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Effects of Heroin/Cocaine Combinations in Rats Trained to Discriminate Heroin or Cocaine from Saline

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LAMAS, X., S. S. NEGUS, M. B. GATCH AND N. K. MELLO. *Effects of heroin/cocaine combinations in rats trained to discriminate heroin or cocaine from saline.* PHARMACOL BIOCHEM BEHAV **60**(2) 357–364, 1998.—The effects of heroin and cocaine administered alone or in combination were examined in rats trained to discriminate either heroin (0.56 mg/kg IP; $n = 6$) or cocaine (5.6 mg/kg IP; $n = 6$) from saline. Heroin (0.032–1.8 mg/kg) substituted completely for the heroin training stimulus in all six heroin-trained rats, but failed to substitute for cocaine in any of the cocaine-trained rats. Cocaine (0.1–32 mg/kg) substituted completely for the cocaine training stimulus in all six cocaine-trained rats, and substituted for heroin in two of six heroin-trained rats. The opioid antagonist naltrexone (0.01–1.0 mg/kg) antagonized the discriminative stimulus effects of heroin, but naltrexone at doses up to 10 mg/kg had no effect on the discriminative stimulus effects of cocaine. The dopamine receptor antagonist flupenthixol (0.032–0.56 mg/kg) attenuated the discriminative stimulus effects of heroin and completely blocked the discriminative stimulus effects of cocaine. When heroin–cocaine combinations were administered to the heroin-trained rats, cocaine (1–5.6 mg/kg) did not significantly alter the mean heroin dose–effect curve. Similarly, in the cocaine-trained rats, heroin (0.1–0.56 mg/kg) did not significantly alter the mean cocaine dose–effect curve. These results suggest that combinations of heroin and cocaine usually produce discriminative stimulus effects similar to either heroin or cocaine alone. © 1998 Elsevier Science Inc.

Heroin Cocaine Drug discrimination Rats

COCAINE and the opioid agonist heroin are among the most widely abused illicit drugs in the United States, and the two drugs are often used together in a drug combination known as "speedball" (32,33). The reasons for this form of polydrug abuse are not well understood. Cocaine–opioid combinations may produce a profile of effects that is different from either drug alone and that contributes to enhanced abuse potential. For example, some drug users have reported that cocaine–opioid combinations produce greater euphoric effects than cocaine or heroin alone or that use of cocaine and opioids in combination ameliorates the undesirable effects of each drug (4,20,21). In agreement with these anecdotal reports, controlled laboratory studies in humans have found that cocaine–opioid combinations produce subjective effects that may differ from the effects produced by either drug alone (13, 14,25,36).

Interactions between cocaine and mu opioid agonists have also been examined in preclinical studies. Both cocaine and mu opioid agonists increase extracellular levels of dopamine in the nucleus accumbens of rats (11), and this neurochemical effect may underlie the high abuse potential of these compounds (19). In addition, combinations of cocaine and the mu agonist buprenorphine were reported to produce greater increases in extracellular dopamine levels than either drug alone, suggesting that cocaine and mu opioids may enhance each other's effects on dopamine release (6). Cocaine and mu opioids may also enhance each other's abuse-related behavioral effects. For example, in squirrel monkeys trained to dis-

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criminate cocaine from saline, morphine and a series of other mu opioid agonists produced leftward shifts in the cocaine dose–effect curve (29,30). These findings suggested that the mu agonists increased the potency of cocaine to produce discriminative stimulus effects.

Few studies have directly assessed the discriminative stimulus effects of heroin–cocaine combinations, although this is the opioid–cocaine combination that is most often abused. Consequently, the purpose of the present study was to evaluate the effects of heroin–cocaine combinations in rats trained to discriminate either heroin or cocaine from saline. Three sets of experiments were conducted. First, the effects of heroin and cocaine alone were examined in both heroin-discriminating and cocaine-discriminating rats to assess the degree to which heroin and cocaine share common discriminative stimulus effects. The second set of experiments examined the ability of the opioid receptor antagonist naltrexone and the dopamine receptor antagonist flupenthixol to antagonize the discriminative stimulus effects of heroin and cocaine. These experiments were conducted to evaluate the role of opioid and dopamine receptors in mediating the discriminative stimulus effects of heroin and cocaine. The final set of experiments examined the effects of heroin–cocaine combinations in both groups of rats to determine the degree to which heroin and cocaine modify each other's discriminative stimulus effects.

METHOD

Animals

Twelve male Sprague–Dawley rats were maintained at approximately 80–85% of their free-feeding weights (range across rats 300–350 g). Each rat was housed individually with free access to water in a temperature- and humidity-controlled colony maintained on a 12 L:12 D cycle (lights on from 0700–1900 h). Animal maintenance and research were conducted in accordance with the guidelines provided by the NIH Committee on Laboratory Animal Resources, and protocols were approved by the Institutional Animal Care and Use Committee. The health of the rats was periodically monitored by consulting veterinarians.

Apparatus

Six operant conditioning chambers (21 × 29.5 × 24.5 cm) were used. Each chamber was equipped with two response levers located on one wall, and these levers were positioned 3 cm above the chamber floor and 1.5 cm from the side walls. A single white stimulus light was located above each lever. A pellet dispenser (ENV-203; MedAssociates, St. Albans, VT) was used to deliver 45 mg food pellets (A/I Rodent Pellets; P. J. Noyes Co., Lancaster, NH) into a pellet receptacle, which was centrally located between the two levers and approximately 2 cm from the chamber floor. Each operant chamber was placed in a sound-attenuating chamber equipped with a houselight and an exhaust fan. The exhaust fan provided ventilation and white noise to mask extraneous sounds. Scheduling of experimental events and data collection were accomplished with a microcomputer and interfacing supplied by MedAssociates Inc. (St. Albans, VT).

Drug Discrimination Procedure

Discrimination training. Following initial shaping of the lever-press response, the rats were divided into two groups. One group of six rats was trained to discriminate 0.56 mg/kg heroin from saline, and a second group of six rats was trained to discriminate 5.6 mg/kg cocaine from saline. These training doses of heroin and cocaine were based on preliminary studies indicating that heroin was approximately 10-fold more potent than cocaine in decreasing rates of food-maintained responding (unpublished results). On training days, rats received an IP injection of either saline or the training dose of heroin or cocaine. A random sequence was used to determine which injection was administered, with the two restrictions that 1) the same injection was not given for more than two consecutive sessions; and 2) during each of the 30 training sessions, the numbers of saline and training drug sessions were approximately equal. Ten minutes after the injection of saline or the training drug a 15-min response period began. During the response period the house light and stimulus lights were illuminated, and 20 food pellets were available under a fixed-ratio (FR) schedule of reinforcement. The fixed ratio was gradually increased from a FR1 to a FR20. When saline was administered, completion of the fixed ratio requirement on one lever (the saline-appropriate lever) resulted in food delivery. When the training dose of the training drug was administered, completion of the fixed ratio requirement on the other lever (the heroin- or cocaine-appropriate lever) resulted in food delivery. The positions of the saline- and drug-appropriate levers were counterbalanced across rats. Responses on the inappropriate lever reset the ratio requirement on the correct lever. If all 20 food pellets were delivered before the end of the 15-min response period, then the house light and stimulus lights were turned off, and responding had no scheduled consequences for the remainder of the 15 min. Training sessions were conducted 5 days per week. Training continued until the following three criteria were met for seven of eight consecutive sessions: 1) percentage of stimulus-appropriate responding prior to delivery of the first reinforcer was $\geqslant$80%; 2) percentage of stimuls-appropriate responding for the entire session was $\geqslant$90%; and 3) response rates were $\geqslant$1.0 resp/s.

Discrimination testing. Once training was completed, three sets of tests were conducted. First, dose–effect curves were determined for heroin alone (0.032–3.2 mg/kg) and cocaine alone (0.1–32 mg/kg) in both the heroin- and cocaine-trained rats. For each group, the dose–effect curve for the training drug was determined first, followed by determination of the dose–effect curve for the alternate drug. Second, the effects of the training dose of heroin in the heroin-trained rats and cocaine in the cocaine-trained rats were redetermined following pretreatment with the opioid receptor antagonist naltrexone (0.01–10 mg/kg) or the dopamine receptor antagonist flupenthixol (0.032–0.56 mg/kg). Naltrexone was administered 30 min prior the administration of either heroin or cocaine, whereas flupenthixol was administered 60 min prior to heroin or cocaine. These pretreatment times were selected on the basis of preliminary studies conducted in our laboratory and on other published findings (2,38). The final set of experiments examined the effects of heroin/cocaine combinations. In the heroin-trained rats, the heroin dose–effect curve was redetermined in combination with 1.0–5.6 mg/kg cocaine. In the cocaine-trained rats, the cocaine dose–effect curve was redetermined in combination with 0.1–0.56 mg/kg heroin. When heroin and cocaine were administered in combination, the two drugs were administered in two separate injections within approximately 10 s, and the training drug was administered in the second of the two injections.

Throughout a test session, the completion of 20 responses on either of two levers resulted in food delivery. Otherwise, conditions during test sessions were identical to those de-

scribed during training sessions. During all phases of the study, testing usually occurred on Tuesdays and Fridays, whereas training sessions were continued on Mondays, Wednesdays, and Thursdays. A test session was conducted in a given rat only if that rat's performance met the three criteria described above for accurate drug discrimination on the training day preceding the test day. If these criteria were not met, then the next scheduled test session was omitted and replaced by a training session.

Data Analysis

Dose–effect curves were plotted to show the mean percent heroin- and cocaine-appropriate responding during the entire session as a function of drug dose (log scale). A drug or drug combination was considered to substitute completely for the training dose of heroin or cocaine if it produced ⩾90% drug-appropriate responding. ED_{50} values were defined as the dose producing 50% drug-appropriate responding, and ED_{50} values and 95% confidence limits were derived mathematically from mean data by linear regression using at least three doses on the linear portion of the dose–effect curve (35). ED_{50} values were considered to be significantly different if 95% confidence limits did not overlap. The percent drug-appropriate responding for a given test session was calculated only if the rat emitted ⩾20 responses (i.e., enough responses to earn at least one food pellet). At least three rats had to meet this criterion for mean data to be included in drug discrimination graphs and ED_{50} analysis. Data from all rats were included in response rate analysis.

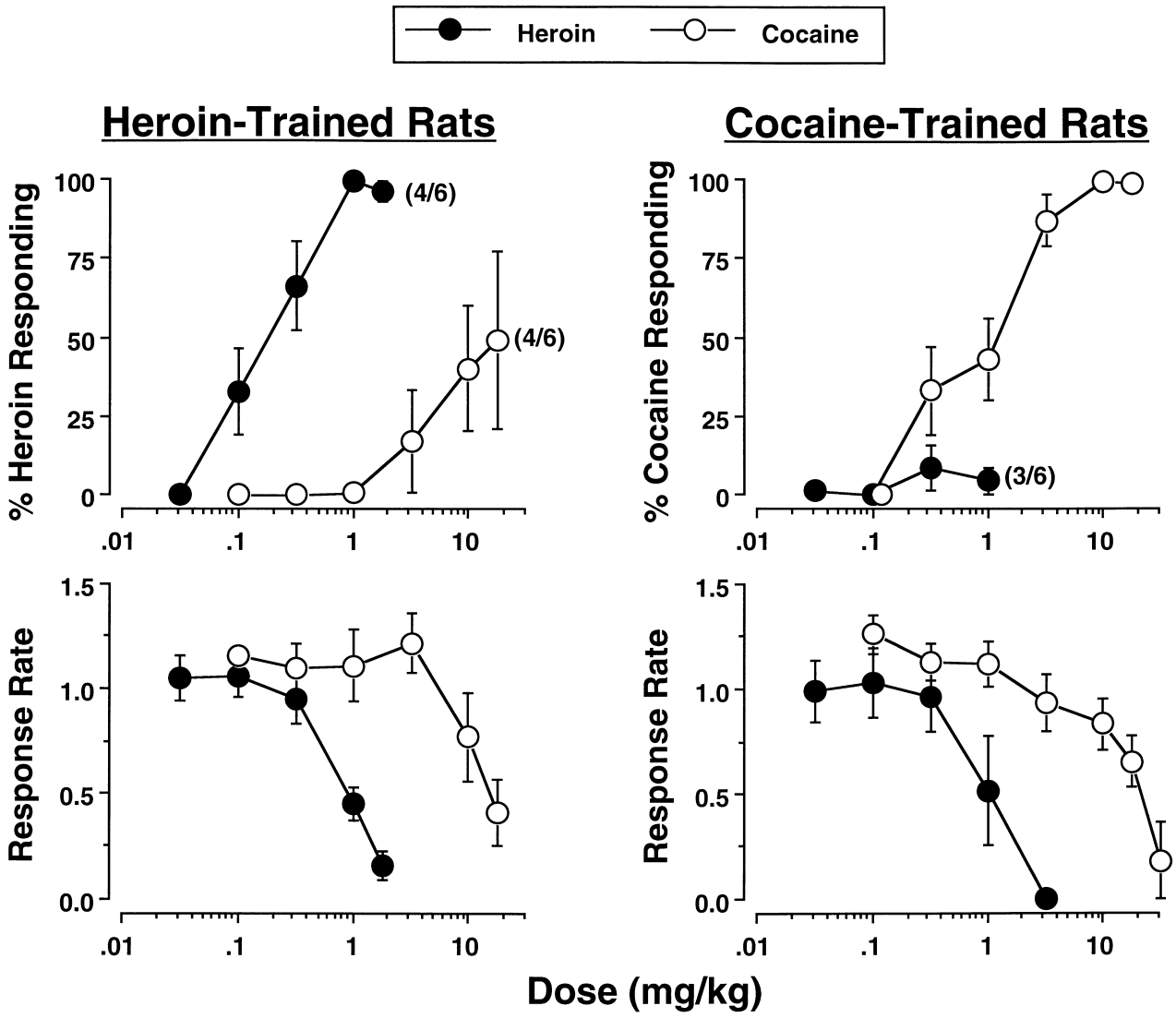

FIG. 1. Effects of heroin and cocaine administered alone in rats trained to discriminate either 0.56 mg/kg heroin (heroin-trained rats; left panels) or 5.6 mg/kg cocaine (cocaine-trained rats; right panels) from saline. Abscissae: dose of heroin or cocaine in mg/kg (log scale). Ordinates (top panels): percent heroin-appropriate responding or cocaine-appropriate responding. Ordinates (bottom panels): response rate in responses/s. Each point shows mean data (±SEM) from six rats except for the highest doses of heroin and cocaine in the upper panels. The number of subjects contributing to these data points are shown in parentheses next to the point. The remaining subjects did not respond.

Drugs

Heroin hydrochloride, cocaine hydrochloride, and naltrexone hydrochloride were obtained from the National Institute on Drug Abuse, and cis-(Z)-flupenthixol dihydrochloride was obtained from Research Biochemicals International, Natick, MA. All drugs were dissolved in sterile saline and administered IP in volumes of 0.1–1.0 ml. Doses for all drugs are expressed in terms of the salt forms described above.

RESULTS

Figure 1 shows the effects of heroin alone (0.032–3.2 mg/kg) and cocaine alone (0.1–32 mg/kg) in the heroin- and cocaine-trained rats. In rats trained to discriminate 0.56 mg/kg heroin from saline (Fig. 1, left panels), heroin produced a dose-dependent and complete substitution to the training dose of heroin in all rats (ED_{50} = 0.18 mg/kg; 95% C.L.= 0.18–0.19 mg/kg). Cocaine produced a dose-dependent but only partial substitution to heroin, reaching a maximum of 49% heroin-appropriate responding at a dose of 18 mg/kg cocaine. This partial substitution of cocaine for the heroin training stimulus resulted from complete substitution of cocaine in two rats; in the other four rats, cocaine produced primarily saline-appropriate responding. In rats trained to discriminate 5.6 mg/kg cocaine from saline (Fig. 1, right panels), cocaine produced a dose-dependent and complete substitution for the training dose of cocaine in all rats (ED_{50} = 1.0 mg/kg; 95% C.L. = 0.64–1.4 mg/kg). Heroin, in contrast, produced prima-

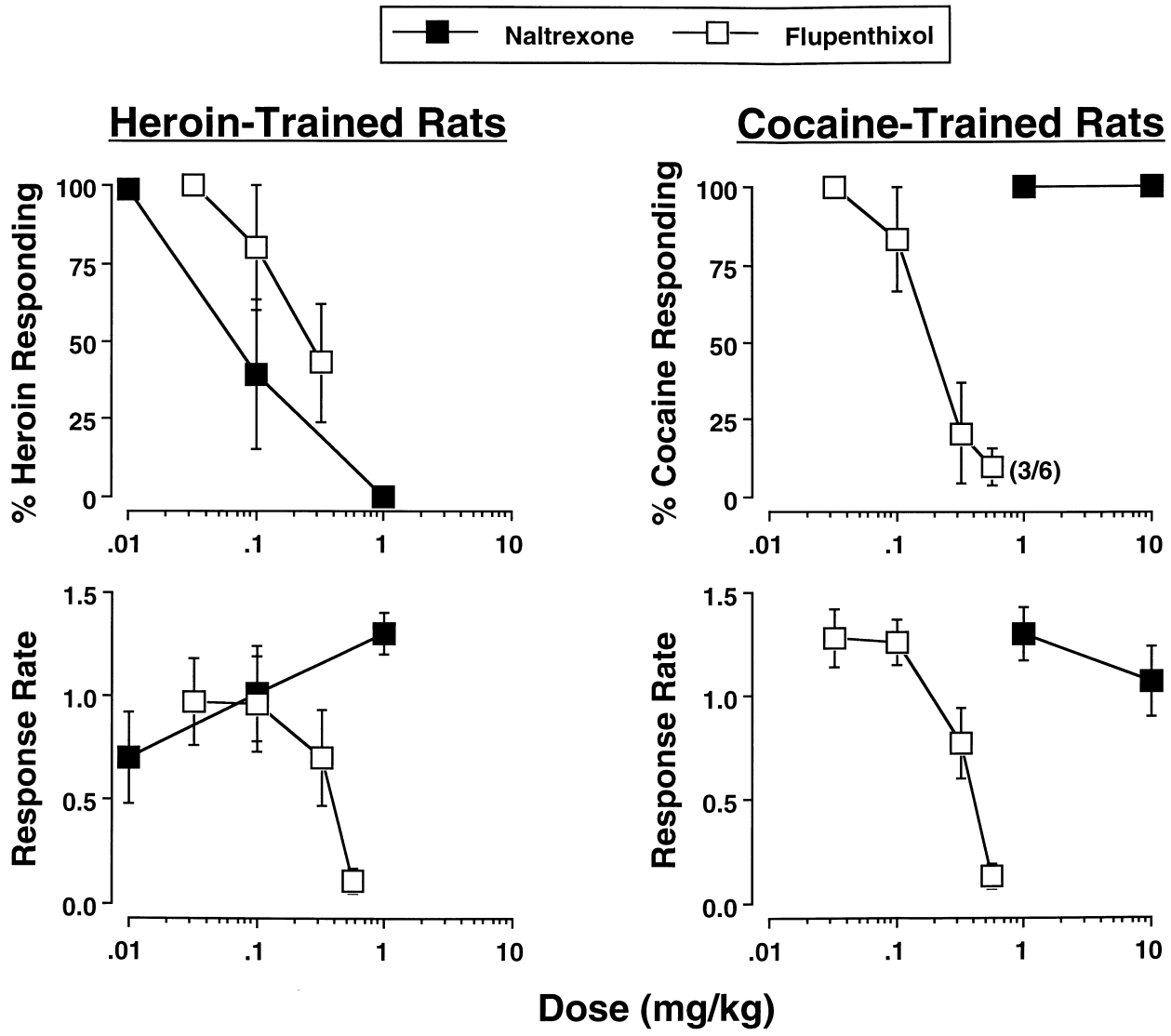

FIG. 2. Effects of the opioid receptor antagonist naltrexone and the dopamine receptor antagonist flupenthixol administered before 0.56 mg/kg heroin in the heroin-trained rats (left panels) or 5.6 mg/kg cocaine in the cocaine-trained rats (right panels). Abscissae: dose of naltrexone or flupenthixol in mg/kg (log scale). Ordinates (top panels): percent heroin-appropriate responding or cocaine-appropriate responding. Ordinates (bottom panels): response rate in responses/s. Each point shows mean data (±SEM) from five or six rats except for the highest dose of flupenthixol in the upper right panel. The number of subjects contributing to this data point is shown in parentheses next to the point. The remaining subjects did not respond.

rily saline-appropriate responding in all six cocaine-trained rats. Both heroin and cocaine produced dose-dependent decreases in response rates in both groups of rats.

Figure 2 shows the antagonist effects of the opioid receptor antagonist naltrexone and the dopamine receptor antagonist flupenthixol. In the heroin-trained rats (Fig. 2, left panels), naltrexone (0.01–1.0 mg/kg) produced a dose-dependent antagonism of the discriminative stimulus effects of heroin, and 1.0 mg/kg naltrexone completely blocked the discriminative stimulus effects of heroin in all six rats. The training dose of heroin alone produced a small decrease in response rates, and naltrexone also antagonized these rate-decreasing effects of heroin. One of the heroin-trained rats died at the conclusion of the naltrexone antagonism experiments, so the remaining experiments were conducted in a group of five rats. Flupenthixol (0.032–0.56 mg/kg) attenuated the discriminative stimulus effects of heroin, but this effect was inconsistent across rats. Specifically, flupenthixol decreased the percent heroin-appropriate responding elicited by 0.56 mg/kg heroin to ⩽20% in three rats, but in the other two rats, flupenthixol had little or no effect on heroin-appropriate responding. Flupenthixol, in combination with the training dose of heroin, produced a dose-dependent decrease in response rates in all five heroin-trained rats.

In the cocaine-trained rats (Fig. 2, right panels), flupenthixol (0.032–0.56 mg/kg) produced a dose-dependent blockade of the discriminative stimulus effects of 5.6 mg/kg cocaine. Doses of 0.32 or 0.56 mg/kg flupenthixol decreased the percent cocaine-appropriate responding elicited by the training dose of cocaine to ⩽22% in all six rats. Flupenthixol,

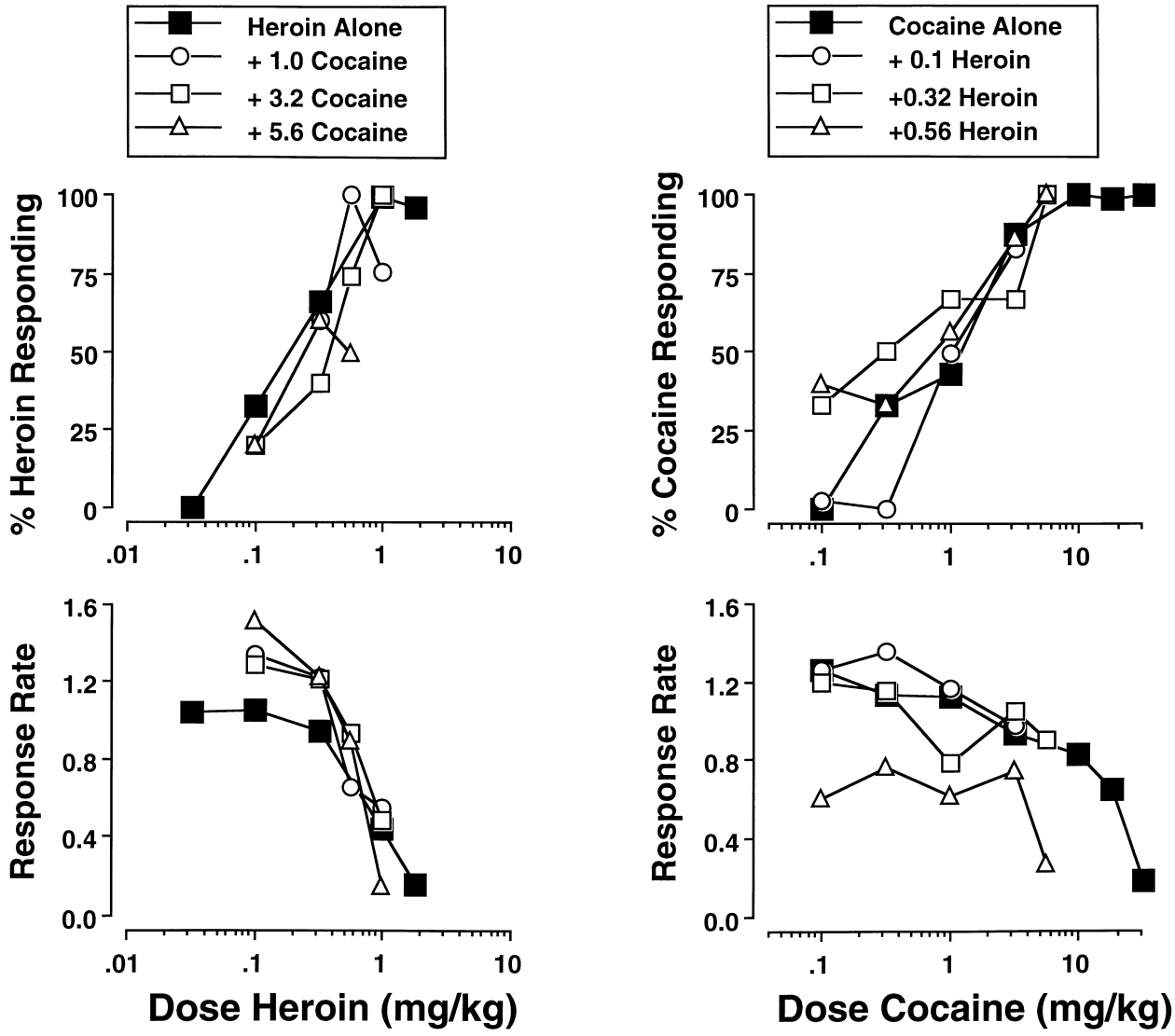

FIG. 3. Effects of heroin–cocaine combinations in heroin-trained rats (left panels) or cocaine-trained rats (right panels). Abscissae: dose of heroin (left panels) or cocaine (right panels) in mg/kg (log scale). Ordinates (top panels): percent heroin-appropriate responding or cocaine-appropriate responding. Ordinates (bottom panels): response rate in responses/s. Most points shows mean data from five rats in the heroin-trained group and six rats in the cocaine-trained group. However, some rats did not respond following administration of heroin-cocaine combinations including the highest doses of heroin (0.56 and 1.0 mg/kg).

in combination with the training dose of cocaine, also produced a dose-dependent decrease in response rates. Naltrexone (1.0–10 mg/kg) had no effect on the discriminative stimulus effects of cocaine or on response rates in the cocaine-trained rats.

The effects of heroin/cocaine combinations are shown in Fig. 3 and Table 1. In the heroin-trained rats, the addition of cocaine (1.0–5.6 mg/kg) had little overall effect on the heroin dose–effect curve (Fig. 3, left panels), and cocaine did not produce a significant change in the heroin ED_{50} value (Table 1). Relative to heroin alone, cocaine tended to increase response rates in combination with low doses of heroin (0.1–0.32 mg/kg). In contrast, a combination of a high dose of heroin (1.0 mg/kg) and a high dose of cocaine (5.6 mg/kg) decreased response rates more than 1.0 mg/kg heroin alone.

When heroin/cocaine combinations were administered to the cocaine-trained rats, heroin had little effect on the dose–effect curve for cocaine discrimination (Fig. 3, right panels), and heroin did not significantly alter the ED_{50} value for cocaine (Table 1). Response rates for combinations of 0.1 and 0.32 mg/kg heroin with cocaine were similar to those following administration of cocaine alone. However, 0.56 mg/kg heroin produced rate-decreasing effects of its own and shifted the dose–effect curve for cocaine-induced rate suppression to the left.

DISCUSSION

Effects of Heroin and Cocaine Alone

When administered alone, heroin dose dependently substituted for the training stimulus in the heroin-trained rats but not in the cocaine-trained rats. Similarly, cocaine dose dependently substituted for the training stimulus in the cocaine-trained rats but not in most heroin-trained rats. These results are consistent with previous findings that mu opioids and cocaine usually produce distinct discriminative stimulus effects in subjects trained to discriminate vehicle from either a mu opioid agonist (7) or cocaine (5,7,12,29,30). However, there was an exception to this general finding in the present study in that cocaine produced a dose-dependent and complete substitution for heroin in two heroin-trained rats. Cross-substitution between mu opioids and cocaine has occasionally been observed in some subjects in previous studies (1,9,16,22,23). For example, cocaine substituted for the low-efficacy mu agonist nalbuphine in one of three monkeys (16). Similarly, the mu agonist fentanyl substituted completely for cocaine in 6 of 10 rats (9), and in rhesus monkeys trained to discriminate cocaine, both heroin and the mu agonist alfentanil substituted completely for cocaine in three of five monkeys (22,23). Thus, although the discriminative stimulus effects of heroin and cocaine are usually distinct from each other, there may be some overlap between the discriminative stimulus effects of heroin and cocaine in some subjects. Interestingly, clinical studies have also reported some overlap between the subjective effects of cocaine and mu opioid agonists. For example, Foltin and Fischman (14) found that while there were many differences in the subjective effects produced by intravenous cocaine and morphine, both drugs produced similar effects on some measures (e.g., increases in subjective measures of "high"), and cocaine also produced a small but significant increase in scores on an Opiate Symptoms Checklist.

TABLE 1

ED_{50} VALUES IN mg/kg (95% CONFIDENCE LIMITS) FOR HEROIN ALONE AND HEROIN + COCAINE (1.0–5.6 MG/KG) IN THE HEROIN-TRAINED RATS AND FOR COCAINE ALONE AND COCAINE + HEROIN (0.1–0.56 mg/kg) IN THE COCAINE-TRAINED RATS

Group	ED_{50} Value
Heroin-trained rats	
Heroin alone	0.18 (0.18–0.19)
Heroin + 1.0 cocaine	0.21 (0.032–1.3)
Heroin + 3.2 cocaine	0.29 (0.13–0.60)
Heroin + 5.6 cocaine	0.32 (0.1–1.0)
Cocaine-trained rats	
Cocaine alone	1.0 (0.64–1.4)
Cocaine + 0.1 heroin	1.0 (0.27 – 5.1)
Cocaine + 0.32 heroin	0.34 (0.1–1.0)
Cocaine + 0.56 heroin	0.69 (0.53–0.99)

Effects of Naltrexone and Flupenthixol on Heroin and Cocaine Discrimination

The discriminative stimulus effects of the training dose of heroin in this study were completely blocked by relatively low doses of the mu-selective opioid receptor antagonist naltrexone, suggesting that the effects of heroin were mediated by mu opioid receptors. This conclusion is consistent with previous studies that have demonstrated that heroin shares discriminative stimulus effects with other mu opioid agonists (3,28); however, this is the first demonstration that the discriminative stimulus effects of heroin in a heroin-trained subject can be blocked by an opioid antagonist. The discriminative stimulus effects of heroin were also attenuated by the dopamine receptor antagonist flupenthixol, suggesting that dopaminergic systems may also have mediated the discriminative stimulus effects of heroin. This finding agrees with previous reports that other dopamine antagonists attenuate the discriminative stimulus effects of heroin and fentanyl in rats (8,10). Moreover, these behavioral studies are consistent with reports that mu opioid agonists may function as indirect dopamine agonists by disinhibiting mesolimbic dopamine neurons and increasing extracellular dopamine levels in the terminal fields of these neurons (11,17). However, these effects of flupenthixol on heroin discrimination should be interpreted with caution for at least two reasons. First, in contrast to naltrexone, flupenthixol did not antagonize the discriminative stimulus effects of heroin in all rats. This suggests that heroin's discriminative stimulus effects may be independent of dopaminergic activity in at least some subjects. Second, flupenthixol's effects on heroin discrimination were observed only at doses that also decreased response rates, suggesting that flupenthixol may have produced nonspecific effects that interfered with accurate discrimination of the heroin stimulus. In accord with this possibility, some studies have found that flupenthixol and other dopamine antagonists may compromise the expression of accurate discrimination behavior regardless of the modality of the stimulus being discriminated (26,37).

The discriminative stimulus effects of cocaine in the present study were not blocked by even high doses of naltrexone, indicating that cocaine's effects were not mediated by opioid receptors. This result is consistent with our previous

finding that the opioid antagonist quadazocine did not block the discriminative stimulus effects of cocaine in rhesus monkeys (22). Moreover, these results indicate that the discriminative stimulus effects of heroin and cocaine are mediated by different pharmacological mechanisms of action. In contrast to naltrexone, flupenthixol produced a dose-dependent and complete blockade of the discriminative stimulus effects of cocaine in all six rats. These findings agree with previous reports that flupenthixol blocks the discriminative stimulus effects of cocaine (2,24,31). These results are also consistent with other evidence indicating that cocaine acts as an indirect dopamine agonist, and that cocaine's discriminative stimulus effects are mediated primarily by its effects on dopaminergic systems (7,18,31). Again, however, it should be noted that the effects of flupenthixol on cocaine discrimination were observed only at doses that also decreased response rates, suggesting that nonspecific effects of flupenthixol may have contributed to its blockade of the discriminative stimulus effects of cocaine.

Effects of Heroin/Cocaine Combinations

This is the first study to describe the effects of heroin–cocaine combinations in heroin-trained rats. Despite the fact that cocaine partially substituted for heroin, the combination of cocaine with heroin did not produce a significant shift in the heroin dose–effect curve. These findings suggest that cocaine does not enhance the discriminative stimulus effects of heroin in rats. Indeed, the primary effect of cocaine was to produce small increases in the ED_{50} value for heroin discrimination, although this effect did not achieve statistical significance. Similarly, cocaine did not alter the discriminative stimulus effects of morphine in rats (34). In another related series of studies, Young and colleagues reported that amphetamine had no effect on the discriminative stimulus effects of morphine in rats trained to discriminate a high dose of morphine (5.6 mg/kg), and amphetamine attenuated the discriminative stimulus effects of a lower training dose of morphine (3.2 mg/kg) (15,38). This latter effect was attributed to either masking of the morphine stimulus by amphetamine or to the creation of a novel amphetamine-morphine stimulus that was distinct from the morphine training stimulus. Taken together, these studies suggest that psychostimulants such as cocaine and amphetamine do not enhance the discriminative stimulus effects of mu agonists.

The present study also found that heroin had little effect on the discriminative stimulus effects of cocaine in rats trained to discriminate cocaine from saline. Although heroin did produce small decreases in the ED_{50} value for cocaine discrimination, these effects were neither statististically significant nor dose-dependent, suggesting that heroin does not enhance the discriminative stimulus effects of cocaine. These findings with heroin extend several previous studies that have examined the effects of other mu opioid agonists on cocaine discrimination, and the results of these previous experiments have been mixed. For example, morphine produced leftward shifts in the cocaine discrimination dose–effect curve in squirrel monkeys (29,30) and rats (34). However, in agreement with the present study, the mu agonist fentanyl did not alter the discriminative stimulus effects of cocaine in rats (5), and the mu agonist buprenorphine increased cocaine-appropriate responding engendered by low doses of cocaine in rats, but decreased cocaine-appropriate responding produced by higher doses of cocaine (12). Finally, in rhesus monkeys discriminating cocaine from saline, mu agonists produced dose-dependent and naltrexone-reversible leftward shifts in the cocaine dose–effect curve in some monkeys, but in other monkeys, mu agonists had little or no effect on the cocaine dose–effect curve (23). Thus, mu agonists are at best inconsistent in their ability to enhance the discriminative stimulus effects of cocaine, and heroin in particular does not appear to enhance cocaine's discriminative stimulus effects.

Because the discriminative stimulus effects of drugs in animals may be related the subjective effects of drugs in humans (27), it is of interest to compare the results of the present drug discrimination study with the findings of clinical studies examining the subjective effects of cocaine/mu agonist combinations. The acute administration of cocaine/mu agonist combinations has been found to produce greater subjective effects than either drug alone on some subjective measures, but the magnitude of these differences has been small and less than would be predicted on the basis of a model of additivity (14,36). For example, both Foltin and Fishman (14) and Walsh et al. (36) found that cocaine/mu agonist combinations produced greater scores on a measure of drug-induced "high" than either drug alone. However, the effects of the combinations were not significantly different from the effects of either drug alone in the Walsh et al. (36) study, and they were less than additive in both studies. Moreover, cocaine and mu agonists do not alter each other's effects on other subjective measures (e.g., the MBG scale of the Addiction Research Center Inventory). Foltin and Fishman (14) concluded that ". . . although some significant differences in subjective effects after the administration of cocaine–morphine combinations compared to cocaine and morphine alone were observed, they were few. Generally, the effects of combining these drugs could be predicted by the effects of the drugs alone."

SUMMARY

The results of this study and previous studies suggest that cocaine and mu opioid agonists produce discriminative stimulus effects that overlap to a small degree (i.e., cross-substitution is occasionally observed) and that may be mediated in part by activation of common dopaminergic systems. However, when cocaine and mu agonists are administered in combination, they do not consistently enhance each other's discriminative stimulus effects under all conditions. Rather, the discriminative stimulus effects of cocaine/mu agonist combinations are often similar to the discriminative stimulus effects of either cocaine or the mu agonist alone.

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