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Behavioral and physiological effects of cocaine in humans following triazolam

Jamie L. Haga[a], Robert W. Baker[b], Craig R. Rush[a,c,d,*]

[a]Department of Behavioral Science, University of Kentucky, Lexington, KY 40536-0086, USA
[b]Eli Lilly, Inc., Indianapolis, IN 46285, USA
[c]Department of Psychiatry, University of Kentucky, Lexington, KY 40536, USA
[d]Department of Psychology, University of Kentucky, Lexington, KY 40536, USA

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Abstract

Rationale: Cocaine abuse represents a significant public health problem. Gamma-aminobutyric acid (GABA) agonists may attenuate the behavioral effects of cocaine and may be effective pharmacotherapies for cocaine abuse and dependence. *Objectives:* The aim of this experiment was to determine the combined effects of oral cocaine (0 and 300 mg) and triazolam (0 and 0.5 mg), a $GABA_A$ modulator, in 10 individuals with recent histories of cocaine use. *Methods:* Volunteers received each of the four possible drug combinations in mixed order. Drug effects were assessed using a battery of subject-rated drug-effect questionnaires and physiological indices. *Results:* Cocaine alone produced prototypical stimulant-like subject-rated drug effects (e.g., increased ratings of High, Like Drug, and Willing to Take Drug Again). Triazolam alone produced sedative-like effects (e.g., increased scores on the Pentobarbital, Chlorpromazine, Alcohol Group [PCAG] scale of the Addiction Research Center Inventory [ARCI]). Triazolam pretreatment did not significantly attenuate the subject-rated effects of cocaine. *Conclusions:* While the results of this study do not support the utility of $GABA_A$ modulators as pharmacotherapies for cocaine abuse, future research should test other benzodiazepines (e.g., alprazolam) using more sophisticated methods (e.g., dose–response curves for the drugs alone and in combination) and behavioral arrangements (e.g., drug discrimination).

Keywords: Cocaine; Triazolam; Humans; Drug abuse; Subjective effects; Physiological effects

1. Introduction

Cocaine abuse continues to represent a significant public health problem. In 2000, for example, approximately 1.5 million Americans had used cocaine in the past month (Substance Abuse and Mental Health Services Administration [SAMHSA], 2003). Alarmingly, between 1995 and 2001 the percentage of high school seniors that had used cocaine at least once increased steadily (National Institute on Drug Abuse, 2002). Because of widespread use and public health concerns, intense research efforts have been aimed at identifying a pharmacotherapy for the treatment of cocaine abuse (Schuster and Snyder, 1990). To date, an effective pharmacotherapy for cocaine abuse and dependence has not yet been identified (for reviews, see Bigelow and Walsh, 1998; Foltin and Fischman, 1998).

Preclinical behavioral pharmacology studies suggest that gamma-aminobutyric acid $(GABA)_A$ receptor modulators may attenuate the behavioral effects of cocaine (Goeders et al., 1989, 1993; Meririnne et al., 1999; Negus et al., 2000; Wilson and Schuster, 1973). The results of one study, for example, suggest that triazolam pretreatment attenuates the discriminative-stimulus effects of cocaine in cocaine-trained rhesus monkeys (Negus et al., 2000). In this experiment, six male rhesus monkeys were trained to discriminate 0.4 mg/kg cocaine from saline. After acquiring the cocaine–saline discrimination, a range of doses of cocaine (0.01–1.3 mg/kg) was tested alone and following pretreatment with triazolam (0.01, 0.1, and 1.0 mg/kg). As expected, cocaine alone dose dependently increased percent cocaine-appropriate responding. Triazolam alone did not occasion significant percent cocaine-appropriate responding, but dose dependently attenuated the discriminative-stimulus effects of cocaine.

* Corresponding author. Department of Behavioral Science, University of Kentucky, Lexington, KY 40536-0086, USA. Tel.: +1-859-323-6130; fax: +1-859-323-5350.
E-mail address: crush2@uky.edu (C.R. Rush).

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The aim of this experiment was to determine the combined effects of oral cocaine (0 and 300 mg) and triazolam (0 and 0.5 mg), a $GABA_A$ modulator, in individuals ($N = 10$) with recent histories of cocaine use. Drug effects were assessed before drug administration and periodically afterwards for 4 h using a battery of subject-rated drug-effect questionnaires and physiological indices previously shown to be sensitive to the behavioral effects of cocaine and triazolam (e.g., Oliveto et al., 1995; Rush and Baker, 2001a,b). The discriminative-stimulus effects of drugs in laboratory animals are thought to be a model of subjective drug effects in humans (for reviews, see Preston and Bigelow, 1991; Schuster and Johanson, 1988; Schuster et al., 1981).

2. Materials and methods

2.1. Volunteers

Ten adult volunteers (8 males and 2 females) with recent histories of cocaine use were recruited via flyers and word of mouth, and paid to participate in this experiment. 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; (4) negative urine pregnancy test for females (Abbott TestPack, + Plus, Abbott Laboratories, Abbott Park, IL); (5) no medical contraindications or prior serious adverse reactions to cocaine or stimulant drugs (e.g., seizure or drug-related admission to an emergency room); and (6) a score of at least 5 on the Drug Abuse Screening Test (DAST) (Skinner, 1982).

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 (R.W.B.). 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 Mississippi Medical Center approved this study, and volunteers gave their written informed consent before participating.

Volunteers ranged in age from 28 to 47 years (mean = 36) and in weight from 56 to 86 kg (mean = 78). All volunteers reported smoking cocaine (i.e., crack), which was their preferred route of administration. One volunteer reported having self-administered cocaine intravenously. In the week preceding admission to this 4-day protocol, volunteers reported using 6–280 "rocks" of cocaine (mean = 68) and scored between 6 and 25 (mean = 13) on the DAST. Volunteers reported consuming 0 to 168 alcohol-containing beverages during the week preceding admission (mean = 60), and scored between 0 and 42 (mean = 15) on the Michigan Alcohol Screening Test (MAST) (Selzer, 1971). Volunteers also reported lifetime experience with a wide range of other substances including amphetamines (0–15 lifetime experiences), benzodiazepines (0–500 lifetime experiences), marijuana (20–10,000 lifetime experiences), and opiates (0–100 lifetime experiences). All volunteers reported smoking tobacco cigarettes daily (range = 1–60/day, mean = 28/day), and consuming approximately 15 to 768 mg caffeine/day (mean = 302 mg/day).

2.2. General procedures

Volunteers resided on the General Inpatient Psychiatry Unit at the University of Mississippi Medical Center while they participated in this experiment, and two volunteers generally participated concurrently. Volunteers completed four experimental sessions across a 6-day period.

Volunteers were informed that during their participation they would receive various drugs and drug combinations including placebo, sedatives, muscle relaxants, anxiolytics, stimulants and weight loss medications, antidepressants, and antihistamines. 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 and drug combinations 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 Inpatient Psychiatry Unit, volunteers provided an expired air specimen that was assayed for the presence of alcohol using a handheld breathalyzer (Alco-Sensor, Intoximeters, St. Louis, MO). A volunteer was not admitted to the General Inpatient Psychiatry Unit if this expired air specimen was positive for alcohol. Volunteers also provided a urine sample, which was screened for the presence of amphetamines, barbiturates, benzodiazepines, cocaine, opioids, and tetrahydrocannabinol (THC). Admission to the General Inpatient Psychiatry Unit was rescheduled if a urine specimen was positive for any substance other than cocaine or THC. Volunteers were then allowed to acclimate to the General Inpatient Psychiatry Unit 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. The acclimation period also helped ensure that a volunteer was not under the influence of any drug not administered

experimentally. 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 laboratory routine. No medications were administered on these days.

Experimental sessions were conducted Monday through Friday. There were no scheduled experimental activities on Saturday and Sunday. On experimental session days, volunteers followed a daily routine. Each experimental session day, volunteers consumed a standard hospital breakfast at approximately 0700 h. Volunteers were then escorted off the General Inpatient Psychiatry Unit and allowed to smoke a tobacco cigarette between 0730 and 0800 h. Volunteers were escorted to the test room at approximately 0815 h. The test room consisted of a desk and chair for the research assistant and nurse, a cushioned chair for the volunteer, an Apple Macintosh microcomputer (Quadra 605, Apple Computer, Cupertino, CA), and an automated blood pressure monitor (DINAMAP XL, Johnson and Johnson, Alexandria, TX). A crash cart was situated immediately outside the test room in case of a medical emergency. Volunteers provided a urine specimen each morning that was screened on an unannounced basis 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 handheld breathalyzer (Alco-Sensor, Intoximeters). These urine specimens were negative except for cocaine or benzoylecgonine, which was most likely due to experimentally administered drug. All expired air specimens were negative.

On experimental session days, volunteers completed the subject-rated drug-effect questionnaires and performance task at approximately 0830 h. Between 0830 and 0900 h volunteers sat quietly in a semireclined positioned and their heart rate and blood pressure were monitored. Experimental drug was not administered if heart rate was >90 bpm, systolic blood pressure was >145 mm Hg, or diastolic blood pressure was >90 mm Hg. Volunteers ingested drug at approximately 0900 h, and completed the subject-rated drug-effect questionnaires and performance task periodically for 4 h after drug administration. A standard hospital lunch was provided after the volunteer completed the subject-rated drug-effect questionnaires and performance task at the 3-h observation (i.e., approximately 1215 h). After completing the subject-rated drug-effect questionnaires and performance task at the 4-h observation, volunteers were escorted back to the General Inpatient Psychiatry Unit. No other activities were scheduled for volunteers for the remainder of the day, but they were encouraged to engage in art and occupational or recreational therapy provided by the staff of the General Inpatient Psychiatry Unit.

2.3. Behavioral measures

Unless otherwise noted, all subject-rated drug-effect questionnaires and performance tasks were completed on an Apple Macintosh microcomputer. Unless stated otherwise, these measures were completed approximately 30 min before drug administration, and at 30-min intervals for 4 h after drug administration.

2.3.1. 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) (Jasinski, 1977; Martin et al., 1971).

2.3.2. Drug-Effect Questionnaire

This questionnaire consisted of 16 items that were presented on the computer, 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).

2.3.3. Side-Effect Questionnaire

This questionnaire consisted of 19 items that were presented on the video screen, one at a time. Volunteers rated each of these items using a 5-point scale identical to the one described above.

2.3.4. End-of-Day Questionnaire

Approximately 4 h after oral drug administration, volunteers completed an End-of-Day Questionnaire that consisted of three parts. The first part consisted of five items: *strength*, *liking*, *good effects*, *bad effects*, and *like to take today's drug again*. These items were rated using a 5-point scale similar to the one described above. The second part of the questionnaire consisted of two items: (1) Estimate the amount of money you think the drug would be worth on the street. (2) Estimate the amount of money that you would personally be willing to pay for the drug on the street. The third part asked volunteers to "select the drug class that best describes the drug you received today" (i.e., blank or placebo, opiate [such as morphine, heroin], stimulant [such as cocaine, amphetamine], speedball [such as heroin and cocaine together], hallucinogen [such as LSD], benzodiazepine [such as Valium] or barbiturate [such as Seconal], alcohol, marijuana, phencyclidine [such as PCP], or antidepressant [such as Elavil]).

2.3.5. 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). The dependent measure was the number of geometric patterns the volunteer entered correctly (i.e., number of trials correct). Previous studies have shown that intranasally and orally administered cocaine improves

DSST performance (Higgins et al., 1990, 1993; Rush and Baker, 2001a), whereas triazolam impairs DSST performance (e.g., Rush and Baker, 2001a,b; Rush et al., 1999a,b). The DSST is also sensitive to the combined effects of stimulants and sedatives (Higgins et al., 1993, 1996; Rush et al., 1994a,b).

2.3.6. Observer-Rated Questionnaire

A research assistant who was blind to the medications and doses being tested completed observer ratings. The research assistant completed the observer-rating scales at approximately the same time the volunteer completed the Drug-Effect Questionnaire. The observer was instructed to base his/her ratings on observation of the volunteer's gross behavior rather than on the volunteer's verbal reports or ratings. The items were rated using a 5-point scale similar to the one described above.

2.4. Physiological measures

Heart rate and blood pressure were recorded using an automated blood pressure monitor (DINAMAP XL, Johnson and Johnson). Heart rate and blood pressure were monitored at 10-min intervals for 30 min before drug administration and at 30-min intervals for 4 h after drug administration. Heart rate and blood pressure were recorded immediately before volunteers completed the subject-rated drug-effect questionnaires and performance tasks described above.

2.5. Drug administration

All drugs were administered orally. Four cocaine–triazolam conditions were studied in the present experiment: (1) 0 mg cocaine and 0 mg triazolam, (2) 300 mg cocaine and 0 mg triazolam, (3) 0 mg cocaine and 0.5 mg triazolam, and (4) 300 mg cocaine and 0.5 mg triazolam. Each volunteer received all four possible cocaine–triazolam combinations in mixed order. A minimum of 24 h separated all experimental sessions. References below to placebo pertain to sessions in which placebo doses of both cocaine and triazolam were administered. References to cocaine or triazolam alone pertain to sessions in which the active dose of one drug was administered in combination with the placebo dose of the other compound.

The cocaine conditions (i.e., 0 and 300 mg) were prepared by encapsulating 100 mg cocaine HCl (Mallinckrodt, St. Louis, MO) in a size 00 capsule. Lactose was used to fill the remainder of all the capsules. Triazolam conditions (i.e., 0 and 0.5 mg) were prepared from commercially available tablets (The Pharmacia Corporation, Peapack, NJ), which were overencapsulated in 00 capsules. Lactose was used to fill the remainder of all the capsules. Placebo capsules contained only lactose. Participants ingested four capsules each experimental session (i.e., three cocaine- or placebo-containing capsules and one triazolam- or placebo-containing capsule). Capsules were taken orally with approximately 150 ml of water.

Oral cocaine and triazolam produce their peak plasma levels and behavioral effects approximately 1 h after administration (e.g., Greenblatt et al., 1989; Oliveto et al., 1995, 1998; Rush and Baker, 2001a; Rush et al., 1999a,b,c; Van Dyke et al., 1978). In order to test the effects of the drug combinations across peak effect, cocaine and triazolam were administered simultaneously. The pharmacodynamic and pharmacokinetic effects of oral cocaine are qualitatively and quantitatively similar to those of intranasally administered cocaine (Oliveto et al., 1995; Van Dyke et al., 1978).

2.6. Data analysis

For all statistical analyses, effects were considered significant for $P \leq .05$. Two sets of analyses were conducted. First, peak effect (i.e., maximum value from 0.5 to 5 h after drug administration) was calculated for each volunteer and analyzed with two-factor repeated measures ANOVA (StatView, Abacus Concepts, Berkeley, CA). Factors for these analyses were Cocaine (0 and 300 mg) and Triazolam (0 and 0.5 mg). The mean square error term for all means was then used to conduct planned comparisons (i.e., Tukey's Honestly Significantly Different [HSD] test). Planned comparisons were used to determine which drug conditions differed significantly from the placebo condition. If the cocaine alone or the triazolam alone condition differed significantly from placebo, these conditions were then compared to the cocaine–triazolam condition. Data from the first two parts of the End-of-Day Questionnaire were analyzed in a similar fashion. Data from the third part of the End-of-Day Questionnaire (i.e., pharmacological class question) were not analyzed statistically. Peak effect was calculated for the DSST using both the maximum and minimum value from 0.5 to 5 h after drug administration. Second, time-course data were analyzed by three-factor, repeated measures ANOVA with Cocaine (0 and 300 mg), Triazolam (0 and 0.5 mg), and Time (predrug, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, and 4 h) as factors. The mean square error term for all means was then used to conduct planned comparisons (i.e. Tukey's HSD).

3. Results

3.1. Peak effect

3.1.1. ARCI

The cocaine alone and the cocaine–triazolam conditions increased A and LSD scores significantly above levels observed with placebo (Tukey's HSD = 0.8 and 1.6, respectively). The cocaine alone and the cocaine–triazolam conditions did not differ significantly from each other on either of these scales. Triazolam alone increased PCAG scores, and this effect was not altered significantly by the concomitant administration of cocaine (Tukey's HSD = 2.8). Fig. 1

shows the effects of placebo, cocaine and triazolam alone, and the cocaine–triazolam combination on each of these scales.

3.1.2. Drug-Effect Questionnaire

Each of the active drug conditions increased ratings of Any Effect, Good Effects, Willing to Take Drug Again, and Talkative-Friendly above placebo levels (Tukey's HSD = 1.0, 0.7, 0.7, and 0.7, respectively). Combining cocaine and triazolam increased ratings of Good Effects significantly above those observed with cocaine alone. Combining cocaine and triazolam increased ratings of Willing to Take Drug Again significantly above those observed with triazolam alone. Fig. 1 shows the effects of placebo, cocaine and triazolam alone, and the cocaine–triazolam combination for each of these items.

The cocaine alone and the cocaine–triazolam conditions increased ratings of Active–Alert–Energetic, Excited–Elated, High, Like Drug, and Motivated significantly above ratings observed with placebo (Tukey's HSD = 0.3, 1.1, 1.2, 1.0, and 0.8, respectively). Combining cocaine and triazolam did not significantly alter the effects observed with

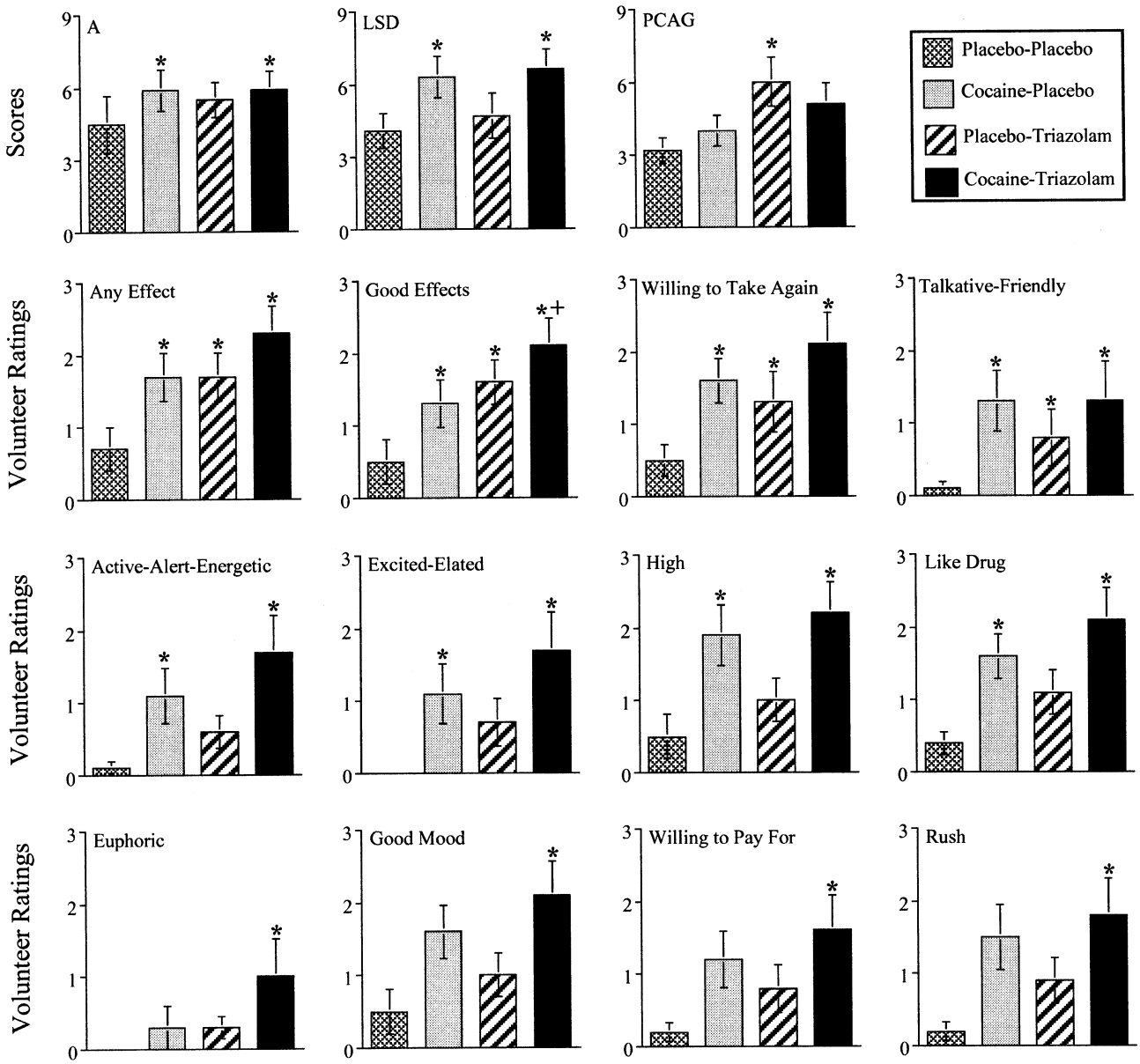

Fig. 1. Effects of placebo, cocaine alone, triazolam alone, and the cocaine–triazolam combination for scores on the A, LSD, and PCAG scales from the ARCI, along with volunteer ratings of Any Effects, Good Effects, Willing to Take Drug Again, Talkative-Friendly, Active-Alert-Energetic, Excited-Elated, High, Like Drug, Euphoric, Good Mood, Willing to Pay For, and Rush from the Drug-Effect Questionnaire. Data points show means of 10 participants. Data are expressed as peak effect. Brackets indicate 1 standard error of the mean (S.E.M.). An asterisk (*) indicates that the drug condition differs significantly from the placebo condition. A plus sign (+) indicates a significant difference between the cocaine alone and cocaine–triazolam conditions.

cocaine alone. Fig. 1 shows the effects of placebo, cocaine and triazolam alone, and the cocaine–triazolam combination for each of these items except for ratings of Motivated. The cocaine–triazolam condition, but not the cocaine or triazolam alone conditions, increased ratings of Euphoric, Good Mood, Willing to Pay For, Relaxed–Carefree, and Rush significantly above ratings observed with placebo (Tukey's HSD = 0.8, 1.4, 1.1, 1.1 and 1.3, respectively). Fig. 1 shows the effects of placebo, cocaine and triazolam alone, and the cocaine–triazolam combination for each of these items except for ratings of Relaxed–Carefree.

3.1.3. Side-Effect Questionnaire

The cocaine alone and the cocaine–triazolam conditions increased ratings of Irregular or Racing Heartbeat significantly above levels observed with placebo (Tukey's HSD= 1.1) (data not shown). Combining cocaine and triazolam did not significantly alter these ratings relative to those observed with cocaine alone. Triazolam alone, but none of the other drug conditions, increased ratings of Sleepy–Tired–Drowsy significantly above ratings observed with placebo (Tukey's HSD = 0.9) (data not shown). Combining cocaine and triazolam did not significantly alter these ratings relative to those observed with triazolam alone. The cocaine–triazolam condition, but not the cocaine or triazolam alone conditions, increased ratings of Sluggish–Lazy and Performance Improved significantly above ratings observed with placebo (Tukey's HSD = 1.1) (data not shown).

3.1.4. End-of-Day Questionnaire

Each of the active drug conditions increased end-of-day ratings of Drug Strength and Like to Take Drug Again significantly above ratings observed with placebo (Tukey's HSD = 0.9 and 0.6, respectively) (data not shown). Combining cocaine and triazolam did not significantly alter the effects observed with the constituent drugs alone.

The cocaine alone and the cocaine–triazolam conditions increased end-of-day ratings of Like Drug, Estimates of Worth on the Street, and Estimates of Amounts Personally Willing to Pay significantly above levels observed with placebo (Tukey's HSD = 0.7, 4.5, and 8.2, respectively) (data not shown). Combining cocaine and triazolam did not significantly alter these ratings relative to those observed with cocaine alone. Cocaine alone increased end-of-day ratings of Bad Effects significantly above ratings observed with placebo (Tukey's HSD = 0.6) (data not shown). Combining cocaine and triazolam did not significantly alter the effects observed with cocaine alone.

Placebo was identified as blank/placebo (9 volunteers) or benzodiazepine/barbiturate (1 volunteer). Cocaine alone was identified as a stimulant (4 volunteers), speedball (2 volunteers), benzodiazepine/barbiturate (2 volunteers), marijuana (1 volunteer), or blank/placebo (1 volunteer). Triazolam alone was identified as alcohol (2 volunteers), benzodiazepine/barbiturate (4 volunteers), marijuana (1 volunteer), stimulant (1 volunteer), or blank/placebo (2 volunteers). The cocaine–triazolam condition was identified as a stimulant (4 volunteers), benzodiazepine/barbiturate (2 volunteers), marijuana (2 volunteers), opioid (1 volunteer), or speedball (1 volunteer).

3.1.5. DSST

None of the drug conditions affected DSST performance to a statistically significant degree.

3.1.6. Observer-Rated Questionnaire

Each of the active drug conditions increased observer ratings of Carefree, Any Drug Effect, and Stimulated (Tukey's HSD = 0.6, 0.9, and 1.0, respectively) (data not shown). Combining cocaine and triazolam did not significantly alter the effects observed with the constituent drugs alone. The cocaine alone and the cocaine–triazolam conditions increased observer ratings of Energetic, High, Like Drug, and Restless significantly above ratings observed with placebo (Tukey's HSD = 0.1, 0.9, 0.7, and 0.1, respectively) (data not shown). Combining cocaine and triazolam did not significantly alter these ratings relative to those observed with cocaine alone.

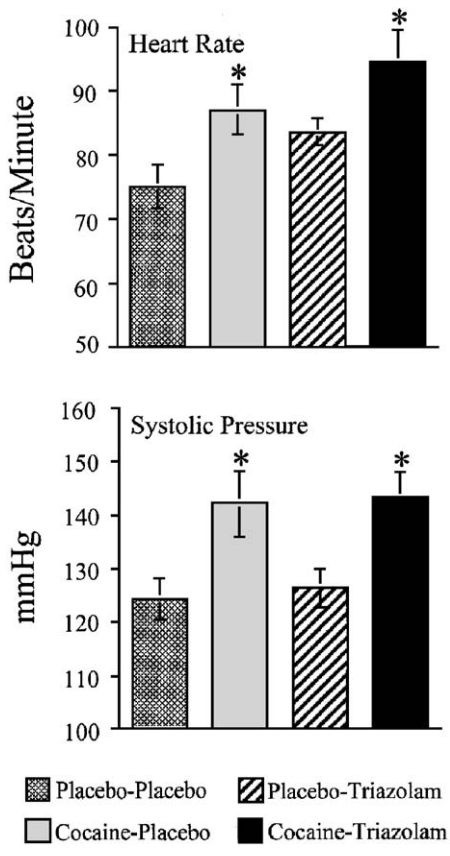

Fig. 2. Effects of placebo, cocaine alone, triazolam alone, and the cocaine–triazolam combination on heart rate and systolic blood pressure. Data points show means of 10 participants. Data are expressed as peak effect. Brackets indicate 1 standard error of the mean (S.E.M.). An asterisk indicates that the drug condition differs significantly from the placebo condition.

Triazolam alone, but none of the other active drug conditions, increased observer ratings of Drowsy and Drunk significantly above levels observed with placebo (Tukey's HSD = 0.5 and 0.4, respectively) (data not shown). Combining cocaine and triazolam significantly reduced these ratings relative to those observed with triazolam alone.

3.1.7. Physiological measures

The cocaine alone and the cocaine–triazolam conditions increased heart rate and systolic blood pressure significantly above levels observed with placebo (Tukey's HSD = 10.3 and 5.9, respectively). Combining cocaine and triazolam did not increase heart rate or systolic blood pressure significantly above levels observed with cocaine alone. None of the drug conditions affected diastolic blood pressure to a statistically significant degree. Fig. 2 shows the effects of placebo, cocaine and triazolam alone, and the cocaine–triazolam combination on heart rate and systolic blood pressure.

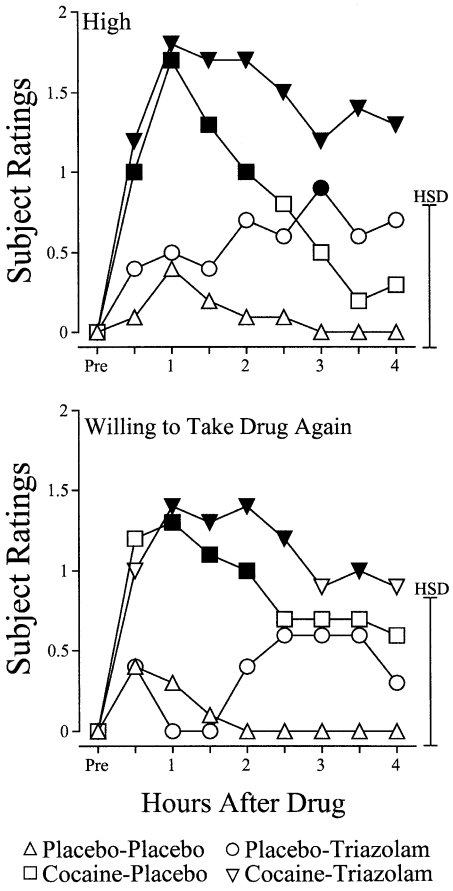

Fig. 3. Time–action functions for placebo, cocaine alone, triazolam alone, and the cocaine–triazolam combination for volunteer ratings of High and Willing to Take Drug Again from the Drug-Effect Questionnaire. Data points show means of 10 participants. *x*-axis: hours after drug. The bracket labeled HSD indicates the critical difference for Tukey's HSD test. These brackets can be used to make pairwise comparisons between means. Means that are separated by a distance larger than the bracket are significantly different according to Tukey's HSD test. Filled symbols are significantly different from the placebo value at the indicated time. Standard error bars are omitted for clarity.

3.2. Time course

The results of analyses conducted on the time-course data were consistent with those conducted on the peak effect data. Fig. 3 shows time-course data for cocaine and triazolam, alone and in combination, for two representative measures: subject ratings of High and Willing to Take Drug Again from the Drug-Effect Questionnaire. This figure shows that cocaine alone increased these ratings as an orderly function of time. Triazolam alone produced only a transient increase in subject ratings of High. Fig. 3 also shows that the magnitude of the effect following the administration of the cocaine–triazolam combination was not significantly different than that observed with cocaine alone. Significant drug effects were observed for a longer period following the concomitant administration of cocaine and triazolam relative to cocaine alone.

4. Discussion

The aim of the present experiment was to determine the combined effects of oral cocaine and triazolam in humans with recent histories of cocaine use because the results of preclinical studies suggest that $GABA_A$ modulators may attenuate the behavioral effects of cocaine (e.g., Goeders et al., 1989, 1993; Meririnne et al., 1999; Negus et al., 2000; Wilson and Schuster, 1973). As expected, oral cocaine alone produced prototypical stimulant-like drug effects (e.g., increased ratings of High, Like Drug, and Willing to Take Drug Again), and increased heart rate and blood pressure. Triazolam alone produced sedative-like drug effects (e.g., increased scores on the PCAG scale of the ARCI). Triazolam pretreatment did not significantly attenuate the behavioral effects of cocaine. Below we discuss these findings in terms of the effects of cocaine alone, triazolam alone, and the effects of the cocaine–triazolam combination.

4.1. Effects of cocaine

Oral cocaine produced stimulant-like subject-rated drug effects (e.g., increased ratings of High, Like Drug, and Willing to Take Drug Again). The present finding that oral cocaine produces prototypical stimulant-like subject-rated drug effects is consistent with previous studies that tested the acute behavioral effects of oral, intranasal, intravenous, and smoked cocaine in humans (e.g., Foltin and Fischman, 1991; Higgins et al., 1990; Oliveto et al., 1995, 1998; Rush and Baker, 2001a; Rush et al., 1999c, 2002a,b; Walsh et al., 1994). Cocaine increased heart rate and blood pressure, which is also concordant with the results of previous studies that tested the effects of oral cocaine. Importantly, however, the magnitude of these effects was not clinically significant.

For example, average maximal heart rate following 300-mg cocaine administration was ~87 bpm, whereas peak systolic blood pressure was ~142 mm Hg. The results of the present study further demonstrate that 300 mg oral cocaine is well tolerated by individuals with recent histories of cocaine use under controlled laboratory and medical conditions (Rush and Baker, 2001a; Rush et al., 1999c, 2002a,b).

4.2. Effects of triazolam

Triazolam alone produced sedative-like subject-rated drug effects. The subject-rated effects observed with 0.5 mg triazolam in the present experiment are concordant with previous studies that tested this dose (e.g., Evans et al., 1990; Rush and Baker, 2001a,b; Rush et al., 1999a,b).

4.3. Effects of combining cocaine and triazolam

Triazolam pretreatment did not significantly attenuate the behavioral effects of cocaine in the present experiment. The finding that triazolam pretreatment did not attenuate the subject-rated effects of cocaine is discordant with the results of a previous study in which the discriminative-stimulus effects of cocaine were assessed in rhesus monkeys following pretreatment with triazolam (Negus et al., 2000). The discriminative-stimulus effects of drugs in laboratory animals are thought to be a model of the subject-rated effects of drugs in humans (for reviews, see Preston and Bigelow, 1991; Schuster and Johanson, 1988; Schuster et al., 1981). As described above, in this previous experiment, six male rhesus monkeys were trained to discriminate cocaine (0.4 mg/kg) from saline (Negus et al., 2000). As expected, cocaine alone (0.01–1.3 mg/kg) dose dependently increased percent cocaine-appropriate responding. Triazolam alone (0.01–1.0 mg/kg) did not occasion significant percent cocaine-appropriate responding, but dose dependently attenuated the discriminative-stimulus effects of cocaine.

The reason for the discrepancy between the present experiment and the previous study conducted with rhesus monkeys is unknown, but may be due to the methods used. First, in the previous study conducted with rhesus monkeys relatively higher doses of triazolam were tested than were used in the present experiment. Perhaps a higher dose of triazolam might attenuate the subject-rated effects of cocaine in humans. Second, as described above, in the previous study conducted with rhesus monkeys, the discriminative-stimulus effects of cocaine were assessed following triazolam pretreatment. In the present experiment, the subject-rated effects of cocaine were assessed following triazolam. While the discriminative-stimulus effects of drugs in laboratory animals and the subject-rated effects of drugs in humans overlap extensively, this relationship is not absolute.

Future studies that assess the efficacy of putative pharmacotherapies for cocaine abuse and dependence should use drug-discrimination procedures adapted for use with humans. The results of two recently published studies collectively suggest that human drug-discrimination procedures in combination with subject-rated drug-effect questionnaires may yield results that are more consistent with the pharmacology of commonly abused stimulants, and, thus, may be particularly well suited for studying the effects of agonist–antagonist combinations in humans (Rush et al., 2003; Wachtel et al., 2002). In the first experiment, the acute subject-rated effects of methamphetamine (0 or 20 mg) were examined alone and following pretreatment with risperidone (0 or 0.75 mg), a $D_2/5HT_2$ receptor antagonist (Wachtel et al., 2002). Methamphetamine alone produced prototypical stimulant-like subject-rated drug effects (e.g., increased ratings of Drug Liking and MBG scores on the ARCI). Risperidone pretreatment did not alter the subject-rated effects of methamphetamine. In the second study, the discriminative-stimulus and subject-rated effects of *d*-amphetamine were assessed following pretreatment with risperidone (Rush et al., 2003). Eight volunteers learned to discriminate 15-mg oral *d*-amphetamine. After acquiring the discrimination (i.e., $\geq$80% correct responding on 4 consecutive days), the effects of a range of doses of *d*-amphetamine (0, 2.5, 5, 10, and 15 mg), alone and following pretreatment with risperidone (0 and 1 mg), were assessed. *d*-Amphetamine alone functioned as a discriminative stimulus and produced stimulant-like self-reported drug effects (e.g., increased ratings of Willing to Take Drug Again, Like Drug, and Good Effects). These effects were generally a function of dose. Risperidone alone did not occasion *d*-amphetamine-appropriate responding, nor did it produce stimulant-like subject-rated effects. Risperidone pretreatment significantly attenuated the discriminative-stimulus and subject-rated effects of *d*-amphetamine.

Although the results of the present experiment do not support the utility of $GABA_A$ modulators as pharmacotherapies for cocaine abuse, at least four caveats of the present experiment need to be considered. First, cocaine was administered orally. Cocaine is not typically abused orally. Future studies should determine if $GABA_A$ modulators attenuate the effects of smoked or intravenous cocaine. Second, triazolam was the $GABA_A$ modulator tested in the present experiment. Perhaps other $GABA_A$ modulators (e.g., alprazolam) might attenuate the subject-rated effects of cocaine. Third, triazolam was administered acutely in the present experiment. Triazolam may need to be administered chronically rather than acutely in order to attenuate the subject-rated effects of cocaine. Fourth, drug plasma concentrations were not assayed following the administration of cocaine and triazolam, alone and in combination. Future studies that examine the effects of triazolam pretreatment on the behavioral effects of cocaine should assay drug plasma concentrations.

In summary, triazolam did not attenuate the acute subject-rated effects of oral cocaine. While the results of the present experiment do not support the utility of $GABA_A$

modulators as pharmacotherapies for cocaine abuse, additional research is needed. In fact, to the best of our knowledge this is the first report in which the effects of cocaine were assessed in humans under controlled laboratory conditions following pretreatment with a $GABA_A$ modulator. Future studies should test the effects of cocaine following pretreatment with $GABA_A$ modulators using more sophisticated behavioral assays such as drug-discrimination procedures developed for use with humans. Future studies should also test the effects of cocaine following pretreatment with $GABA_A$ modulators using more rigorous methods such as dose–response curves for both cocaine and the $GABA_A$ modulator, alone and in combination. 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). Finally, future studies might test the effects of cocaine alone and following pretreatment with a $GABA_B$ agonist (e.g., baclofen) or a GABA transaminase inhibitor. The results of rigorous preclinical studies suggest that $GABA_B$ agonists and GABA transaminase inhibitors attenuate the behavioral effects of cocaine under a variety of behavioral arrangements (for reviews, see Cousins et al., 2002; Dewey et al., 1998; Kushner et al., 1999).

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