–S52.

Kilbey MM and Ellinwood EH Jr (1979) Discriminative stimulus properties of psychomotor stimulants in the cat. *Psychopharmacology (Berl)* **63:**151–153.

Kollins SH and Rush CR (1999) Effects of training dose on the relationship between discriminative-stimulus and self-reported drug effects of d-amphetamine in humans. *Pharmacol Biochem Behav* **64:**319–326.
Lamb RJ and Henningfield JE (1994) Human *d*-amphetamine drug discrimination: methamphetamine and hydromorphone. *J Exp Anal Behav* **61:**169–180.
Martin WR, Sloan JW, Sapira JD, and Jasinski DR (1971) Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine and methylphenidate in man. *Clin Pharmacol Ther* **12:**245–258.
McLeod DR, Griffiths RR, Bigelow GE, and Yingling JE (1982) An automated version of the digit symbol substitution test (DSST). *Behav Res Methods Instr* **14:**463–466.
Mechanic JA, Wasielewski JA, Carl KL, and Holloway FA (2002) Attenuation of the amphetamine discriminative cue in rats with the atypical antipsychotic olanzapine. *Pharmacol Biochem Behav* **72:**767–777.
Meert TF (1991) Application of drug discrimination with drugs of abuse to develop new therapeutic agents. *NIDA Res Monogr* 307–323.
Meert TF (1996) Serotonin mechanisms in antipsychotic treatment: evidence from drug discrimination studies, in *Serotonin in Antipsychotic Treatment. Mechanisms and Clinical Practice* (Kane JM, Moller HJ, and Awouters F eds) pp 109–130, Marcel Dekker, Inc., New York.
Nielsen EB and Jepsen SA (1985) Antagonism of the amphetamine cue by both classical and atypical antipsychotic drugs. *Eur J Pharmacol* **111:**167–176.
Oliveto AH, Bickel WK, Hughes JR, Higgins ST, and Badger G (1997) Functional antagonism of the caffeine-discriminative stimulus by triazolam in humans. *Behav Pharmacol* **8:**124–138.
Oliveto AH, Bickel WK, Hughes JR, Shea PJ, Higgins ST, and Fenwick JW (1992) Caffeine drug discrimination in humans: acquisition, specificity and correlation with self-reports. *J Pharmacol Exp Ther* **261:**885–894.
Perkins KA, Sanders M, Fonte C, Wilson AS, White W, Stiller R, and McNamara D (1999) Effects of central and peripheral nicotinic blockade on human nicotine discrimination. *Psychopharmacology (Berl)* **142:**158–164.
Physician's Desk Reference (2003) Medical Economics Company, Inc., Oradell, NJ.
Rush CR and Baker RW (2001) Behavioral pharmacological similarities between methylphenidate and cocaine in cocaine abusers. *Exp Clin Psychopharmacol* **9:**59–73.
Rush CR, Kelly TH, Hays LR, and Wooten AF (2002) Discriminative-stimulus effects of modafinil in cocaine-trained humans. *Drug Alcohol Depend* **67:**311–322.
Rush CR, Kollins SH, and Pazzaglia PJ (1998) Discriminative-stimulus and participant-rated effects of methylphenidate, bupropion and triazolam in d-amphetamine-trained humans. *Exp Clin Psychopharmacol* **6:**32–44.
Wachtel S, Ortengren A, and Wit H (2002) The effects of acute haloperidol or risperidone on subjective responses to methamphetamine in healthy volunteers. *Drug Alcohol Depend* **68:**23–33.

Address correspondence to: Dr. Craig R. Rush, Department of Behavioral Science, University of Kentucky, Lexington, KY 40536-0086. E-mail: crush2@uky.edu