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EFFECTS OF COCAINE AND ALCOHOL, ALONE AND IN COMBINATION, ON HUMAN LEARNING AND PERFORMANCE

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The acute effects of cocaine hydrochloride (4 to 96 mg/70 kg) and alcohol (0 to 1.0 g/kg), administered alone and in combination, were assessed in two experiments with human volunteers responding under a multiple schedule of repeated acquisition and performance of response chains. Subjects were intermittent users of cocaine and regular drinkers who were not cocaine or alcohol dependent. Alcohol was mixed with orange juice and ingested in six drinks within 30 min; cocaine was administered intranasally 45 min after completion of drinking. In each component of the multiple schedule, subjects completed response sequences using three keys of a numeric keypad. In the acquisition component, a new sequence was learned each session. In the performance component, the response sequence always remained the same. Results were consistent in both experiments, despite variations in the order in which the drugs were tested alone and in combination. Alcohol administered alone increased overall percentage of errors and decreased rates of responding in the acquisition component, whereas responding in the performance component generally was unaffected. Cocaine administered alone decreased rates of responding but did not affect accuracy of responding in the acquisition component, and enhanced accuracy of responding without affecting rates of responding in the performance component. The combined doses of cocaine and alcohol attenuated the effects observed with alcohol and cocaine alone. These results suggest that, under the conditions investigated in this study, (a) alcohol produces greater behavioral disruption than cocaine or cocaine–alcohol combinations, (b) cocaine and alcohol each attenuate effects of the other, and (c) such attenuation is most pronounced for cocaine attenuating the disruptive effects of alcohol.

Key words: repeated acquisition, cocaine, alcohol, drug interactions, learning, performance, humans

Combined use of cocaine and alcohol is widespread in the United States (Grant & Harford, 1990). Approximately 70% to 90% of individuals receiving inpatient treatment and 50% of those receiving outpatient treatment for cocaine dependence are also alcohol dependent (Higgins et al., 1991; Miller, Belkin, & Gold, 1990). In national surveys, more than 90% of those who report current cocaine use also report current alcohol use (Grant & Harford, 1990). Combined use of cocaine and alcohol is prominent in drug-related problems in emergency rooms and in drug-related deaths (Drug Abuse Warning Network, 1988).

Despite such widespread use, little scientific information is available on the behavioral effects of combined use of cocaine and alcohol (cf. Kreek, 1987). To our knowledge, only one study has been published describing the behavioral effects of cocaine–alcohol combinations in humans (Foltin & Fischman, 1989). In that study, subjects were tested with alcohol (19 to 58 g) and intranasal cocaine (4 to 96 mg), alone and in combination, while responding under a modified repeated-acquisition procedure. Subjects responded on three response keys (left, center, and right). Correct responses produced an asterisk on a video screen, whereas incorrect responses produced a brief timeout. Points exchangeable for money were delivered contingent on emitting predetermined response sequences on the three keys. The length of the response sequence to be acquired increased progressively to a maximum of 25 responses. Alcohol alone significantly decreased the maximum length of the response sequence acquired and rates of correct responding, whereas cocaine alone produced no significant effects on these measures. Combining the drugs did not alter the effects of alcohol alone to a statistically significant degree, but a trend towards less disruption with the drug combinations versus alcohol alone was evident.

To our knowledge, only three studies have been reported on the behavioral effects of cocaine and alcohol combinations with nonhu-

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mans. Results from those studies suggest that effects of the combinations vary dependent on (a) environmental conditions, (b) the effects of the constituent drugs administered alone, and, perhaps, (c) species. In the first study, doses of cocaine that had no effect on rotarod performance when administered alone were combined with an active dose of alcohol using rats and mice as subjects (Rech, Vomachka, & Rickert, 1978). The combinations disrupted rotarod performance of rats above levels observed with alcohol alone, whereas with mice, the combination produced no clear evidence of exacerbation or attenuation. In the second study, cocaine, at doses that were inactive when administered alone, attenuated the rate-enhancing effects of alcohol on punished responding by rats in one component of a multiple schedule. In the other component, cocaine exacerbated the rate-suppressing effects of alcohol on responding under a random-interval schedule of reinforcement (Aston-Jones, Aston-Jones, & Koob, 1984). In the third study, activity levels of mice were measured after they received alcohol alone and in combination with varying doses of cocaine (Masur, Souza-Formigoni, & Pires, 1989). Both compounds increased activity when administered alone, and combining them resulted in additive increases.

This dearth of scientific information on the behavioral effects of this commonly used drug combination is surprising. Certainly the acute behavioral impairment resulting from combined use could have important implications for traffic, occupational, and other areas of safety (cf. Grant & Harford, 1990). Recent evidence indicates that cocaine and alcohol combinations result in the production of a novel metabolite, cocaethylene, that is behaviorally active in nonhumans (Hearn et al., 1991; Jatlow et al., 1991; Katz, Terry, & Witkin, 1992). How that metabolite may affect human behavior is unknown. Finally, understanding the behavioral effects of cocaine and alcohol combinations may provide insights into why the drugs often are used together.

The purpose of this study was to characterize the acute effects of cocaine and alcohol, alone and in combination, on discriminated operant behavior of adult humans. Discriminated operants are a fundamental element of many forms of complex human behavior. Thus, the results of this study should have potential generalizability to many forms of naturalistic human behavior. A two-component multiple schedule of repeated acquisition and performance of behavioral chains was employed. This baseline permits an assessment of drug effects on responding in transition (i.e., learning) contrasted with steady-state (i.e., performance) conditions. Drug effects often differ for these two conditions (e.g., Bickel, Higgins, & Griffiths, 1989; Desjardins, Moerschbaecher, Thompson, & Thomas, 1982; Higgins, Woodward, & Henningfield, 1989), and, thus, inclusion of both conditions provides for a more comprehensive characterization of the effects of this commonly used drug combination than either condition alone. In addition, in prior studies with humans the repeated-acquisition and performance procedure has been sensitive to the acute effects of cocaine and alcohol alone, which makes it an interesting baseline on which to study the effects of these drugs in combination (e.g., Fischman, 1984; Higgins, Bickel, O'Leary, & Yingling, 1987; Higgins, Bickel, et al., 1989).

EXPERIMENT 1

METHOD

Subjects

Subjects were 6 healthy men and 2 healthy women recruited via newspaper ads who received monetary compensation ($5.90 per hour) for time spent in experimental sessions. Performance-based payment was also obtained as outlined below. Average age and body weight were 21.5 years (range, 21 to 24) and 75.8 kg (range, 58 to 88). All subjects were Caucasian. Average educational level was 15 years (range, 14 to 16). Subjects completed questionnaires assessing drug use and psychiatric and medical histories, and were interviewed by a licensed psychologist. They also received a physical exam, laboratory screening, and 10 hr of continuous EKG monitoring, and provided written informed consent prior to participating in the study. Individuals who reported evidence of current or past drug dependence, other than tobacco dependence, or who reported current or past psychiatric problems were excluded. Medical problems contraindicating psychomotor stimulant use were also grounds for exclusion. None of the subjects were on medication during the study (except S7, who used an oral contraceptive).

All subjects were recent but occasional users of cocaine. They reported an average of 6.4 weeks since last instance of cocaine use (range, 1 to 16 weeks). All used cocaine intranasally and none reported experience with smoked or intravenous cocaine use. All reported current use of alcohol (range, 12 to 30 drinks per week), 5 reported current use of hallucinogens (range, 24 to 94 weeks since last use), 7 reported daily use of caffeinated beverages, and none were current cigarette smokers.

Drug

Drugs were administered under medical supervision. Ethyl alcohol (95%) was administered in six drinks during a 30-min period. The doses were placebo and 0.5 and 1.0 g/kg of body weight. Tap water was added to the placebo and 0.5 g/kg drinks to be equal in volume with the 1.0 g/kg dose. Reduced-acid orange juice was added to the drinks at a ratio of five parts orange juice per one part alcohol/water. One milliliter of alcohol was floated on the surface of placebo drinks, which otherwise contained only tap water and orange juice. Cocaine hydrochloride was administered intranasally at doses of 4, 48, and 96 mg/70 kg of body weight. Doses were calculated on the basis of the salt. Lactose was added to the lower doses to maintain a constant weight equal to the high dose. The 4 mg/70 kg dose served as placebo, because it is reported to produce a numbing sensation in the nasal mucosa without producing measurable cocaine blood levels (Javaid, Fischman, Schuster, Dekirmenjian, & Davis, 1978). Subjects received their doses on a mirror (30 cm by 30 cm) with a straight-edge razor and a straw (7.5 cm in length and 7.0 mm in diameter). Subjects prepared the cocaine in "lines" using the razor, and, when instructed by the nurse, inhaled them via the straw within 60 s (Foltin & Fischman, 1989; Higgins et al., 1990). Cocaine was inhaled 45 min after completion of the last alcohol drink. The timing of alcohol and cocaine administration was arranged to have their behavioral effects achieve peak levels at approximately the same time (Higgins et al., 1987, 1990). Subjects received all possible dose combinations. For safety purposes, subjects were tested with alcohol and cocaine alone, in a randomized order, prior to testing with the drug combinations. The combined dose of 1.0 g/kg of alcohol and 96 mg/70 kg of cocaine was tested only following testing with the other combinations. One subject (S2) did not receive the high-dose combination due to safety concerns raised during testing of the low-dose combinations. All other subjects received all of the nine dose conditions.

Staff members knew that cocaine and alcohol were being studied, but did not know the schedule of administration of the different doses. Subjects were told that they might receive caffeine, cocaine, *d*-amphetamine, placebo, or alcohol, and that they might receive the drugs alone or a stimulant–alcohol combination. They were not informed of which stimulant they actually received. Subjects received drinks and cocaine during each test session to maintain staff and subject blindness as to whether drugs were being administered alone or in combination (i.e., a single-blind, single-dummy dosing regimen). References below to cocaine or alcohol administered alone pertain to instances in which an active dose of one compound was administered in combination with a placebo dose of the other compound. References to placebo sessions pertain to sessions in which placebo doses of both compounds were administered.

Procedure

General procedures. Subjects participated as outpatients in the General Clinical Research Center of the Medical Center Hospital of Vermont. They were instructed to refrain from all illicit and prescription drug use for the duration of the study, and from alcohol for 12 hr and caffeine and solid food for 4 hr prior to their scheduled sessions. Subjects ate a meal consisting of skim milk and unbuttered toast 1 hr before alcohol administration to prevent nausea. To monitor compliance with restrictions on drug use, breath alcohol levels and urine specimens were screened. Breath and urine test results confirmed compliance with our instructions. Sessions generally were conducted at the same time of day for each subject (weekdays only) with at least 48 hr between sessions. Sessions were conducted in a quiet room, with a maximum of 2 subjects participating simultaneously. A research nurse was present at all times during test sessions. Behavioral procedures were presented and data recorded via an Apple IIe® monochromatic video screen and microprocessor. A numeric keypad served as the response panel.

Experimental sessions. Test sessions generally lasted 6.0 hr, during which subjects remained seated except for a brief visit to the bathroom. The first hour was devoted to subject preparation, the next 0.5 hr to collection of baseline measures, and the subsequent 4.5 hr to drug administration and monitoring.

Multiple schedule. The multiple schedule of repeated acquisition and performance of response chains procedure used in this study has been described previously (Higgins et al., 1987). Subjects performed under a multiple schedule of repeated acquisition and performance of 10-response sequences. Each schedule component was paired with the following distinct visual stimuli: The word "Learning" appeared on the video screen in reverse-contrast print during the acquisition component, and the word "Performance" appeared on the video screen in standard print during the performance component. In each schedule component, points were earned contingent on subjects emitting a 10-response sequence using Keys 1, 2, and 3 of the numeric keypad. The key had to be depressed in a predetermined order (e.g., 2, 1, 3, 1, 3, 2, 1, 3, 2, 1) in the presence of the video screen numbers 0 through 9, which appeared sequentially in the center of the video screen. That is, as each number appeared in the center of the video screen in the 0 through 9 sequence, it was necessary to depress the correct key in order to advance to the next step in the sequence. Incorrect responses initiated a 2-s timeout, during which the word "incorrect" appeared in the center of the video screen in reverse contrast; completion of the timeout period returned the program to the step in the response sequence at which an error was made. Each completed sequence added 1 point to a running counter shown at the top of the video screen and returned the number in the center of the screen to 0 for the start of the next sequence. Points were redeemable for money at the end of the study at a rate of 1 cent per point.

In the acquisition component, reinforcement was contingent on subjects acquiring a new 10-response sequence each time they did the task. In the performance component, the response sequence remained the same throughout the experiment. Each time subjects performed this task, they had 20 trials to acquire the new sequence in the acquisition component and 20 trials of performing the same sequence in the performance component. Subjects always completed all 40 trials, which required approximately 3 to 5 min. Subjects responded under the repeated-acquisition and performance schedule before drug administration, every 15 min for the first hour, and every 30 min during the second and third hours after cocaine administration (total of nine observations per session). Data collected during these different observation times were treated separately in the analyses (i.e., they were not averaged).

In addition to the repeated-acquisition and performance procedure, subjects also completed the Digit Symbol Substitution Test (McLeod, Griffiths, Bigelow, & Yingling, 1982). Visual-analog scales and breath-alcohol levels (BALs) were recorded at each of the observation times mentioned above. Noninvasive physiological monitoring (e.g., electrocardiogram) was conducted throughout the experimental session. Those results will be included in a separate report. The order of behavioral testing was visual-analog scales first, followed by the repeated-acquisition procedure and then the Digit Symbol Substitution Test.

Training sessions. Subjects completed an average of 43 (range, 33 to 51) practice sessions on the repeated-acquisition and performance procedure prior to beginning drug testing. Drug testing began only after responding was judged to be stable via visual inspection (i.e., there were no discernible trends in accuracy or rates of responding).

Data Analysis

Data from each component of the multiple schedule were analyzed separately. Errors were defined as responses on any key other than the one designated as correct at a particular step in a response sequence and were analyzed as overall percentage of errors by dividing the total number of errors in a component by the total number of responses in that component and multiplying by 100. A within-session analysis of errors was conducted for the acquisition component by estimating quarter-life values (Gollub, 1964). Subjects had a maximum of 20 trials to acquire a new response sequence at each observation time. Quarter-life values in this analysis represent the percentage of trials elapsed in making 25% of the total number of errors per each observation

time (Higgins et al., 1987). Quarter-life values were not calculated in the performance component due to the relatively low number of errors in that component, which can obscure a quarter-life analysis. Overall rates of responding in each component were analyzed as responses per second by dividing the total number of responses in each component by the total number of seconds in each component. The 2-s timeouts that followed errors were excluded in calculations of response rate.

Within-subject analyses were conducted across all measures and drug doses. A drug dose was deemed to have an effect in an individual when the peak effect of that dose on absolute scores exceeded the range of values observed during placebo-control sessions. At each dose, peak effect was defined as the value observed after drug administration that represented the largest change from the value observed immediately prior to drug administration during that session. To assess statistical significance, area-under-the-time-action-curve (AUC) values were analyzed in a two-way, repeated measures analysis of variance (ANOVA) for each measure using alcohol and cocaine as factors, with each drug having three levels (i.e., placebo, low dose, high dose). AUC values were calculated by the trapezoidal rule (Dixon, 1988). AUC values, instead of peak effects, were used in the statistical analysis because they represent the overall profile of effects during the repeated observations conducted throughout an experimental test session. We decided against statistically analyzing both peak-effect and AUC values to avoid the errors that may result from conducting multiple statistical tests. Duncan's multiple range test was used to test for differences between the dose conditions when a significant main effect occurred in the ANOVA. Effects were considered statistically significant at $p \leq .05$. Results from the subject who, for safety reasons, did not receive all of the dose conditions were omitted from the statistical analyses.

Results

Breath-Alcohol Levels

BALs increased as an orderly function of alcohol dose, $F(2, 12) = 207.3$, $p < .001$, and there were no significant differences between BALs observed with alcohol administered alone or in combination with the 48 mg or 96 mg/70 kg doses of cocaine. Average peak effects for the 0.5 g and 1.0 g/kg doses administered alone were 28 ± 9 mg/dL and 87 ± 10 mg/dL; administered in combination with the 48 mg/70 kg dose of cocaine they were 26 ± 6 mg/dL and 81 ± 17 mg/dL; and administered in combination with the 96 mg/70 kg dose they were 25 ± 8 mg/dL and 79 ± 16 mg/dL.

Overall Percentage of Errors

Acquisition. During baseline sessions (i.e., placebo sessions), mean overall percentage of errors in the acquisition component ranged across subjects from 0.5% to 7.4% (Figure 1). During peak effects of the 0.5 g and 1.0 g/kg doses of alcohol administered alone, overall percentage of errors increased above the range of placebo levels with 4 and 7 of 8 subjects, respectively. The peak effects of cocaine administered alone on this measure were variable across subjects and generally were not dose dependent. Combinations of cocaine and alcohol produced less behavioral disruption than either dose of alcohol administered alone. The peak effects of the 0.5 g/kg dose of alcohol on overall percentage of errors were less when administered in combination with the 48 mg or 96 mg/70 kg doses of cocaine for 6 and 5 of 8 subjects, respectively. Similarly, effects of the 1.0 g/kg dose of alcohol administered in combination with the 48 mg and 96 mg/70 kg doses of cocaine were less than the effects of the same dose of alcohol administered alone in 6 of 8 and 7 of 7 subjects, respectively (S2 did not receive the highest dose combination).

The results of the AUC statistical analysis on this measure are consistent with the above results. There were significant main effects of alcohol, $F(2, 12) = 7.8$, $p < .01$, and cocaine, $F(2, 12) = 9.1$, $p < .01$, and a significant alcohol–cocaine interaction, $F(4, 24) = 5.8$, $p < .01$ (see Figure 2, upper left panel). In post hoc testing, the two doses of alcohol administered alone differed from placebo and each other. Cocaine alone produced no significant effects. Combining the 0.5 g/kg or 1.0 g/kg doses of alcohol with either dose of cocaine decreased errors significantly below levels observed with those doses of alcohol alone.

The time course of the interaction between alcohol and cocaine is best illustrated by contrasting the effects on percentage of errors of the 1.0 g/kg dose of alcohol administered alone

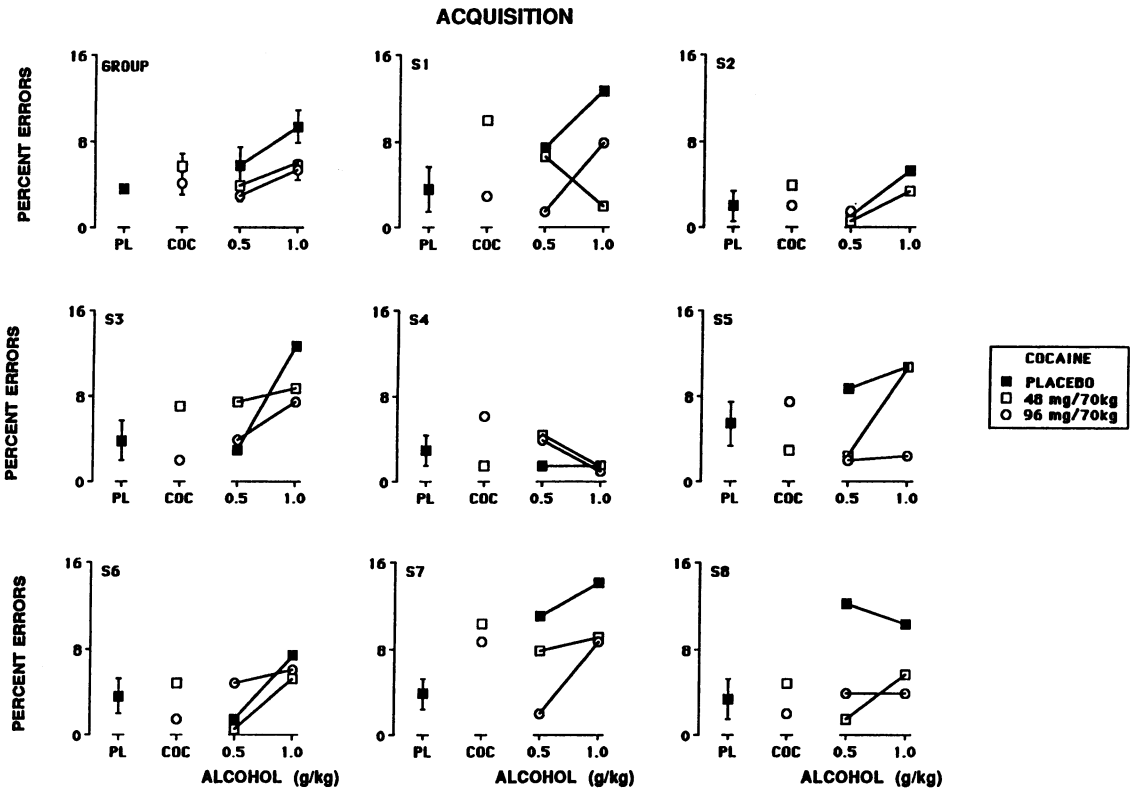

Fig. 1. Overall percentage of errors in the acquisition component are shown for subjects as a group (upper left panel) and for individual subjects as a function of alcohol dose. Group averages are based on results from the 7 subjects who received all dose conditions. Data points above PL represent placebo-control values. Data points above COC represent the effects of cocaine administered alone. Connected data points represent the effects of the two alcohol doses alone (closed squares), and in combination with the 48 mg/70 kg (open squares) and 96 mg/70 kg (open circles) doses of cocaine. Data points across all dose conditions except PL represent peak effects (i.e., largest changes from predrug values). Data points above PL represent the midpoint of the range of values observed with individual subjects during placebo-control sessions. Brackets in the group function represent ±1 *SEM*, and those in the individual-subject functions represent the range of placebo-control values.

with the effects on this measure in combination with the 96 mg/70 kg doses of cocaine (Figure 3). Note that when alcohol was administered alone, errors increased above placebo levels from the 30-min through the 90-min observation. When alcohol was combined with either dose of cocaine, by contrast, errors remained at placebo levels. This pattern of effects was evident for both group data (upper panel) and individual-subject data (lower panel).

Performance. Baseline error levels in the performance component were substantially lower than those in the acquisition component. Mean percentage of errors in the performance component ranged across subjects from 0 to 2.9% (Figure 4). Alcohol alone had relatively little effect on accuracy of responding in the performance component. The 0.5 g and 1.0 g/kg doses increased errors above the range of placebo levels with only 1 (S2) and 3 (S1, S2, S8) of 8 subjects, respectively. No consistent effects of cocaine alone on this measure were discernible in the peak-effect analysis. With the dose combinations, one observation was consistent across all subjects: Overall percentage of errors was the same or lower when the 96 mg/70 kg dose of cocaine was combined with the 1.0 g/kg dose of alcohol than when that same dose of alcohol was administered alone.

In the AUC statistical analysis of this measure, there were significant main effects of alcohol, $F(2, 12) = 5.3$, $p = .02$, and cocaine, $F(2, 12) = 0.02$, $p < .02$, but there was not a

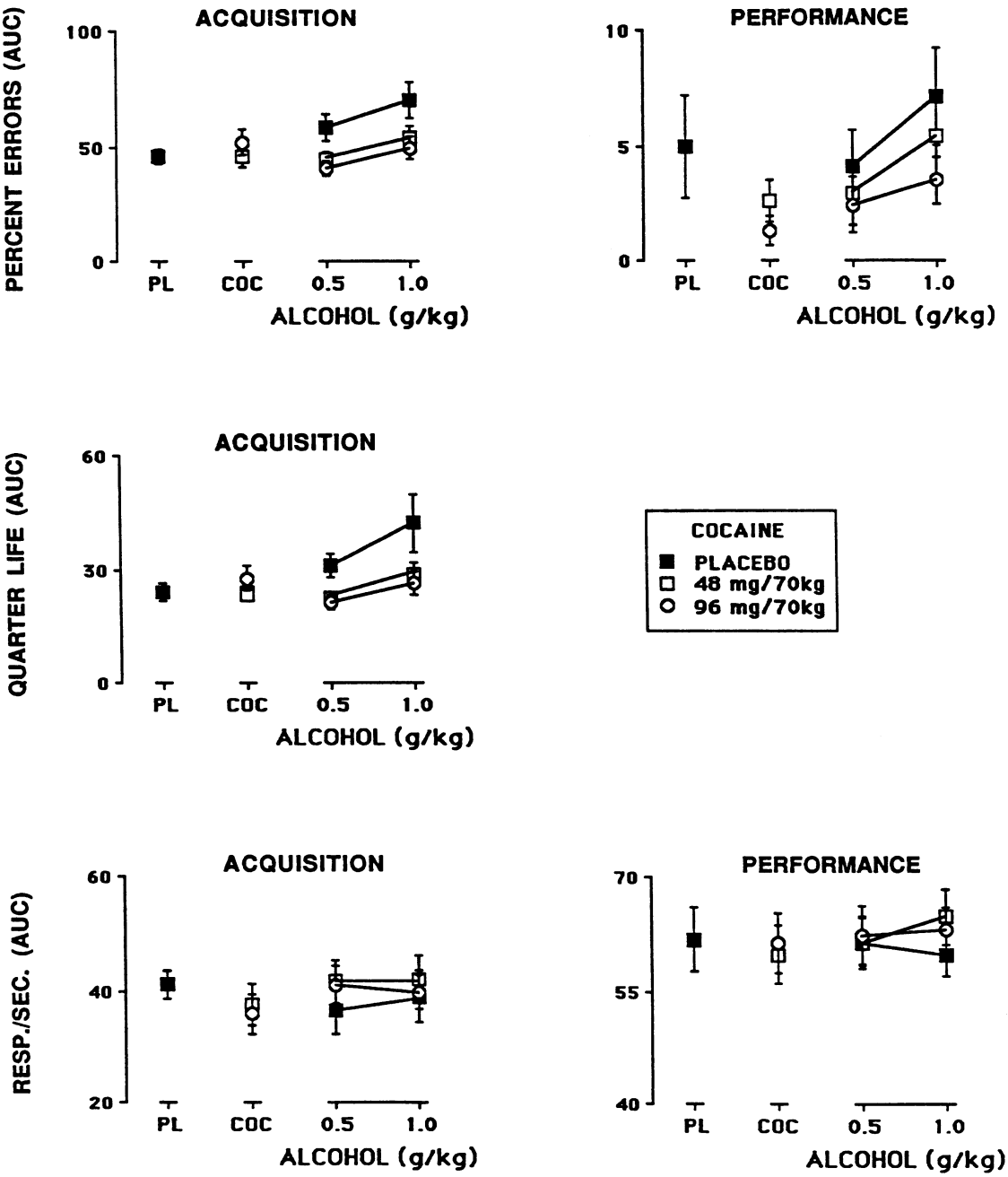

Fig. 2. Area-under-the-time-action-curve values averaged across the 7 subjects who received all dose conditions are shown as a function of alcohol dose. Drug doses are represented by the same symbols as in Figure 1. Percentage of errors in the acquisition component are shown in the upper left panel, percentage of errors in the performance component are shown in the upper right panel, quarter-life values in the acquisition component are shown in the middle panel, rates of responding in the acquisition component are shown in the lower left panel, and rates of responding in the performance component are shown in the lower right panel. Brackets represent ±1 *SEM*.

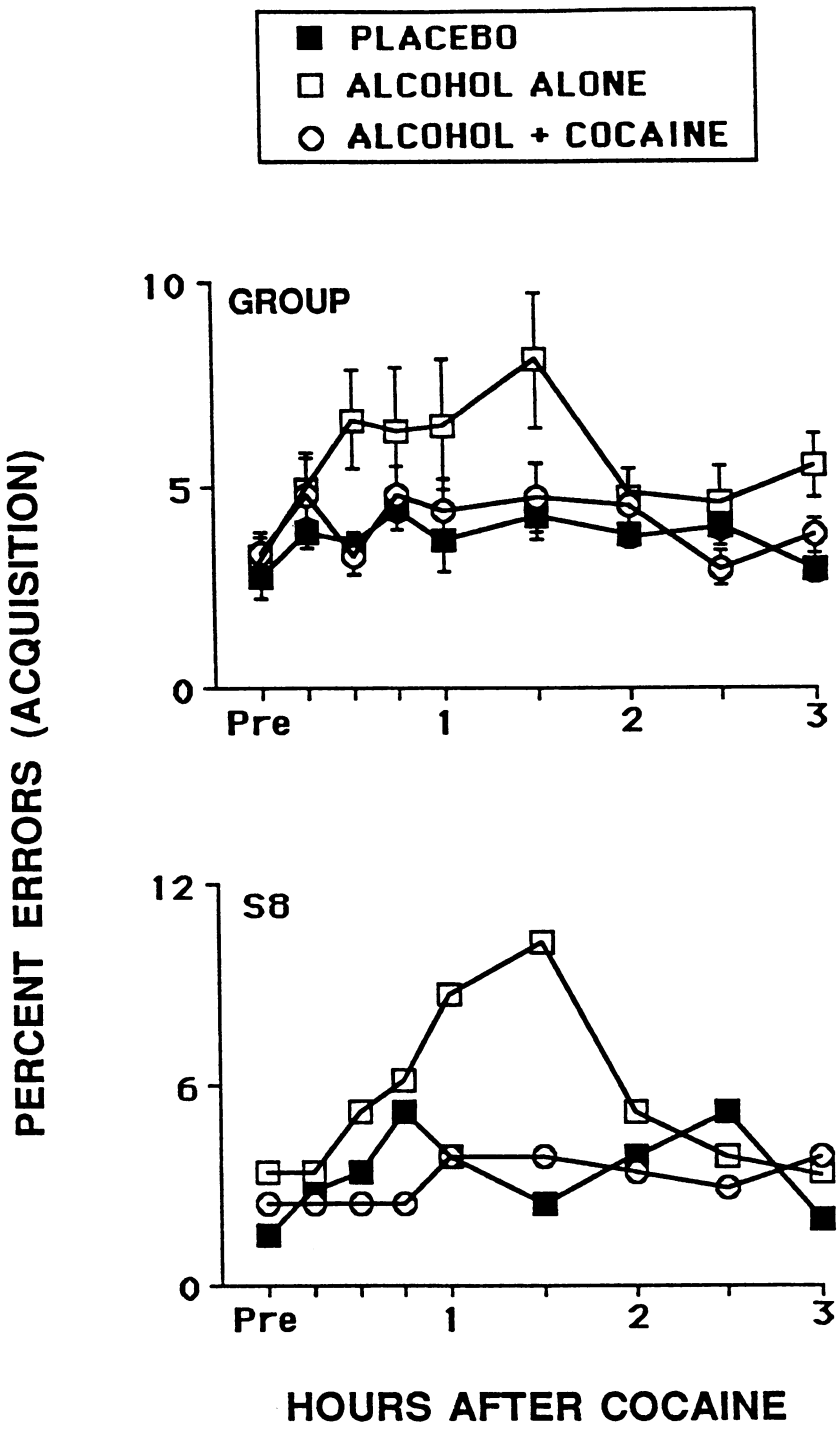

Fig. 3. Percentage of errors in the acquisition component are shown as a function of hours since cocaine administration. The placebo-control dose is represented by closed squares, the 1.0 g/kg dose of alcohol alone by the open squares, and the 1.0 g/kg dose of alcohol in combination with the 96 mg/70 kg dose of cocaine by the open circles. The upper panel shows a group function based on the 7 subjects who received all dose conditions, and the lower panel is a function from a selected individual subject.

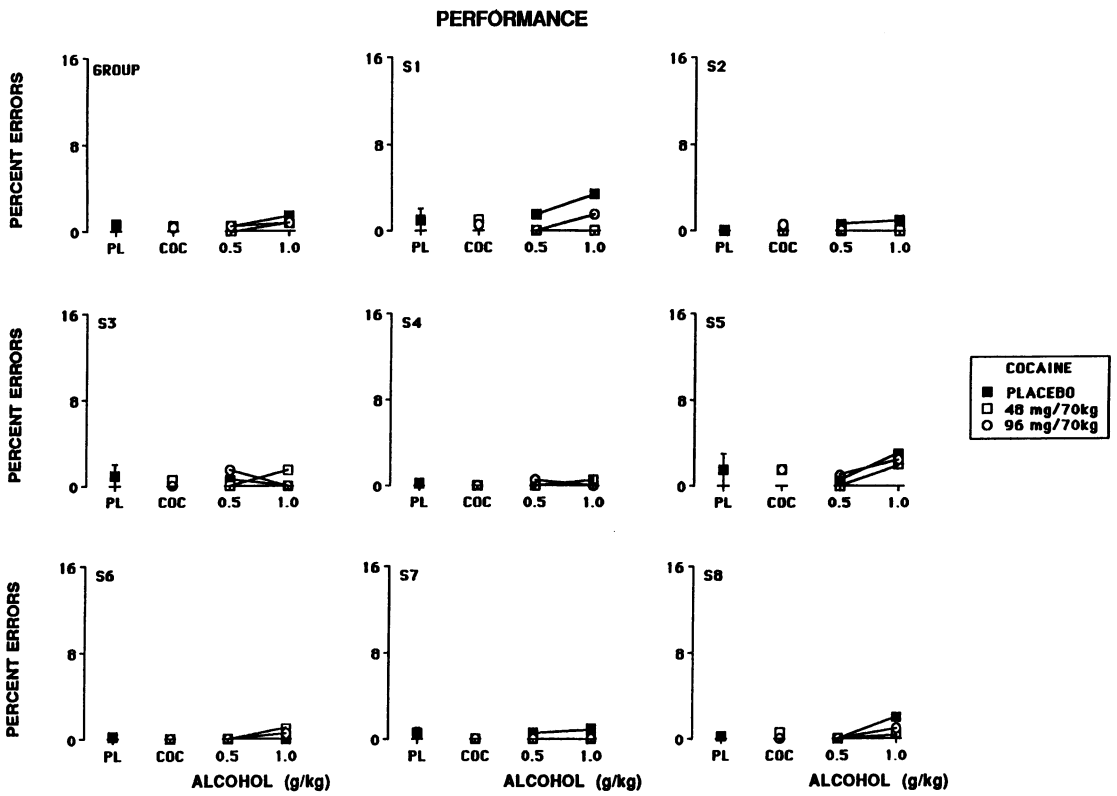

Fig. 4. Overall percentage of errors during peak effect in the performance component are shown for subjects as a group (upper left panel) and for individual subjects as a function of alcohol dose; all else is the same as in Figure 1.

significant alcohol–cocaine interaction, $F(4, 24) = 0.33$, n.s. (see Figure 2, upper right panel). In post hoc testing, neither dose of alcohol alone differed significantly from placebo levels. The 96 mg/70 kg dose, but not the 48 mg/70 kg dose, of cocaine alone decreased errors below placebo levels. Combining the 96 mg/70 kg dose of cocaine with the 1.0 g/kg dose of alcohol increased errors significantly above levels observed with that dose of cocaine administered alone.

Quarter-Life Values

Quarter-life values less than 25% indicate that within-session cumulative errors were negatively accelerated; that is, learning occurred. Values equal to or greater than 25% represent constant and positively accelerated error patterns, respectively, indicating that no learning occurred.

Baseline quarter-life values ranged across subjects from 1.3 to 3.8% (Figure 5). Consistent with the increases observed in overall percentage of errors in the acquisition component, within-session learning was disrupted as an orderly function of alcohol dose. Administration of either dose of alcohol alone increased quarter-life values above placebo levels in 6 of 8 subjects. Although learning was disrupted by alcohol, values remained below 25%, indicating that some acquisition still occurred. Administration of either dose of cocaine alone generally did not affect this measure. Cocaine-produced attenuation of the disruptive effects of alcohol was discernible in the 4 subjects (S3, S5, S7, S8) who exhibited the largest effects from alcohol alone.

In the AUC statistical analysis on this measure, there were significant main effects of alcohol, $F(2, 12) = 8.0$, $p < .01$, and cocaine, $F(2, 12) = 6.8$, $p < .01$, and a significant interaction of the two drugs, $F(4, 24) = 3.7$, $p < .01$ (see Figure 2, middle panel). In post hoc testing, the 1.0 g/kg dose of alcohol alone differed from the 0.5 g/kg and placebo doses, but the latter two did not differ. Cocaine alone

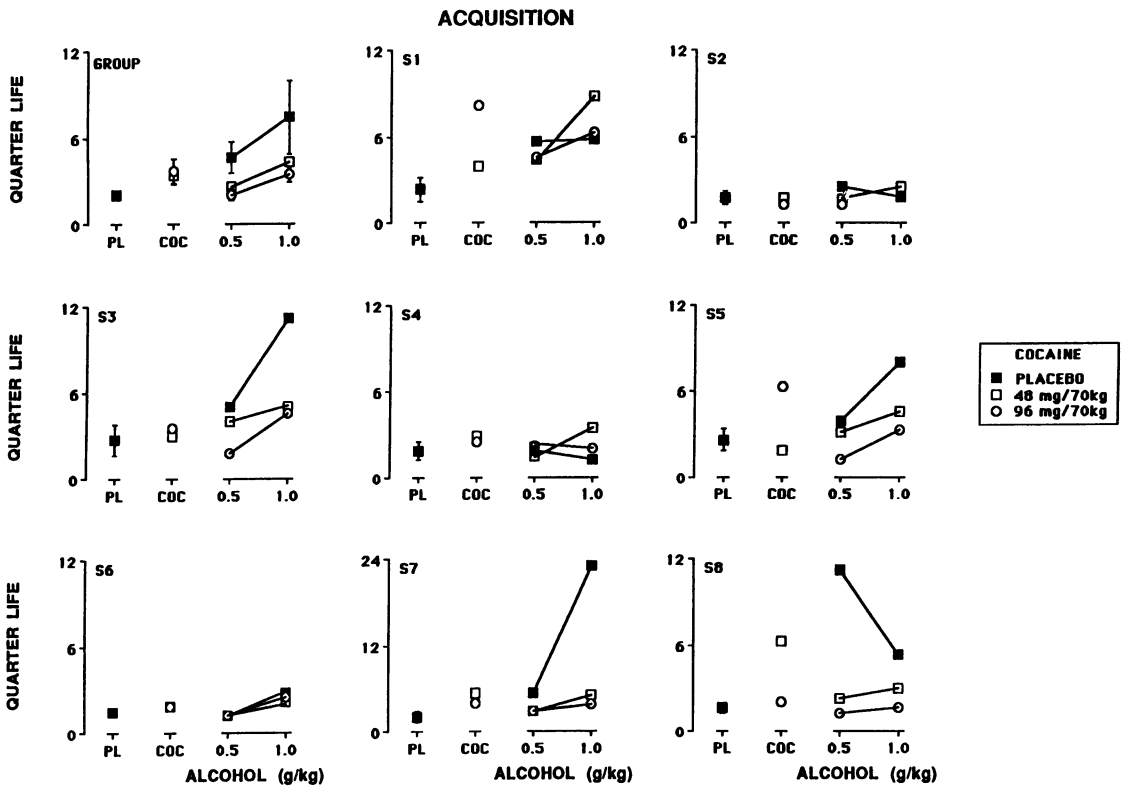

Fig. 5. Quarter-life values in the acquisition component during peak effect are shown for subjects as a group (upper left panel) and for individual subjects as a function of alcohol dose; all else is the same as in Figure 1.

produced no significant effects. Combining the 0.5 g/kg dose with 96 mg/70 kg, but not 48 mg/70 kg, of cocaine decreased values below levels observed with that dose of alcohol alone. Combining the 1.0 g/kg dose of alcohol with either dose of cocaine decreased values below levels observed with that dose of alcohol alone.

The time course of effects on this measure (not shown) corresponded to that described above for overall percentage of errors (Figure 3).

Overall Rates of Responding

Acquisition. Average rates of responding in the acquisition component ranged across subjects from 2.5 to 5.0 responses per second (Figure 6). The effects of alcohol alone on overall rates of responding were inconsistent across subjects and generally were not an orderly function of dose. Administration of the 0.5 g and 1.0 g/kg doses alone decreased rates of responding below placebo levels with 4 (S4, S5, S7, S8) and 3 (S1, S5, S7) subjects, respectively. Administration of the 48 mg and 96 mg/70 kg doses of cocaine alone decreased rates of responding in the acquisition component below placebo levels with 1 (S8) and 4 (S1, S3, S5, S8) of the 8 subjects, respectively.

Combining alcohol and cocaine attenuated the decreases in rates of responding observed in half the subjects when the 0.5 g/kg dose of alcohol or the 96 mg/70 kg dose of cocaine was administered alone. That is, in the 4 subjects (S4, S5, S7, S8) who exhibited rate decreases with the 0.5 g/kg dose of alcohol alone, combining it with either dose of cocaine increased rates above levels observed with that dose of alcohol alone. Similarly, in the 4 subjects (S1, S3, S5, S8) who exhibited rate decreases with the 96 mg/70 kg dose of cocaine alone, combining it with either dose of alcohol increased rates above levels observed with that dose of cocaine alone. It is noteworthy that such attenuation occurred in 2 of these subjects (S5 and S8) even though the drugs alone both decreased rates of responding.

In the AUC statistical analysis, there were no significant main effects of alcohol or co-

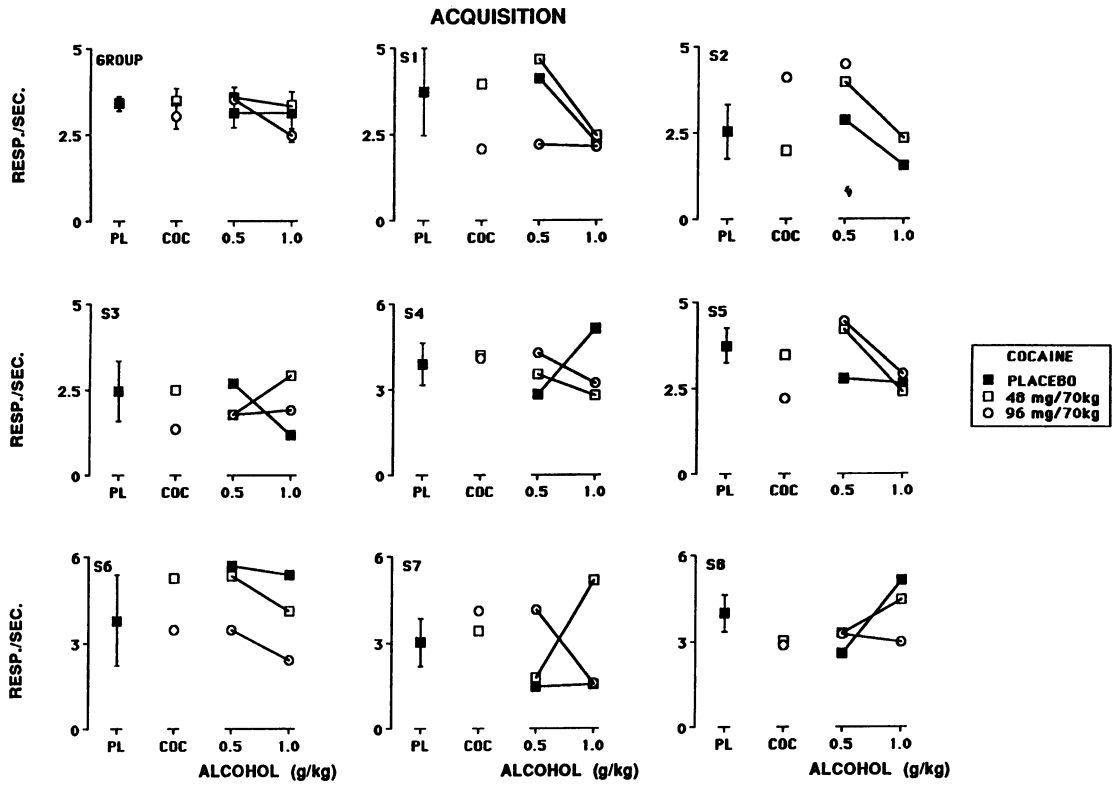

Fig. 6. Rates of responding in the acquisition component during peak effect are shown for subjects as a group (upper left panel) and for individual subjects as a function of alcohol dose; all else is the same as in Figure 1.

caine, but there was a significant drug interaction, $F(4, 24) = 3.7, p < .02$. The interaction appeared to be due to the drug combinations attenuating the decreasing trends evident with the 0.5 g/kg dose of alcohol and the 96 mg/70 kg dose of cocaine administered alone (see Figure 2, lower left panel).

Performance. As expected, overall mean rates of responding in the performance component generally were higher than rates in the acquisition component, with values ranging across subjects from 2.9 to 7.8 responses per second (not shown). Neither drug administered alone or in combination produced effects that were consistent across subjects or statistically significant (see Figure 2, lower right panel).

EXPERIMENT 2

Although the results from Experiment 1 suggested that alcohol and cocaine in combination attenuated the behavioral effects of the drugs alone, an alternative interpretation is that the dose combinations produced less of an effect due to dosing order. That is, cocaine and alcohol were always tested in combination after being studied alone, and perhaps the attenuation was due to repeated exposure to cocaine and alcohol (e.g., tolerance). Experiment 2 was conducted to test this possibility directly.

METHOD

Subjects

Four healthy men and 1 healthy woman participated after providing written informed consent. Subjects S5 and S8 participated in Experiment 1, and the others were new subjects. Average age and body weight were 23 years (range, 22 to 25) and 76.5 kg (range, 68 to 82). All subjects were Caucasian. Average educational level was 16 years (range, 15 to 16). All subjects were recent but occasional users of cocaine. They reported an average of 11 weeks since last instance of cocaine use (range, 1 to 18 weeks). All used cocaine intranasally, 1 reported experience with smoked

cocaine, and none reported experience with intravenous cocaine use. All reported current use of alcohol (range, 10 to 22 drinks per week); all reported current or past use of hallucinogens (range, 1 to 104 weeks since last use); 4 reported daily use of caffeinated beverages; none were cigarette users, although 1 was a regular user of chewing tobacco. No restrictions were placed on tobacco use between sessions. To prevent tobacco withdrawal during sessions, this subject was required to chew for 15 min beginning 45 min before each session, but was not permitted to use tobacco again during experimental sessions. None of the subjects were on medication during the study.

Drug

Four dose conditions were studied in this experiment: placebo alcohol in combination with placebo cocaine (i.e., placebo), the 1.0 g/kg dose of alcohol in combination with cocaine placebo (i.e., alcohol alone), the 96 mg/70 kg dose of cocaine in combination with the placebo dose of alcohol (i.e., cocaine alone), and the the 1.0 g/kg dose of alcohol in combination with the 96 mg/70 kg dose of cocaine (i.e., drug combination). Drug preparation and administration were the same as in Experiment 1. Subjects S5 and S8 were tested first with a placebo dose to reacquaint them with the protocol, and were then tested with the four doses described above. Results from the first placebo session were discarded. S9 was first tested under alcohol alone, and S10 and S11 were tested under alcohol alone and cocaine alone to ensure they could safely tolerate the drugs; data from those sessions were discarded. S9 received cocaine in a prior study; thus, his ability to tolerate it had been established. These 3 subjects were subsequently tested with the four doses outlined above. Subjects received the final four doses in a Latin-square design. The 5th subject (S11) was an extra in the 4 × 4 Latin-square design. He was assigned to a dosing order in which the alcohol–cocaine combination was administered prior to alcohol alone, in keeping with the purpose of this experiment.

Procedure

All experimental procedures remained the same as in Experiment 1.

Data Analysis

Results from this experiment were analyzed as peak-effect and AUC values. Inferential statistics were omitted due to the small sample size.

Results and Discussion

Breath-Alcohol Levels

Consistent with results from Experiment 1, BALs observed with alcohol alone were not altered by combining it with cocaine. When the 1.0 g/kg dose of alcohol was administered alone and in combination with cocaine, average peak effects were 87 ± 10 mg/dL and 81 ± 10 mg/dL, respectively.

Overall Percentage of Errors

Acquisition. The results observed with percentage of errors in the acquisition condition were consistent with those observed in Experiment 1. The 1.0 g/kg dose of alcohol administered alone increased percentage of errors above placebo levels in all subjects in the peak-effect and AUC analyses (Figure 7). Cocaine alone increased errors in both analyses with S8 and S9, but effects were variable for the other subjects. Most important to the purposes of this experiment, error scores were lower with the drug combination than alcohol alone for 4 of the 5 subjects in the peak-effect and AUC analyses.

As in Experiment 1, differences between alcohol alone and the drug combination were evident across several observation times. When alcohol was administered alone, errors increased above placebo levels from the 30-min through the 60-min observation (Figure 8). When alcohol was combined with the 96 mg/70 kg dose of cocaine, by contrast, errors remained within placebo levels. Also consistent with results from Experiment 1, this was evident for both the group (upper panel) and the individual data (lower panel).

Performance. Consistent with the results observed in Experiment 1, drug effects on accuracy of responding in the performance component were of relatively small magnitude (Figure 7). Alcohol alone increased errors above placebo levels for 3 (S8, S10, S11) of the 5 subjects in the peak-effect and AUC analyses. Cocaine alone did not alter percentage of errors in any subject in the peak-effect analysis, but decreased errors in all subjects in the AUC analysis. For the 3 subjects in whom alcohol alone increased errors (S8, S10, S11), the drug combination resulted in less disruption in both analyses. With S9, who did not exhibit an effect with alcohol alone, the drug combination

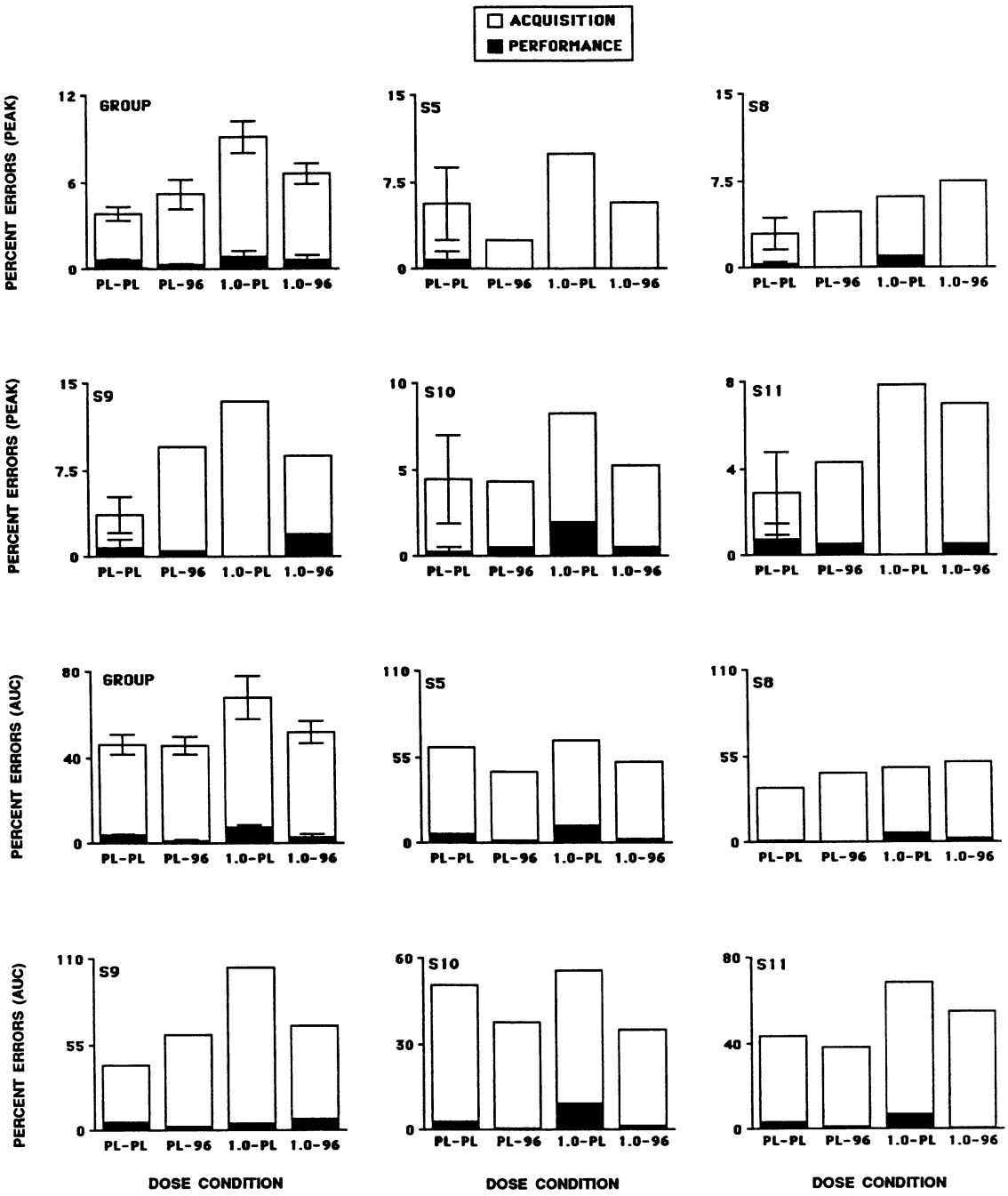

Fig. 7. Overall percentage of errors in the acquisition (open bars) and performance (closed bars) components are presented as peak-effect values in the upper two rows of panels and area-under-the-time-action-curve values in the lower two rows of panels. In each set of panels, group data are shown in the upper left panel and individual-subject data in the remaining panels. Bars above PL-PL represent placebo-control values, bars above PL-96 represent the 96 mg/70 kg dose of cocaine administered alone, bars above 1.0-PL represent the 1.0 g/kg dose of alcohol administered alone, and bars above 1.0-96 represent the 1.0 g/70 kg dose of alcohol and the 96 mg/70 kg dose of cocaine administered in combination. Brackets in the group panel represent ±1 *SEM*, and those in the individual-subject panels for peak effects represent the range of placebo-control values.

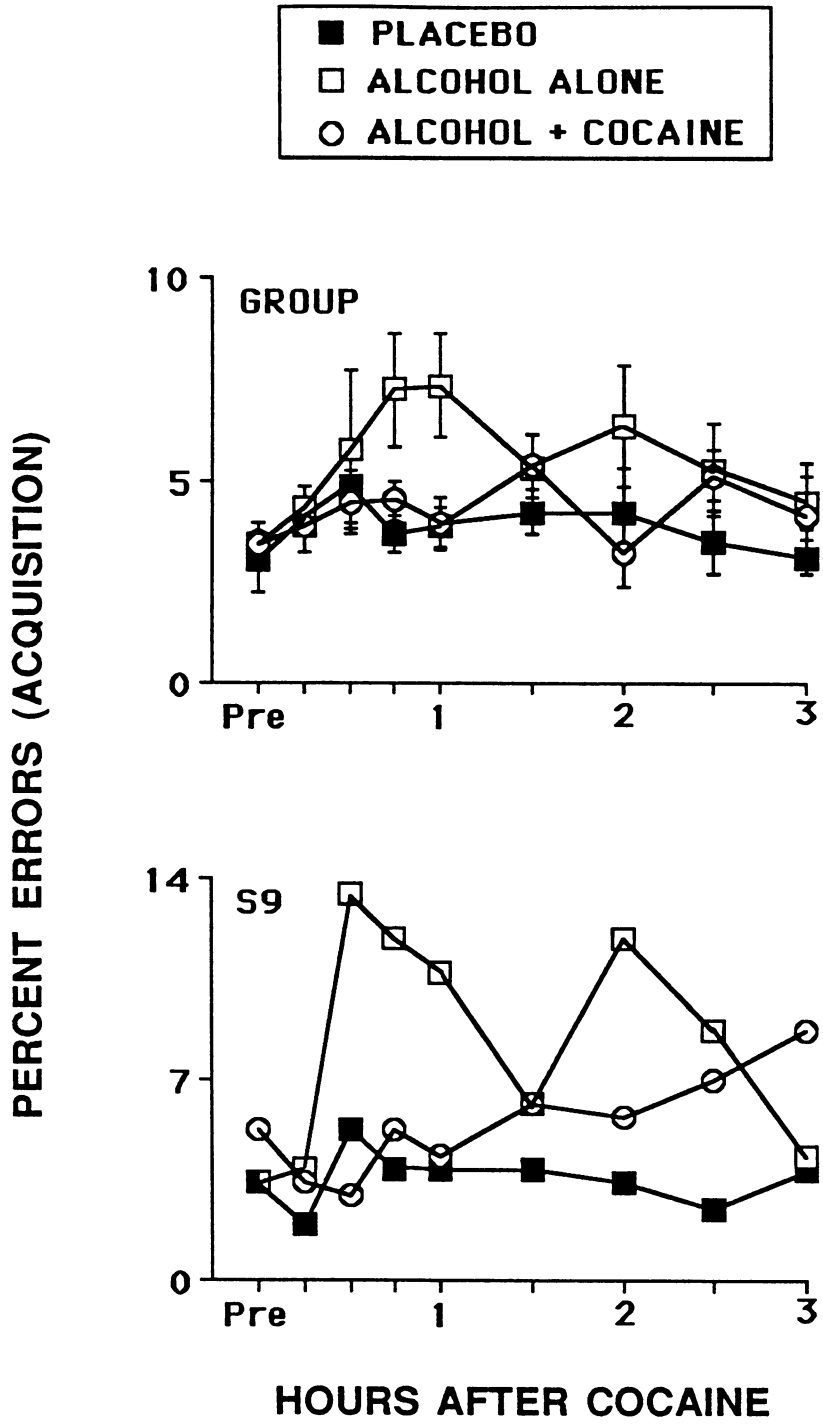

Fig. 8. Percentage of errors in the acquisition component are shown as a function of hours since cocaine administration. The placebo-control dose is represented by closed squares, the 1.0 g/kg dose of alcohol alone by the open squares, and the 1.0 g/kg dose of alcohol in combination with the 96 mg/70 kg dose of cocaine by the open circles. The upper panel shows a group function based on all subjects, and the lower panel is a function from a selected individual subject.

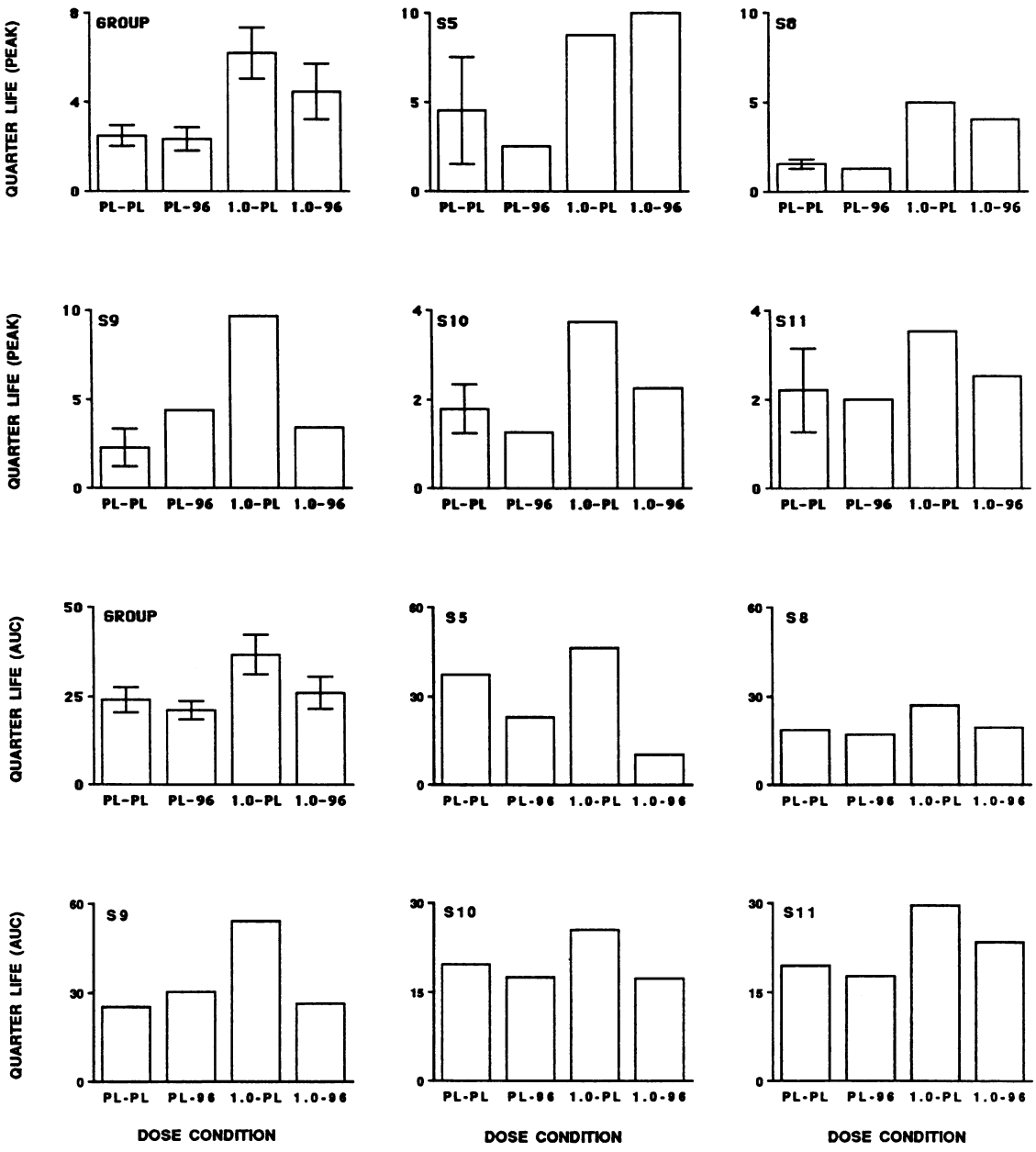

Fig. 9. Quarter-life values in the acquisition component are presented as peak-effect values in the upper two rows of panels and area-under-the-time-action-curve values in the lower two rows of panels; all else is the same as in Figure 7.

resulted in more errors than were observed with any of the other doses, but errors still never exceeded 2%.

Quarter-Life Values

Consistent with results observed in Experiment 1, alcohol alone increased quarter-life values in the acquisition component above placebo levels for all subjects (Figure 9). Cocaine alone had no effect in the majority of subjects in the peak-effect analysis, but decreased AUC values in 4 of 5 subjects. The drug combination decreased quarter-life values below those observed with alcohol alone for 4 of the 5 subjects in the peak-effect analysis and all subjects in the AUC analysis.

Table 1

Overall rates of responding in the acquisition and performance components expressed as peak-effect and AUC values.

	S5	S8	S9	S10	S11	*M*	*SEM*
Acquisition (peak effect)							
Placebo–placebo	3.39 (2.61–4.16)[a]	4.48 (3.80–5.15)	4.67 (3.87–5.46)	3.32 (2.55–4.08)	3.21 (2.77–3.64)	3.81	4.31
Placebo–96 mg cocaine	4.43	3.43	2.75	3.07	2.60	3.26	4.31
1.0 g alcohol–placebo	3.10	4.50	2.14	4.51	2.57	3.36	4.31
1.0 g alcohol–96 mg cocaine	2.47	4.60	4.28	4.44	2.57	3.67	4.31
Performance (peak effect)							
Placebo–placebo	4.40 (3.99–4.80)	5.83 (4.96–6.70)	5.50 (5.06–5.93)	4.34 (3.90–4.78)	4.63 (4.13–5.13)	4.94	4.31
Placebo–96 mg cocaine	4.19	6.33	5.65	5.12	5.47	5.35	4.31
1.0 g alcohol–placebo	4.40	6.39	5.24	4.95	5.28	5.25	4.31
1.0 g alcohol–96 mg cocaine	3.90	6.49	5.96	4.91	5.54	5.36	4.31
Acquisition (AUC)							
Placebo–placebo	41.50	55.70	51.13	39.01	37.98	45.06	4.31
Placebo–96 mg cocaine	45.87	47.08	45.69	40.55	42.61	44.36	3.64
1.0 g alcohol–placebo	43.86	49.10	33.94	36.18	36.03	39.82	3.46
1.0 g alcohol–96 mg cocaine	36.09	47.43	42.94	39.01	37.98	40.69	4.07
Performance (AUC)							
Placebo–placebo	53.49	75.32	68.55	53.54	59.37	62.05	4.31
Placebo–96 mg cocaine	51.81	71.24	70.04	58.45	64.21	63.15	3.64
1.0 g alcohol–placebo	51.03	67.38	68.19	53.83	59.99	60.08	3.46
1.0 g alcohol–96 mg cocaine	49.40	70.97	69.32	56.10	63.81	61.92	4.07

[a] Values in parentheses represent the range of values observed with individual subjects during placebo-control sessions.

Overall Rates of Responding

Acquisition. Effects of alcohol alone, cocaine alone, and the drug combination on rates of responding were variable. Alcohol alone decreased rates of responding across the peak-effect and AUC analyses in only 2 subjects (S9 and S11) (Table 1). Cocaine alone decreased rates in both analyses with 2 subjects (S8 and S9), increased them in 1 subject (S5), and produced inconsistent effects in 2 subjects (S10 and S11). When the drug combination was administered to S9 and S11, who had exhibited decreases with both alcohol alone and cocaine alone, rates were above those observed with alcohol alone.

Performance. Consistent with results observed in Experiment 1, overall mean rates of responding in the performance component generally were unaffected by the drugs administered alone or in combination (Table 1).

GENERAL DISCUSSION

Considered together, the results from Experiments 1 and 2 provide a detailed characterization of the acute effects of alcohol and cocaine, alone and in combination, on human learning and performance. When administered alone, alcohol significantly disrupted accuracy, and sometimes rates of responding, in the acquisition component. These effects replicate prior findings with humans and nonhumans (Barthalmus, Leander, & McMillan, 1978; Higgins et al., 1987; Higgins, Bickel, et al., 1989). Also consistent with prior findings, responding in the performance component was less sensitive to the disruptive effects of alcohol than responding in the acquisition component, although in some subjects responding in both schedule components was disrupted by the highest dose (Barthalmus et al., 1978; Higgins et al., 1987; Higgins, Bickel, et al., 1989).

Cocaine administered alone did not consistently disrupt accuracy of responding in the acquisition or performance components; accuracy of responding in the performance component was often enhanced by the 96 mg/70 kg dose of cocaine. The absence of significant disruption with intranasal cocaine at the doses studied in this report replicates prior findings (Foltin & Fischman, 1989; Higgins et al., 1990). However, it is important to note that

cocaine can disrupt discriminated-operant responding under some circumstances. For example, a transient increase in errors occurred with some subjects in the present study and in prior studies on the effects of the same or comparable doses of intranasal cocaine (Fischman, 1984; Higgins et al., 1990). Also, disruptions in accuracy and rates of responding in this procedure have been observed with humans who received intravenous injections of cocaine (Fischman, 1984), and with pigeons and monkeys that received intramuscular injections of cocaine (Moerschbaecher & Thompson, 1980; Thompson, 1977).

The enhancement by cocaine in accuracy of responding in the performance component and the decreases in rates of responding in the acquisition component are effects that were not observed in a prior study using these procedures and doses of intranasal cocaine (Higgins et al., 1990). In that study, neither of these measures was significantly affected by cocaine. However, performance in the Digit Symbol Substitution Test was enhanced in that study. The Digit Symbol Substitution Test can be considered to be a discriminated-operant procedure; thus, there is precedent for these doses of intranasal cocaine to enhance some aspects of discriminated-operant responding in human subjects who are not sleep deprived. Comparable doses of intranasal cocaine produce clear improvements in reaction time with sleep-deprived humans (Fischman & Schuster, 1980).

In the present study, combining alcohol and cocaine significantly attenuated the disruption of accuracy and rates of responding observed when alcohol was administered alone. Similarly, combining alcohol and cocaine attenuated the enhanced accuracy of responding in the performance component and the decreases in rates of responding in the acquisition component observed when cocaine was administered alone. The consistency of the results across Experiments 1 and 2 suggests dosing order was not a confounding factor.

The profile of behavioral effects of cocaine and alcohol combinations observed here is consistent with the observation of less behavioral disruption with cocaine–alcohol combinations versus alcohol alone noted in the only prior report on this topic in humans (Foltin & Fischman, 1989). It is also consistent with cocaine's attenuation of alcohol's effects on punished responding in rats (Aston-Jones et al., 1984). Conversely, the present results are inconsistent with cocaine's exacerbation of alcohol's effects on rotarod performance and responding maintained under a random-interval schedule of reinforcement, noted previously in rats (Aston-Jones et al., 1984; Rech et al., 1978), and the additive effects reported with these compounds on locomotor behavior in mice (Masur et al., 1989). However, as the Aston-Jones et al. (1984) study illustrated, cocaine can attenuate or exacerbate the behavioral effects of alcohol depending on the schedule of reinforcement under which responding is maintained. Clearly a great deal more research must be conducted before a complete understanding of the environmental determinants of the behavioral effects of cocaine and alcohol combinations emerges.

Because cocaine has a relatively short duration of action, attenuation of alcohol's behavioral effects by cocaine would be expected to be of brief duration and, in that sense, potentially dangerous. For example, the attenuation may be of sufficient duration to permit an individual to begin to operate a motor vehicle, but the effects would quickly dissipate, leaving an impaired driver on the road. The present results are inconsistent with the prediction. Less behavioral disruption was observed with the drug combinations versus alcohol alone throughout the time course of alcohol's effects. This observation is consistent with prior findings that intranasal administration of the 96 mg/70 kg dose of cocaine improved performance in the Digit Symbol Substitution Test for several hours after cocaine administration (Higgins et al., 1990).

Interestingly, the attenuation observed between cocaine and alcohol in Experiment 1 was not consistently dose dependent. That is, there were no consistent differences observed in the efficacy of the 48 mg and 96 mg/70 kg doses of cocaine in attenuating the effects of either dose of alcohol, nor were there clear differences between the efficacy of the 0.5 g and 1.0 g/kg doses of alcohol in attenuating the effects of either dose of cocaine. Whether this lack of dose responsivity is an artifact of testing a narrow dose range or is a reliable characteristic of this drug combination is unclear. Alcohol dose was not manipulated in any of the published studies on cocaine–alcohol interactions conducted with nonhumans, but cocaine dose was manipulated in two studies

conducted with rodents (Masur et al., 1989; Rech et al., 1978). In those studies, there were few discernible differences between cocaine doses with regard to how they interacted with a constant dose of alcohol, except at the highest cocaine doses tested (25 and 30 mg/kg); these produced larger magnitude effects than the other doses.

Importantly, the effects of the drug combination in this study often were not predictable based on the effects of the compounds administered alone. For example, doses of cocaine that produced no significant effects when administered alone nevertheless attenuated the effects of alcohol. This is consistent with prior findings on the effects of cocaine and other stimulants in combination with alcohol (e.g., Holloway & Holloway, 1979; Rech et al., 1978). Such findings underscore the necessity of directly assessing the effects of drug combinations as opposed to predicting effects based on the effects of the drugs alone.

The mechanism(s) for the opposing behavioral effects of cocaine and alcohol observed in the present study are unknown. There were no discernible changes in alcohol metabolism that would account for the effects observed. BALs in Experiments 1 and 2 did not differ when alcohol was administered alone or in combination with cocaine. Cocaine serum levels were not assessed in this study; thus, whether an alcohol-produced alteration in cocaine metabolism may have contributed to the results observed is unknown. To our knowledge, the influence of alcohol on cocaine metabolism has not been reported, although alcohol has been demonstrated to inhibit the metabolism of other psychomotor stimulants such as amphetamine (Jonsson & Lewander, 1973; Rech et al., 1978). Considering that either attenuation or exacerbation of effects can be seen with cocaine–alcohol combinations depending on environmental factors (Aston-Jones et al., 1984) and the absence of reliable dose-dependent relationships, a physiological rather than a competitive type of antagonism may be operating. What role, if any, is played by the novel metabolite cocaethylene in the behavioral effects of cocaine–alcohol combinations is unknown.

The generality of the present findings to other behavioral arrangements, drug doses, dosing regimens, and routes of administration is an important topic for future studies. Another important topic for future study is how combining cocaine and alcohol influences rates and patterns of self-administration of each compound. For example, if cocaine increases rates of alcohol self-administration, individuals using these combinations may ultimately ingest enough alcohol to surmount any practical benefits to be derived from cocaine's ability to attenuate alcohol's disruptive effects. Such studies will contribute immensely to our overall understanding of the behavioral pharmacology of cocaine–alcohol combinations.

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