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The Effects of Cocaine in Combination With Other Drugs of Abuse on Schedule-Controlled Behavior in the Pigeon

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EVANS, E. B. AND G. R. WENGER. *The effects of cocaine in combination with other drugs of abuse on schedule-controlled behavior in the pigeon.* PHARMACOL BIOCHEM BEHAV **37**(2) 349–357, 1990.—The present experiment sought to provide information regarding the consequences of combining cocaine with other drugs of abuse. The effects of cocaine alone and in combination with *d*-amphetamine, caffeine, morphine or delta-9-tetrahydrocannabinol were determined in five male white Carneaux pigeons responding under a multiple fixed-ratio 30, fixed-interval 600 schedule (mult FR FI). Drug interactions were studied by redetermining the cocaine dose-response curve in the presence of various fixed doses of the other drugs. Under the mult FR FI schedule, when cocaine (1 to 10 mg/kg) was combined with inactive doses of *d*-amphetamine (0.1, 0.3, 1.0, and 1.8 mg/kg), caffeine (10, 30, and 100 mg/kg), morphine (0.3, and 1.0 mg/kg), and delta-9-tetrahydrocannabinol (0.1 mg/kg), the FR and FI response rate dose-response curves were not shifted relative to the cocaine-alone curves. When cocaine was combined with an active dose of a drug which decreased response rate when given alone (0.3 mg/kg delta-9-tetrahydrocannabinol and 3 mg/kg morphine), the position of the response rate dose-response curves shifted compared to the cocaine-alone curves. The most frequent and consistent outcome of these interactions can be described as less than or approximately equal to an effect-additive interaction. Thus, these data indicate that the potential consequences of coabusing cocaine with the drugs tested in the present experiment can most often be predicted from the effects of each drug when taken alone.

Cocaine Morphine Caffeine *d*-Amphetamine Delta-9-tetrahydrocannabinol Pigeons Drug interactions Behavior Effect-addition

POLYDRUG use can be defined as the use of more than one drug simultaneously and with a certain frequency (34). Polydrug use can result from intentionally combining two or more drugs, or the unintentional administration of two or more drugs due to the adulteration of street-acquired drugs. It is well established that polydrug use is common among cocaine users (2, 5, 14, 27, 29, 33, 34, 36–38). The primary reasons expressed by users for combining drugs with cocaine are to combat unpleasant effects, to alleviate anxiousness often felt when cocaine's initial euphoria dissipates, and to reduce the overstimulation experienced during periods of intensified cocaine use (14, 28, 37). Drugs are also often combined to enhance or supplement the "high." For example, cocaine is combined with an opiate such as heroin to produce a more intensely pleasurable "rush" (8, 13, 41). Finally, as mentioned above, polydrug use is also observed as a consequence of the adulteration of street acquired cocaine (28,37). Illicitly acquired cocaine has been found to be adulterated with procaine, lidocaine, phenylpropanolamine, heroin, caffeine, amphetamines, lactose, and mannitol (13, 17, 37).

It is surprising that with polydrug use among cocaine users so widespread and well documented little is known concerning the potential consequences. It is even more alarming since it has been suggested that polydrug use may be responsible for many of the adverse effects associated with cocaine use (1, 2, 6, 8, 10). Therefore, the purpose of the present experiment was to investigate possible interactions between cocaine and other commonly abused drugs. Specifically, this study provides a systematic description of the effects of cocaine in combination with other drugs of abuse on schedule-controlled behavior in pigeons.

To measure the effects of the drug combinations on behavior

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the mult fixed-ratio 30, fixed-interval 600 second (mult FR 30, FI 600) schedule of reinforcement was chosen. The mult FR 30, FI 600 schedule was selected to measure the consequences of the drug combinations since the individual components of the schedule provide two baselines of behavior which are differentially affected by drugs thereby increasing the ability to detect possible cocaine-drug interactions.

Drugs frequently combined with cocaine include alcohol, marijuana, stimulants, sedatives, and opiates (2, 5, 14, 27, 36). These patterns of polydrug abuse indicate that drugs taken in conjunction with cocaine represent many pharmacological classes. Based on this pattern of human polydrug use, drugs from various pharmacological classes were chosen to combine with cocaine. The drugs chosen to combine with cocaine were *d*-amphetamine, caffeine, morphine, and delta-9-tetrahydrocannabinol. Separate dose-response curves for cocaine and each of these drugs were determined. Subsequently, the effects of cocaine were redetermined in the presence of selected doses of *d*-amphetamine, caffeine, morphine, and delta-9-tetrahydrocannabinol. The effects of the cocaine drug combinations were measured by comparing the cocaine dose-response curve in the presence and absence of different doses of each of these drugs.

METHOD

Subjects

Five adult male White Carneaux pigeons with free-feeding weights between 531–645 g were used. Four of the subjects were experimentally naive at the start of the experiment. One of the subjects (P153) had previously performed under various schedules of food presentation. For the experiment, the weights of the subjects were reduced to 80% of their free-feeding weights. They were subsequently maintained at this weight for the duration of the study. Water and grit were continuously available in their home cages. The home cages were located in a room devoted solely to pigeon housing, and the room lights were scheduled on a 12-hour light-dark cycle, with the lights on from 7:00 a.m.–7:00 p.m.

Apparatus

The apparatus consisted of a standard one-key pigeon chamber (Model G7311, Gerbrands Corp., Arlington, MA). The single, 2 cm in diameter, response key was located in the center of the front wall, 22 cm above the chamber floor. A force of at least 0.17 N was required to open the key contacts and define the response. The response key could be transilluminated by lights mounted behind the keys. Located below the response key, 5 cm above the wire mesh floor, was a rectangular opening through which the pigeon could be given access to Purina pigeon checkers (food aperture). The chamber was illuminated by two bulbs (No. 1819) mounted on the ceiling of the chamber (houselights). The chamber was housed in a separate ventilated, sound- and light-attenuating enclosure (Model G7211, Gerbrands Corp., Arlington, MA). External noises were further masked by random noise from a speaker located in the experimental room. Programming of the schedule and recording of responses were accomplished by a microcomputer located in a separate room (TRS-80, Model 4, Tandy Corp., Fort Worth, TX).

Procedure

The schedule was a multiple fixed-ratio 30, fixed-interval 600 second (mult FR 30, FI 600) schedule of reinforcement. To signal the start of the session the houselights were illuminated, and the response key was transilluminated green. In the presence of the green stimulus, 30 responses resulted in 5-second access to food (FR 30). During food presentation, the key and houselights were extinguished, and the food aperture was illuminated. Following the 5-second access to the food, the houselights were reilluminated, and the response key was transilluminated red. In the presence of the red stimulus, the first response emitted after the elapse of 600 seconds resulted in 5-second access to food (FI 600). Under both components, a 60-sec limited-hold was in effect. That is, if no response occurred during a 60-sec period following the elapse of the 600-sec interval, or if 30 responses were not emitted in 60 sec during the presentation of the green stimulus, the schedule progressed to the next component of the schedule. The stimulus colors and their associated components alternated after each food presentation or after the elapse of the 60-sec limited-hold. The session ended when each component had been presented 7 times (approximately 72 min).

The drugs and vehicles were administered by deep intramuscular injection into the pectoral muscle. Following drug administration, the subject was placed in a darkened experimental chamber (except for caffeine and delta-9-THC; see below). The session began after the elapse of the appropriate pressession time allowing for the onset of drug effect. The presession times were: 10 minutes for morphine sulfate, and 5 minutes for cocaine hydrochloride and *d*-amphetamine sulfate. Following the administration of caffeine or delta-9-THC, due to the lengthy presession time (90 minutes for delta-9-THC, 30 minutes for caffeine sodium benzoate) the subject was returned to the home cage until five minutes before the completion of the presession time, at which time the subject was placed in the experimental chamber. Each pigeon began drug testing at a different dose and progressed in either an ascending or descending dosage sequence. The birds were tested between 08:30 and 17:00 hours, Monday through Friday. Drug effects were tested on Tuesday and Friday with Thursdays used as a vehicle test day.

The drugs that were coadministered with cocaine will be referred to as: *combination drugs*. The combination drugs were: morphine, *d*-amphetamine, caffeine, and delta-9-THC. Prior to testing drug combinations, acute dose-response curves were determined for cocaine and each of the combination drugs. After completing acute dose-response curves, the cocaine dose-response curve was redetermined prior to testing any drug combinations. From the acute dose-response curves of the combination drugs, doses were selected to combine with cocaine. To perform the cocaine-drug combinations a selected dose of the combination drug was kept constant and was coadministered separately with each dose from the cocaine dose-response curve. Once all combinations of cocaine and the fixed dose of the combination drug were tested, another dose of the combination drug was chosen to combine with cocaine. The initial dose of combination drug used in combination with cocaine was the highest dose which had no effect on the rate or pattern of responding. Additional doses, smaller or larger, of the combination drug were selected based on the results obtained from the initial cocaine combination drug dose-response results. Two to four doses of each combination drug were coadministered with cocaine. Additionally, the effect of the selected doses of the combination drugs were redetermined in the presence of a control injection of saline.

The terminology used to summarize each drug combination was adopted from Fingl and Woodbury (9). The effects of coadministering two behaviorally active drugs are compared to the separate effect of each drug when given alone. The outcome of coadministering two drugs is referred to as effect-addition when the effect of the drug combination is equal to the sum of the effects of each drug when given alone. Variation of results from effect-addition are described as greater or less than the simple addition or summation of the effect of each drug alone.

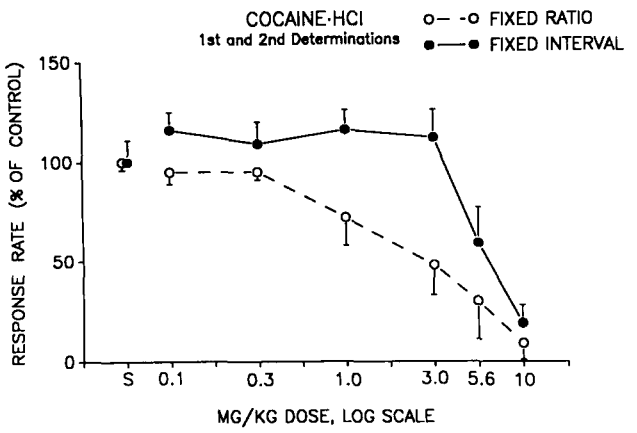

FIG. 1. Effects of cocaine·HCl on the rate of responding under the mult FR 30, FI 600 schedule of food presentation. Abscissa: cocaine dose, log scale. Ordinate: overall response rate expressed as a percentage of saline control rate. Points above S represent the mean ± S.E.M. from 10 saline sessions in each of the 5 pigeons. Points and vertical lines represent the mean ± S.E.M. of two observations in each of the 5 pigeons.

Drugs

The drug forms administered and from which the doses were calculated were as follows: cocaine hydrochloride, morphine sulfate, *d*-amphetamine sulfate, caffeine sodium benzoate, and delta-9-tetrahydrocannabinol (delta-9-THC) (200 mg/ml in ethanol, supplied by the National Institute on Drug Abuse). All drugs were dissolved in physiologic saline (except delta-9-THC) to a concentration that permitted the desired dose to be injected at a volume of 1 ml/kg body weight. Delta-9-THC, after evaporation of the alcohol, was suspended in 7 drops of Triton X-100, absolute ethyl alcohol in a 2% concentration (calculated as volume percent) and distilled water to a volume which permitted the administration of the desired dose in a volume of 1 ml/kg of body weight. Physiologic saline was used for control injections. The Triton X-100, ethyl alcohol solution was administered to determine the effects of the delta-9-THC vehicle.

Data Analysis

Average rates of responding during FR and FI components were calculated in responses per second by dividing the total number of responses emitted during the respective component by the total elapsed-time during each component (not including access time to reinforcer).

The group data were analyzed by comparing drug and drug interaction effects to the mean of five to fifteen saline control sessions. The saline sessions bracketed each dose-response determination, that is, saline sessions were run before, during, and after each dose-response determination. In addition, the effects of the drug combinations were also compared to effects of each of the drugs when given alone. Drug and drug combination effects on the rates of responding are expressed as percent of control. Control rates for each bird were determined by calculating the mean response rate of the saline sessions which bracketed each dose-response determination. To determine the statistical significance of individual dose combinations compared to the individual doses administered separately, an analysis of variance (ANOVA) was conducted on the data for the individual dose combination in question, the data for the same doses of both drugs given separately, and the saline control group. Those effects producing significant F-ratios were further evaluated by the Bonferroni *t*-test between selected pairs of means using the pooled degrees of freedom and residual variance values from the analysis of variance (18). All measures were determined to be significant at $p \leq 0.05$.

RESULTS

Acute Effects of Cocaine Administered Alone

The effect of cocaine on the mult FR 30, FI 600 responding of pigeons was determined twice: once as the first drug tested for acute effects, and a second time after the acute effects of all drugs in the study had been determined but before any combination had been studied. No statistical significances were observed between the two cocaine determinations. Therefore, data from both cocaine determinations were combined and are presented as the mean of the two determinations. Figure 1 illustrates the results of the two determinations of the effects of cocaine administration on FR and FI mean rate of responding. Doses of 0.1 to 3.0 mg/kg cocaine had no effect on FI rate of responding while higher doses decreased responding in a dose-dependent manner. Low doses of 0.1 and 0.3 mg/kg cocaine produced no change in FR rate of responding from saline control rate. Higher doses of cocaine (1 to 10 mg/kg) decreased FR responding.

The effects of each combination drug when coadministered with saline shown in Figs. 2–5 are representative of those observed when the acute dose-response curves were determined. Therefore, the acute dose-response curve for each combination drug is not shown. The range of doses tested in each acute dose-response curve was: *d*-amphetamine 0.1 to 3.0 mg/kg, caffeine 1.0 to 180 mg/kg, morphine 0.01 to 3.0 mg/kg, and delta-9-THC 0.03 to 1.8 mg/kg.

Effects of Cocaine Plus Combination Drugs

Cocaine plus selected doses of d-*amphetamine.* Redeterminations of the cocaine dose-response curve in the presence of various doses of *d*-amphetamine are illustrated in Fig. 2. Doses of 0.1, 0.3, 1.0, and 1.8 mg/kg *d*-amphetamine (coadministered with an injection of saline) had no significant effect on FR or FI rate. Combinations of cocaine with doses of *d*-amphetamine produced effects on FR and FI rate of responding that were no different from those of cocaine given alone. Combinations of cocaine + *d*-amphetamine tested did not shift the FR or FI response rate dose-response curve relative to the cocaine-alone curve. The resultant effects of the cocaine + *d*-amphetamine combinations tested could be predicted according to the effects produced by each drug when given alone (effect-additive). Only the 10 mg/kg cocaine + 0.1 mg/kg *d*-amphetamine, and 0.3 mg/kg cocaine + 1.8 mg/kg *d*-amphetamine dose combinations resulted in effects that could not be predicted from the effects of each drug alone. The 10 mg/kg cocaine + 0.1 mg/kg *d*-amphetamine combination lessened the severe FI rate decreases produced by 10 mg/kg cocaine given alone (top left panel), and the combination of 0.3 mg/kg cocaine + 1.8 mg/kg *d*-amphetamine significantly reduced FR rate of responding (lower right panel).

Cocaine plus selected doses of caffeine. Redeterminations of the cocaine dose-response curve in the presence of various doses of caffeine are illustrated in Fig. 3. The doses of 10, 30, and 100 mg/kg caffeine administered alone produced no significant changes in FR or FI rate. The majority of the cocaine + caffeine dose combinations tested produced no shift in the FR response rate dose-response curve relative to the cocaine alone curve (effect-additive). Only 3 mg/kg cocaine interacted with 30 mg/kg caffeine in a less than additive manner by eliminating the decrease in FR rate produced when 3 mg/kg cocaine was given alone (center

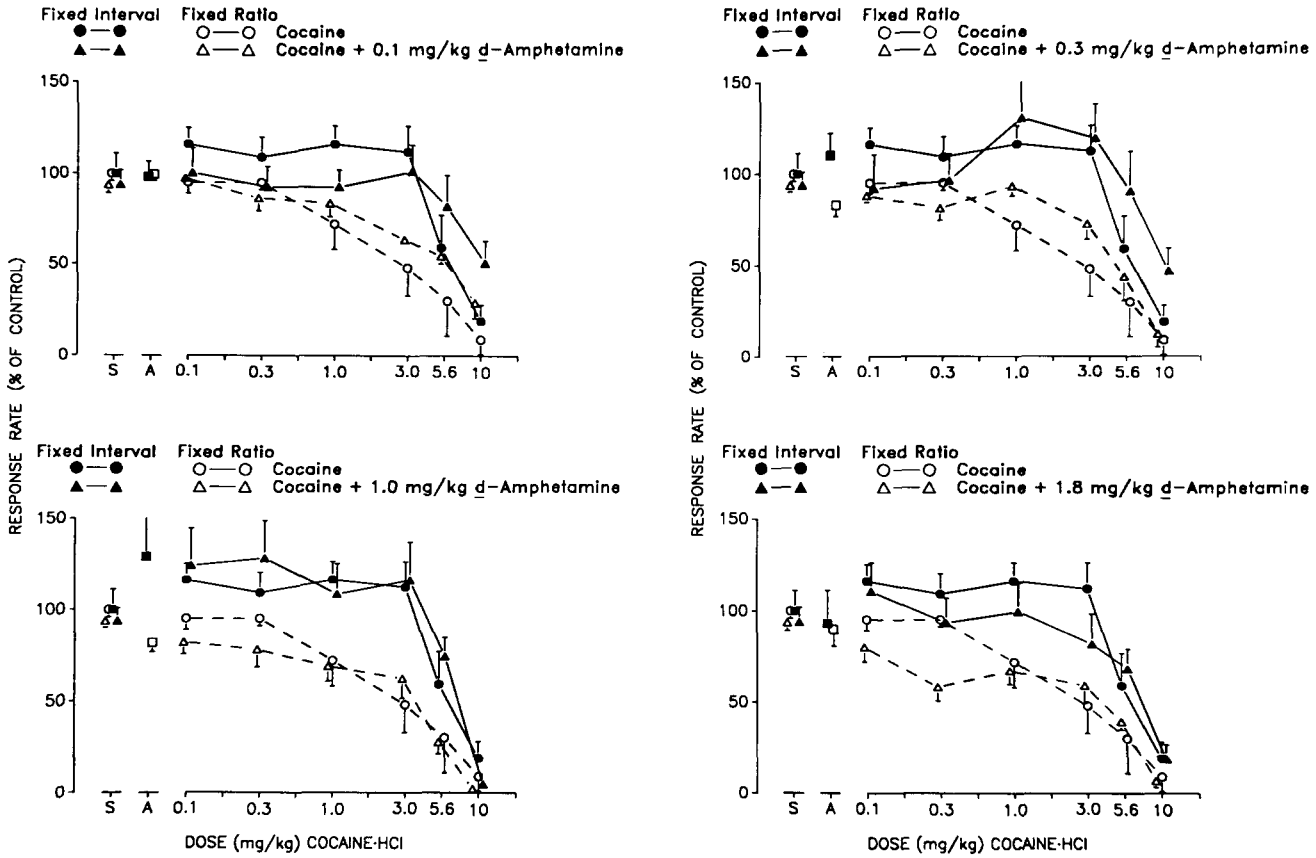

FIG. 2. Effects of cocaine alone and in combination with doses of *d*-amphetamine on responding under the mult FR 30, FI 600 schedule of food presentation. Abscissa: cocaine dose, log scale. Ordinate: overall rate of responding expressed as a percentage of saline control rate. Points above S represent the mean ± S.E.M. from 14 saline sessions in each of 5 pigeons. Points above A show the effects the various doses of *d*-amphetamine coadministered with an injection of saline. Points and vertical lines for *d*-amphetamine coadministered with an injection of saline and cocaine in combination with *d*-amphetamine represent the mean ± S.E.M. of single observations in 5 pigeons. Points and vertical lines for cocaine represent the mean ± S.E.M. of two observations in 5 pigeons.

panel). Like the effects of the cocaine + caffeine combinations on FR rate, low doses of cocaine (0.1 to 3.0 mg/kg) in combination with doses of caffeine also had no effect on FI rate compared to cocaine given alone (effect-additive). However, when higher doses of 5.6 and 10 mg/kg cocaine were combined with 10 and 30 mg/kg caffeine, the FI response rate decreases produced by cocaine alone were diminished or eliminated, resulting in a shift to the right in the dose-response curve (top and center panel). Similarly, 10 mg/kg cocaine + 100 mg/kg caffeine diminished the decrease in FI rate observed when 10 mg/kg of cocaine was given alone (bottom panel). These combinations all resulted in less than effect-additive interactions by eliminating the substantial FI response rate decrease observed when these doses of cocaine were given alone. It should be noted that a greater shift to the right of the FI response rate dose-response curve was generated by either 5.6 or 10 mg/kg cocaine + 30 mg/kg caffeine than by 5.6 and 10 mg/kg cocaine + 10 mg/kg caffeine.

Cocaine plus selected doses of morphine. Redeterminations of the cocaine dose-response curve in the presence of various doses of morphine are illustrated in Fig. 4. The dose of 0.3 mg/kg morphine alone had no effect on FR and FI rate. Combining this dose of morphine with cocaine produced effects on both FR and FI rates of responding that were no different than those resulting from administering cocaine alone (top panel). Similarly, a larger dose of 1.0 mg/kg morphine also had no effect when given alone, and produced no shift in the cocaine + morphine dose-response curves for both FR and FI rate as compared to the cocaine-alone curves (center panel). When 3.0 mg/kg morphine was coadministered with an injection of saline, the apparent decrease in FI and FR rate was not statistically significant (bottom panel). The combination of 3 mg/kg morphine with cocaine shifted both FR and FI response rate dose-response curves to the left compared to the cocaine-alone curves, although none of the effects on FR rate produced when cocaine was combined with 3 mg/kg morphine were significantly different from cocaine given alone. However, doses of 0.1, 0.3, 1.0, and 3.0 mg/kg cocaine in combination with 3 mg/kg morphine resulted in greater than effect-additive interactions by decreasing FI rate compared to the effect (or no effect on FI rate) of these doses of cocaine given alone. All other cocaine + 3 mg/kg morphine dose combinations produced effects on FI rate no different than cocaine given alone. The substantial, but not statistically significant, decrease of FR and FI responding at 5.6 or 10 mg/kg cocaine + 3 mg/kg morphine reflects the apparent rate suppressing effects of 3 mg/kg of morphine added to rate-suppressing doses of cocaine. In summary, excluding the effects of cocaine (0.1 to 3.0 mg/kg) + 3 mg/kg morphine on FI rate,

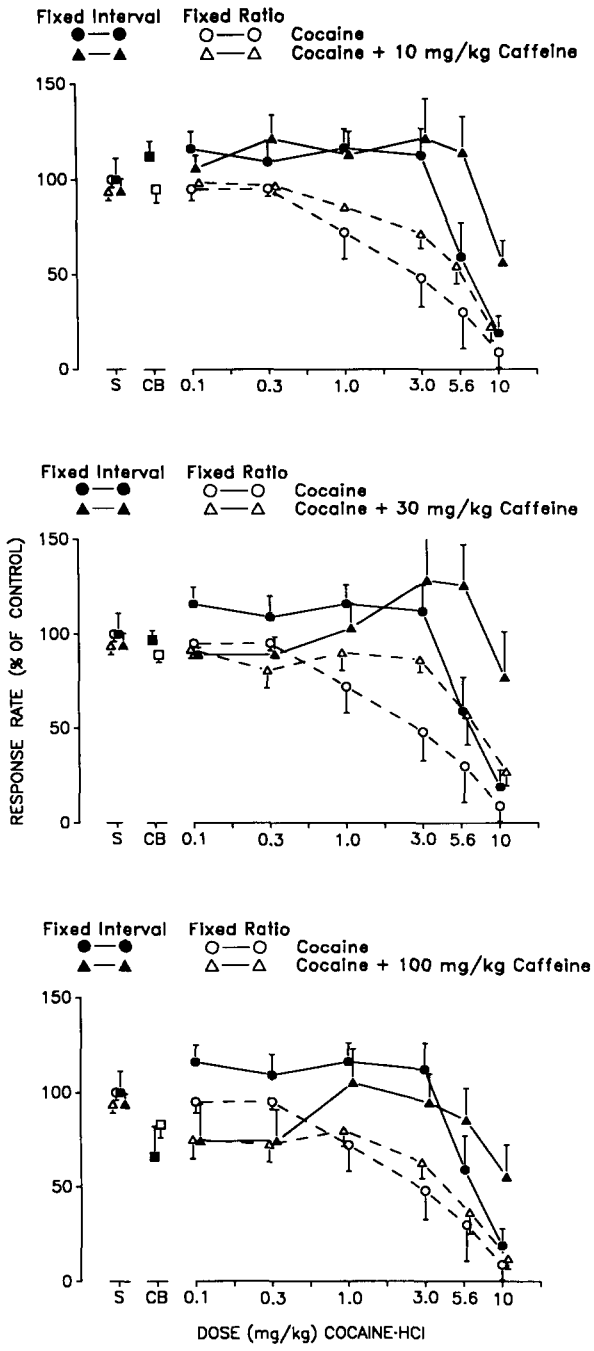

FIG. 3. Effects of cocaine alone and in combination with doses of caffeine Na·benzoate on responding under the mult FR 30, FI 600 schedule of food presentation. Abscissa: cocaine dose, log scale. Ordinate: overall rate of responding expressed as a percentage of saline control rate. Points above S represent the mean ± S.E.M. from 15 saline sessions in each of 5 pigeons. Points above CB show the effects the various doses of caffeine Na·benzoate coadministered with an injection of saline. Points and vertical lines for caffeine Na·benzoate coadministered with an injection of saline and cocaine in combination with caffeine Na·benzoate represent the mean ± S.E.M. of single observations in 5 pigeons. Points and vertical lines for cocaine represent the mean ± S.E.M. of two observations in 5 pigeons.

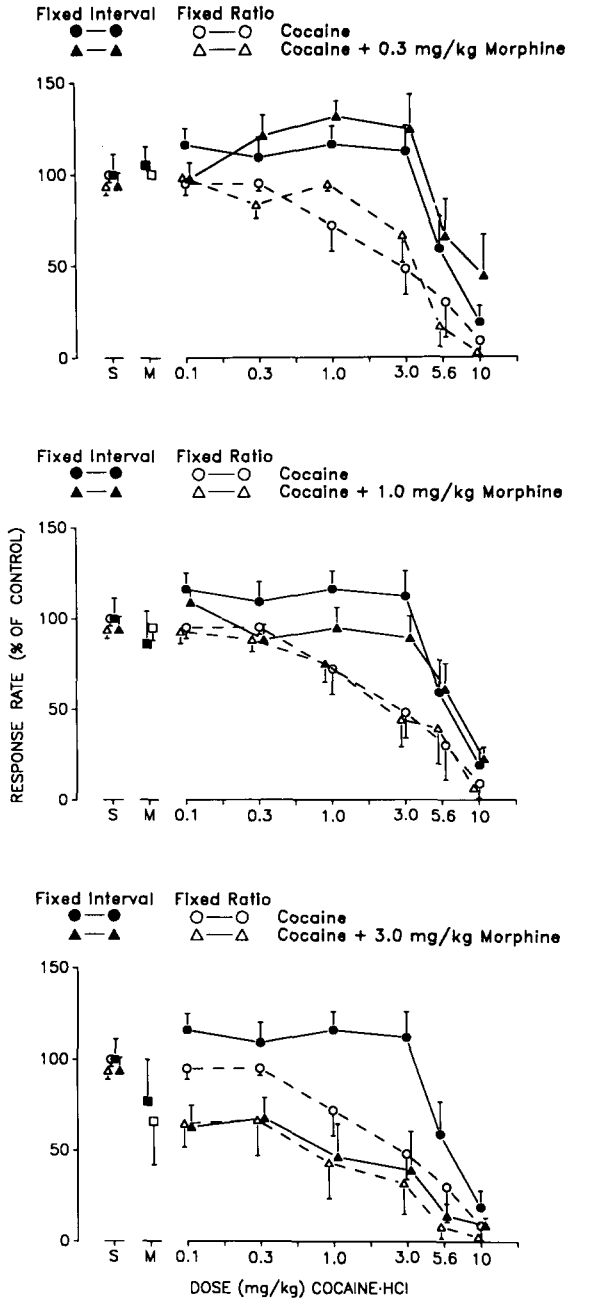

FIG. 4. Effects of cocaine alone and in combination with doses of morphine·SO_4 on responding under the mult FR 30, FI 600 schedule of food presentation. Abscissa: cocaine dose, log scale. Ordinate: overall rate of responding expressed as a percentage of saline control rate. Points above S represent the mean ± S.E.M. from 15 saline sessions in each of 5 pigeons. Points above M show the effects the various doses of morphine·SO_4 coadministered with an injection of saline. Points and vertical lines for morphine·SO_4 coadministered with an injection of saline and cocaine in combination with morphine·SO_4 represent the mean ± S.E.M. of single observations in 5 pigeons. Points and vertical lines for cocaine represent the mean ± S.E.M. of two observations in 5 pigeons.

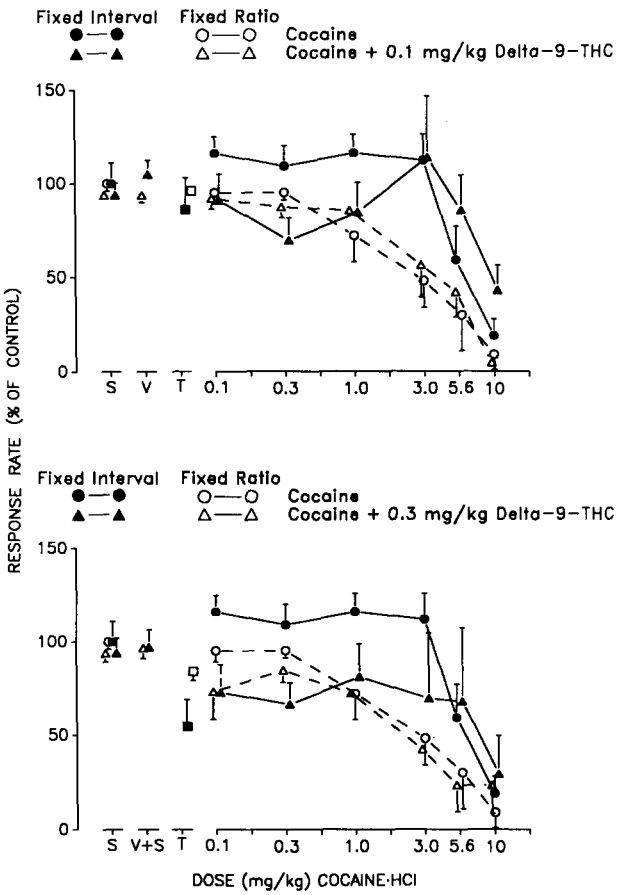

FIG. 5. Effects of cocaine alone and in combination with doses of delta-9-THC on responding under the mult FR 30, FI 600 schedule of food presentation. Abscissa: cocaine dose, log scale. Ordinate: overall rate of responding expressed as a percentage of saline control rate. Points above S represent the mean ± S.E.M. from 13 saline sessions in each of 5 pigeons. Points above V represent the mean ± S.E.M. of 5 delta-9-THC vehicle sessions in each of 5 pigeons. Points above V+S represent the mean ± S.E.M. from 5 sessions in each of 5 pigeons where delta-9-THC vehicle was coadministered with an injection of saline. Points above T show the effects the various doses of delta-9-THC coadministered with an injection of saline. Points and vertical lines for delta-9-THC coadministered with an injection of saline and cocaine in combination with delta-9-THC represent the mean ± S.E.M. of single observations in 5 pigeons. Points and vertical lines for cocaine represent the mean ± S.E.M. of two observations in 5 pigeons.

which were greater than effect-additive, the interactions between cocaine and morphine were effect-additive.

Cocaine plus selected doses of delta-9-THC. Redeterminations of the cocaine dose-response curve in the presence of various doses of delta-9-THC are illustrated in Fig. 5. The combination of 0.1 mg/kg delta-9-THC, a dose which had no effect when given alone, with cocaine produced effects on FR and FI rate of responding that were not significantly different from giving cocaine alone (top panel). A deviation from this trend was noted following the administration of 0.1 mg/kg delta-9-THC with 0.3 mg/kg cocaine, although this decrease in FI rate was not significant. The dose of 0.3 mg/kg delta-9-THC given alone had no effect on FR rate while decreasing the rate of FI responding (bottom panel). The combination of cocaine + 0.3 mg/kg delta-9-THC produced no shift in the FR response rate dose-response curve relative to the cocaine-alone curve. When 0.1 and 0.3 mg/kg cocaine were combined with 0.3 mg/kg delta-9-THC the FI response rate was decreased compared to effects of these doses of cocaine given alone. Higher doses of cocaine (1.0 to 10 mg/kg) combined with 0.3 mg/kg delta-9-THC produced effects on FI rate no different than cocaine given alone. In summary, the effects of cocaine + 0.1 mg/kg delta-9-THC on FI and FR rate and cocaine + 0.3 mg/kg delta-9-THC on FR rate were effect-additive. Effects on FI rate of low doses of cocaine in combination with 0.3 mg/kg delta-9-THC were effect-additive interactions. Effects of higher doses of cocaine + delta-9-THC on FI rate were less than effect-additive.

DISCUSSION

In the present study, the consequences of combining cocaine with commonly abused drugs at doses that did not affect behavior did not reveal significant changes in the behavioral effect compared to cocaine alone. Similarly, the combination of cocaine with active doses of commonly abused drugs resulted in effects similar to the effects of the interacting drugs alone. The effects of the majority of combinations could be predicted on the basis of the effects of each of the drugs when given alone; i.e., the combinations afforded effect-additive interactions.

In the present study, combinations of cocaine together with another CNS stimulant, either caffeine or *d*-amphetamine, were tested. Many people who abuse cocaine may often combine cocaine with another stimulant. In some instances this combination may be unintentional since cocaine acquired from illicit sources is often adulterated with amphetamines and caffeine (17). Additionally, since caffeine is consumed by a broad spectrum of the population in coffee, tea, cola beverages, and cocoa, many cocaine abusers also intentionally combine cocaine and caffeine (15,36). In general, in the model employed in this study the effects of combinations of cocaine with either caffeine or *d*-amphetamine were no different than those observed with the administration of cocaine alone. Infrequently, caffeine or *d*-amphetamine in combination with cocaine resulted in effects different from cocaine given alone. In these instances, the combinations of cocaine with either caffeine or *d*-amphetamine resulted in an attenuation of the behavioral effects of cocaine.

It is often difficult to satisfactorily explain the cellular basis of a drug's effect on a behavior. However, cocaine, caffeine, and *d*-amphetamine, over a certain dose range, would all be expected to potentiate the actions of catecholamines in the central nervous system. Cocaine, a CNS stimulant, facilitates neuronal transmission generally by blocking reuptake of catecholamines at presynaptic neurons thereby increasing neurotransmitter levels within the synapse (32,39). *d*-Amphetamine appears to exert its effects in the CNS by releasing biogenic amines from their storage sites in the nerve terminals (3,40). Caffeine's stimulatory effects on CNS may result from enhancement of neuronal calcium uptake (19), decreased phosphodiesterase activity, and adenosine receptor antagonism (16,31). In light of these CNS stimulatory actions, it would have been difficult to predict the overall lack of greater than additive interactions observed in this study.

Other investigators have used various behavioral models to study possible interactions between cocaine and either *d*-amphetamine or caffeine. In these studies cocaine in combination with caffeine or *d*-amphetamine resulted in greater than additive effects. For example, in a study by Schekel and Boff (35), rats responded under a continuous avoidance procedure to postpone the onset of shock for 40 seconds. The combination of an inactive dose of *d*-amphetamine significantly reduced the minimal dose of cocaine which increased avoidance responding. However, the results are difficult to interpret since dose-response functions of the drugs alone and in combination were not presented. Cocaine

and *d*-amphetamine combinations also generally had greater than additive effects on milk drinking in the rat (11). Intraperitoneal (0.5 to 2.0 mg/kg) and intragastric (8 and 16 mg/kg) administration of *d*-amphetamine in combination with cocaine produced leftward shifts of the cocaine dose-response curve for milk intake. The shifts in the cocaine dose-response curve were greater than predicted by the sum of effects of either drug given alone. In another study, Misra *et al.* (24) reported that pretreatment of rats with a behaviorally active dose of caffeine (20 mg/kg) increased cocaine locomotor stimulant activity.

The significant interaction between cocaine and *d*-amphetamine in the Scheckel and Boff study and the overall lack of interaction observed between these drugs in the present results may be attributed to differences in the ongoing rate of behavior and events maintaining behavior. The differences in experimental results between the effects of cocaine combined with either caffeine or *d*-amphetamine in this study and those observed on locomotor activity (24) and milk drinking (11) may be due to differences in experimental methods, subjects, and end points. In the Misra *et al.* and Foltin *et al.* studies the cocaine-drug combinations were administered to rats by the intraperitoneal and/or intragastric route and the effects on unconditioned behavior were measured. In contrast, in the present study the drug combinations were administered by intamuscular injection to pigeons and the effects on operant behavior were recorded.

However, similar to the results of the present experiment, cocaine-caffeine combinations had varied effects in an experiment by Logan *et al.* (21) using rats responding under an FI 600 second schedule of food reinforcement. These investigators found that cocaine (10 mg/kg) coadministered with caffeine (10 mg/kg) reduced high rates of responding produced when caffeine was given alone. These results are similar to our results where caffeine (30 mg/kg) coadministered with an inactive dose of cocaine (3 mg/kg) suppressed high rates of responding characteristic of FR control rates. Logan *et al.* also found that concomitant administration of cocaine and caffeine slightly attenuated decreases in FI response rate produced by 32 mg/kg caffeine administered alone. These results are comparable to our results where caffeine (10, 30, and 100 mg/kg) plus cocaine (5.6 and/or 10 mg/kg) attenuated the suppression of FI rates produced by these high doses of cocaine when given alone.

Most of the effects of cocaine-morphine interactions under the multiple schedule demonstrated that when inactive doses of morphine were combined with cocaine, the effects were no different from those of cocaine alone. Similar effects on operant behavior were found when cocaine and methadone were coadministered in rhesus monkeys chronically maintained on methadone (7). Cocaine administered in conjunction with the daily dose of methadone did not significantly alter baseline rate of responding. However, it is surprising that cocaine-morphine combinations produced effects no different than those of cocaine alone, since cocaine and morphine combinations often result in a potentiation of effects when other physiological and toxicological responses are examined. For example, cocaine users often combine cocaine with heroin, an opiate similar to morphine, to intensify the initial "rush" associated with cocaine administration (8, 13, 41). In the human population, there is also evidence that morphine coadministered with cocaine can increase toxicity. In cocaine-related fatalities, blood cocaine concentrations have been found to be significantly lower in those cases where morphine was also detected (10). This finding suggests that the presence of morphine was an important factor in toxicity. This view is supported by animal studies where morphine augmented the lethality of cocaine in both rats and mice (4). Additionally, a combination of cocaine and morphine has been taken orally for many years, as the Brompton cocktail, in treatment of chronic pain due to the belief that morphine analgesia is potentiated by cocaine (23,25). Likewise, cocaine coadministered with morphine to mice potentiates analgesia as evidenced by an increase in reaction time of the tail-flick response subsequent to immersion in hot water (26).

It should be mentioned that in the rhesus monkey, cocaine self-administration was disrupted by buprenorphine treatment (22). A single dose of buprenorphine decreased cocaine-maintained responding and consequently decreased the number of cocaine injections received daily. Comparison of this interaction with the present cocaine-morphine combination is difficult. The effects of either drug alone or in combination on the rate of responding were not presented, furthermore, buprenorphine is a mixed opioid agonist-antagonist, while morphine is an opioid agonist.

Under the multiple FR FI schedule, the majority of the cocaine and delta-9-THC combinations failed to produce effects any different than cocaine alone. However, when an active dose of delta-9-THC was combined with cocaine the effects on FI response rate resembled those of delta-9-THC given alone. These results support previous findings on combinations of cocaine and delta-9-THC in rats responding under a signalled-avoidance paradigm (30). Cocaine did not significantly influence the impairment of the conditioned avoidance response caused by behaviorally active doses of delta-9-THC. Similarly, in the Pryor *et al.* experiment, behaviorally active doses of delta-9-THC in combination with cocaine resulted in effects on motor activity which were like those of delta-9-THC given alone. Thus, in laboratory animals, the effects of behaviorally active doses of delta-9-THC coadministered with cocaine on multiple FR FI responding and those reported in the literature suggest that the effects of delta-9-THC predominate over those of cocaine.

In contrast, in human subjects, the cardiovascular effects of intravenous cocaine and smoked marijuana in combination were unlike those of marijuana given alone (12). Cocaine plus marijuana increased heart rate to a larger extent than the increase observed when either cocaine or marijuana was administered separately. Cocaine plus marijuana also increased mean arterial blood pressure above cocaine-alone elicited increases (marijuana alone had little or no effect on mean arterial blood pressure), however, this was only observed at the highest cocaine-marijuana dose combination. The discrepancies between the effects in humans and those observed in laboratory animals may be due to the obvious difference in species or the experimental measures (behavioral versus cardiovascular).

The majority of the results reported here in pigeons revealed that cocaine-drug combinations resulted in direct behavioral effects which could be predicted using the effect-addition model. Thus, these data do not support the suggestion that the adverse consequences observed with cocaine use is attributable to a greater than additive effect as a result of polydrug use with cocaine. However, it must be remembered that the relations between drugs and behavior are not only a function of the drug but also of the conditions under which the behavior is generated (20). Therefore, since drug effects are not confined to one specific behavior-environment contingency and will vary depending upon the conditions under which the drug is administered, the effects of cocaine when coadministered with other drugs of abuse in the human population may be different than that predicted by an effect-additive model.

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