Discriminative Stimulus Effects of Morphine in Squirrel Monkeys: Stimulants, Opioids, and Stimulant-Opioid Combinations

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ABSTRACT
Morphine and other μ-opioids mimic and/or modulate the discriminative stimulus (DS) effects of cocaine, possibly reflecting mutual stimulation of mesolimbic dopamine activity. Less is known about the capacity of cocaine and related stimulants to modulate the DS effects of morphine. The present study investigated the effects of cocaine, amphetamine, and reference drugs, administered alone and with morphine, in squirrel monkeys trained to discriminate morphine from vehicle. Additional studies determined the ability of opioid and dopamine receptor antagonists to attenuate the DS effects of morphine and the morphine-like effects of other drugs. The DS effects of morphine were mimicked by the μ-opioid agonist fentanyl but not the δ-opioid agonists SNC 80 and BW 373U86 or the κ-opioid agonist U50,488H, and were antagonized by the opioid antagonist naltrexone but not the dopamine antagonist flupenthixol.

In three of five monkeys, the DS effects of morphine also were mimicked by cocaine, amphetamine, and the dopamine transport inhibitor GBR 12909 but not the norepinephrine transport inhibitor talsupram or the serotonin transport inhibitor fluoxetine, and were antagonized by flupenthixol but not naltrexone. In this subgroup, pretreatment with cocaine or amphetamine enhanced the DS effects of morphine, whereas in the other two monkeys pretreatment with either stimulant attenuated the DS effects of morphine. The results demonstrated individual differences in morphine-like DS effects of stimulants that are mirrored by individual differences in their interactions with morphine. Furthermore, different mechanisms appear to mediate the DS effects of morphine and the morphine-like DS effects of cocaine and amphetamine.

Converging evidence suggests that the abuse-related effects of cocaine and amphetamine are mediated by enhanced mesolimbic dopamine (DA) activity as a result of inhibited DA uptake and/or stimulated DA release (see Wise and Bozarth, 1987; Koob and Bloom, 1988; and Woolverton and Johnson, 1992, for review). Morphine and other μ-opioid agonists also have been shown to stimulate release of DA in mesolimbic regions (Di Chiara and Imperato, 1988; Spanagel et al., 1990) and to enhance cocaine-induced increases in extracellular DA (Brown et al., 1991; Zernig et al., 1997; Hemby et al., 1998). Given the likely importance of DA systems in mediating the behavioral effects of stimulants and μ opioids (Wise and Bozarth, 1987; Koob and Bloom, 1988; Di Chiara and North, 1992), the possibility of reciprocal enhancement of the behavioral effects of these two classes of drugs has been explored using procedures that model different aspects of the addiction process (e.g., drug discrimination and drug self-administration: Spealman and Bergman, 1992; Mello et al., 1995). Using drug discrimination procedures, morphine and related drugs have been shown to enhance, in a largely additive manner, the discriminative stimulus (DS) effects of cocaine in squirrel monkeys (Spealman and Bergman, 1992, 1994; Rowlett and Spealman, 1998). These results support the idea that μ opioids and cocaine given in combination can result in enhanced behavioral effects, perhaps mediated by their mutual ability to augment DA neurotransmission. Other studies, however, have reported less consistent effects of stimulant-opioid combinations. In rats, for example, clear-cut enhancement of the DS effects of cocaine by morphine has been observed by Suzuki et al. (1997) and Kantak et al. (1994) but not by others (Dykstra et al., 1992; Broadbent et al., 1995). Similarly, in rhesus monkeys enhancement of the DS effects of cocaine by μ opioids has been reported in approximately half the subjects tested (Mello et al., 1995; Negus et al., 1998). In addition, several μ opioids engendered appreciable cocaine-like responding.

ABBREVIATIONS: DA, dopamine; DS, discriminative stimulus; NE, norepinephrine; 5-HT, 5-hydroxytryptamine; FR, fixed ratio; ED50, dose producing 50% morphine lever responding.
when tested alone in these latter studies. Together, these findings suggest that individual differences may play a role in the capacity of μ opioids to either mimic or modulate the DS effects of cocaine in some instances.

Although opioid modulation of the DS effects of cocaine has received considerable attention, only a few studies have specifically investigated the ability of stimulants to modulate the DS effects of opioids. In two such experiments, Suzuki et al. (1995) and Lamas et al. (1998) observed no consistent modulation by cocaine of the DS effects of either morphine or heroin in rats. On the other hand, an earlier study by Gauvin and Young (1989a) demonstrated that amphetamine typically enhanced the DS effects of morphine at a relatively low training dose in pigeons; whereas both enhancement and blockade of the DS effects of morphine were evident in individual subjects trained to discriminate higher doses of morphine. In human drug abusers, cocaine also has been found to enhance morphine- or hydromorphone-induced subjective ratings of "high" and "drug effect", whereas it reduced opioid-induced sedation and "noding" (Foltin and Fischman, 1992; Walsh et al., 1996).

The purpose of the present study was to investigate the ability of cocaine and related drugs to mimic and/or modulate the DS effects of the prototypic μ agonist morphine in squirrel monkeys. Monkeys were trained to discriminate morphine from vehicle injections, using a procedure similar to one used previously to investigate stimulant-opioid interactions in monkeys trained to discriminate cocaine (Spealman and Bergman, 1992, 1994; Rowlett and Spealman, 1998). Cocaine, amphetamine, and several reference drugs were studied for their ability to engender morphine-appropriate responding when administered alone as well as for their capacity to alter the morphine dose-response function when administered as pretreatments. Reference drugs included selective μ-, δ-, and κ-opioid agonists; selective DA, norepinephrine (NE), and 5-hydroxytryptamine (5-HT) uptake inhibitors; and sedative/anxiolytics. Finally, antagonism studies with the opioid receptor antagonist naltraxone and the DA receptor antagonist flupenthixol were conducted to evaluate the role of opioid and DA receptor mechanisms in the DS effects of morphine and the morphine-like stimulus effects of other drugs.

Materials and Methods

Subjects. Five adult male squirrel monkeys (Saimiri sciureus) were studied in daily experimental sessions. Between sessions, monkeys lived in individual home cages and had unlimited access to water. Each monkey was maintained at 85 to 90% of its free-feeding body weight (750–900 g) by adjusting its access to food (Purina Monkey Chow;Ralston Purina, St. Louis, MO; Teklad Monkey Diet; Teklad Premier Laboratory Diets, Madison, WI; and fruit). With the exception of one monkey (S-288), all were experimentally naive at the beginning of the study. Monkey S-288 had been trained previously under a punishment procedure and tested with γ-aminobutyric acid (GABA) modulators. All animals were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and the Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare Publication No. (National Institutes of Health) 85-23, as revised in 1985. Research protocols were approved by the Harvard Medical School Institutional Animal Care and Use Committee.

Apparatus. During experimental sessions, monkeys were seated in Plexiglas chairs similar to the one described by Spealman and Bergman (1992). Two response levers (model 121-05; BRS/LVE, Beltville, MD) were mounted 15 cm apart on the wall of the chair in front of the monkey. Each press of a lever produced an audible feedback click and was recorded as a response. Red lights mounted at eye level behind the front panel of the chair could be illuminated to serve as a visual stimulus associated with consecutive components of the session (see below). Sucrose pellets (190 mg; P.J. Noyes Co., Inc., Lancaster, NH) could be delivered to a tray that was accessible through an opening in the front panel of the chair. Each chair was enclosed in a ventilated, sound-attenuating chamber, which was equipped with white noise to mask external sounds.

Drug-Discrimination Procedure. Monkeys were trained to discriminate morphine from saline, using procedures similar to those used in previous studies with cocaine (Spealman and Bergman, 1992). After i.m. injection of morphine, 10 consecutive responses [fixed ratio (FR) 10] on one lever produced food, whereas after injection with saline, 10 consecutive responses on the other lever produced food. Responses on the incorrect lever reset the FR requirement. Daily training sessions consisted of a variable number of components (n = 1–3) of the FR schedule. Each component ended after the completion of the tenth FR 10 or after 5 min had elapsed, whichever occurred first. A 20-min timeout period, during which the lights were off and responding had no programmed consequences, preceded each component. During most training sessions, saline was injected during timeout periods preceding the first n – 1 components, and morphine was injected before the final component of the session. Periodically, saline was injected before each of the three components of a training session to prevent an invariant association between drug and the third component. Injections of morphine or saline were made in a thigh or calf muscle of either leg during min 5 of the 20-min timeout periods.

The training dose of morphine initially was 0.3 mg/kg for all subjects, but it subsequently was increased in one-fourth log-unit steps to either 0.56 mg/kg (monkeys S-204 and S-288) or 1.0 mg/kg (monkeys S-89, S-95, and S-221) to achieve consistent stimulus control of behavior. These relatively low training doses of morphine, compared with the 3.0 mg/kg training dose used in a previous study with squirrel monkeys (Schaefe and Holtzman, 1977; Teal and Holtzman, 1980a,b), were selected to minimize the development of tolerance over the course of the study as well as to avoid any adverse physical effects such as respiratory depression. The total training time varied from 135 to 210 sessions, depending on the monkey. Drug testing began once monkeys consistently made ≥80% of responses on the injection-appropriate lever during at least 4 of the previous 5 training days.

Drug-Testing Procedure. Drug test sessions were conducted once or twice per week with training sessions scheduled on intervening days. Test sessions consisted of three FR components, each preceded by a 20-min timeout period. In each component, completion of 10 consecutive responses on either lever produced food. Dose-response functions were determined for test drugs, using a cumulative dosing procedure similar to the one described by Spealman and Bergman (1992). Incremental doses were injected i.m. during min 5 of the 20-min timeout periods that preceded each FR component, permitting a three-point cumulative dose-response function to be determined in a single session. In most cases, four or more different doses of a drug were studied by administering overlapping ranges of cumulative doses during test sessions on different days, and the effects of each active dose typically were determined twice in each subject.

In experiments involving pretreatments with opioid or DA receptor antagonists, a fixed dose of naltrexone (0.3 mg/kg) or flupenthixol (0.1 mg/kg) was administered either 30 min (cf. Dykstra, 1990) or 60 min (cf. Spealman et al., 1991), respectively, before the experimental session, and cumulative doses of cocaine, amphetamine, or morphine were administered during the session as described above. In exper-
iments involving pretreatments with stimulants, fixed doses of cocaine (0.1–0.3 mg/kg) or amphetamine (0.03–0.3 mg/kg) were administered at the start of the experimental session, and cumulative doses of morphine were administered during the session.

Analysis of Drug Effects. The percentage of responses on the morphine-associated lever was calculated for individual subjects in each component of a test session by dividing the number of responses on that lever by the total number of responses on both levers and multiplying by 100. The overall rate of responding in each component was computed by dividing the total number of responses in a component (regardless of lever) by the total component duration. The doses of a drug estimated to engender 50% morphine-appropriate responding ($ED_{50}$) were determined for individual subjects by linear regression analysis in cases where the linear portion of the log dose-response function was defined by three or more data points and by linear interpolation in cases in which the linear portion of the log dose-response function was defined best by two points.

Drugs. Morphine sulfate (Merck, Sharpe and Dohme, West Point, PA); (+)-amphetamine sulfate (Sigma, St. Louis, MO); cocaine HCl (National Institute on Drug Abuse, Rockville, MD); midazolam base (Hoffman-LaRoche, Basel, Switzerland); cis-(-)-flupenthixol - 2 HCl, fentanyl citrate, and naltrexone HCl (Research Biochemicals, Inc., Natick, MA); SNC 80 base (Tocris Cookson, Inc., Ballwin, MO); sodium pentobarbital (Abbott Laboratories, Chicago, IL); and U50,488H methanesulfonate (Research Biochemicals, Inc.) were dissolved in sterile water or 0.9% saline solution. GBR 12909 (Hoffman-LaRoche, Basel, Switzerland); aminorex HCl (National Institute on Drug Abuse, Rockville, MD); midazolam base (Abbott Laboratories, Chicago, IL); and U50,488H methanesulfonate (Research Biochemicals, Inc.) were dissolved in sterile water or 0.9% saline solution. GBR 12909 - 2 HCl (Research Biochemicals), fluoxetine HCl (Eli Lilly and Co., Indianapolis, IN), and talsupram HCI (Lundbeck A/S, Copenhagen, Denmark) were dissolved in small amounts of warm 0.1 N HCl or acetic acid and diluted with 0.9% saline solution. BW 373U86 HCl (Research Biochemicals) was dissolved in a small amount of dimethyl sulfoxide and 0.1 M NaHCO$_3$ and diluted with 0.9% saline solution.

Results

Effects of Morphine. Morphine at the final training doses of 0.56 or 1.0 mg/kg maintained consistent control of behavior over the course of the study. Averaged across all training sessions that preceded drug test sessions ($n = 44–53$), individual monkeys made 94 to 99% responses on the morphine-associated lever after injection of morphine and 1 to 4% responses on this lever after injection of saline (Table 1). The average rate of responding after injection of morphine (0.8–2.9 responses/s for individual monkeys) was comparable to the average response rate after injection of saline (0.9–2.5 responses/s), and subjects typically completed all 10 FRs in each component of a training session.

Under test conditions, increasing cumulative doses of morphine (0.03–1.0 mg/kg) engendered dose-related increases in the percentage of responses on the morphine-associated lever (Fig. 1, top). Dose-response functions determined at the beginning of the study (solid circles) did not differ systematically from those determined more than 1 year later at the end of the study (open circles). In each case, low doses of morphine (0.03–0.1 mg/kg) engendered little or no responding on the morphine-associated lever, whereas an intermediate dose of 0.3 mg/kg morphine engendered 39 to 68% morphine-lever responses, and 1.0 mg/kg morphine engendered 88 to 100% morphine-lever responses for individual subjects. Similar dose-response functions for morphine were obtained during the middle portion of the experiment in those monkeys tested with morphine on three separate occasions (S-95, S-204, and S-288; not shown). Comparing across subjects, the average response rate was not affected systematically by morphine over the range of doses tested, and no dose of morphine decreased the response rate to <50% of the rate after saline administration in any subject (Fig. 1, bottom).

Effects of Other Opioids and Reference Drugs. The selective µ-opioid agonist fentanyl had DS effects that were qualitatively similar to those of morphine (Fig. 1, solid triangles). Increasing cumulative doses of fentanyl (0.003–0.01 mg/kg) engendered dose-related increases in the percentage of responses on the morphine-associated lever, with one or more doses occasioning full substitution for morphine (i.e., >80% morphine responses) in each monkey. As in the case of morphine, these DS effects were observed after administration of doses of fentanyl that did not systematically alter the response rate for the group of five monkeys, although some doses of fentanyl either increased or decreased response rate in individual subjects (Fig. 1, bottom).

As shown in Fig. 2, pretreatment with naltrexone (0.3 mg/kg) antagonized the DS effects of morphine, resulting in overall rightward shifts in the morphine dose-response function for each monkey. Antagonism of the DS effects of morphine by naltrexone could be fully or partially surmounted by increasing the dose of morphine to a maximum of 10.0 mg/kg. In combination with naltrexone, morphine usually had only small effects on the average response rate, although decreases in response rate were observed in two monkeys after 10.0 mg/kg morphine and in a third monkey after lower doses of morphine.

Unlike morphine and fentanyl, the k-receptor agonist U50,488H and the δ-receptor agonists BW 373U86 and SNC 80 did not engender consistent responding on the morphine-associated lever regardless of dose (Table 2). Reference compounds from other pharmacological classes, including the NE-uptake inhibitor talsupram, the 5-HT-uptake inhibitor fluoxetine, and the sedative/anxiolytic drugs midazolam and pentobarbital also failed to engender consistent responding on the morphine-associated lever over a 10- to 30-fold range of doses (Table 2).

Effects of Cocaine, Amphetamine, and GBR 12909. Unlike the other drugs studied, cocaine, amphetamine, and the selective DA-uptake inhibitor GBR 12909 had qualitatively different DS effects in different subjects (Fig. 3). In three of the five monkeys (S-204, S-288, and S-221), all three drugs engendered dose-related increases in the percentage of responses on the morphine-associated lever, reaching maxima of 77 to 99% morphine-lever responses for the individ-

<table>
<thead>
<tr>
<th>Monkey</th>
<th>Training Condition*</th>
<th>Morphine-Lever Responses</th>
<th>Responses/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-204</td>
<td>Morphine</td>
<td>94 (3)</td>
<td>2.9 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>2 (2)</td>
<td>0.6 (0.6)</td>
</tr>
<tr>
<td>S-288</td>
<td>Morphine</td>
<td>97 (2)</td>
<td>1.2 (0.1)</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>4 (3)</td>
<td>1.1 (0.1)</td>
</tr>
<tr>
<td>S-221</td>
<td>Morphine</td>
<td>95 (5)</td>
<td>2.3 (0.4)</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>1 (1)</td>
<td>1.7 (0.3)</td>
</tr>
<tr>
<td>S-95</td>
<td>Morphine</td>
<td>99 (1)</td>
<td>0.8 (0.3)</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>2 (2)</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td>S-89</td>
<td>Morphine</td>
<td>97 (3)</td>
<td>2.9 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>2 (2)</td>
<td>2.5 (0.6)</td>
</tr>
</tbody>
</table>

* Training dose of morphine was 0.56 mg/kg for monkeys S-204 and S-228 and 1.0 mg/kg for monkeys S-221, S-95, and S-89.
ual subjects. In the remaining two monkeys (S-95 and S-89), however, none of the drugs engendered substantial morphine-lever responding regardless of dose. In general, doses of cocaine, amphetamine, and GBR 12909 that engendered maximum percentages of morphine-lever responses also decreased the overall response rate (Fig. 3, bottom). GBR 12909, however, either had little effect on or increased the rate of responding in monkeys S-221 and S-95, as did cocaine and amphetamine in monkey S-95.

As shown in Table 3, the morphine-like DS effects of cocaine and amphetamine were not altered systematically by pretreatment with naltrexone in the two monkeys showing full substitution of these drugs for morphine (S-204 and S-288). In contrast, the DS effects of morphine itself were consistently attenuated by naltrexone, resulting in a rightward shift in the morphine dose-response function (Fig. 2) accompanied by a 12-fold or greater increase in ED_{50} (Table 3). Pretreatment with the DA-receptor antagonist flupenthixol, on the other hand, consistently attenuated the morphine-like DS effects of cocaine and amphetamine, re-

![Fig. 1. Percentage of morphine-lever responding (top) and response rate (bottom) engendered by fentanyl and morphine in squirrel monkeys trained to discriminate morphine from saline. Each column of panels represents data from an individual monkey, identified at the top of each column. Morphine dose-response functions were determined at the beginning of the study (○) and at the end of the study (□). Horizontal bars (bottom) represent mean response rates after the morphine training dose; horizontal dashed lines represent mean response rates after saline.](image)

![Fig. 2. Percentage of morphine-lever responding (top) and response rate (bottom) engendered by morphine in squirrel monkeys in the presence and absence of 0.3 mg/kg naltrexone. See legend of Fig. 1 for other details.](image)
sulting in a 3- to 13-fold increase in the ED₅₀ for cocaine and a 5- to >14-fold increase in the ED₅₀ for amphetamine (Table 3). Flupenthixol pretreatment, however, did not systematically alter the DS effects of morphine.

**Effects of Morphine Combined with Cocaine and Amphetamine.** In the monkeys (S-204, S-228, and S-221) for which both stimulants exhibited full or partial substitution for morphine, combined administration of either cocaine or amphetamine with morphine had qualitatively different effects compared with monkeys S-95 and S-89 (Figs. 4 and 5). In the former three monkeys, pretreatment with 0.1 to 0.3 mg/kg cocaine or 0.03 to 0.3 mg/kg amphetamine produced an overall enhancement of the DS effects of morphine such that doses of morphine <1.0 mg/kg engendered a larger percentage of morphine-lever responses in the presence of either cocaine or amphetamine than in their absence. The degree to which cocaine or amphetamine enhanced the DS effects of morphine in these monkeys depended on the particular subject and pretreatment dose, but in no case was there evidence that either cocaine or amphetamine attenuated the DS effects of morphine. In the remaining two monkeys (S-95 and S-89), however, neither cocaine nor amphetamine enhanced the DS effects of morphine regardless of dose. Instead, pretreatment with at least one dose of either stimulant attenuated the DS effects of morphine in these subjects such that doses of morphine ≥0.3 mg/kg engendered a reduced percentage of morphine-lever responses in the presence compared with the absence of cocaine or amphetamine. Pretreatment with cocaine or amphetamine did not result in response rates that were invariably greater than or less than those observed with morphine alone, although lower response rates were observed in most subjects after pretreatment with one or more doses of amphetamine (Fig. 5, bottom) and both increases and decreases in response rate were observed in some instances after pretreatment with cocaine (Fig. 4, bottom).

**Discussion**

**Opioid Mechanisms in the DS Effects of Morphine.** Morphine is thought to exert its behavioral effects largely via stimulation of μ-opioid receptors (Martin et al., 1976; Woods et al., 1992). Consistent with this view, the DS effects of morphine in the present study were mimicked fully by the selective μ agonist fentanyl and antagonized by naltrexone. In contrast, the DS effects of morphine were not mimicked by the κ agonist U50,488H. These findings corroborate existing data indicating that κ-opioid receptors do not play a critical role in the DS effects of morphine (Teal and Holtzman, 1980a,b). The δ agonists BW 373U86 and SNC 80 also did not mimic the DS effects of morphine in the present study, suggesting that δ-opioid receptor mechanisms do not play a critical role in transduction of the interoceptive effects of morphine. Consistent with this view, Negus et al. (1994) found that BW 373U86 similarly did not share DS effects with the μ agonist alfentanil in rhesus monkeys, and Jowell et al. (1996) demonstrated that the μ-selective peptide [D-Ala²-N-Me-Phe⁴-Met(O)⁵-(ol)]-enkephalin did not substitute for the δ-selective peptide [D-Pen⁵-D-Pen⁶]-enkephalin in pigeons. The present results, however, differ in some respects from previous findings with δ-opioid agonists in other experiments. For example, morphine and BW 373U86 show considerable cross-substitution in pigeons trained to discriminate either morphine or BW 373U86 from vehicle (Comer et al., 1993). Similarly, the δ-selective peptide [D-Ala²,N-Leu⁶]-enkephalin substituted fully for morphine in morphine-trained rats (Locke and Holtzman, 1986). Although our results provide no support for a primary involvement of δ receptors in the DS effects of morphine in monkeys, the results with pigeons and rats raise the possibility that δ-receptor mechanisms contribute in some way to the DS effects of morphine in other species.

**Individual Differences in Shared DS Effects of Stimulants and Opioids.** Clear differences in the substitution profiles for cocaine and amphetamine were observed among individual subjects in our study. In three of five monkeys, both stimulants fully or partially mimicked the DS effects of morphine, but neither drug engendered appreciable morphine-appropriate responding in the other monkeys. Individual differences in the degree to which cocaine and amphetamine share DS effects with μ opioids also have been noted previously. For example, subgroups of pigeons trained to discriminate either morphine or butorphanol from vehicle showed full substitution for the training drug when tested with amphetamine or cocaine, whereas other subjects showed little or no substitution (Gauvin and Young, 1989a; Cook and Picker, 1988). Similarly, in heroin-trained rats, cocaine partially substituted for the training drug in approximately one-third of the subjects tested (Lamas et al., 1998). Although the DS effects of morphine itself appear to be mediated primarily by μ-opioid mechanisms (see above), the morphine-like DS effects of cocaine and amphetamine do not. In this regard, the DS effects of neither cocaine nor amphetamine were altered appreciably by naltrexone in the present study at doses that clearly antagonized the DS effects of morphine. This observation is concordant with previous findings that opioid-receptor antagonists do not alter the DS effects of cocaine or amphetamine in rats or monkeys trained to discriminate either of these drugs from vehicle (Mello et al., 1995; Woolfolk and Holtzman, 1996; Rowlett and Spealman, 1998).

Because both cocaine and amphetamine act as indirect monoaminergic agonists, we were interested in determining the ability of selective DA, NE, and 5-HT uptake inhibitors to mimic the DS effects of morphine. Of the drugs tested, only the selective DA-uptake inhibitor GBR 12909 engendered morphine-like responding in the subgroup of monkeys for which cocaine and amphetamine also substituted for morphine. These findings suggest that DA rather than 5-HT or NE mechanisms played a key role in the morphine-like DS effects of cocaine or amphetamine in the presence compared with vehicle (Mello et al., 1995; Woolfolk and Holtzman, 1996; Rowlett and Spealman, 1998).

**TABLE 2**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range Tested</th>
<th>Maximum Morphine-Lever Responses</th>
<th>n</th>
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<tbody>
<tr>
<td>U50,488H</td>
<td>0.03–0.3 mg/kg</td>
<td>17 ± 12 (0.1 mg/kg)</td>
<td>5</td>
</tr>
<tr>
<td>BW 373U86</td>
<td>0.003–0.3 mg/kg</td>
<td>26 ± 20* (0.3 mg/kg)</td>
<td>5</td>
</tr>
<tr>
<td>SNC 80</td>
<td>0.1–3.0 mg/kg</td>
<td>15 ± 7 (1.0 mg/kg)</td>
<td>5</td>
</tr>
<tr>
<td>Talsupram</td>
<td>0.3–5.6 mg/kg</td>
<td>24 ± 15 (3.0 mg/kg)</td>
<td>5</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1.0–10.0 mg/kg</td>
<td>16 ± 3 (1.0 mg/kg)</td>
<td>5</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.03–1.0 mg/kg</td>
<td>15 ± 9 (1.0 mg/kg)</td>
<td>4</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>0.3–5.6 mg/kg</td>
<td>1 ± 3 (3.0 mg/kg)</td>
<td>4</td>
</tr>
</tbody>
</table>

* Values in parentheses show doses at which the maximum percentages of morphine-lever responses were observed for the group. ** >80% morphine-lever responses in one of five subjects.
effects of cocaine andamphetamine. Furthermore, in these same subjects, the morphine-like DS effects of cocaine and amphetamine were antagonized by the DA-receptor antagonist flupenthixol. In contrast, the DS effects of morphine itself were not altered systematically by flupenthixol, suggesting that augmented dopaminergic activity does not provide an exclusive explanation for the shared DS effects of morphine, cocaine, and amphetamine.

During the initial determination of the morphine dose-response function, morphine produced increases in response rate in the three monkeys for which the DS effects of morphine generalized to cocaine and amphetamine. Because cocaine and amphetamine can also have pronounced rate-increasing effects on operant behavior (e.g., Spealman et al., 1989), it is possible that the generalization of morphine to cocaine and amphetamine in these monkeys was mediated by a common capacity of these drugs to increase response rate. Although this explanation cannot be ruled out entirely, it is noteworthy that the rate-increasing effects of morphine observed initially were not preserved over the course of the study in these monkeys (cf. Fig. 1). Moreover, with the exception of monkey S-221, neither cocaine nor amphetamine consistently increased rates of responding (cf. Fig. 3).

One possible factor contributing to the individual differences observed in our study is the training dose of morphine used to establish stimulus control in different subjects. Although the two training doses (0.56 and 1.0 mg/kg) differed by only one-fourth log unit, cocaine and amphetamine engendered morphine-like DS effects in the two monkeys trained with the lower dose of morphine, whereas neither drug engendered appreciable morphine-lever responding in two of the three monkeys trained with the higher dose of morphine. However, the third monkey trained with the higher morphine dose displayed a profile of DS effects similar to that exhibited by monkeys trained with the lower dose. These observations suggest that training dose per se was not a crucial factor determining individual differences in the substitution profiles for cocaine and amphetamine. Nevertheless, it has been demonstrated that the training dose can affect the shape and position of the dose-response function in opioid discrimination studies (Colpaert et al., 1980) as well as the likelihood that a particular opioid DS will generalize to other drugs (Young et al., 1992; Cook and Picker, 1998). It is possible, therefore, that the number of subjects exhibiting morphine-like stimulus effects after administration of cocaine or amphetamine might be altered systematically by either increasing or decreasing the training dose of morphine. In addition, the extent to which cocaine and amphetamine engender morphine-like stimulus effects could be influenced by other aspects of the training or testing procedures. Although the available literature does not permit explicit evaluation of these possibilities, it is notable that Schaefer and Holtzman (1977) observed partial substitution of d-amphetamine for morphine, indicative of individual dif-

### TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>ED50 mg/kg</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>S-204</td>
<td>S-288</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.11</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Cocaine + naltrexone</td>
<td>0.17 (1.5)*</td>
<td>0.24 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Cocaine + flupenthixol</td>
<td>1.45 (13.2)</td>
<td>0.46 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Amphetamine</td>
<td>0.06</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Amphetamine + naltrexone</td>
<td>0.02 (0.3)</td>
<td>0.06 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Amphetamine + flupenthixol</td>
<td>0.33 (5.5)</td>
<td>&gt;1.00 (&gt;14.3)</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>0.25</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Morphine + naltrexone</td>
<td>3.03 (12.1)</td>
<td>7.11 (23.7)</td>
<td></td>
</tr>
<tr>
<td>Morphine + flupenthixol</td>
<td>0.45 (1.8)</td>
<td>0.19 (0.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Values in parentheses show ED50 ratios compared with cocaine, amphetamine, and morphine alone.
ferences, in a group of six squirrel monkeys trained to discriminate a relatively high dose of morphine (3.0 mg/kg) by use of a shock-avoidance rather than a food-reinforcement paradigm and a single-dose rather than a cumulative-dose testing procedure.

**Individual Differences in Interactions between Stimulants and Opioids.** In the subgroup of monkeys for which cocaine and amphetamine substituted for morphine, the DS effects of morphine were enhanced after pretreatment with either stimulant. Gauvin and Young (1989a) similarly have shown that amphetamine enhances the DS effects of morphine in pigeons that also showed substitution of amphetamine for morphine. In the two monkeys for which the stimulants did not substitute for morphine, however, pretreatment with either cocaine or amphetamine resulted in rightward and downward shifts in the morphine dose-response functions. Although the possibility of pharmacological antagonism of the DS effects of morphine by cocaine and
amphetamine cannot be ruled out, it seems more likely that the attenuated effects of morphine in these subjects was due to perceptual masking of the DS effects of morphine by the two stimulants (cf. Gauvin and Young, 1989a,b). Perceptual masking has been inferred from demonstrations of attenuation of the DS effects of a drug without concomitant attenuation of its rate-altering effects. Although morphine itself did not alter response rates systematically, rate-decreasing effects were observed in both monkeys when morphine was combined with 0.1 or 0.3 mg/kg amphetamine and in monkey S-95 when morphine was combined with 0.1 mg/kg cocaine. Enhanced rate-decreasing effects as a result of combining the drugs would not be expected if attenuation of the effects of morphine was due primarily to pharmacological antagonism (e.g., as in the case of morphine combined with naltrexone).

There is now considerable evidence supporting the idea that enhancement of mesolimbic DA activity contributes importantly to the abuse-related effects of stimulants and opioids (Wise and Bozarth, 1987; Koob and Bloom, 1988; Di Chiara and North, 1992). On the basis of such findings, a reciprocal enhancement of the DS effects of stimulants and morphine might be expected. In the present study, however, cocaine and amphetamine enhanced the DS effects of morphine in some subjects but not in others. The reasons for these individual differences are unknown, but they could reflect corresponding differences in the effects of stimulants and morphine on mesolimbic DA activity among subjects. In this regard, individual differences in both basal and cocaine-stimulated levels of extracellular DA in the nucleus accumbens have been documented using in vivo microdialysis and are correlated with individual differences in locomotor response to a novel environment in rats (Hooks et al., 1992). Glick et al. (1992) similarly found a positive correlation between individual differences in levels of extracellular DA metabolites in the nucleus accumbens and corresponding differences in i.v. self-administration of morphine. These findings encourage speculation that there may be a direct relationship between individual variation in the capacity of stimulants and opioids to enhance mesolimbic DA activity and individual differences in the interaction between these drugs at the behavioral level. Regardless of ultimate relationship, however, our findings suggest that there may be important individual differences in the subjective effects of stimulant-opioid (speedball) combinations in human polydrug abusers. Such differences could have implications for the management of speedball abuse among individuals who combine stimulants and opioids for ostensibly different reasons [i.e., to enhance the subjective state of euphoria or to attenuate the undesirable effects of the individual drugs (Kosten et al., 1986; Foltin and Fischman, 1992; Walsh et al., 1996)].

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References


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