ABSTRACT

Cocaine and heroin often are abused together in a combination known as a “speedball,” but relatively little is known about ways in which cocaine and heroin may interact to modify each other’s abuse-related effects. The present study evaluated the discriminative stimulus effects of a speedball combination of cocaine and heroin. Three rhesus monkeys were trained to discriminate vehicle from a 10:1 ratio of cocaine (0.4 mg/kg) in combination with heroin (0.04 mg/kg). Both cocaine alone and heroin alone substituted completely for the cocaine/heroin combination, although cocaine and heroin were more potent when administered together than when administered alone. Combined pretreatment with the dopamine antagonist flupenthixol and the opioid antagonist quadafoxetine dose-dependently antagonized the discriminative stimulus effects of the cocaine/heroin combination, but pretreatment with either antagonist alone was less effective. These findings suggest that either cocaine or heroin alone was sufficient to substitute for the cocaine/heroin training combination. To characterize the discriminative stimulus properties of this speedball more fully, a series of cocaine-like and heroin-like agonists were studied in substitution tests. The indirect dopamine agonists CFT, amphetamine and bupropion and the mu opioid agonists alfentanil, fentanyl and morphine produced high levels of speedball-appropriate responding. However, the indirect dopamine agonist GBR12909, the D1 dopamine agonist SKF82958, the D2 dopamine agonist quinpirole and the partial mu opioid agonist nalbuphine did not substitute for the cocaine/heroin combination. Because these compounds produce discriminative stimulus effects similar to either cocaine or mu opioid agonists alone, these findings suggest that the discriminative stimulus effects of the cocaine/heroin combination do not overlap completely with the effects of cocaine and heroin alone. Finally, a series of compounds that produce partial or no substitution for cocaine or mu opioid agonists alone also did not substitute for the cocaine/heroin combination, which indicates that the discriminative stimulus effects of the combination were pharmacologically selective. Taken together, these findings suggest that a combination of cocaine and heroin produces a pharmacologically selective discriminative stimulus complex that includes aspects of both component drugs.

Psychostimulants such as cocaine and opioid agonists such as heroin often are abused together in a drug combination known as a “speedball.” Recent studies suggest that the incidence of this form of polydrug abuse may be relatively high. For example, 45% to 63% of intravenous drug users in large, urban samples reported use of cocaine/heroin speedball combinations (Schutz et al., 1994; Metzger et al., 1996). The reasons for combined cocaine and heroin abuse are not well understood. Users of stimulant/opioid combinations have reported that these drugs enhance each other’s euphoric effects and/or ameliorate each other’s unpleasant effects (Brecher, 1972; Kosten et al., 1986, 1987; Tutton and Crayton, 1993). Some users also have reported that cocaine attenuates signs and symptoms of opioid withdrawal during heroin dose reduction (Hunt et al., 1984; Strug et al., 1985).

Taken together, these findings suggest that combinations of stimulants and opioids may produce subjective experiences that are different from those produced by either drug alone. In agreement with these anecdotal reports, controlled clinical studies have found that after acute administration, stimulants and opioids may modify each other’s physiological and subjective effects. For example, the effects of cocaine and morphine administered alone or in combination were examined in polydrug abusers with histories of both cocaine and heroin use (Foltin and Fischman, 1992). When administered alone, cocaine and morphine produced different but overlapping profiles of subjective effects. For example, cocaine produced increases in ratings of “stimulated,” morphine produced increases in ratings of “sedated” and both drugs increased ratings of “high.” When cocaine and morphine were administered together, they modified each other’s effects on some endpoints but not on others. For example, some dose combinations produced greater ratings of high than either drug alone and lower ratings of sedated than morphine alone.
In general, though, the effects of combining cocaine and morphine were less than would be expected from an effect addition model of drug interaction. Similar results were obtained with combinations of cocaine and hydromorphone (Walsh et al., 1996). These combinations produced greater effects on such endpoints as “drug effect” and stimulated than either cocaine or hydromorphone alone and smaller effects on respiration or observer-rated “nodding” than hydromorphone alone. For many other effects, however, cocaine/hydromorphone combinations produced effects similar to those of either cocaine or hydromorphone alone. Both studies concluded that the primary outcome of combining cocaine and opioids was not a change in the magnitude of effects of the component drugs but rather the production of a compound stimulus that incorporated both stimulant and opioid effects.

Preclinical studies have examined the reinforcing effects of cocaine/heroin speedball combinations in assays of drug self-administration to determine the degree to which cocaine and heroin modify each other’s reinforcing effects (Mello et al., 1995; Hemby et al., 1996; Rowlett and Woolverton, 1997). We evaluated drug self-administration maintained by cocaine and heroin alone and by nine different combinations of cocaine and heroin in rhesus monkeys (Mello et al., 1995). In general, drug self-administration maintained by the different cocaine/heroin combinations was similar to self-administration of either cocaine or heroin alone, which suggests that these doses of cocaine and heroin did not modify each other’s reinforcing effects. Similar results were reported for self-administration of cocaine/heroin combinations in rats (Hemby et al., 1996). In rhesus monkeys responding under a progressive ratio schedule, however, low doses of heroin that did not maintain self-administration alone produced small leftward shifts in the cocaine dose-effect curve in some monkeys (Rowlett and Woolverton, 1997). Taken together, these findings suggest that cocaine and heroin may enhance each other’s reinforcing effects under some conditions, but these effects are small and are not always observed.

Interactions between cocaine and opioids also have been examined in preclinical studies of drug discrimination, in which subjects were trained to discriminate either cocaine or a mu opioid agonist from vehicle. Cocaine and mu agonists alone usually produce different discriminative stimulus effects and fail to cross-substitute in animals trained to discriminate either cocaine (Colpaert, 1978; Dykstra et al., 1992; Spealman and Bergman, 1992, 1994; Broadbent et al., 1995) or an opioid agonist (Gerak and France, 1996; Suzuki et al., 1995, 1997; Woolfolk and Holtzman, 1997; Lamas et al., in press). However, there are several exceptions to this general finding (Ando and Yanagita, 1978; Colpaert et al., 1979; Mello et al., 1995; Negus et al., 1998a). For example, in rhesus monkeys trained to discriminate 0.4 mg/kg cocaine i.m. from vehicle, both heroin and alfentanil substituted completely for cocaine in 3 of 5 monkeys (Mello et al., 1995; Negus et al., 1998a). Similarly, cocaine substituted for the mu opioid agonist nalbuphine in 1 of 3 monkeys (Gerak and France, 1996) and for heroin in 2 of 6 rats (Lamas et al., in press). When mu opioid agonists are administered as pretreatments to cocaine in cocaine-trained subjects, they sometimes enhance the discriminative stimulus effects of cocaine, as evidenced by leftward shifts in the cocaine dose-effect curves (Dykstra et al., 1992; Spealman and Bergman, 1992, 1994; Suzuki et al., 1995, 1997; Negus et al., 1998a). However, the magnitude of these effects usually has been small, and in many instances, pretreatments with mu agonists that failed to substitute for cocaine also failed to alter the discriminative stimulus effects of cocaine (Broadbent et al., 1995; Mello et al., 1995; Woolfolk and Holtzman, 1997; Negus et al., 1998a; Lamas et al., in press). Similarly, cocaine pretreatment apparently does not alter the discriminative stimulus effects of mu opioid agonists in opioid-trained subjects (Suzuki et al., 1995; Lamas et al., in press). Thus, these preclinical drug discrimination studies agree with both clinical studies and preclinical drug self-administration studies in finding that cocaine and opioid agonists may weakly modify each other’s effects, but these changes are relatively small and are not observed consistently under all conditions.

All previous drug discrimination studies that have examined cocaine/opioid interactions were conducted in subjects trained to discriminate either cocaine or an opioid from vehicle. Consequently, these studies were limited to an investigation of the ability of one drug to modify the discriminative stimulus effects produced by the other. However, these procedures do not permit an evaluation of the overall discriminative stimulus effects produced by a drug combination. An alternative approach to the study of cocaine/opioid interactions is to train subjects to discriminate a combination of the two drugs and to evaluate the discriminative stimulus effects of the drug combination directly. Such studies may be particularly informative, because as noted above, clinical studies have suggested that the most important consequence of combining stimulants and opioids may be the production of a compound stimulus that includes aspects of both drugs.

The present study is the first evaluation of the discriminative stimulus effects of a cocaine/heroin speedball combination in rhesus monkeys. Three rhesus monkeys were trained to discriminate a 10:1 combination of 0.4 mg/kg cocaine and 0.04 mg/kg heroin from vehicle in a two-lever, food-reinforced drug discrimination procedure. Subsequently, three sets of experiments were conducted. In the first set of experiments, the potency and time course of the 10:1 cocaine/heroin training combination were determined and compared with the effects of cocaine alone, heroin alone and other cocaine/heroin combinations. The second set of experiments examined the ability of the dopamine receptor antagonist flupenthixol and the mu selective opioid antagonist quazadocine to antagonize the effects of the 10:1 cocaine/heroin training combination. These antagonists were selected for study because the abuse-related effects of cocaine, including its discriminative stimulus effects, are mediated primarily by cocaine’s blockade of dopamine reuptake and subsequent indirect dopamine agonist effects (Ritz et al., 1987; Koob and Bloom, 1988; Johnson and Fischman, 1989; Woolverton and Johnson, 1992), whereas the behavioral effects of heroin are thought to be mediated primarily by mu opioid receptors (Way et al., 1960; Inturrisi et al., 1983; Jaffe and Martin, 1985; Bertalmio et al., 1992). The effects of flupenthixol and quazadocine administered alone and in combination were evaluated.

The final series of experiments investigated the pharmacological selectivity of the cocaine/heroin discriminative stimulus by examining the ability of a range of other compounds to substitute for the cocaine/heroin training combination. The indirect dopamine agonists CPT, amphetamine, bupropion and GBR12909, the D1 dopamine receptor agonist SKF82958 and the D2 dopamine receptor agonist quinpirole
were examined because these compounds previously had been found to produce high levels of cocaine-appropriate responding in cocaine-trained primates (Kleven et al., 1990; Speelman et al., 1991; Speelman, 1993; Lamas et al., 1996; Negus et al., 1998a). Because cocaine also blocks the reuptake of norepinephrine and serotonin (Koe, 1976; Reith, 1988), the norepinephrine reuptake blocker nisoxetine and the serotonin reuptake blocker clomipramine also were studied. The discriminative stimulus effects of heroin alone have not been characterized thoroughly, but the effects of heroin are thought to be mediated primarily by mu opioid receptors (Way et al., 1960; Inturrisi et al., 1983; Jaffe and Martin, 1985; Bertalino et al., 1992). Accordingly, we evaluated the effects of the other mu opioid agonists alfentanil, fentanyl, morphine and nalbuphine. The kappa opioid agonist U50,488 and the delta opioid agonist SNC80 also were studied as representative agonists for the other two principal opioid receptor types. Finally, the barbiturate pentobarbital was studied as a behaviorally active control compound that does not act through monoamine or opioid systems and that does not substitute for cocaine in cocaine-trained subjects (de la Garza and Johanson, 1983) or for mu opioid agonists in opioid-trained subjects (Picker et al., 1990; Young et al., 1992). Selected indirect dopamine agonists and mu agonists also were administered together to determine the degree to which other dopamine agonist/mu agonist combinations could reproduce the discriminative stimulus effects of the cocaine/heroin combination.

Methods

Subjects. Three male rhesus monkeys (Macaca mulatta) were studied. All three monkeys had previous experience in behavioral procedures involving cocaine- and food-maintained responding; however, none of the monkeys had previous drug discrimination experience. Monkeys weighed 6.0 to 8.0 kg and were maintained on a diet of multiple vitamins, fresh fruit, vegetables and Lab Diet Jumbo Monkey biscuits (PMI Feeds, Inc., St. Louis, MO). In addition, mon-

Apparatus. Drug discrimination procedures were similar to those used in our previous studies of cocaine discrimination (Lamas et al., 1995; Mello et al., 1995; Negus et al., 1995). Each monkey was housed individually in a well-ventilated, stainless steel chamber (56 × 71 × 69 cm). The home cages of all monkeys were modified to include an operant panel (28 × 28 cm) mounted on the front wall. Three square translucent response keys (6.4 × 6.4 cm) were arranged 2.54 cm apart in a horizontal row 3.2 cm from the top of the operant panel. Each key could be transilluminated by red or green stimulus lights (Superbright LEDs). The operant panel also supported an externally mounted pellet dispenser (Gerbrands, model G9210) that delivered 1-g fruit-flavored food pellets to a food receptacle mounted on the cage beneath the operant response panel. Operation of the operant panels and data collection were accomplished with IBM compatible computers (MED Associates Inc., Georgia, VT) located in a separate room.

Discrimination training. Experimental sessions were composed of individual cycles and were conducted 5 days per week. Each cycle consisted of a 15-min time-out period followed by a 5-min response period. During the time-out, all stimulus lights were off, and responding had no scheduled consequences. During the response period, the right and left response keys were transilluminated red or green, and monkeys could receive up to 10 food pellets by responding under a fixed ratio 30 (FR30) schedule of food presentation. For two of the three monkeys, the left key was illuminated green and the right key was illuminated red. For the other monkey, the colors of the response keys were reversed. The center key was not illuminated at any time, and responding on the center key had no scheduled consequences. If all available food pellets were delivered before the end of the 5-min response period, the stimulus lights transilluminating the response keys were turned off, and responding had no scheduled consequences for the remainder of that response period.

Monkeys were trained to discriminate a speedball combination of cocaine and heroin. Specifically, the drug stimulus used in discrimination training consisted of a mixture of 0.40 mg/kg cocaine and 0.04 mg/kg heroin administered in a single i.m. injection. This 10:1 ratio of cocaine and heroin doses was selected on the basis of preliminary observational studies as well as previous drug self-administration studies, which indicated that cocaine is approximately 10-fold less potent than heroin in maintaining drug self-administration (Mello et al., 1995). The absolute doses used as components of the training stimulus were selected on the basis of our previous finding that 0.4 mg/kg cocaine serves as a robust and reliable discriminative stimulus in rhesus monkeys (Lamas et al., 1995; Mello et al., 1995; Negus et al., 1995).

On training days, monkeys were given an i.m. injection of either vehicle (distilled water) or the cocaine/heroin training combination 5 min after the beginning of each time-out period (i.e., 10 min before the response period). After the administration of vehicle, responding on only the green key (the vehicle-appropriate key) produced food, whereas after administration of the cocaine/heroin training combination, only responding on the red key (the drug-appropriate key) produced food. Responses on the inappropriate key reset the FR requirement on the appropriate key.

Experimental sessions consisted of one to five cycles each day. Initially, experimental sessions consisted of only one cycle each day, and during this first phase of training, key-pressing behavior was shaped and the ratio value was increased gradually to the terminal FR30. During the second phase of training, the maximum number of cycles per session was increased to 2, and during the final phase of training, the maximum number of cycles per session was increased to 5. If the training dose of the cocaine/heroin combination was administered, it was administered only during the last cycle. This design assured a constant interval between drug administration and onset of response periods during which responding on only the drug-appropriate key produced food.

During the response period of each cycle, three dependent variables were determined: 1) percent injection-appropriate responding before delivery of the first reinforcer [(Injection-appropriate responses emitted before 1st reinforcer) ÷ Total responses emitted before delivery of 1st reinforcer] × 100; 2) percent injection-appropriate responding for the entire response period [(Injection-appropriate responses emitted during response period) ÷ Total responses emitted during response period] × 100; and 3) response rate (Total responses emitted during response period ÷ Total time stimulus lights were illuminated).

Monkeys were considered to have acquired the discrimination when the following three criteria were met for seven of eight consecutive training sessions: 1) the percent injection-appropriate responding before delivery of the first reinforcer was greater than or equal to
80% for all cycles; 2) the percent injection-appropriate responding for the entire cycle was greater than or equal to 90% for all cycles; 3) response rates during vehicle training cycles were greater than 0.5 responses per second.

**Discrimination testing.** Once monkeys met criterion levels of discrimination, testing began. Test sessions were identical to training sessions except that responding on either key produced food, and test drugs were administered i.m. as described below. Training sessions usually were conducted on Mondays, Wednesdays and Thursdays, and test sessions were conducted on Tuesdays and Fridays. Test sessions were conducted only if the three criteria listed as “Criteria for Discrimination” were met during the training day immediately preceding the test day. If responding did not meet criterion levels of discrimination performance, then training was continued until criterion levels of performance were obtained for at least two consecutive days. Three series of experiments were conducted to characterize the discriminative stimulus effects of the cocaine/heroin combination.

The first series of experiments examined the effects of various cocaine/heroin combinations and of cocaine and heroin alone. Initially, the potency and time course of the 10:1 cocaine/heroin training combination were determined. To examine the potency of this combination, the dose ratio of cocaine to heroin was maintained at 10:1, and increasing doses of this combination were administered by a cumulative dosing procedure. In this procedure, a dose of the cocaine/heroin combination was administered instead of vehicle or the training combination during the time-out period of each cycle, and each successive injection increased the cumulative dose by 1/2 log units. To examine the time course of the cocaine/heroin combination, a single dose of the training combination of 0.4 mg/kg cocaine and 0.04 mg/kg heroin was administered, and response periods were scheduled to begin after 3, 10, 18, 30, 56 and 100 min. The effects of the combination at 3, 18 and 56 min after injection were determined during one test session, and the effects at 10, 30 and 100 min after injection were determined during a separate test session. Once the potency and time course of the 10:1 cocaine/heroin training combination had been determined, the effects of cocaine alone and heroin alone were examined. Finally, the effects of other cocaine/heroin combinations in ratios of 30:1 and 3:1 cocaine/heroin were determined using cumulative dosing procedures. The 30:1 cocaine/heroin combination was selected as a combination with a relatively high ratio of cocaine, which was intermediate between the 10:1 training combination and cocaine alone. Similarly, the 3:1 cocaine/heroin combination was selected as a combination with a relatively high ratio of heroin, which was intermediate between the 10:1 training combination and heroin alone.

The second set of experiments examined the effects of the opioid antagonist quazadocine and the dopamine antagonist fluoxetine administered alone or in combination on the cumulative dose-effect curve of the 10:1 cocaine/heroin combination. Quazadocine and fluoxetine were administered with pretreatment times of 30 min and 3 hr, respectively. These pretreatment times were based on previous studies that examined the opioid antagonist effects of quazadocine (Negus et al., 1993) and the cocaine antagonist effects of fluoxetine (Negus et al., 1996a) in rhesus monkeys.

The third set of experiments examined the ability of various test drugs or drug combinations to substitute for the 10:1 cocaine/heroin training combination. All test drugs or drug combinations were administered by cumulative dosing procedures identical to those described above. In the drug combination experiments, we studied a 1:10 combination of amphetamine/morphine and a 1:1 combination of GBR12909/nalbuphine. The dose ratios for these combinations were based on relative potencies observed during initial experiments with these drugs alone and on previous studies examining the relative potencies of these compounds (e.g., Gatch et al., 1998; Negus et al., 1998a).

Substitution and antagonist tests for all drugs or drug combinations were conducted at least twice in each monkey, with the exception of U50,488 and clomipramine. These two compounds were studied only once in each subject, because during the first determination, they produced almost exclusively vehicle-appropriate responding.

**Data analysis.** The percent drug-appropriate responding was calculated for a given test cycle only if the monkey emitted enough responses to earn at least one reinforcer (i.e., 30 responses). A test drug or drug combination was considered to substitute for the training combination in a monkey if at least some dose produced ≥90% drug-appropriate responding. The ED_{50} value was defined as the dose of a drug or component doses of a drug combination that produced 50% drug-appropriate responding. An ED_{50} value was determined for any drug or drug combination in a given monkey that produced a dose-dependent increase in drug-appropriate responding to a level ≥50%. ED_{50} values were derived mathematically (least-squares method) by log-linear interpolation with two to three points on the ascending limb of the dose-effect curve. For drugs and drug combinations producing ≥50% drug-appropriate responding in at least two monkeys, the mean ED_{50} value and 95% confidence limits were calculated.

ED_{50} values for cocaine administered alone were compared with ED_{50} values for cocaine as a component drug in various cocaine/heroin mixtures (30:1 cocaine/heroin, 10:1 cocaine/heroin, 3:1 cocaine/heroin) by a one-factor, repeated measures analysis of variance. A significant analysis of variance was followed by individual means comparisons by paired t tests. ED_{50} values for heroin administered alone or as a component drug in the cocaine/heroin mixtures were compared similarly. The level of significance was set a priori at P < .05.

**Drugs.** (-)-Cocaine HCl, heroin HCl, CFT, alfentanil HCl and morphine sulfate were supplied by the National Institute on Drug Abuse (Bethesda, MD). Quadazocine methanesulfonate was generously supplied by Sanofi Pharmaceuticals (Malvern, PA), and SNC80 was kindly provided by Dr. K. Rice (NIH, Bethesda, MD). Fluoxetine dihydrochloride, S(+)-amphetamine sulfate, bupropion HCl, GBR12909 dihydrochloride, SKF82958 HBr, (-)-quinpirole HCl, nisoxetine HCl, clomipramine HCl, fentanyl citrate, nalbuphine HCl and (±)-trans-U50488 methanesulfonate were purchased from Research Biochemicals International (Natick, MA). Pentobarbital sodium was purchased from Sigma Chemical Co. (St. Louis, MO). All drugs were dissolved in sterile water except GBR12909, which was dissolved in a vehicle of 50% propylene glycol and 50% water, and pentobarbital, which was dissolved in sterile saline. All drugs were administered i.m. Injections sites were varied from day to day, and there was no evidence of tissue damage at the injection sites at any time during the study.

**Results**

**Acquisition of cocaine/heroin discrimination and control performance.** All three monkeys readily acquired the discrimination between vehicle and the cocaine/heroin combination. The mean number of training sessions required to meet the criterion was 78 (range, 50–102). Control performance in each monkey during training sessions that preceded test sessions is shown in table 1. During training sessions, all monkeys responded almost exclusively on the vehicle key during vehicle training cycles and almost exclusively on the drug key during speedball training cycles. Mean response rates during vehicle training cycles ranged from 1.36 to 3.33 responses per second in individual monkeys, and the effects of the training dose of 0.4 mg/kg cocaine/0.04 mg/kg heroin on response rates varied across monkeys.

**Effects of cocaine/heroin combinations and cocaine and heroin alone.** The dose-effect curves for the 10:1 cocaine/heroin combination on discrimination and response rates are shown in figure 1 (left panels). Cumulative admin-
istration of the cocaine/heroin combination produced a dose-
dependent increase in drug-appropriate responding, with
complete substitution occurring at the training dose of 0.4
mg/kg cocaine + 0.04 mg/kg heroin. The mean ED$_{50}$ value for
the combination was 0.19 mg/kg cocaine/0.019 mg/kg heroin
(see table 2). The cocaine/heroin combination also produced a
dose-dependent decrease in response rates. The highest dose
of the combination (1.3 mg/kg cocaine + 0.13 mg/kg heroin)
decreased response rates to approximately 50% of control
levels.

Figure 1 also shows the time course of the cocaine/heroin
training combination (right panels). After 3 min, the cocaine/
heroin combination produced a mean of 83% drug-appropriate
responding, with complete substitution in two of the
three monkeys. Complete substitution was observed in all
three monkeys after 10 min, which was the pretreatment
interval used during training sessions. The discriminative
stimulus effects of the combination then diminished over
time, and after 56 min, all monkeys responded primarily on
the vehicle-appropriate key.

<table>
<thead>
<tr>
<th>Monkey</th>
<th>Vehicle Training Cycles</th>
<th>Speedball Training Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% DAR</td>
<td>Rate</td>
</tr>
<tr>
<td>163F</td>
<td>0.3 (0.3)</td>
<td>3.33 (0.77)</td>
</tr>
<tr>
<td>90B147</td>
<td>0.1 (0.1)</td>
<td>1.36 (0.11)</td>
</tr>
<tr>
<td>90B164</td>
<td>0.8 (0.4)</td>
<td>1.71 (0.11)</td>
</tr>
</tbody>
</table>

* Values show mean (95% confidence limits) of 58 training sessions in each
monkey: % DAR, percent drug-appropriate responding; rate, response rate in re-
sponse/sec.

#### TABLE 1
Control percent drug-appropriate responding and response rates during vehicle and speedball training cycles in individual monkeys

Figure 2 and table 2 show the effects of cocaine and heroin administered alone or in combinations consisting of various ratios of cocaine to heroin. Administration of cocaine alone and heroin alone substituted completely for the 10:1 cocaine/
heroin combination in all three monkeys. However, cocaine
and heroin were significantly less potent when administered
alone than when administered in any of the combinations
(table 2). In general, increasing the proportion of one drug
produced dose-dependent leftward shifts in the discrimination
dose-effect curve and decreases in the ED$_{50}$ value for the
other drug.

**Effects of the dopamine antagonist flupenthixol and the opioid antagonist quadazocine on cocaine/heroin discrimination.** Pretreatment with the dopamine receptor
antagonist flupenthixol produced a dose-dependent attenua-
tion of the discriminative stimulus effects of the 10:1 cocaine/
heroin training combination, but these effects on cocaine/
heroin discrimination were accompanied by decreases in
response rates (fig. 3, left panel). A dose of 0.01 mg/kg flupen-
thixol had no effect either on cocaine/heroin discrimina-
tion or on response rates. Flupenthixol (0.018 mg/kg) de-
creased drug-appropriate responding produced by 0.4/0.04
and 1.3/0.13 mg/kg cocaine/heroin, but this dose of flupen-
thixol eliminated responding at lower doses of cocaine/
heroin. Pretreatment with the highest dose of flupenthixol,
0.032 mg/kg, eliminated responding at all doses of cocaine/
heroin. In contrast to flupenthixol, the opioid antagonist
quadazocine had little effect on cocaine/heroin discrimination
or response rates at doses up to 0.32 mg/kg (fig. 3, center
panel).

Pretreatment with both flupenthixol and quadazocine was
more effective than either antagonist alone in blocking the
effects of the cocaine/heroin combination (fig. 3, right panel).
Pretreatment with doses of flupenthixol (0.01 mg/kg) and
quadazocine (0.1 mg/kg) that had no effect alone produced an
approximately 3-fold rightward shift in the dose-effect curves
for cocaine/heroin on both drug-appropriate responding and
response rates (fig. 3, right panel). Pretreatment with 0.032
mg/kg flupenthixol and 0.32 mg/kg quadazocine eliminated
responding at doses up to 0.04/0.004 mg/kg cocaine/heroin.
However, monkeys began to respond after administration of
higher doses of the cocaine/heroin combination, and monkeys
responded exclusively on the vehicle-appropriate key at
doses up to 1.3/0.13 mg/kg cocaine/heroin.

**Effects of substituting indirect and direct dopamine agonists.** The effects of substituting indirect and direct dop-
amine agonists in individual monkeys are shown in figures.

**TABLE 2**
Mean ED$_{50}$ values and 95% confidence limits for cocaine and heroin administered alone or in various combinations in substituting for the 10:1 cocaine/heroin training combination

<table>
<thead>
<tr>
<th>Test Drug or Drug Combination</th>
<th>ED$_{50}$ (mg/kg)</th>
<th>95% Confidence Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine alone</td>
<td>0.48</td>
<td>0.23-0.99</td>
</tr>
<tr>
<td>Heroin alone</td>
<td>0.20</td>
<td>0.16-0.26</td>
</tr>
<tr>
<td>30:1 cocaine/heroin</td>
<td>0.20 cocaine*</td>
<td>0.10-0.39</td>
</tr>
<tr>
<td></td>
<td>0.0067 heroin†</td>
<td>0.0035-0.013</td>
</tr>
<tr>
<td>10:1 cocaine/heroin</td>
<td>0.19 cocaine*</td>
<td>0.12-0.23</td>
</tr>
<tr>
<td></td>
<td>0.019 heroin†</td>
<td>0.019-0.020</td>
</tr>
<tr>
<td>3:1 cocaine/heroin</td>
<td>0.080 cocaine*</td>
<td>0.037-0.22</td>
</tr>
<tr>
<td></td>
<td>0.030 heroin†</td>
<td>0.012-0.072</td>
</tr>
</tbody>
</table>

* Significantly different from cocaine alone (P < .05).
† Significantly different from heroin alone (P < .05).
4 and 5, and mean ED₅₀ values are shown in Table 3. The highest levels of drug-appropriate responding were produced by CFT and amphetamine. CFT substituted completely for the training combination in all three monkeys, whereas amphetamine substituted completely in monkeys 90B147 and produced 80% drug-appropriate responding in monkey 90B164. Bupropion substituted completely only in monkeys 163F and 90B164. In monkey 90B147, bupropion produced only vehicle-appropriate responding up to a dose (10 mg/kg) that eliminated responding. In contrast to the other indirect dopamine agonists, GBR12909 did not substitute for the cocaine/heroin combination in any of the monkeys at doses up to 10 mg/kg. Higher doses of GBR12909 were not tested in all monkeys because of the limited solubility and availability of the compound; however, a dose of 18 mg/kg GBR12909 was tested in monkey 163F, and this dose also produced only vehicle-appropriate responding (data not shown). These indirect dopamine agonists produced only rate-decreasing effects in monkey 163F, the monkey that had the highest base-line response rates. However, in monkeys 90B147 and 90B164, intermediate doses of the indirect dopamine agonists tended to increase response rates. The relative potencies of the indirect dopamine agonists in producing drug-appropriate responding and/or changes in response rates were CFT ≥ amphetamine > bupropion ≥ GBR12909.

In contrast to the high levels of drug-appropriate responding produced by most of the indirect dopamine agonists, the direct D₂ dopamine receptor agonist quinpirole and the D₁ dopamine receptor agonist SKF82958 did not substitute for the cocaine/heroin combination in any of the monkeys up to doses that eliminated responding (Fig. 5). The highest level of drug-appropriate responding (84%) was produced by 0.32 mg/kg quinpirole in monkey 90B164. Unlike the indirect dopamine agonists, the direct dopamine agonists produced only dose-dependent decreases in response rates in all three monkeys.

Effects of substituting mu opioid agonists. The effects of mu opioid agonists in individual monkeys are shown in Figure 6, and mean ED₅₀ values are shown in Table 3. The highest levels of drug-appropriate responding were produced by the high-efficacy mu agonists alfentanil and fentanyl. Alfentanil substituted completely for the cocaine/heroin combination in monkey 163F and produced >80% drug-appropriate responding in monkey 90B147. Bupropion substituted completely only in monkeys 163F and 90B147. In monkey 90B164, bupropion produced only vehicle-appropriate responding up to a dose (10 mg/kg) that eliminated responding. In contrast to the other indirect dopamine agonists, GBR12909 did not substitute for the cocaine/heroin combination in any of the monkeys at doses up to 10 mg/kg. Higher doses of GBR12909 were not tested in all monkeys because of the limited solubility and availability of the compound; however, a dose of 18 mg/kg GBR12909 was tested in monkey 163F, and this dose also produced only vehicle-appropriate responding (data not shown). These indirect dopamine agonists produced only rate-decreasing effects in monkey 163F, the monkey that had the highest base-line response rates. However, in monkeys 90B147 and 90B164, intermediate doses of the indirect dopamine agonists tended to increase response rates. The relative potencies of the indirect dopamine agonists in producing drug-appropriate responding and/or changes in response rates were CFT ≥ amphetamine > bupropion ≥ GBR12909.

In contrast to the high levels of drug-appropriate responding produced by most of the indirect dopamine agonists, the direct D₂ dopamine receptor agonist quinpirole and the D₁ dopamine receptor agonist SKF82958 did not substitute for the cocaine/heroin combination in any of the monkeys up to doses that eliminated responding (Fig. 5). The highest level of drug-appropriate responding (84%) was produced by 0.32 mg/kg quinpirole in monkey 90B164. Unlike the indirect dopamine agonists, the direct dopamine agonists produced only dose-dependent decreases in response rates in all three monkeys.

Fig. 2. Effects of cocaine/heroin combinations and cocaine and heroin alone. Abscissae (left panels): Dose of cocaine in mg/kg. Abscissae (right panels): Dose of heroin in mg/kg. Ordinates (top panels): Percent drug-appropriate responding. Ordinates (bottom panels): response rate in responses/sec. Data show mean results from four determinations (10:1 cocaine/heroin) or two determinations (all other treatments) in each of three monkeys. The data for the 10:1 cocaine/heroin combination are the same as in figure 1, and these data are included here for comparison.

Fig. 3. Antagonism of the effects of the 10:1 cocaine/heroin training combination. Abscissae: Doses of cocaine and heroin in mg/kg. Ordinates (top panels): Percent drug-appropriate responding. Ordinates (bottom panels): response rate in responses/sec. The open circles show the effects of the 10:1 cocaine/heroin combination alone, and these data are the same as in figure 1. Closed symbols show the effects of the cocaine/heroin combination after pretreatment with the dopamine antagonist flupenthixol alone (left panels), the opioid antagonist quazaxcine alone (center panels) or flupenthixol + quazaxcine (right panels).
at 

mu receptors, also substituted completely in monkeys 163F and 90B147, but in monkey 90B164, morphine produced primarily saline-appropriate responding up to a dose (10 mg/kg) that eliminated responding. Alfentanil, fentanyl and morphine produced primarily dose-dependent decreases in response rates, and doses of these 

mu agonists that produced high levels of drug-appropriate responding also usually decreased response rates. The relative potency of these compounds to produce drug-appropriate responding and/or decrease response rates was fentanyl > alfentanil > morphine. In contrast to the other 

mu agonists, the low efficacy 

mu agonist nalbuphine at doses up to 10 mg/kg failed to substitute for the cocaine/heroin combination or alter response rates in any of the monkeys. However, all doses of nalbuphine produced intermediate levels of drug-appropriate responding in monkey 90B147.

Effects of substituting dopamine agonist/mu opioid agonist combinations. The effects of substituting a 1:10 amphetamine/morphine combination and a 1:1 GBR12909/nalbuphine combination are shown in figure 7. The amphetamine. Abscissae: Dose in mg/kg. Ordinates (top panels): Percent drug-appropriate responding. Ordinates (bottom panels): response rate in responses/sec. Each panel shows data for one monkey, and the identification number of the monkey is shown above the top panels. Different symbols represent data for different test compounds.

Fig. 4. Effects of the indirect dopamine agonists CFT, bupropion, GBR12909 and amphetamine. Abscissae: Dose in mg/kg. Ordinates (top panels): Percent drug-appropriate responding. Ordinates (bottom panels): response rate in responses/sec. Each panel shows data for one monkey, and the identification number of the monkey is shown above the top panels. Different symbols represent data for different test compounds.

Fig. 5. Effects of the D₁ dopamine agonist SKF82958 and the D₂ dopamine agonist quinpirole. Details are as in figure 4.
The amphetamine/morphine combination substituted completely for the cocaine/heroin combination in all three monkeys. In addition, the ED₅₀ values for amphetamine and morphine were lower when these drugs were administered in combination than when they were administered alone (table 3). Although GBR12909 and nalbuphine administered alone did not substitute for the cocaine/heroin training combination in any monkeys, a 1:1 combination of GBR12909/nalbuphine substituted completely in monkeys 163F and 90B. This combination produced only partial substitution up to doses that eliminated responding in monkey 90B.

Effects of substituting other test compounds. Figure 8 (left panels) shows the effects of the norepinephrine reuptake inhibitor nisoxetine and the serotonin reuptake inhibitor clomipramine. Nisoxetine produced a maximum of 62% drug-appropriate responding at a dose of 3.2 mg/kg, and complete substitution of nisoxetine for the cocaine/heroin combination was observed in monkey 90B164. The serotonin reuptake inhibitor clomipramine, in contrast, produced primarily vehicle-appropriate responding up to a dose of 10 mg/kg. Response rates were not affected by clomipramine, but these doses of clomipramine have been found to produce other behavioral effects in rhesus monkeys (i.e., antinociception; Gatch et al., 1998).

The effects of the delta opioid agonist SNC80 and the kappa opioid agonist U50,488 are shown in figure 8 (center panels). SNC80 produced a maximum of 72% drug-appropriate responding at a dose of 3.2 mg/kg, and SNC80 substituted completely for the cocaine/heroin combination in one monkey (90B164). U50,488 produced only vehicle-appropriate responding up to doses that eliminated responding. Like U50,488, the barbiturate pentobarbital also produced only vehicle-appropriate responding up to doses that eliminated responding (fig. 8, right panels).

### Table 3
Mean ED₅₀ values and 95% confidence limits for dopaminergic and opioid drugs and drug combinations in substituting for the 10:1 cocaine/heroin training combination

<table>
<thead>
<tr>
<th>Test Drug or Drug Combination</th>
<th>ED₅₀ (mg/kg)</th>
<th>95% Confidence Limit</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFT</td>
<td>0.13</td>
<td>0.057–0.27</td>
<td>3</td>
</tr>
<tr>
<td>Bupropion</td>
<td>3.2</td>
<td>2.7–3.9</td>
<td>2</td>
</tr>
<tr>
<td>GBR12909</td>
<td>ND⁹</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>0.18</td>
<td>0.15–0.21</td>
<td>3</td>
</tr>
<tr>
<td>Quinpirole</td>
<td>ND⁹</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SKF82958</td>
<td>ND⁹</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>0.023</td>
<td>0.011–0.034</td>
<td>3</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.011</td>
<td>0.008–0.015</td>
<td>3</td>
</tr>
<tr>
<td>Morphine</td>
<td>4.6</td>
<td>1.7–12</td>
<td>2</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>ND⁹</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1:10 Amphetamine/morphine</td>
<td>0.079</td>
<td>0.033–0.19</td>
<td>3</td>
</tr>
<tr>
<td>1:1 GBR12909/nalbuphine</td>
<td>0.79</td>
<td>0.33–1.9</td>
<td>2</td>
</tr>
</tbody>
</table>

⁹ The number of monkeys contributing to each mean ED₅₀ value (i.e., the number of monkeys showing >50% mixture-appropriate responding) is shown under “N” for each drug or drug combination.

*Not determined because the test compound did not produce >50% mixture-appropriate responding in at least two monkeys.*

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Fig. 6. Effects of the mu opioid agonists alfentanil, fentanyl, morphine and nalbuphine. Details are as in figure 4.
This study characterized the discriminative stimulus effects of a cocaine/heroin speedball combination in rhesus monkeys. The results of these experiments suggest four major conclusions. First, monkeys were readily trained to discriminate the cocaine/heroin combination, which suggests that this drug combination produces robust discriminative stimulus effects. This finding is expected insofar as many previous studies have demonstrated that either cocaine (e.g., Kleven et al., 1990; Negus et al., 1995, 1996a) or mu opioid agonists (e.g., Bertalmio and Woods, 1987; Gerak and France, 1996) alone can serve as discriminative stimuli in rhesus monkeys. Moreover, the rapid onset of action of this...
cocaine/heroin combination also was expected, because we have reported previously that both i.m. cocaine (Lamas et al., 1995) and i.m. heroin (Negus et al., 1998a) produce maximal effects in less than 10 min in rhesus monkeys. Second, the discriminative stimulus effects of the cocaine/heroin combination used in this study included aspects of both component drugs. High levels of speedball-appropriate responding were produced both by cocaine and several other indirect dopamine agonists (i.e., CFT, amphetamine and bupropion) and by heroin and several other mu opioid agonists (i.e., alfentanil, fentanyl and morphine). Moreover, administration of flupenthixol and quazadacine in combination was more effective than either antagonist alone in blocking the discriminative stimulus effects of the combination. These findings indicate that the presence of either cocaine-like or heroin-like effects was sufficient to produce full substitution for the training combination. Third, although administration of either cocaine or heroin was sufficient to substitute for the cocaine/heroin combination, the two drugs were more potent when administered in combination than when administered alone. These results suggest that cocaine and heroin mutually enhanced each other’s ability to produce speedball-appropriate responding. Similar results were obtained with two other combinations of an indirect dopamine agonist and a mu opioid agonist (i.e., amphetamine/morphine and GBR12909/nalbuphine). Finally, a range of other behaviorally active drugs produced only partial substitution or no substitution for the cocaine/heroin combination. These findings indicate that the discriminative stimulus effects of the cocaine/heroin combination were pharmacologically selective. The implications of these conclusions are discussed in the next section.

Comparison with the Discriminative Stimulus Effects of Cocaine and Mu Opioid Agonists Alone

Effects of dopamine agonists and mu opioid agonists. These findings complement and extend previous studies that examined the discriminative stimulus effects of cocaine and mu agonists in subjects trained to discriminate either cocaine alone or a mu agonist alone from vehicle. The discriminative stimulus effects of the cocaine/heroin combination examined in this study differ from the discriminative stimulus effects produced by either cocaine or a mu agonist alone in at least two respects. First, when cocaine or mu agonists are administered alone, they do not substitute consistently for each other in subjects trained to discriminate either cocaine (Colpaert, 1978; Dykstra et al., 1992; Spealman and Bergman, 1992, 1994; Broadbent et al., 1995; Mello et al., 1995; Negus et al., 1998a; Lamas et al., in press) or a mu agonist (Gerak and France, 1996; Suzuki et al., 1995; Lamas et al., in press), although high levels of cross-generalization are observed occasionally in some subjects. For example, we recently reported that the ability of mu agonists to produce cocaine-like discriminative stimulus effects in rhesus monkeys may be related to the rate of onset of drug effects, with rapid-onset mu agonists such as heroin and alfentanil being more likely than slower-onset mu agonists such as fentanyl and morphine to substitute for cocaine (Negus et al., 1998a). However, even rapid-onset mu agonists failed to substitute for cocaine in all subjects (Negus et al., 1998a). In contrast to the occasional cross-generalization between cocaine and mu agonists observed in subjects trained to discriminate cocaine or a mu agonist alone, both cocaine and heroin substituted fully for the cocaine/heroin combination in the present study. In addition, many cocaine-like and heroin-like drugs also produced high levels of substitution for the cocaine/heroin combination. Thus, the combination of cocaine and heroin used in this study produced discriminative stimulus effects that included aspects of both component drugs.

Although most cocaine-like dopamine agonists and heroin-like mu opioid agonists tested in this study substituted for the cocaine/heroin combination, there were several exceptions. In contrast to the other dopamine agonists, the selective dopamine reuptake inhibitor GBR12909 and the direct dopamine receptor agonists SKF82958 and quinpirole failed to substitute for the cocaine/heroin combination in any of the monkeys. All of these compounds have been reported to substitute partially or fully for cocaine in subjects trained to discriminate cocaine alone (Kleven et al., 1990; Spealman et al., 1991; Spealman, 1993; Lamas et al., 1996). Moreover, we have found that all of these compounds produced high levels of cocaine-appropriate responding (i.e., complete substitution in >75% of subjects) in rhesus monkeys trained to discriminate 0.4 mg/kg cocaine (i.m.) from vehicle under conditions similar to those used in this study (Lamas et al., 1996; Negus SS and Mello NK, unpublished observations). Thus, these compounds produce cocaine-like discriminative stimulus effects, but unlike cocaine in the present study, they did not substitute for the cocaine/heroin combination. The failure of these compounds to substitute for the cocaine/heroin combination was probably not a result of testing inadequate doses. Both SKF82958 and quinpirole were tested up to doses that eliminated responding, which indicates that behaviorally active doses were investigated. GBR12909 did not eliminate response rates across the dose range tested (1–10 mg/kg; 18 mg/kg tested in one monkey), but it is approximately 10-fold less potent than cocaine in producing cocaine-like discriminative stimulus and other stimulant effects in monkeys (Bergman et al., 1989; Kleven et al., 1990; Spealman, 1993). Given that the ED50 value of cocaine alone in substituting for the cocaine/heroin combination was 0.48 mg/kg, GBR12909 would have been expected to produce behavioral effects within the dose range tested.

The only mu agonist that failed to substitute for the cocaine/heroin discriminative stimulus was nalbuphine. Nalbuphine shares discriminative stimulus effects with other mu agonists under many conditions (Young et al., 1992; Picker et al., 1993; Walker et al., 1994; Gerak and France, 1996). However, in subjects trained to discriminate high doses of relatively high efficacy mu agonists, nalbuphine does not always produce complete substitution (Young et al., 1992; Picker et al., 1993), and these findings have been interpreted to suggest that nalbuphine has relatively low efficacy at mu opioid receptors. The effects of nalbuphine in rhesus monkeys trained to discriminate heroin alone are not known, but in the present study, the low efficacy of nalbuphine at mu opioid receptors may have limited its ability to produce cocaine/heroin-like discriminative stimulus effects. Taken together, the failure of GBR12909, SKF82958, quinpirole and nalbuphine to substitute for the cocaine/heroin training combination suggests that the discriminative stimulus effects of the combination cannot be described as a simple union of the discriminative stimulus effects of the two component drugs. Rather, the cocaine/heroin combination produces discrimina-
tive stimulus effects that do not overlap completely with the discriminative stimulus effects of cocaine and heroin alone.

A second difference between the discriminative stimulus effects of cocaine or heroin alone and the cocaine/heroin combination was revealed by the administration of cocaine and heroin in combination. As noted in the introduction, mu agonists administered either in combination with or as pretreatments to cocaine occasionally have been reported to produce leftward shifts in the cocaine dose-effect curve in cocaine-trained subjects, but these shifts are usually small and are not observed consistently under all conditions (Dykstra et al., 1992; Spealman and Bergman, 1992, 1994; Broadbent et al., 1995; Mello et al., 1995; Suzuki et al., 1995, 1997; Woofolk and Holtzman, 1997; Negus et al., 1989a; Lamas et al., et al., in press). These findings suggest that mu agonists produce at best only a small and inconsistent enhancement of the discriminative stimulus effects of cocaine. Moreover, in subjects trained to discriminate a mu opioid agonist, the addition of cocaine has not been found to alter the dose-effect curve of the opioid, which suggests that cocaine does not enhance the discriminative stimulus effects of mu opioids (Suzuki et al., 1995; Lamas et al., in press). These relatively weak interactions between cocaine and mu opioid agonists in subjects trained to discriminate cocaine or a mu agonist alone contrast with the effects of cocaine/heroin combinations in the present study, in which cocaine and heroin consistently enhanced each other’s ability to produce cocaine/heroin-appropriate responding. In all monkeys in the present study, both cocaine and heroin were more potent in producing cocaine/heroin-appropriate responding when the two drugs were administered together than when they were administered alone. This enhanced potency was observed not only with the training combination of 10:1 cocaine/heroin, but also with 30:1 and 3:1 combinations of cocaine/heroin. Moreover, combinations of other dopamine agonists and mu agonists (i.e., amphetamine/morphine and GBR12909/nalbuphine) were also more potent and/or effective than the component drugs alone in producing drug-appropriate responding. This was especially evident with the 1:1 combination of GBR12909 and nalbuphine, because neither drug alone substituted for the cocaine/heroin combination in any monkeys, but coadministration of both drugs substituted completely in two monkeys.

**Effects of dopamine and mu opioid antagonists.** The discriminative stimulus effects of the cocaine/heroin combination also differed from the effects of cocaine and heroin alone in their sensitivity to antagonists. Doses of the dopamine antagonist flupenthixol (0.01 mg/kg) or the mu opioid antagonist quazadocine (0.1–0.32 mg/kg) that are sufficient to antagonize the discriminative stimulus effects of cocaine alone (Negus et al., 1996a) or mu agonists alone (Bertalmio and Woods, 1987), respectively, did not alter the dose-effect curve for the cocaine/heroin combination. A higher dose of flupenthixol (0.018 mg/kg) alone did produce a rightward shift in the cocaine/heroin dose-effect curve, but even in this case, the dose-effect curve was located to the left of the dose-effect curve for heroin alone. Relative to the effects of either antagonist alone, combined pretreatment with flupenthixol and quazadocine was more effective in antagonizing the discriminative stimulus effects of the cocaine/heroin combination. These findings suggest that antagonism of either cocaine alone (by flupenthixol) or heroin alone (by quazadocine) is relatively ineffective in reducing the discriminative stimulus effects of the cocaine/heroin combination, presumably because the presence of the drug which is not antagonized is sufficient to produce cocaine/heroin-appropriate responding. This conclusion is consistent with the substitution studies described above, which indicated that the presence of either cocaine-like effects or heroin-like effects is sufficient to produce cocaine/heroin-appropriate responding.

**Effects of other psychoactive drugs.** In addition to evaluating the effects of dopamine agonists and mu opioid agonists, the present study also examined the effects of a series of other compounds. The norepinephrine reuptake inhibitor nisoxetine and the serotonin reuptake inhibitor clomipramine were evaluated because they share cocaine’s ability to block reuptake of these monoamines. The delta opioid agonist SNC80 and the kappa opioid agonist U50,488 were studied as representative agonists selective for the principal non-mu opioid receptor types. Finally, the barbiturate pentobarbital was studied as a psychoactive compound that has a mechanism of action distinct from that of cocaine and opioid agonists. Clomipramine, U50,488 and pentobarbital all produced primarily vehicle-appropriate responding. These results agree with the finding that serotonin reuptake inhibitors, kappa agonists and barbiturates produce primarily vehicle-appropriate responding in animals trained to discriminate either cocaine alone (de la Garza and Johanson, 1983; Kleven et al., 1990; Spealman, 1993, 1995; Spealman and Bergman, 1992) or a mu agonist alone (Herling and Woods, 1981; Picker et al., 1990; Negus et al., 1991). Moreover, the failure of these psychoactive compounds to produce cocaine/heroin-appropriate responding provides additional evidence of the pharmacological selectivity of the cocaine/heroin stimulus.

Both nisoxetine and SNC80 produced intermediate levels (62–72%) of cocaine/heroin-appropriate responding. Previous studies have found that nisoxetine and other norepinephrine reuptake inhibitors produce intermediate to high levels of cocaine-appropriate responding in subjects trained to discriminate cocaine alone, especially when the training dose of cocaine is relatively low (Terry et al., 1994; Spealman, 1995). Similarly, delta opioid agonists have been reported to produce intermediate to high levels of drug-appropriate responding in subjects trained to discriminate either cocaine (Ukai et al., 1993; Suzuki et al., 1997) or a mu agonist (Comer et al., 1993; Negus et al., 1996b). We reported previously that the prototype nonpeptidic delta agonist BW373U86 did not substitute for cocaine or the mu agonist fentanyl in rhesus monkeys, but this negative finding may have resulted from the relatively low efficacy of BW373U86 at delta receptors (Negus et al., 1994, 1995). In more recent studies, we found that SNC80 substituted for cocaine in 5 of 7 cocaine-trained monkeys (Negus et al., 1998b). Thus, the relatively high levels of cocaine/heroin-appropriate responding produced by nisoxetine and SNC80 may have resulted from their ability to produce cocaine-like and/or heroin-like discriminative stimulus effects.

**Comparison with the Subjective and Reinforcing Effects of Cocaine and Mu Opioid Agonists.**

The present findings complement previous clinical studies that have compared the subjective and physiological effects of cocaine and mu opioid agonists administered alone or in
Combination drugs are typically less potent in substituting for the component drug is usually sufficient to produce high levels of effects that include aspects of both cocaine and the mu agonist (Foltin and Fischman, 1992; Walsh et al., 1996). Moreover, as in the present study, the subjective effects and physiological effects of cocaine/mu agonist combinations only partially overlapped with the effects of either drug alone. For example, cocaine/mu agonist combinations have been found to produce less sedation and less respiratory depression than the mu agonist alone (Foltin and Fischman, 1992; Walsh et al., 1996). Finally, the study by Walsh et al. (1996) included a drug identification questionnaire that asked subjects to choose the category of drug most similar to the test injection. Subjects frequently identified cocaine alone as a speedball combination of cocaine and a mu agonist. This finding is similar to the results of the present study, in which cocaine alone produced complete substitution for the cocaine/heroin combination. However, polydrug abusers rarely identified the mu agonist hydromorphone alone as a speedball, a finding that contrasts with our observation that heroin also substituted for the cocaine/heroin combination. Subjects could choose between only two options, the vehicle-appropriate key or the cocaine/heroin-appropriate key. Overall, then, there was a high degree of concordance between the findings of the present drug discrimination study and previous studies in humans that have examined the reinforcing effects of cocaine/mu agonist combinations.

These findings also extend previous studies that have examined the reinforcing effects of cocaine/opioid combinations. In our previous studies examining cocaine/heroin speedball self-administration, we found that self-administration of cocaine/heroin combinations was similar to self-administration of either cocaine or heroin alone (Mello et al., 1995). These findings in rhesus monkeys were consistent with other studies that have compared self-administration of cocaine alone, heroin alone and cocaine/heroin speedball combinations (Hemby et al., 1996; Rowlett and Woolverton, 1997). Thus, studies of the reinforcing, subjective and discriminative stimulus effects of cocaine/opioid speedball combinations consistently find that these combinations produce an overall profile of effects that includes aspects of either drug alone.

Comparison with the Discriminative Stimulus Effects of Other Drug Combinations

To our knowledge, this is the first study to characterize the discriminative stimulus effects of a cocaine/heroin speedball combination. However, the discriminative stimulus effects produced by combinations of other psychoactive drugs have been examined previously (Stolerman et al., 1987; 1991; Garcha and Stolerman, 1989; Mariathasan et al., 1991; McMillan and Snodgrass, 1993), and in many respects, the results of the present study agree with these previous findings. As in the present study, these previous studies reported that either component drug is usually sufficient to produce high levels of drug-appropriate responding in subjects trained to discriminate a drug combination from vehicle. Moreover, the component drugs are typically less potent in substituting for the drug combination when they are administered alone than when they are administered in combination. For example, Stolerman and colleagues (1987) trained rats to discriminate a 2:1 combination of nicotine (0.4 mg/kg) and midazolam (0.2 mg/kg) from saline and subsequently compared the effects of the training combination with the effects of nicotine and midazolam alone. Both nicotine and midazolam produced dose-dependent increases in drug-appropriate responding. However, both compounds were approximately two to four times less potent when administered alone than when administered in combination.

Previous studies also found that antagonists of the component drugs in a drug combination were less effective in blocking the discriminative stimulus effects of the combination when the antagonists are administered alone than when they were administered together (Stolerman et al., 1987, 1991; Mariathasan et al., 1997). For example, Stolerman et al. (1987) evaluated the effects of the nicotinic acetylcholine receptor antagonist mecamylamine and the benzodiazepine receptor antagonist flumazenil on the discriminative stimulus effects of the 2:1 nicotine/midazolam combination. When administered alone, relatively high doses of mecamylamine (1.0 mg/kg) and flumazenil (20 mg/kg) produced only a modest antagonism of the discriminative stimulus effects of the nicotine/midazolam training combination. However, when the two antagonists were administered together, they completely blocked the effects of the combination. Finally, the discriminative stimulus effects of other drug combinations also have been shown to be pharmacologically selective (Stolerman et al., 1991; Garcha and Stolerman, 1989). More specifically, drugs that do not substitute for either component drug also usually fail to substitute for a combination of the component drugs. For example, amphetamine and morphine do not share discriminative stimulus effects with either nicotine or midazolam, and in rats trained to discriminate a combination of nicotine (0.32 mg/kg) and midazolam (0.1 mg/kg), neither amphetamine nor morphine substituted for the training combination (Garcha and Stolerman, 1989). Taken together, these findings suggest that the profile of discriminative stimulus effects produced by the cocaine/heroin combination in the present study may reflect a more general set of principles that determines the discriminative stimulus effects of many drug combinations (see Stolerman et al., 1991, for discussion).

Summary

In summary, this study found that a cocaine/heroin speedball combination produced robust discriminative stimulus effects that included aspects of both component drugs. Substitution and antagonist tests indicated the either cocaine-like or heroin-like effects were usually sufficient to produce cocaine/heroin-appropriate responding. Some drugs that share discriminative stimulus effects with either cocaine or mu opioid agonists alone did not share discriminative stimulus effects with the cocaine/heroin combination. These findings suggest that the discriminative stimulus effects of the cocaine/heroin combination did not overlap completely with the discriminative stimulus effects of both component drugs. Finally, drugs that do not share discriminative stimulus effects with either cocaine or mu opioid agonists also failed to produce high levels of cocaine/heroin speedball-appropriate responding, which suggests that the effects of the cocaine/
heroin combination were pharmacologically selective. These preclinical findings in rhesus monkeys agree with clinical studies which suggest that combinations of cocaine and a mu agonist produce a compound set of subjective effects that includes aspects of both cocaine and the mu agonist.

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References


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