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Discriminative-stimulus effects of modafinil in cocaine-trained humans

Craig R. Rush [a,b,c,*], Thomas H. Kelly [a,c], Lon R. Hays [b], Adam F. Wooten [b]

[a] *Department of Behavioral Science, University of Kentucky, Lexington, KY 40536-0086, USA*
[b] *Department of Psychiatry, University of Kentucky, Lexington, KY 40536, USA*
[c] *Department of Psychology, University of Kentucky, Lexington, KY 40536, USA*

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Abstract

Modafinil is a novel stimulant that is effective in the treatment of narcolepsy and excessive daytime sleepiness. In vitro and in vivo neuropharmacological data suggest that the mechanism of action of modafinil is distinct from that of prototypical abused stimulants like cocaine and *d*-amphetamine. In the present experiment, six human volunteers with recent histories of cocaine use learned to discriminate 150 mg oral cocaine HCL. After acquiring the discrimination (i.e. $\geq$80% correct responding on 4 consecutive days), a range of doses of oral cocaine (50, 100, and 150 mg), modafinil (200, 400, and 600 mg), and placebo were tested to determine if they shared discriminative-stimulus and self-reported effects with 150 mg cocaine. Methylphenidate (60 mg) and triazolam (0.5 mg) were included as positive and negative controls, respectively. Cocaine and methylphenidate, but neither modafinil nor triazolam, produced cocaine-like discriminative-stimulus, subject-rated, and cardiovascular effects. The results of the present experiment suggest that cocaine discrimination in humans is pharmacologically specific within and across drug classes. © 2002 Published by Elsevier Science Ireland Ltd.

Keywords: Modafinil; Cocaine; Stimulants; Discriminative effects; Subjective effects

1. Introduction

Stimulants are widely used clinically. *d*-Amphetamine and methylphenidate, for example, are commonly prescribed for sleep disorders (e.g. excessive daytime sleepiness or narcolepsy), Attention Deficit Hyperactivity Disorder (ADHD), appetite suppression, and antidepressant augmentation (e.g. for a review see Holmes, 1995). While stimulants like *d*-amphetamine and methylphenidate are effective in the management of these clinical conditions, their use can be problematic. Most notably, *d*-amphetamine and methylphenidate have abuse potential and dependence liability (for reviews see Kollins et al., 2001; Seiden et al., 1993).

The problems associated with *d*-amphetamine and methylphenidate have led to the development and marketing of novel stimulants. Modafinil, for example, is structurally and chemically unrelated to amphetamine and is clinically effect in the treatment of narcolepsy or excessive daytime sleepiness (Broughton et al., 1997; Moldofsky et al., 2000; US Modafinil in Narcolepsy Multicenter Study Group, 2000). In addition to narcolepsy, modafinil is also being tested in the treatment of disorders for which other stimulants (e.g. *d*-amphetamine and methylphenidate) are traditionally prescribed. Two recently published studies, for example, reported that modafinil is effective in the treatment of ADHD in children and adults (Rugino and Copley, 2001; Taylor and Russo, 2000). Modafinil has also been used successfully to augment the effects of antidepressants in depressed patients (Menza et al., 2000). Finally, modafinil has been shown to suppress food intake in healthy volunteers (Makris et al., 2001).

The neuropharmacologic mechanisms that mediate the stimulant effects of modafinil are unknown. Modafinil, however, appears to differ pharmacologically from prototypical stimulants like cocaine, *d*-amphetamine, and methylphenidate (e.g. Akaoka et al., 1991;

* Corresponding author. Tel.: +1-859-323-6130; fax: +1-859-323-5350
E-mail address: crush2@uky.edu (C.R. Rush).

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Ferraro et al., 1997; Lin et al., 1996; Mignot et al., 1994). Modafinil binds with weak affinity to the dopamine transporter (DAT), while cocaine binds with high affinity (Mignot et al., 1994). Modafinil only weakly increases dopamine release in the nucleus accumbens, while *d*-amphetamine produces potent increases (Ferraro et al., 1997). Finally, analysis of whole-brain metabolic activity using c-*fos* expression suggests that modafinil and commonly prescribed stimulants like *d*-amphetamine and methylphenidate differentially affect global neuronal functioning and act in varying brain nuclei (Lin et al., 1996).

Consistent with the biochemical differences noted above, laboratory studies with non-human laboratory animals suggest that the behavioral effects of modafinil differ from those of commonly abused stimulants like cocaine (Gold and Balster, 1996). In this experiment, six rats were trained to discriminate 10 mg/kg cocaine. After acquiring the discrimination, a range of doses of modafinil (3–100 mg/kg) was tested to determine if they shared discriminative-stimulus effects with cocaine. On average, the highest dose of modafinil tested engendered 67% drug-appropriate responding even though it substantially reduced rates of responding. We are not aware of any published studies in which the discriminative-stimulus effects of modafinil were assessed in cocaine-trained primates.

The results of laboratory studies conducted with humans are mixed regarding the behavioral effects of modafinil relative to commonly abused stimulants like cocaine and methylphenidate (Jasinski, 2000; Rush et al., 2002). In the first study, the acute behavioral effects of modafinil (200, 400 and 800 mg), methylphenidate (45 and 90 mg), and placebo were assessed in volunteers with histories of stimulant abuse with a battery of self-reported drug-effect questionnaires (Jasinski, 2000). Modafinil and methylphenidate dose-dependently increased ratings of Feel the Drug, Like the Drug, and High. The two higher doses of modafinil and both doses of methylphenidate differed significantly from placebo on each of these measures. The absolute magnitude of this effect following the administration of the two higher doses of modafinil was comparable to that observed following the administration of the two higher methylphenidate doses. In the second study, the acute behavioral effects of oral modafinil (200, 400, and 600 mg), cocaine (100, 200, and 300 mg), and placebo were assessed in volunteers with recent histories of cocaine abuse using a battery of self-reported drug-effect questionnaires (Rush et al., 2002). Cocaine produced robust stimulant-like self-reported drug effects (e.g. increased ratings of High, Rush, and Stimulated). Modafinil, by contrast, was nearly devoid of psychoactive effects.

The aim of the present experiment was to assess further the behavioral effects of modafinil in humans. To accomplish this aim, individuals with recent histories of cocaine use learned to discriminate 150 mg oral cocaine. After acquiring the oral cocaine discrimination, a range of doses of oral cocaine (50, 100, and 150 mg), modafinil (200, 400, and 600 mg), and placebo were tested to determine if they shared discriminative-stimulus effects with the training dose. Single doses of methylphenidate (60 mg) and triazolam (0.5 mg) were tested to determine if they also shared discriminative-stimulus effects with 150 mg oral cocaine. Methylphenidate, a piperidine derivative that blocks the DAT, was included as a positive control (e.g. Gatley et al., 1999; Ritz et al., 1987; Volkow et al., 1999a,b). Triazolam, a triazolobenzodiazepine hypnotic that exerts its effects at the benzodiazepine recognition site of the gamma-aminobutyric acid-A ($GABA_A$) receptor complex, was included as a negative control (Hobbs et al., 1996). Previous human drug-discrimination experiments have shown that methylphenidate and triazolam occasion high (i.e. $>80\%$) and low ($<25\%$) levels, respectively, of drug-appropriate responding in volunteers trained to discriminate oral cocaine (Oliveto et al., 1995; Rush and Baker, 2001).

Drug-discrimination procedures have been used extensively with animals to characterize the interoceptive-stimulus effects of cocaine, but much less so with humans. Conducting drug-discrimination experiments with humans is important to determine to what extent findings with laboratory animals generalize to humans. Moreover, because drug-discrimination procedures involve extensive training before novel doses and drugs are tested, presumably between-subject variability should be decreased. However, to characterize more fully the behavioral effects of these compounds, a battery of traditional self-reported drug-effect questionnaires previously shown to be sensitive to the acute effects of stimulant and sedative compounds was used (e.g. Rush and Baker, 2001; Rush et al., 1999a,b, 2001). A performance task and physiological indices were also included.

2. Methods

2.1. Volunteers

Six adult volunteers 2 females and 4 males with recent histories of cocaine use were recruited via flyers and word-of-mouth, and were paid (i.e. $20 per session and up to $20 per session based on their performance on the drug-discrimination task described below) to participate in this experiment. Another female volunteer was enrolled, but she was unable to discriminate 150 mg oral cocaine. A final male volunteer was enrolled, but was discharged before completing all of his scheduled experimental sessions because of behavioral problems at the General Clinical Research Center. Data from these

volunteers were excluded from all analyses. Volunteers had to meet the following inclusion criteria: (1) self-reported recent cocaine use, (2) confirmation of recent cocaine use (i.e. positive urine for cocaine or benzoylecgonine during the initial screening interview [ONTRAK Abusscreens, Roche Diagnostic Systems, Nutley, NJ]), (3) no significant medical or psychiatric disorders, other than substance abuse or dependence, and (4) no medical contraindications or prior serious adverse reactions to cocaine or stimulant drugs (e.g. seizure or drug-related admission to an emergency room).

Prior to participation, all potential volunteers completed a comprehensive medical-history questionnaire, drug-use questionnaire, a mini-mental status examination and vital sign assessment, and were examined by a psychiatrist (L.R. Hays or A.F. Wooten). Routine clinical laboratory blood chemistry tests and an electrocardiogram were conducted on all potential volunteers. Potential volunteers with histories of serious physical disease, current physical disease, impaired cardiovascular functioning, chronic obstructive pulmonary disease, seizure, head trauma or CNS tumors, or current or past histories of serious psychiatric disorder (i.e. Axis I, DSM IV), other than substance abuse or dependence, were excluded from participation. All volunteers were in good health with no contraindications to stimulant or sedative drugs. The Institutional Review Board of the University of Kentucky Medical Center approved this study, and volunteers gave their written informed consent prior to participating.

Volunteers ranged in age from 38 to 45 years (mean = 42) and in weight from 52 to 99 kg (mean = 70). The Body Mass Index for these volunteers ranged from 20 to 30 (mean = 24). All volunteers reported smoking cocaine (i.e. crack). In the month preceding admission to this protocol, these volunteers reported using cocaine on 15–30 days (mean = 23) and scored between 5 and 21 (mean = 12) on the Drug Abuse Screening Test (DAST; Skinner, 1982). These volunteers reported consuming alcohol on 12–30 days (mean = 23) and scored between 4 and 45 (mean = 23) on the MAST (Selzer, 1971). Volunteers also reported lifetime experience with a wide range of other substances including amphetamines, barbiturates, benzodiazepines, marijuana and opiates. All volunteers reported smoking tobacco cigarettes daily (range = 20–40/day, mean = 26/day), and consuming 0–322 mg caffeine/day (mean = 117 mg/day).

2.2. General procedures

Volunteers resided at the General Clinical Research Center at the University of Kentucky Medical Center while they participated in this experiment, and one to two volunteers generally participated concurrently. Volunteers completed 16–22 (mean = 18) daily experimental sessions.Volunteers were informed that during their participation they would receive various drugs and that these could include placebo, sedatives or hypnotics, prescription stimulants and weight loss medications, or illicit stimulants. Other than receiving this general information, volunteers were blind to the type of drug administered. Volunteers were told that the purpose of the study was to see how different drugs affect mood and behavior. Other than this general explanation of purpose, volunteers were given no instruction of what they were 'supposed' to do or of what outcomes might be expected.

On the day of admission to the General Clinical Research Center, volunteers provided a urine sample that was screened for the presence of amphetamines, barbiturates, benzodiazepines, cocaine, opioids and THC. Volunteers were then allowed to acclimate to the General Clinical Research Center for at least 1 day. During this acclimation period, volunteers were observed for signs of drug or alcohol withdrawal. All volunteers were without evidence of physiological dependence. During the acclimation period, volunteers completed at least one 'practice' session. These 'practice' sessions were used to familiarize volunteers with the behavioral measures and daily routine. No medications were administered on these days.

Experimental sessions were conducted daily. Volunteers followed a daily routine. Each experimental session day volunteers consumed a low-fat breakfast at approximately 07:00 h. Volunteers were then escorted from the General Clinical Research Center and allowed to smoke tobacco cigarettes between 07:30 and 08:00 h. Volunteers were not allowed to smoke again until after completing the daily experimental session.

Volunteers were escorted to the test room at approximately 08:15 h. The test room consisted of a table and chair for the research assistant, a hospital bed for the volunteer, an Apple Macintosh microcomputer (Apple Computer, Inc., Cupertino, CA) and an automated blood pressure monitor (DINAMAP Model 9300, Johnson and Johnson Medical Inc., Tampa, FL). A crash cart was available in case of a medical emergency. Volunteers provided a urine sample each morning that was screened for the presence of amphetamines, barbiturates, benzodiazepines, cocaine, opioids and THC. Volunteers also provided an expired air specimen that was assayed for the presence of alcohol using a hand-held Breathalyzer (Alco-Sensor, Intoximeters, Inc., St. Louis, MO). All urine specimens were negative for all drugs other than those administered experimentally. All expired air specimens were negative.

On experimental session days, volunteers completed the self-reported drug-effect questionnaires and performance task at approximately 08:30 h. Between 08:30 and 09:00 h volunteers sat quietly in the hospital bed in a semi-reclined positioned while blood pressure and heart

rate were monitored. Experimental drug was not administered if systolic blood pressure was >145 mmHg, diastolic blood pressure was >90 mmHg, or heart rate was >90 bpm. Volunteers ingested drug at approximately 09:00 h, and completed the drug-discrimination task, self-reported drug-effect questionnaires and performance measure periodically for 4 h after drug administration. A standard hospital lunch was provided after the volunteer completed the drug-discrimination measure, self-reported drug-effect questionnaires, and performance task at the 3 h observation (i.e. approximately 12:15 h). No other experimental activities were scheduled for volunteers for the remainder of the day after they completed the drug-discrimination measure, self-reported drug-effect questionnaires, and performance task at the 4 h observation

2.3. Drug discrimination procedures

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

2.3.1. Sampling phase

All volunteers completed two sampling sessions to acquaint them with the drug effects. Volunteers completed the self-reported drug-effect questionnaires and performance task described below before drug administration and periodically afterwards for 4 h. During each sampling session, volunteers ingested three capsules that contained a total of 150 mg cocaine. Cocaine was identified by letter code (e.g. DRUG A), but the volunteers were not explicitly informed of the capsules' contents. Below are the instructions given to each volunteer during the sampling phase. These instructions were printed on a piece of paper, and volunteers were instructed to carefully read them prior to each sampling session. Cocaine (150 mg) is identified as DRUG A for illustrative purposes only. A unique letter code was used for each volunteer.

2.3.1.1. Instructions (sampling sessions 1–2). 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 or not 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.

2.3.2. Test-of-acquisition phase

Following the sampling phase, a test-of-acquisition phase was conducted to determine if volunteers could reliably discriminate 150 mg cocaine. On test-of-acquisition days, volunteers ingested capsules under double-blind conditions, but were not told whether the capsules contained 150 mg cocaine (e.g. DRUG A) or placebo (e.g. NOT DRUG A). After capsule administration, volunteers completed the drug-discrimination measure, self-reported drug-effect questionnaires, and performance task periodically for 4 h. Volunteers were instructed that they could change their responses on the drug-discrimination task between 0.5, 1, 2, 3 and 4 h based on what they believed at the time. After completing the drug-discrimination task, self-reported drug-effect questionnaires and performance task at the 4 h observation, volunteers opened a sealed envelope that informed the volunteer 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 $\geq 80\%$ correct responding on four consecutive sessions on the drug-discrimination task described below. The order of drug administration was random except that each volunteer received each training condition, 150 mg cocaine and placebo, at least twice.

Below are the instructions given to each volunteer during the test-of-acquisition phase. These instructions were printed on a piece of paper and volunteers were told to carefully read them prior to each experimental session. These instructions were also used during the test-of-novel-doses-and-novel-drugs phase described below.

2.3.2.1. Instructions (test-of-acquisition and test-of-novel-doses-and-novel-drugs 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 if 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 total amount of money you earned on both the Drug A and Not Drug A button.

2.3.3. Test-of-novel-doses-and-drugs phase

Following the test-of-acquisition phase, volunteers entered a test-of-novel-doses-and-drugs phase to determine whether other doses of cocaine, modafinil, methylphenidate, and triazolam shared discriminative-stimulus effects with the training dose. Experimental sessions conducted during the test-of-novel-doses-and-drugs phase were identical to those conducted during the test-of-acquisition phase except that volunteers did not receive any feedback concerning their drug-discrimination performance and they received the total amount of money earned on both response options.

Drugs tested during the test-of-novel-doses-and-drugs phase included cocaine (50, 100, and 150 mg), modafinil (200, 400, and 600 mg), methylphenidate (60 mg), triazolam (0.5 mg), and placebo. 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. To accommodate this criterion, placebo was tested two to three times. Each active drug dose was administered once.

2.4. Drug-discrimination measure

The drug-discrimination task was completed 0.5, 1, 2, 3 and 4 h after oral drug administration on an Apple Macintosh microcomputer. In this procedure, the volunteer distributed 100 points between two options (i.e. DRUG A or NOT DRUG A) (Rush and Baker, 2001; Rush et al., 1997, 1998). Points accumulated on the correct option were exchangeable for money at a rate of $0.04 per point. Thus, volunteers were able to earn a maximum of $20.00 per session on this task. The dependent measure in this procedure was percent cocaine-appropriate responding.

2.5. Self-reported drug-effect questionnaires and performance task

The self-reported drug-effect questionnaires and performance task were administered on an Apple Macintosh microcomputer in fixed order. Unless otherwise stated, these questionnaires were completed approximately 30 min before drug administration, and 0.5, 1, 2, 3 and 4 h after drug administration.

2.5.1. Addiction-Research-Center Inventory

The short form of the Addiction-Research-Center Inventory (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] (Jasinski, 1977; Martin et al., 1971).

2.5.2. Drug-Effect Questionnaire

This questionnaire consisted of 22 items that were presented on the video screen, one at a time. Volunteers 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). The items rated were: Any effect; Bad effects; Good effects; Like drug; High; Willing to take again; Willing to pay for; Performance impaired; Performance improved; Active, alert or energetic; Stimulated; Crave cocaine; Elated; Euphoric; Excited; Good mood; Motivated; Powerful; Relaxed or carefree; Rush; Talkative or friendly; and Tingle.

2.5.3. Side-Effect Questionnaire

This questionnaire consisted of 23 items that were presented on the video screen, one at a time. Volunteers rated each adjective with a 5-point scale similar to the one described above. The items rated were: More hungry; Less hungry; Fearful; Bad mood; Seeing or hearing unusual things; Shaky or jittery; Agitated; Suspicious; Clumsy or difficulty walking; Dizzy; Confused, dazed or spaced out; Sleepy, tired or drowsy; Depressed; Irregular or racing heartbeat; Thirsty or dry mouth; Muscles twitching; Nauseated, queasy or sick to your stomach; Drunk; Nervous or anxious; Irritable; Restless; Sluggish, fatigued or lazy; and Sweaty.

2.5.4. Cocaine-Sensitive-Adjective Scale

The cocaine adjective rating scales consisted of 21 items that have previously been shown to be sensitive to acute administrations of intravenously administered cocaine HCL (Di Marino et al., 1998). Volunteers rated each adjective with a 5-point scale similar to the one described above. Responses to individual items were summed to produce a total score, so the maximum possible score was 84.

2.5.5. End-of-Day Questionnaire

Approximately 4 h after oral drug administration, volunteers completed an End-of-Day Questionnaire that consisted of two parts. The first part consisted of five items that were rated using a 5-point scale similar to the

one described above. The items rated were: Drug Strength, Good Effects, Bad Effects, Drug Liking, and Willing to Take Again. The second part of the questionnaire asked the volunteer to estimate the amount of money they thought the drug would be worth on the street, and the amount of money that they would personally be willing to pay for the drug on the street. Volunteers used the numeric keypad on the computer keyboard to input any numeric value in dollars and cents.

2.5.6. Digit-Symbol-Substitution Test

A computerized version of the Digit-Symbol-Substitution Test (DSST), which has been described previously, was used in this experiment (McLeod et al., 1982). Briefly, volunteers used a numeric keypad to enter a geometric pattern associated with one of nine digits displayed on a video screen. Volunteers had 90 s to enter as many geometric patterns as possible. The dependent measures were the number of geometric patterns the volunteer attempted to enter (i.e. trials completed) and the number of patterns the volunteer entered correctly (i.e. trials correct). The DSST has previously been shown to be sensitive to the performance-enhancing effects of cocaine (Higgins et al., 1990, 1993; Rush and Baker, 2001; Stillman et al., 1993), and the performance-impairing effects of triazolam (e.g. Rush et al., 1997, 1998, 1999b, 2000).

2.6. Physiological measures

Blood pressure and heart rate were recorded using an automated blood-pressure monitor. Blood pressure and heart rate were monitored every 10 min for 0.5 h before drug administration and every 30 min afterwards for 4 h. Blood pressure and heart rate were recorded immediately before volunteers completed the drug-discrimination task, self-reported drug-effect questionnaires and performance measure described above.

2.7. Drug administration

All drug conditions were administered in a double-blind fashion. Cocaine (Mallinckrodt, St. Louis, MO), modafinil (Cephalon, Inc., West Chester, PA), methylphenidate (Ciba Pharmaceutical Company, Buffalo Grove, IL), and triazolam (Pharmacia and Upjohn Company, Kalamazoo, MI) doses were prepared by encapsulating commercially available preparations (i.e. powder or tablets in a size 00 capsule). Each cocaine, modafinil, methylphenidate, and triazolam capsule contained 50, 200, 20, and 0.25 mg, respectively. Lactose was used to fill the remainder of all the capsules. Placebo capsules contained only lactose.

During each experimental session volunteers ingested three capsules. Administering the appropriate number of active and placebo capsules resulted in different cocaine, modafinil, methylphenidate, and triazolam doses. Capsules were taken orally with approximately 150 ml of water. Drug administration procedures were designed to ensure that volunteers swallowed the capsules and did not open them in their mouths and taste the contents (Abreu and Griffiths, 1996). To accomplish this, the research assistant: (a) watched the volunteer to ensure that he swallowed the capsules and did not remove them from his mouth, (b) conducted a brief oral examination to ensure that the volunteer was not hiding the capsules under his tongue, and (c) spoke with the volunteer to determine if she/he had anything in his mouth.

2.8. Data analysis

Statistical analyses of group data were conducted to examine drug effects on the drug-discrimination measure, self-reported drug-effect questionnaires, performance task, and physiological indices. Data were analyzed statistically as raw scores.

Data for the 150 mg cocaine and placebo conditions were averaged across the final four sessions during the test-of-acquisition phase during which the volunteers met the discrimination criteria, as well as all exposures to these conditions during the test-of-novel doses-and-novel-drugs phase. Drug-discrimination, subject-rated, performance, and physiological data from the 1 h observation were then analyzed with two separate repeated measure analysis of variance (ANOVA). We chose the 1 h observation because plasma levels of oral cocaine and the test drugs would be expected to be near peak and the results of previous studies suggest that the discriminative-stimulus effects of drugs do not vary as a function of time using the procedures described above (e.g. Rush and Baker, 2001; Rush et al., 1997, 2000). Preliminary analyses of the present data also suggest that the report of the discriminative-stimulus effects of drugs did not vary as a function of time. The first analyses employed a one-factor repeated measure ANOVA to compare the effects of placebo, 150 mg cocaine, 600 mg modafinil, 0.5 mg triazolam, and 60 mg methylphenidate. If the effect of dose attained statistical significance in this analysis, the mean square error term was used to conduct Fisher's Protected LSD post hoc test comparing each dose condition with the placebo condition. The second analysis employed a two-factor repeated-measure ANOVA with drug (cocaine and modafinil) and dose (Dose 1 ×, Dose 2 ×, and Dose 3 ×) as factors. Placebo data were omitted from these analyses. Between-drug differences were inferred if the main effect of drug or the interaction of drug and dose attained statistical significance.

3. Results

3.1. Drug-discrimination performance

The six volunteers met the discrimination criterion in eight, four, ten, five, four and four (mean = 5.8) sessions. The one-factor repeated-measure ANOVA that included the placebo, 150 mg cocaine, 0.5 mg triazolam, and 60 mg methylphenidate conditions revealed a significant effect of dose for percent cocaine-appropriate responding ($F_{4,20} = 3.2$, $P < 0.04$). Post-hoc analysis revealed that 150 mg cocaine and 60 mg methylphenidate, but neither 0.5 mg triazolam nor 600 mg modafinil, increased drug-appropriate responding significantly above levels observed with placebo (Fig. 1). The two-factor repeated measure ANOVA that compared the cocaine and modafinil dose-response functions revealed a significant effect of drug ($F_{1,5} = 20.0$, $P < 0.01$).

3.2. ARCI

There were no significant effects on any of the scales on the ARCI.

3.3. Drug-Effect Questionnaire

The one-factor repeated-measure ANOVA that included the placebo, 150 mg cocaine, 0.5 mg triazolam, and 60 mg methylphenidate conditions revealed a significant effect of dose on seven items from the Drug-Effect Questionnaire: Active/Alert/Energetic, Any Effects, Good Effects, High, Like Drug, Stimulated, and Take Again ($F_{4,20}$ values > 3.6, $P < 0.03$). Post-hoc analysis revealed that 150 mg cocaine and 60 mg methylphendiate, but neither 600 mg modafinil nor 0.5 mg triazolam, increased ratings of Any Effects; Good Effects; High; Like Drug; Stimulated; and Take Again significantly above levels observed with placebo. Only 150 mg cocaine increased ratings of Active/Alert/Energetic significantly above levels observed with placebo. The two-factor repeated measure ANOVA that compared the cocaine and modafinil dose-response functions revealed a significant effect of drug on five of the measures listed above: Any Effects, Good Effects, High, Like Drug, and Take Again ($F_{1,5}$ values > 8.0, $P < 0.04$).

3.4. Side-Effect Questionnaire

The one-factor repeated-measure ANOVA that included the placebo, 150 mg cocaine, 0.5 mg triazolam, and 60 mg methylphenidate conditions revealed a significant effect of dose on three items from the Side-Effect Questionnaire: Irregular/Racing Heart, Nervous–Shaky, and Thirsty–Dry Mouth ($F_{4,20}$ values > 3.2, $P < 0.04$) (data not shown). Post-hoc analysis revealed that 150 mg cocaine, but not 600 mg modafinil, 60 mg methylphenidate nor 0.5 mg triazolam, increased ratings on each of these items significantly above levels observed with placebo. The two-factor repeated measure ANOVA that compared the cocaine and modafinil dose-response functions revealed a significant effect of drug ($F_{1,5} = 12.5$, $P < 0.02$), for ratings of Thirsty–Dry Mouth, but not ratings of Irregular/Racing Heart nor Nervous–Shaky.

3.5. Cocaine-Sensitive-Adjective Scale

The one-factor repeated-measure ANOVA that included the placebo, 150 mg cocaine, 0.5 mg triazolam, and 60 mg methylphenidate conditions revealed a significant effect of dose for scores on the Cocaine-Sensitive-Adjective Scale ($F_{4,20} = 4.1$, $P < 0.02$) (data not shown). Post-hoc analysis revealed that 150 mg cocaine and 60 mg methylphenidate, but neither 600 mg modafinil nor 0.5 mg triazolam, increased scores significantly above levels observed with placebo. The two factor repeated measure ANOVA that compared the cocaine and modafinil dose-response functions revealed a significant effect of drug ($F_{1,5} = 12.5$, $P < 0.02$).

3.6. End-of-Day Questionnaire

The one-factor repeated-measure ANOVA that included the placebo, 150 mg cocaine, 0.5 mg triazolam, and 60 mg methylphenidate conditions revealed a significant effect of dose on four items from the End-of-Day Questionnaire: Drug Strength, Drug Liking, Good Effects, and Willing to Take Again ($F_{4,20}$ values > 3.4, $P < 0.03$) (Fig. 1). In each case, post-hoc analysis revealed that 150 mg cocaine and 60 mg methylphendiate, but neither 600 mg modafinil nor 0.5 mg triazolam, increased ratings significantly above levels observed with placebo. The two-factor repeated measure ANOVA that compared the cocaine and modafinil dose-response functions revealed a significant effect of drug on each of the items listed above ($F_{1,5} = 7.8$, $P < 0.04$).

3.7. DSST

The one-factor repeated-measure ANOVA that included the placebo, 150 mg cocaine, 0.5 mg triazolam, and 60 mg methylphenidate conditions revealed a significant effect of dose for trials completed and trials correct on the DSST ($F_{4,20} = 9.2$ and 14.2, respectively, $P < 0.01$). In both cases, post-hoc analysis revealed that 0.5 mg triazolam, but neither 150 mg cocaine, 600 mg modafinil, nor 60 mg methylphenidate, significantly impaired performance relative to placebo (data not

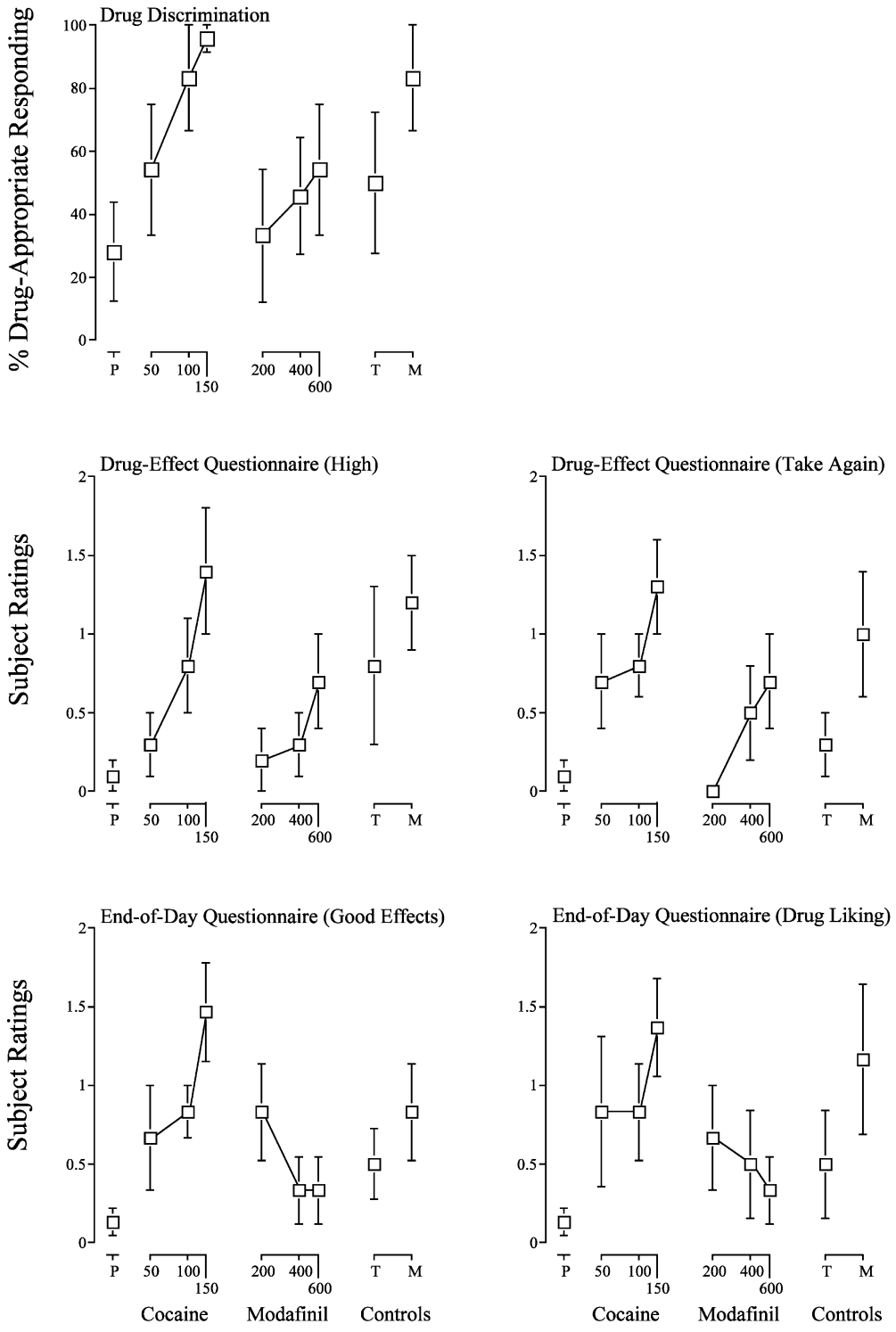

Fig. 1. Percent drug-appropriate responding for cocaine (50, 100, and 150 mg), modafinil (200, 400, and 600 mg), triazolam (0.5 mg), methylphenidate (60 mg) from the 1 h observation along with subject ratings of High and Take Again from the Drug-Effect Questionnaire, and Good Effects and Drug Liking from the End-of-Day Questionnaire. Data points above P, T and M designate placebo, triazolam and methylphenidate values, respectively. Data for the placebo and 150 mg cocaine conditions were averaged across the final four sessions during the test-of-acquisition phase during which the volunteers met the discrimination criteria, as well as all exposures to these conditions during the test-of-novel doses-and-novel-drugs phase. *X*-axes: dose in mg. Data points show means of six subjects; brackets show 1 S.E.M.

shown). There were no other statistically significant effects on the DSST.

3.8. Physiological measures

The one-factor repeated-measure ANOVA that included the placebo, 150 mg cocaine, 0.5 mg triazolam, and 60 mg methylphenidate conditions revealed a significant effect of dose for diastolic blood pressure ($F_{4,20} = 4.7$, $P < 0.01$). Post-hoc analysis revealed that 150 mg cocaine and 60 mg methylphenidate, but neither 600 mg modafinil nor 0.5 mg triazolam, increased diastolic pressure significantly above levels observed with placebo (data not shown). The two factor repeated measure ANOVA that compared the cocaine and modafinil dose-response functions failed to reveal a significant effect of drug or an interaction of drug and dose on diastolic blood pressure.

4. Discussion

The present experiment examined the discriminative-stimulus, self-reported and physiological effects of a range of doses of cocaine and modafinil in volunteers trained to discriminate 150 mg oral cocaine. Single doses of methylphenidate and triazolam were tested as positive and negative controls, respectively. Cocaine, but not modafinil, dose-dependently increased cocaine-appropriate responding. Methylphenidate, but not triazolam, increased cocaine-appropriate responding significantly above placebo levels. Cocaine and methylphenidate produced a similar constellation of self-reported drug effects.

Oral cocaine readily functioned as a discriminative stimulus and dose-dependently increased drug-appropriate responding in the present study, which is concordant with previous human drug-discrimination experiments (Epstein et al., 1999; Jones et al., 2001; Oliveto et al., 1995, 1998; Rush and Baker, 2001). Oral cocaine produced prototypical stimulant-like self-reported drug effects (e.g. increased ratings of Like Drug and Willing to Take Again) and increased blood pressure, which is also concordant with the results of several previous studies (Epstein et al., 1999; Jones et al., 2001; Oliveto et al., 1995, 1998; Rush and Baker, 2001; Smith et al., 2001). Importantly, however, the magnitude of the effect of cocaine on blood pressure was not clinically significant. The results of the present study demonstrate that oral cocaine is well tolerated by individuals with histories of recent cocaine use, and can be administered safely under controlled conditions.

Modafinil did not occasion a significant level of cocaine-appropriate responding in the present experiment. The present findings are concordant with previous studies that examined the discriminative-stimulus effects of modafinil in rodents (Gold and Balster, 1996). As noted above, in rats trained to discriminate 10 mg/kg cocaine, the highest dose of modafinil tested engendered only 67% drug-appropriate responding. The highest dose of modafinil tested in the present experiment, 600 mg, engendered approximately 55% cocaine-appropriate responding. Worth noting is that the highest dose of modafinil substituted fully (i.e. 100% drug-appropriate responding) for cocaine in three volunteers. Similarly, in the previous study with rodents the highest dose of modafinil substituted fully (i.e. $\geq 80\%$ drug-appropriate responding) for cocaine in four of the six rats tested. Whether higher doses of modafinil would substitute more fully for cocaine in humans is unknown. Doses of modafinil up to 800 mg have been administered safely to humans, so future drug-discrimination studies with humans should obviously test higher doses (Jasinski, 2000).

Consistent with the drug-discrimination data, modafinil did not produce cocaine-like self-reported drug effects. In fact, modafinil was devoid of psychoactive effects as measured by several self-reported drug-effect questionnaires. These findings are concordant with the previous study conducted in our laboratory that directly compared the self-reported effects of oral cocaine and modafinil (Rush et al., 2002). As noted above, in this previous study the acute behavioral effects of oral modafinil (200–600 mg), cocaine (100–300 mg), and placebo were assessed in volunteers with recent histories of cocaine abuse using self-reported drug-effect questionnaires. Cocaine produced robust stimulant-like self-reported drug effects (e.g. increased ratings of High, Rush, and Stimulated), while modafinil was nearly devoid of psychoactive effects.

The results of the present experiment are, however, discordant with those from a previously published experiment in which the self-reported effects of modafinil (200, 400 and 800 mg), methylphenidate (45 and 90 mg), and placebo were assessed in volunteers with histories of stimulant abuse (Jasinski, 2000). Modafinil, like methylphenidate, dose-dependently increased ratings of Feel the Drug, Like the Drug, High, and Nervous significantly above placebo levels. The most obvious reason for the discrepancy between the results of the present experiment and those from the previous experiment is that in the prior study a higher dose of modafinil, 800 mg, was tested.

Overall, then, modafinil did not produce cocaine-like discriminative-stimulus or self-reported drug effects. These observations extend findings from previous human drug-discrimination experiments that found that the discriminative-stimulus and self-reported effects of stimulant drugs often covary (e.g. Chait and Johanson, 1988; Chait et al., 1986; Heishman and Henningfield, 1991; Rush and Baker, 2001). The results of the present experiment also suggest that the interoceptive effects of

modafinil are distinguishable from those of commonly abused stimulants, which is concordant with the findings of previously published studies (Rush et al., 2002; Jasinski, 2000). The results of the present experiment extend these previous findings by demonstrating that the interoceptive-stimulus effects of modafinil and cocaine are distinguishable under a different behavioral arrangement. Since modafinil apparently does not share interoceptive-stimulus effects with commonly abused stimulants like cocaine, it may, by inference, have less abuse potential. However, more research is needed. Additional abuse potential and dependence liability studies are particularly important because modafinil is being used more for the treatment of conditions ADHD and augmentation of antidepressant therapy) for which other stimulants have traditionally been prescribed (Menza et al., 2000; Rugino and Copley, 2001; Taylor and Russo, 2000).

A single dose of methylphenidate, 60 mg, produced significant levels of cocaine-appropriate responding in the present study. Consistent with the drug-discrimination data, methylphenidate produced self-reported drug effects that generally overlapped with those observed with cocaine. The observation that methylphenidate and cocaine produce similar discriminative and self-reported effects is concordant with the results of a previous study (Rush and Baker, 2001). The present findings add to a growing body of literature that suggests the behavioral and neuropharmacological effects of methylphenidate overlap extensively with those of cocaine (for a review see Kollins et al., 2001).

A single dose of triazolam (0.5 mg), a triazolobenzodiazepine hypnotic, did not produce significant levels of cocaine-appropriate responding and impaired DSST performance in the present experiment, which is concordant with the results of several previous studies (e.g. Rush and Baker, 2001; Oliveto et al., 1995, 1998). Worth mentioning is that this dose of triazolam occasioned intermediate levels of cocaine-appropriate responding (i.e. approximately 50%), which was attributable to triazolam occasioning 100% drug-appropriate responding in three of the six volunteers. This dose of triazolam has previously been shown to occasion maximal drug-appropriate responding in some cocaine-trained humans (Oliveto et al., 1995, 1998). Whether this effect is unique to triazolam, or also occurs with other benzodiazepines, is unknown. Future research should assess the discriminative-stimulus effects of other benzodiazepines, like diazepam and alprazolam, in cocaine-trained humans.

The results of the present experiment and previous human drug-discrimination studies are generally consistent with the notion that the cocaine discrimination is pharmacologically specific because other stimulants (i.e. *d*-amphetamine and methylphenidate), but not sedatives (i.e. triazolam), engender significant levels of drug-appropriate responding (Oliveto et al., 1995, 1998; Rush and Baker, 2001). To date, however, there has not been a clear demonstration that the discriminative-stimulus effects of cocaine in humans are pharmacologically specific among central nervous system stimulants thought to act primarily via central dopamine systems. A previous human cocaine-discrimination experiment was unable to demonstrate significant differences between cocaine, *d*-amphetamine, and caffeine (Oliveto et al., 1998), even though these stimulants are thought to have varying effects in the central nervous system (for reviews see Johanson and Fischman, 1989; Nehlig et al., 1992; Seiden et al., 1993). The authors of this report hypothesized that the discriminative-stimulus effects of cocaine would more likely generalize to *d*-amphetamine, an indirect dopamine agonist like cocaine, than caffeine, an adenosine antagonist (Oliveto et al., 1998). However, both drugs increased cocaine-appropriate responding as a function of dose, and the highest dose of *d*-amphetamine (20 mg/70 kg) and caffeine (600 mg/70 kg) substituted fully (i.e. $\geq$80% drug-appropriate responding) for the training dose of cocaine. The authors of this report concluded that the cocaine discriminative stimulus is not pharmacologically specific to stimulants that act primarily via dopamine systems at an 80 mg/70 kg training dose.

The results of the present study suggest that the cocaine discriminative stimulus is pharmacologically specific to stimulants that act primarily via dopamine systems in that methylphenidate, a dopaminergic stimulant, but not modafinil, a non-dopaminergic stimulant, substituted fully for the cocaine discriminative stimulus. This observation is obviously discordant with the results of the study described above. The reason for the discrepancy between the present and previous experiments is unknown, but could be due to two notable methodological differences. First, a higher training dose was used in the present experiment (150 mg) than was employed in the previous study (i.e. 80 mg/70 kg). Previous studies with laboratory animals have demonstrated that the pharmacological specificity of the training drug increases as a function of dose (Colpaert et al., 1980; Shannon and Holtzman, 1979; Stolerman et al., 1984; Terry et al., 1994). Future studies with humans should systematically examine the influence of training dose on the generalization of other stimulant drugs to the training condition. Second, the present and previous experiments differed in terms of the instructions used. Volunteers were trained to discriminate between 'Drug A' and 'Not Drug A' in the present experiment, while in the previous experiment volunteers were trained to discriminate between 'Drug A' and 'Drug B' (Oliveto et al., 1998). The results of a recent study suggest that the discriminative-stimulus effects of drugs may correlate more closely with their receptor mechanisms under a Drug A/Not Drug A procedure relative to a Drug A/Drug B procedure (Preston and Bigelow, 2000). Future

studies with humans should systematically examine the influence of instructions on the generalization of other stimulant drugs to the training condition.

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References

Abreu, M.E., Griffiths, R.R. 1996. Drug tasting may confound human drug discrimination studies. Psychopharmacology 125, 255–257.

Akaoka, H., Roussel, B., Lin, J.S., Chouvet, G., Jouvet, M. 1991. Effect of modafinil and amphetamine on the rat catecholaminergic neuron activity. Neurosci. Lett. 123, 20–22.

Broughton, R.J., Fleming, J.A., George, C.F., Hill, J.D., Kryger, M.H., Moldofsky, H., Montplaisir, J.Y., Morehouse, R.L., Moscovitch, A., Murphy, W.F. 1997. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology 49, 444–451.

Chait, L.D., Johanson, C.E. 1988. Discriminative stimulus effects of caffeine and benzphetamine in amphetamine-trained volunteers. Psychopharmacology 96, 302–308.

Chait, L.D., Uhlenhuth, E.H., Johanson, C.E. 1986. The discriminative stimulus and subjective effects of phenylpropanolamine, mazindol and *d*-amphetamine in humans. Pharmacol. Biochem. Behav. 24, 301–306.

Colpaert, F.C., Niemegeers, C.J., Janssen, P.A. 1980. Factors regulating drug cue sensitivity: the effect of training dose in fentanyl-saline discrimination. Neuropharmacology 19, 705–713.

Di Marino, M.E., Haberny, K.A., Felch, L.J., Walsh, S.L., Preston, L.K., Bigelow, G.E., 1998. Development of a subjective rating scale sensitive to acute cocaine administration. In: Harris L (ed.), Problems of Drug Dependence, 1997: Proceedings of the 59th Annual Scientific Meeting National Institute on Drug Abuse Research Monograph Series, 178, p. 139.

Epstein, D.H., Silverman, K., Henningfield, J.E., Preston, K.L. 1999. Low-dose oral cocaine in humans: acquisition of discrimination and time-course of effects. Behav. Pharmacol. 10, 531–542.

Ferraro, L., Antonelli, T., O'Connor, W.T., Tanganelli, S., Rambert, F.A., Fuxe, K. 1997. Modafinil: an antinarcoleptic drug with a different neurochemical profile to *d*-amphetamine and dopamine uptake blockers. Biol. Psychiatry 42, 1181–1183.

Gatley, S.J., Volkow, N.D., Gifford, A.N., Fowler, J.S., Dewey, S.L., Ding, Y.S., Logan, J. 1999. Dopamine-transporter occupancy after intravenous doses of cocaine and methylphenidate in mice and humans. Psychopharmacology 146, 93–100.

Gold, L.H., Balster, R.L. 1996. Evaluation of the cocaine-like discriminative stimulus effects and reinforcing effects of modafinil. Psychopharmacology 126, 286–292.

Heishman, S.J., Henningfield, J.E. 1991. Discriminative stimulus effects of *d*-amphetamine, methylphenidate, and diazepam in humans. Psychopharmacology 103, 436–442.

Higgins, S.T., Bickel, W.K., Hughes, J.R., Lynn, M., Capeless, M.A., Fenwick, J.W. 1990. Effects of intranasal cocaine on human learning, performance and physiology. Psychopharmacology 102, 451–458.

Higgins, S.T., Rush, C.R., Hughes, J.R., Bickel, W.K., Lynn, M., Capless, M.A. 1993. Acute behavioral and cardiac effects of cocaine and alcohol combinations in humans. Psychopharmacology 111, 285–294.

Hobbs, W.R., Rall, T.W., Verdoorn, T.A. 1996. Hypnotics and sedatives; ethanol. In: Hardman, J.G., Limbird, L.E., Molinoff, P.B., Ruddon, R.W., Gilman, A.G. (Eds.), Goodman's and Gilman's: The Pharmacological Basis of Therapeutics, ninth ed.. McGraw-Hill, New York, pp. 361–398.

Holmes, V.F. 1995. Medical use of psychostimulants: an overview. Int. J. Psychiatry Med. 25, 1–19.

Jasinski, D. 1977. Assessment of the abuse potentiality of morphine-like drugs (methods used in man). In: Martin, W.R. (Ed.), Drug Addiction I. Springer, New York, pp. 197–258.

Jasinski, D.R. 2000. An evaluation of the abuse potential of modafinil using methylphenidate as a reference. J. Psychopharmacol. 14, 53–60.

Johanson, C.E., Fischman, M.W. 1989. The pharmacology of cocaine related to its abuse. Pharmacol. Rev. 41, 3–52.

Jones, H.E., Garrett, B.E., Griffiths, R.R. 2001. Reinforcing effects of oral cocaine: contextual determinants. Psychopharmacology 154, 143–152.

Kollins, S.H., MacDonald, E.K., Rush, C.R. 2001. Assessing the abuse potential of methylphenidate in nonhumans and human subjects: a review. Pharmacol. Biochem. Behav. 68, 611–627.

Lin, J.S., Hou, Y., Jouvet, M. 1996. Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness, evidenced by c-*fos* immunocytochemistry in the cat. Proc. Natl. Acad. Sci. 93, 14128–14133.

Makris, A.M., Kelly, T.H., Wilson, J. 2001. The effects of modafinil on food intake, verbal reports of drug effect, performance and cardiovascular activity in normal, healthy men and women. Drug Alcohol Dependence 63, S96.

Martin, W.R., Sloan, J.W., Sapira, J.D., Jasinski, D.R. 1971. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. Clin. Pharmacol. Ther. 12, 245–258.

McLeod, D.R., Griffiths, R.R., Bigelow, G.E., Yingling, J.E. 1982. An automated version of the digit symbol substitution test (DSST). Behav. Res. Methods Instru. 14, 463–466.

Menza, M.A., Kaufman, K.R., Castellanos, A. 2000. Modafinil augmentation of antidepressant treatment in depression. J. Clin. Psychiatry 61, 378–381.

Mignot, E., Nishino, S., Guilleminault, C., Dement, W.C. 1994. Modafinil binds to the dopamine uptake carrier site with low affinity. Sleep 17, 436–437.

Moldofsky, H., Broughton, R.J., Hill, J.D. 2000. A randomized trial of the long-term, continued efficacy and safety of modafinil in narcolepsy. Sleep Med. 1, 109–116.

Nehlig, A., Daval, J.L., Debry, G. 1992. Caffeine and the central nervous system: mechanisms of action, biochemical metabolic and psychostimulant effects. Brain Res. Rev. 17, 139–170.

Oliveto, A.H., Rosen, M.I., Woods, S.W., Kosten, T.R. 1995. Discriminative stimulus, self-reported and cardiovascular effects of orally administered cocaine in humans. J. Pharmacol. Exp. Ther. 272, 231–241.

Oliveto, A.H., McCance-Katz, E., Singha, A., Hameedi, F., Kosten, T.R. 1998. Effects of *d*-amphetamine and caffeine in humans under a cocaine discrimination procedure. Behav. Pharmacol. 9, 207–217.

Preston, K.L., Bigelow, G.E. 2000. Effects of agonist-antagonist opioids in humans trained in a hydromorphone/not hydromorphone discrimination. J. Pharmacol. Exp. Ther. 295, 114–124.

Ritz, M.C., Lamb, R.J., Goldberg, S.R., Kuhar, M.J. 1987. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237, 1219–1223.

Rugino, T.A., Copley, T.C. 2001. Effects of modafinil in children with Attention-Deficit/Hyperactivity Disorder: an open-label study. J. Am. Acad. Child Adolesc. Psychiatry 40, 230–235.

Rush, C.R., Baker, R.W. 2001. Behavioral pharmacological similarities between methylphenidate and cocaine in cocaine abusers. Exp. Clin. Psychopharmacol. 9, 59–73.

Rush, C.R., Madakasira, S., Goldman, N.H., Woolverton, W.L., Rowlett, J.K. 1997. Discriminative-stimulus effects of zolpidem in pentobarbital-trained subjects: II. Comparison with triazolam and caffeine in humans. J. Pharmacol. Exp. Ther. 280, 174–188.

Rush, C.R., Kollins, S.H., Pazzaglia, P.J. 1998. Discriminative-stimulus and participant-rated effects of methylphenidate, bupropion and triazolam in *d*-amphetamine-trained humans. Exp. Clin. Psychopharmacol. 6, 32–44.

Rush, C.R., Baker, R.W., Wright, K. 1999a. Acute physiological and behavioral effects of oral cocaine in humans: a dose-response analysis. Drug Alcohol Depend. 55, 1–12.

Rush, C.R., Baker, R.W., Wright, K. 1999b. Trazodone, zolpidem, and triazolam in humans: acute behavioral effects and abuse potential. Psychopharmacology 144, 220–233.

Rush, C.R., Baker, R.W., Rowlett, J.K. 2000. Discriminative-stimulus effects of zolpidem, triazolam, pentobarbital and caffeine in zolpidem-trained humans. Exp. Clin. Psychopharmacol. 8, 22–36.

Rush, C.R., Essman, W.D., Simpson, C.A., Baker, R.W. 2001. Reinforcing and subject-rated effects of methylphenidate and *d*-amphetamine in non-drug-abusing volunteers. J. Clin. Psyhopharmacol. 21, 273–286.

Rush, C.R., Kelly, T.H., Hays, L.R., Baker, R.W., Wooton, A.F. 2002. Acute behavioral and physiological effects of modafinil in drug abusers. Behav. Pharmacol. 13, 105–116.

Seiden, L.S., Sabol, K.E., Ricaurte, G.A. 1993. Amphetamine: effects on catecholamine systems and behavior. Ann. Rev. Pharmacol. Toxicol. 33, 639–677.

Selzer, M.L. 1971. The Michigan Alcoholism Screening Test: the quest for a new diagnostic instrument. Am. J. Psychiatry 127, 1653–1658.

Shannon, H.E., Holtzman, S.G. 1979. Morphine training dose: a determinant of stimulus generalization to narcotic antagonists in the rat. Psychopharmacology 61, 239–244.

Skinner, H.A. 1982. The drug abuse screening test. Addict. Behav. 7, 363–371.

Smith, B.J., Jones, H.E., Griffiths, R.R. 2001. Physiological, subjective and reinforcing effects of oral and intravenous cocaine in humans. Psychopharmacology 156, 435–444.

Stillman, R., Jones, R.T., Moore, D., Walker, J., Welm, S. 1993. Improved performance 4 h after cocaine. Psychopharmacology 110, 415–420.

Stolerman, I.P., Garcha, H.S., Pratt, J.A., Kumar, R. 1984. Role of training dose in discrimination of nicotine and related compounds by rats. Psychopharmacology 84, 413–419.

Taylor, F.B., Russo, J. 2000. Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults. J. Child Adolesc. Psychopharmacol. 10, 311–320.

Terry, P., Witkin, J.M., Katz, J.L. 1994. Pharmacological characterization of the novel discriminative stimulus effects of a low dose of cocaine. J. Pharmacol. Exp. Ther. 270, 1041–1048.

US Modafinil in Narcolepsy Multicenter Study Group 2000. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology 54, 1166–1175.

Volkow, N.D., Wang, G.J., Fowler, J.S., Fischman, M., Foltin, R., Abumrad, N.N., Gatley, S.J., Logan, J., Wong, C., Gifford, A., Ding, Y.S., Hitzemann, R., Pappas, N. 1999a. Methylphenidate and cocaine have a similar in vivo potency to block dopamine transporters in the human brain. Life Sci. 65 (1), 7–12.

Volkow, N.D., Fowler, J.S., Gatley, S.J., Dewey, S.L., Wang, G.J., Logan, J., Ding, Y.S., Franceschi, D., Gifford, A., Morgan, A., Pappas, N., King, P. 1999b. Comparable changes in synaptic dopamine induced by methylphenidate and by cocaine in the baboon brain. Synapse 31, 59–66.