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Behavioral Effects of Cocaine and Its Interaction With *d*-Amphetamine and Morphine in Rats

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WENGER, G. R. AND D. W. WRIGHT. *Behavioral effects of cocaine and its interaction with* d-*amphetamine and morphine in rats.* PHARMACOL BIOCHEM BEHAV **35**(3) 595–600, 1990.—Drugs of abuse are commonly co-abused, and frequently these combinations produce effects which cannot be predicted by studying the effects of the individual drugs. To investigate the behavioral interactions which occur following combinations of cocaine plus amphetamine or cocaine plus morphine, rats were trained to respond under a differential reinforcement of low rates (DRL) schedule (10–14 sec). Cocaine (0.1–10 mg/kg) and *d*-amphetamine (0.1–3 mg/kg) decreased the percentage of reinforced responses (efficiency) at doses which had no effect on overall rate of responding. Following moderate doses of either drug, the interresponse time (IRT) distribution showed an increase in the percentage of shorter (<10 sec) IRT's. Morphine (0.1–10 mg/kg) also decreased efficiency, but the decrease which occurred was only observed at doses which also decreased overall response rates. As might be expected, the IRT distribution for morphine showed a dose-related increase in the percentage of long IRT's (>14 sec). When doses of morphine which had no significant effect when administered alone (1 or 3 mg/kg) were combined with cocaine, the cocaine dose-response curve for efficiency was shifted down and to the left and response rates were increased. Analysis of the IRT distribution showed that the combination of an ineffective dose of cocaine, 1 mg/kg, plus 3 mg/kg morphine produced a shift in the IRT distribution to the left (an increase in the percentage of short IRT's). When cocaine was combined with 0.3 mg/kg *d*-amphetamine, a dose which had no effect when given alone, no significant interactions were observed on efficiency or overall rate of responding. A higher dose of *d*-amphetamine (0.56 mg/kg) which significantly decreased efficiency and response rates when given alone, did not result in a greater effect when given in combination with cocaine.

Cocaine Amphetamine Morphine Rat DRL Reinforcement

AMONG cocaine addicts, polydrug abuse is a common phenomena (19, 20, 22), and drugs representing a wide range of pharmacological classes are frequently combined with cocaine. The list of drugs frequently combined with cocaine includes: alcohol, marijuana, opiates, sedatives of various types, and stimulants including amphetamines (3, 10, 17, 22). The primary reasons expressed by users for polydrug use ranged from: combating unpleasant side effects, to alleviating feelings of anxiety when cocaine's initial euphoria dissipates, to reducing the intensity of the cocaine high, to enhancing the cocaine high (9, 10, 18, 23, 25). In some cases the combining of drugs is intentional. For example, the combination of narcotics with cocaine, "speedballing," is quite common and reportedly is used to produce a more intensely pleasurable "rush" (5, 9, 25). Other combinations are used unintentionally by addicts. For example, in an attempt to reduce ("cut") the amount of "active" agent being sold, amphetamines are frequently used to substitute for a reduced amount of cocaine (15). Street samples of cocaine have been found to contain: procaine, lidocaine, phenylpropanolamine, heroin, caffeine, amphetamines, lactose, and mannitol (9, 11, 24). Interestingly, addicts may not be aware that the purchased cocaine has been "cut," and addicts using cocaine "cut" with amphetamine may not be able to distinguish it from pure cocaine. Studies with experienced addicts have shown that the subjective effects produced by amphetamine and cocaine were very similar, and most addicts could not distinguish the two drugs (8).

In spite of the frequency of multiple drug use, the majority of the drug abuse literature is concerned with the effects of single agents, and only a limited number of studies reporting the effects of drug combinations appear in the literature. Of the few studies which have been done in laboratory animals, some have been concerned with whether or not cocaine altered the response of animals to another drug. For example, cocaine has been shown to potentiate the toxicity of morphine in rats and mice (2) and to increase the analgesic properties of morphine (14,16). Other studies have reported on the ability of a second drug to alter cocaine's effects. Amphetamine (21), caffeine (13) and morphine (2) are all reported to increase the response to cocaine in rodents.

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In the present study, dose-response curves were determined for cocaine, *d*-amphetamine, and morphine in rats trained to respond under a differential reinforcement of low rate (DRL) schedule of reinforcement. The DRL schedule is reported to measure an animal's ability to discriminate the passage of time, and, thus, it was selected for study because of our interest in the disruption of temporal discrimination by drugs of abuse. Under this schedule only those responses separated by more than 10, but less than 14 sec, produced a food pellet. In addition, to determine if morphine and *d*-amphetamine were capable of altering the cocaine dose-response curve, combinations of cocaine plus selected doses of morphine or cocaine plus selected doses of *d*-amphetamine were examined.

METHOD

Subjects

Six adult (410–415 g), male CD rats (Charles River Breeding Laboratories, Portage, MI) were food deprived to a body weight equivalent to 80% of their free-feeding weights. They were maintained at that weight throughout the experiment by postsession feeding. The rats were housed individually with water freely available in the home cages. Relative humidity and temperature were maintained at 50% and 22°C, respectively. A 12-hour light/dark cycle was maintained with the lights on from 0700 to 1900 hours.

Schedule

Rats were trained to temporally space their responses under a differential reinforcement of low rates (DRL) schedule. Under this schedule a response separated from the beginning of the experimental session or from the previous response by a minimum interval of 10 sec, but less than 14 sec (DRL 10–14 sec), produced a 97-mg food pellet (Noyes Lab Animal Food; P. J. Noyes Co., Lancaster, NH). Responses separated by less than 10 sec or by more than 14 sec reset the timing cycle, but had no additional consequences. Test sessions were conducted 5 days/week, Monday through Friday, and were 45 minutes in duration.

Apparatus

Rats were tested in a standard rat test cage (Gerbrands Model G7322; Gerbrands Corp., Arlington, MA). In the center of the front panel approximately 2 cm from the floor, a rectangular opening provided access to a food tray into which the 97-mg food pellets were dropped. A lever was mounted on either side of the rectangular opening. A downward force on the levers of approximately 0.15 N closed the contacts and defined the response. Only responses on the right-hand lever produced reinforcement, and responses on the left-hand lever had no programmed consequences. Two 28-V DC bulbs (No. 1819) were located above the right-hand lever. Two additional 28-V DC bulbs (No. 1819) were located in the ceiling of the chamber (houselight). At all times, except for a brief instant during the operation of the pellet feeder, the houselight and the lights above the right-hand lever were illuminated. Experimental programming and data collection were controlled by a TRS-80, Model III microcomputer (Tandy Corp.) housed in an adjoining room.

Drugs

The drugs used in this study were: cocaine·HCl, morphine·SO_4, and *d*-amphetamine·SO_4. All drugs were administered 5 min before the start of the experimental session. When cocaine was administered along with morphine or *d*-amphetamine, both drugs were administered 5 min before the start of the session. All drugs were dissolved in normal saline (0.9%) and administered by the IP route in a volume of 1 ml/kg of body weight. Doses of all drugs were calculated and expressed as the salt. Drugs were never administered more frequently than twice/week, typically Tuesday and Friday. Saline (1 ml/kg) was administered on Thursday of each week as a vehicle control.

Measurement of Drug Effects

The "efficiency" of responding under the DRL schedule was determined by dividing the total number of reinforced responses by the total number of all responses during the session. This value was then multiplied by 100 to convert it to a percentage. Response rate was determined by dividing the total number of responses by the total session time (45 min) and is expressed as responses/second. In addition, a measure of the rat's ability to space its responses in real time was determined by measuring the duration between responses (interresponse times, IRT's). Responses of a given IRT class were accumulated in each of 10 bins, each bin representing consecutive 2-sec IRT's. Thus, the number of responses separated by 0–2 sec were accumulated in bin 1, responses separated by 2–4 sec were accumulated in bin 2, responses separated by 4–6 sec were accumulated in bin 3, etc. Thus, reinforced responses were accumulated in bins 6 (10–12 sec) and bin 7 (12–14 sec). Responses separated by 18 sec or more were accumulated in bin 10. The percentage of responses separated by different IRT values was then determined by dividing the number of responses in each bin by the total number of responses in the session.

The standard error of the mean for saline control data was calculated by determining the total standard deviation $(n-1)$ for all saline values in all rats and dividing by the square root of n, where n represents the number of rats used in the study.

RESULTS

Performance under the DRL 10–14 sec schedule of reinforcement stabilized after approximately 8 weeks of training, and no consistent increases or decreases were observed in the rate of responding or the percentage of total responses which produced a food pellet (efficiency). The mean percent efficiency following saline control injections in the six rats ranged from 44.1% to 66.1% and the mean rate of responding ranged from 0.068 to 0.092 responses/second.

Initially, dose-response curves were determined for cocaine, morphine, and *d*-amphetamine alone. When cocaine was tested over a dose range of 0.1–10 mg/kg, no effects were observed below doses of 3 mg/kg (Fig. 1). At doses of 3 mg/kg and higher, a dose-related decrease in the percent efficiency was observed without a significant change in overall response rate. Analysis of the effects of cocaine on the IRT distribution is shown in Fig. 2. Cocaine produced no effect on the IRT distribution at doses below 3 mg/kg. However, at doses of 5.6 and 10 mg/kg there was an increase in the percentage of IRT's of less than 10–14 sec, and a decrease in the percentage of longer IRT's. Thus, the decrease in efficiency observed at 3, 5.6 and 10 mg/kg resulted from a greater percentage of the responses occurring with IRT's of less than 10 sec.

Following doses of morphine ranging from 0.1–10 mg/kg, no effects were observed at doses below 3 mg/kg (Fig. 3). At doses above 3 mg/kg, dose-related decreases were observed for both the percent efficiency and the rate of responding. Analysis of the IRT distribution showed (Fig. 4) that increasing doses of morphine

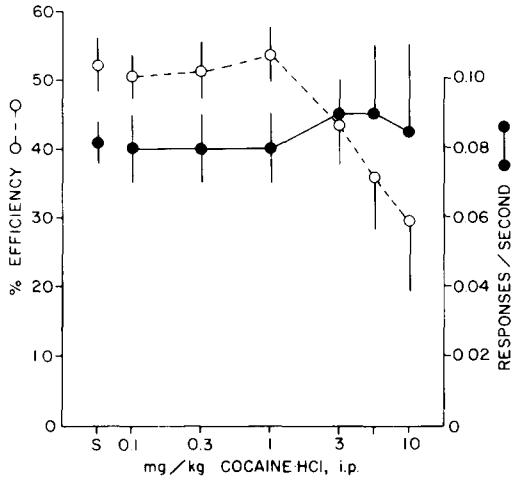


FIG. 1. Effect of cocaine·HCl on the efficiency and rate of responding of rats responding under the DRL 10–14 sec schedule of reinforcement. Abscissa: dose in mg/kg on a log scale; ordinate (left): efficiency of responding defined as the number of responses with IRT's of 10–14 sec divided by the total number of responses in the session expressed as a percentage; ordinate (right); rate of responding as responses/second. Points and brackets represent the mean of single determinations in each of 6 rats ±S.E. Points above S represent the mean of all saline determinations in each of 6 rats ±S.E. (see the Method section).

produced a decrease in the percentage of IRT's falling within the 10–14 sec time interval (bins 6 and 7), and an increase in IRT's of 18 sec and longer. Unlike cocaine, morphine produced no increases in the percentage of shorter IRT's.

The effects of *d*-amphetamine (0.1–3 mg/kg) were somewhat similar to cocaine. At doses of 1 mg/kg and higher, decreases in the percent efficiency were observed without a corresponding change in overall response rate (Fig. 5). Analysis of the IRT distribution (Fig. 6) showed that the effects of doses of 1 mg/kg and higher were to increase the percentage of IRT's of less than 10 sec in length and to decrease the percentage of IRT's of more than 10 sec in length. The net effect of these changes was a broadening of the discrimination peak similar to that seen with cocaine.

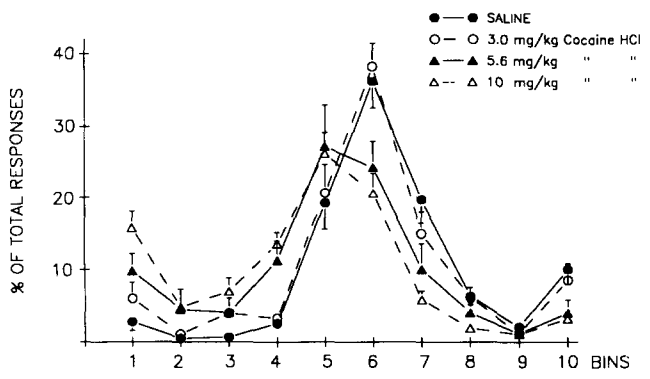


FIG. 2. Effect of cocaine·HCl on the percentage of total responses in a given IRT class. Abscissa: IRT classes representing consecutive 2-sec periods (see the Method section); ordinate: the percentage of total responses. Points and brackets represent the mean of single determinations in each of 6 rats ±S.E. Points and brackets for saline represent the mean of all saline determinations in each of 6 rats ±S.E. (see the Method section).

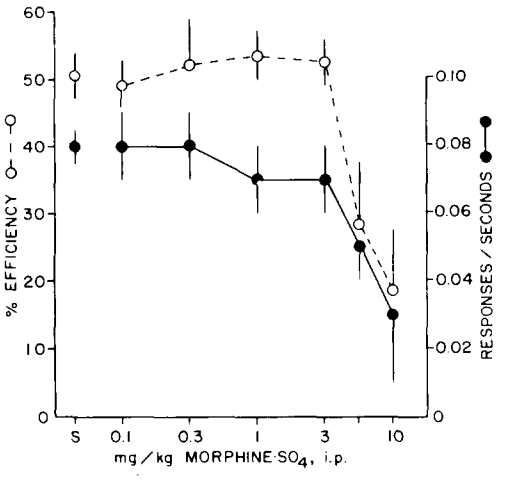


FIG. 3. Effect of morphine·SO_4 on the efficiency and rate of responding of rats under the DRL 10–14 sec schedule of reinforcement. Data expressed as in Fig. 1. n=6.

To study the interactions which may occur between cocaine and morphine, doses of morphine were selected which had relatively little, if any, effect when given by themselves. Thus, the cocaine dose-response curve was redetermined in the presence of either 1 or 3 mg/kg morphine. When 1 mg/kg morphine was combined with cocaine, the combination produced no differences in percent efficiency, rate of responding or the IRT distribution (data not shown) compared to cocaine alone. However, when 3 mg/kg morphine (the highest dose which produced no significant effects when given alone) was combined with cocaine, a considerable degree of shift was observed in the dose-response curves for efficiency and rate of responding (Fig. 7). The dose-response curve for efficiency was shifted down and to the left. The curve for response rate showed that the combination, compared to the effects of cocaine alone, produced increases in the rate of responding at low to moderate doses of cocaine and a decrease at the highest dose of cocaine, 10 mg/kg. These changes were associated with changes in the IRT distribution. Figure 8 shows the IRT distribution for saline, each drug combined with saline, and 3 mg/kg morphine combined with either 1 or 3 mg/kg cocaine. As can be seen the combinations of 3 mg/kg morphine with either 1 or 3 mg/kg cocaine produced a higher percentage of shorter IRT's compared to cocaine alone or saline. Following the combi-

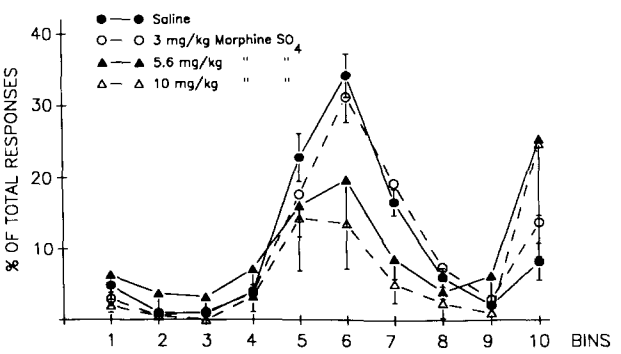


FIG. 4. Effect of morphine·SO_4 on the percentage of total responses in a given IRT class. Data expressed as in Fig. 2. n=6.

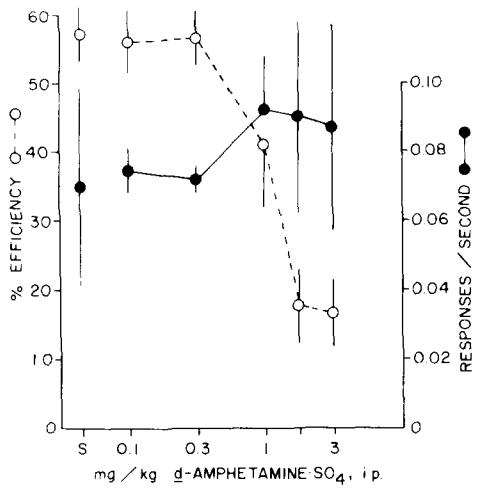


FIG. 5. Effect of *d*-amphetamine·SO_4 on the efficiency and rate of responding of rats under the DRL 10–14 sec schedule of reinforcement. Data expressed as in Fig. 1. n = 6.

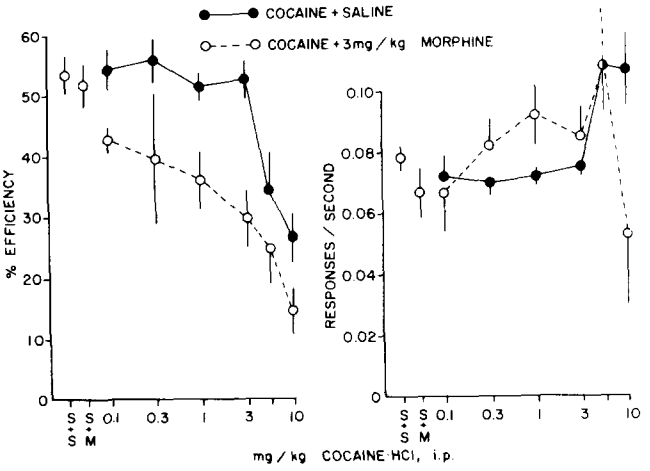


FIG. 7. Effect of cocaine·HCl plus saline and cocaine·HCl plus 3 mg/kg morphine·SO_4 on the efficiency (left) and on the rate of responding (right) of rats under the DRL 10–14 sec schedule of reinforcement. Data expressed as in Fig. 1. n = 6.

nation of 3 mg/kg morphine with 5.6 mg/kg cocaine, there was no change in the percentage of short IRT's compared to cocaine alone, but there was a decrease in the percentage of longer IRT's (data not shown). However, these effects were the same as those produced by 5.6 mg/kg cocaine plus saline.

A similar interaction was not observed when selected doses of *d*-amphetamine were combined with cocaine. When 0.3 mg/kg *d*-amphetamine (a dose which when combined with saline produced a minimal decrease in efficiency and no change in response rate) was combined with cocaine, the combination decreased efficiency compared to cocaine alone. However, the combination did not decrease efficiency compared to 0.3 mg/kg *d*-amphetamine alone until a cocaine dose of 3 mg/kg was given in combination (Fig. 9). A similar effect of the combination is seen in the rate of responding (Fig. 9). These affects can be seen in slightly greater detail in an analysis of the IRT distribution following combinations of 0.3 mg/kg *d*-amphetamine with either 1 or 3 mg/kg cocaine (Fig. 10). Although the distribution is shifted to the left compared to saline or cocaine + saline, there were very few instances where the combination of cocaine and *d*-amphetamine was significantly different from *d*-amphetamine alone.

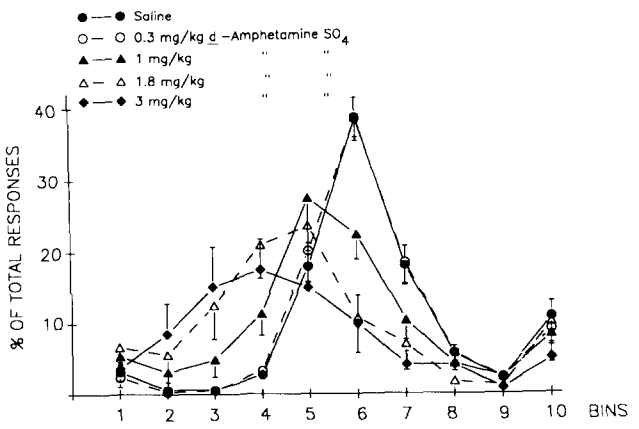
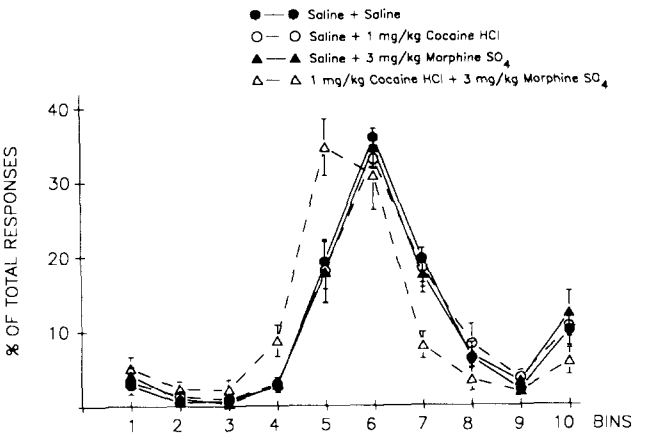


FIG. 6. Effect of *d*-amphetamine·SO_4 on the percentage of total responses in a given IRT class. Data expressed as in Fig. 2. n = 6.



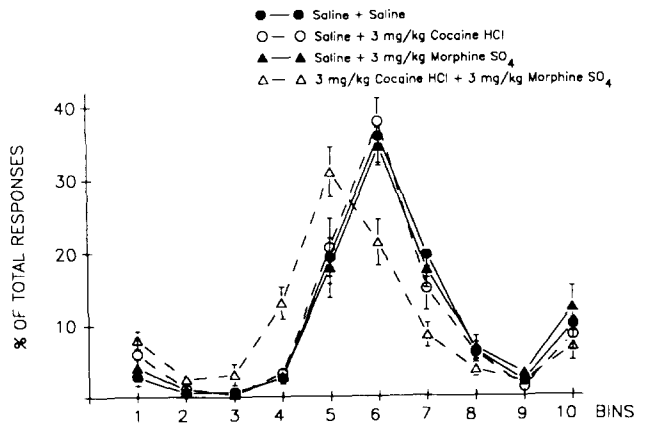


FIG. 8. Effect of saline, saline plus cocaine·HCl, saline plus morphine·SO_4, and cocaine·HCl plus morphine·SO_4 on the percentage of total responses in a given IRT class. Data expressed as in Fig. 2. n = 6.

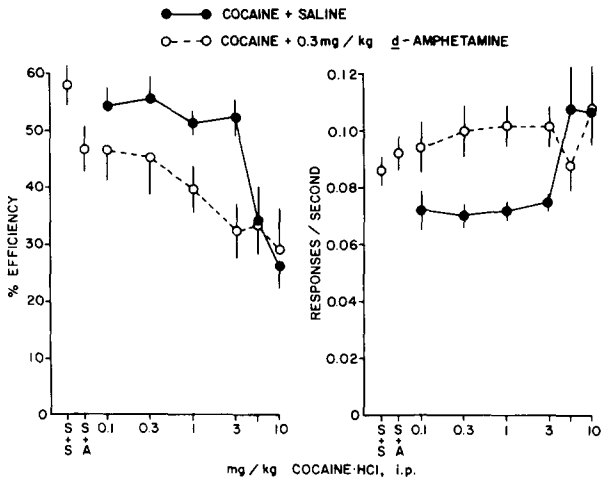


FIG. 9. Effect of cocaine·HCl plus saline and cocaine·HCl plus 0.3 mg/kg *d*-amphetamine·SO_4 on the efficiency (left) and on the rate of responding (right) of rats under the DRL 10–14 sec schedule of reinforcement. Data expressed as in Fig. 1. n=6.

A combination of 0.56 mg/kg *d*-amphetamine with cocaine also failed to show a significant degree of interaction (data not shown). The dose of 0.56 mg/kg *d*-amphetamine decreased efficiency by about 20% compared to saline, and when the cocaine dose-response curve was redetermined in the presence of 0.56 mg/kg *d*-amphetamine, no dose combination produced an affect on efficiency which was different than 0.56 mg/kg *d*-amphetamine alone. In a similar manner 0.56 mg/kg *d*-amphetamine increased the rate of responding compared to saline, but no combination of cocaine and 0.56 mg/kg *d*-amphetamine produced a different affect.

DISCUSSION

These data clearly show that the combination of cocaine and morphine produce an effect which is greater than either drug given alone. The effect is also different than what would be expected based on simple response additivity. For example, cocaine at doses below 5.6 mg/kg had no effect on response rate or efficiency. At higher doses, 5.6 and 10 mg/kg, cocaine increased response rate and decreased efficiency. Morphine had no effect at doses below 5.6 mg/kg, but in contrast, decreased response rate and efficiency at doses of 5.6 and 10 mg/kg. Thus, at doses of 3 mg/kg and lower of both drugs little effect is observed. However, it is over this low dose range where the most interesting interactions occurred. When doses of 1 and 3 mg/kg cocaine, which have no effect when given alone, are combined with an ineffective dose of morphine, response rate is increased, efficiency is decreased, and the IRT distribution is altered. The interactions at higher doses of cocaine are also significant, but they are complicated by the fact that cocaine was shown to have effects at these doses. However, even at 5.6 and 10 mg/kg cocaine, the addition of an ineffective dose of morphine (3 mg/kg), produced a greater effect on efficiency than was observed with cocaine alone.

Similar interactions have been reported in laboratory animals using other endpoints. Blumberg and Ikeda (2) reported that cocaine potentiated the morphine-induced loss of righting reflex in rats, potentiated the Straub tail response of morphine in mice, and increased the acute toxicity of morphine in mice and rats. There have also been several reports of cocaine potentiating the analgesic effects of morphine in laboratory animals (14,16). The results in

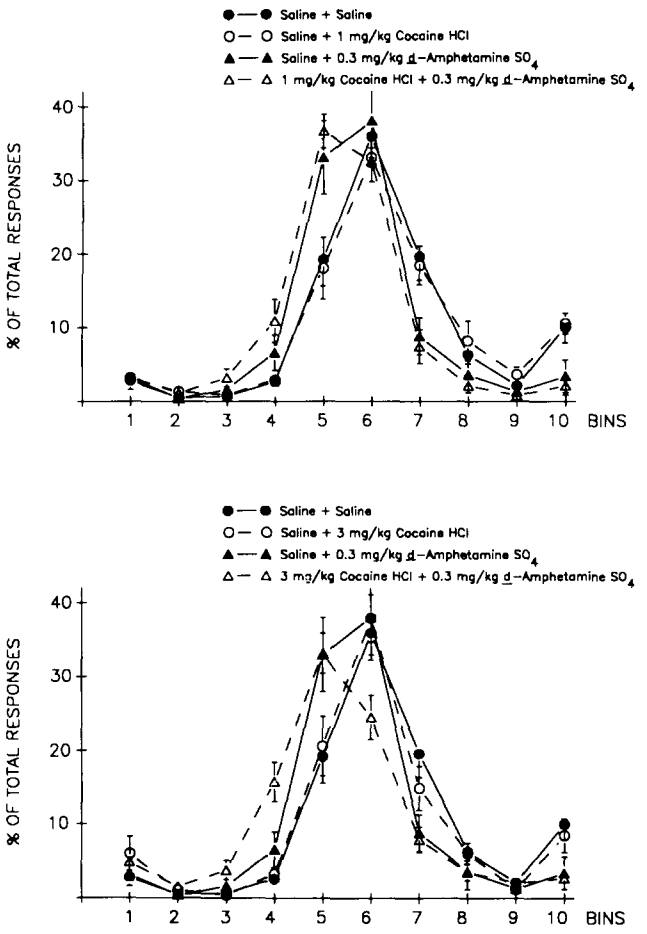


FIG. 10. Effect of saline, saline plus cocaine·HCl, saline plus *d*-amphetamine·SO_4, and cocaine plus *d*-ampethamine·SO_4 on the percentage of total responses in a given IRT class. Data expressed as in Fig. 2. n=6.

the present study along with the previous reports in the literature are somewhat supportive of the reports of addicts that use cocaine and narcotics in combination. The combination of cocaine and a narcotic ("speedball") is said to result in a greater "rush" than that reported with heroin alone (5,25). Likewise, it has been suggested that the lethal effects of combinations of cocaine and morphine are greater than cocaine alone (7). In a survey of drug-related deaths, blood levels of cocaine, upon autopsy, were found to be lower in those cases involving both morphine and cocaine than those cases in which cocaine was the only drug involved. It is difficult to explain the greater than additive interaction between cocaine and morphine observed in the present study. Based upon our present understanding, there is little if any similarity in the mechanism of action of morphine and cocaine, and they do not produce similar drug-induced stimulus states in laboratory animals or man.

The present data also clearly show that the combination of cocaine with *d*-amphetamine does not always produce an additive effect. In the present study, if there was any interaction, it was less than additive. No combination of cocaine and *d*-amphetamine in this study produced an effect which was greater than that produced by either agent alone. The failure to see significant interactions between cocaine and *d*-amphetamine, in this study, is surprising in light of the similarities in their known pharmacology, the similar-

ities in the subjective effects of IV cocaine and *d*-amphetamine in human addicts (8) and in similar tests in laboratory animals trained to discriminate drug-induced stimulus states (4, 6, 12), and in light of previous reports of significant interactions (21). Based upon these reports, one might have predicted additive effects when cocaine was combined with *d*-amphetamine, but little evidence exists for an additive effect of this combination in this study. The reasons for this failure to see significant interactions are not clear, but they may relate to the behavior being studied, or the order and timing of drug administration.

The failure to see additive interactions is interesting in light of the work of Azzaro *et al.* (1) who reported that the release of norepinephrine by amphetamine from chopped rat cerebral cortex is inhibited by high concentrations of cocaine or desmethylimipramine. The same concentrations of cocaine did not affect the release of norepinephrine by KCl. This antagonism by cocaine of the effects of amphetamine is thought to be due to cocaine's ability to block the uptake of amphetamine into the neuron thereby preventing amphetamine from releasing intraneuronal stores of norepinephrine. Such an interaction between amphetamine and cocaine may be the mechanism responsible for the failure to see additive interactions in the present behavioral study.

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REFERENCES

1. Azzaro, A. J.; Ziance, R. J.; Rutledge, C. O. The importance of neuronal uptake of amines for amphetamine-induced release of ^{3}H-norepinephrine from isolated brain tissue. J. Pharmacol. Exp. Ther. 189:110–118; 1974.
2. Blumberg, H.; Ikeda, C. Naltrexone, morphine and cocaine interactions in mice and rats. J. Pharmacol. Exp. Ther. 206:303–310; 1978.
3. Clayton, R. R.; Cocaine use in the United States: In a blizzard or just being snowed. In: Kozel, N. J.; Adams, E. G., eds. Cocaine use in America: Epidemiologic and clinical perspectives. Research Monograph No. 61. Rockville, MD: National Institute on Drug Abuse; 1985:8–34.
4. D'Mello, G. D.; Stolerman, I. P. Comparison of the discriminative stimulus properties of cocaine and amphetamine in rats. Br. J. Pharmacol. 61:415–422; 1977.
5. Ellinwood, E. H., Jr.; Eibergen, R. D.; Kilbey, M. M. Stimulants: Interactions with clinically relevant drugs. Ann. NY Acad. Sci. 281:393–408; 1976.
6. Emmett-Oglesby, M. W.; Wurst, M.; Lal, H. Discriminative stimulus properties of a small dose of cocaine. Neuropharmacology 22:97–101; 1983.
7. Finkle, B. S.; McCloskey, K. L. The forensic toxicology of cocaine. In: Petersen, R. C.; Stillman, R. C., ed. Cocaine: 1977. Research Monograph No. 13. Rockville, MD: National Institute on Drug Abuse; 1977:153–192.
8. Fischman, M. W.; Schuster, C. R.; Resnekov, L.; Shick, J. F. E.; Krasnegor, N. A.; Fennell, W.; Freedman, D. X. Cardio-vascular and subjective effects of intravenous cocaine administration in humans. Arch. Gen. Psychol. 33:983–989; 1976.
9. Gay, G. R.; Inaba, S. S.; Sheppard, C. W.; Newmeyer, J. A. Cocaine: History, epidemiology, human pharmacology, and treatment. A perspective on a new debut for an old girl. Clin. Toxicol. 8:149–178; 1975.
10. Gold, M. S.; Washton, A. M.; Dackis, C. A. Cocaine abuse: Neurochemistry phenomenology, and treatment. In: Kozel, N. J.; Adams, E. G., eds. Cocaine use in America: Epidemiologic and clinical perspectives. Research Monograph No. 61. Rockville, MD: National Institute on Drug Abuse; 1985:130–150.
11. Hawks, R. Cocaine: The material. In: Petersen, R. C.; Stillman, R. C., eds. Cocaine: 1977. Research Monograph No. 13. Rockville, MD: National Institute on Drug Abuse; 1977:47–61.
12. Huang, J. T.; Ho, B. T. Discriminative stimulus properties of *d*-amphetamine and related compounds in rats. Psychopharmacology (Berlin) 36:243–253; 1974.
13. Misra, A. L.; Vadlamani, N. L.; Pontani, R. B. Effect of caffeine on cocaine locomotor stimulant activity in rats. Pharmacol. Biochem. Behav. 24:761–764; 1986.
14. Misra, A. L.; Pontani, R. B.; Vadlamani, N. L. Stereospecific potentiation of opiate analgesia by cocaine: predominant role of noradrenaline. Pain 28:129–138; 1987.
15. Morbidity and Mortality Weekly Report. Center for Disease Control, Atlanta. 31:265–273; 1982.
16. Nott, M. W. Potentiation of morphine analgesia by cocaine in mice. Eur. J. Pharmacol. 5:93–99; 1968.
17. O'Malley, P. M.; Johnston, L. D.; Bachman, J. G. Cocaine use among American adolescents and young adults. In: Kozel, N. J.; Adams, E. G., eds. Cocaine use in America: Epidemiologic and clinical perspectives. Research Monograph No. 61. Rockville, MD: National Institute on Drug Abuse; 1985:50–75.
18. Phillips, J. L.; Wynne, R. D. Sociological aspects of cocaine use and abuse. In: Mulé, S. J., ed. Cocaine: Chemical, biological, clinical, social and treatment aspects. Cleveland, OH: CRC Press Inc.; 1976:232–241.
19. Roehrich, H.; Gold, M. S. 800-Cocaine: Origin, significance and findings. Yale J. Biol. Med. 61:149–155; 1988.
20. Sample, J. C. Concept of polydrug use. In: Richards, L. G.; Blevens, L. B., eds. The epidemiology of drug abuse. Research Monograph No. 10. Rockville, MD: National Institute on Drug Abuse; 1977: 19–31.
21. Scheckel, C. L.; Boff, E. Behavioral effects of interacting imipramine and other drugs with *d*-amphetamine, cocaine, and tetrabenazine. Psychopharmacologia 5:198–208; 1964.
22. Schuster, C. R.; Fischman, M. W. Characteristics of humans volunteering for a cocaine research project. In: Kozel, N. J.; Adams, E. G., eds. Cocaine use in America: Epidemiologic and clinical perspectives. Research Monograph No. 61. Rockville, MD: National Institute on Drug Abuse: 1985:158–170.
23. Siegel, R. K. Changing patterns of cocaine use: Longitudinal observations, consequences, and treatment. In: Grabowski, J., ed. Cocaine: Pharmacology, effects and treatment of abuse. Research Monograph No. 50. Rockville, MD: National Institute on Drug Abuse; 1984: 204–220.
24. Siegel, R. K. Cocaine smoking disorders: Diagnosis and treatment. Psychiat. Ann. 14:728–732; 1984.
25. Wesson, D. R.; Smith, D. E. Cocaine: Its use for central nervous system stimulation including recreational and medical uses. In: Petersen, R. C.; Stillman, R. C., eds. Cocaine: 1977. Research Monograph No. 13. Rockville, MD: National Institute on Drug Abuse; 1977:137–152.