Self-Administration of Cocaine-Opioid Combinations by Rhesus Monkeys: Evaluation of the Role of \(\mu\) Receptor Efficacy Using Labor Supply Analysis

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ABSTRACT

Cocaine and heroin often are abused by self-administering the drugs in combination as a “speedball”. We evaluated the extent to which intrinsic efficacy at the \(\mu\)-opioid receptor influences combined cocaine-opioid self-administration and used the behavioral economic model termed “labor supply” to quantitatively evaluate the reinforcing effects of cocaine-opioid combinations. Rhesus monkeys \((n = 8)\) were trained under a progressive-ratio schedule of i.v. cocaine injection in which the response requirement increased during the experimental session and the initial response requirement was varied. Combination of cocaine with heroin enhanced self-administration compared with the drugs individually, with ineffective doses of both drugs maintaining self-administration when combined. These effects also were observed with the high-efficacy \(\mu\) agonist alfentanil and low-efficacy agonist nalbuphine. Using the labor supply economic model, combinations of heroin, alfentanil, or nalbuphine with relatively low doses of cocaine were found to increase the number of injections per session (“income”) and total responses per session (“labor”). Combination of a relatively high dose of cocaine with either heroin or alfentanil, but not nalbuphine, also resulted in only a small reduction in income concomitant with increased labor, suggesting that heroin and alfentanil made cocaine consumption more resistant to increasing response costs, or more “inelastic.” Collectively, these findings suggest that speedball self-administration may occur even with relatively low levels of intrinsic efficacy at \(\mu\)-opioid receptors and that an inelastic relationship between drug consumption and labor may contribute to the persistence of speedball abuse.

Many polydrug abusers take cocaine in combination with heroin by self-administering the drugs together in the form of speedballs. Research efforts focused on understanding speedball abuse have yet to reveal clear neuropharmacologic mechanisms underlying this prevalent form of polydrug addiction. Preclinical investigations have implicated brain dopamine and opioid systems as important in modulating the abuse-related effects of stimulants and opioids when used singly (Koob and Bloom, 1988; Di Chiara and North, 1992), and speedballs may engender their effects via an interaction of these neurotransmitter systems (for review, see Leri et al., 2003).

Several studies evaluating the discriminative stimulus effects of cocaine with opioids have provided evidence that the effects of speedballs involve an interaction of \(\mu\)-opioid receptors with dopamine systems (Mello et al., 1995; Negus et al., 1998; Rowlett et al., 1998a). However, the extent to which \(\mu\)-opioid receptors contribute to the enhanced self-administration of speedballs is not yet understood fully, although most reports have implicated primarily the \(\mu\)-opioid receptor subtype. For example, with a progressive-ratio schedule of i.v. drug injection, Rowlett et al. (1998b) demonstrated that dose-response functions consisting of cocaine-heroin combinations could be attenuated by administration of the opioid antagonist naltrexone. Moreover, in vivo apparent \(pA_2\) analysis of these results showed apparent affinity estimates consistent with blockade at the \(\mu\)-receptor subtype. Others have found similar findings using different procedures and species (Hemby et al., 1999). In other studies, however, the opioid antagonist dextromethorphan was ineffective at attenuating self-administration of speedball combinations unless combined with a dopamine antagonist (Mello and Negus, 1999). Because of these differences across studies, a broader understanding of the contribution of the \(\mu\)-opioid receptor to the reinforcing effects of speedball combinations is clearly warranted.

ABBREVIATIONS: IRR, initial response requirement; ANOVA, analysis of variance.

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Considerable research has focused on identifying receptor mechanisms underlying the addictive and therapeutic effects of opioid receptor agonists (Woods et al., 1992; Dykstra et al., 1997). A well-documented observation is that μ agonists with comparatively low intrinsic efficacy as determined in vitro by cAMP production or G protein binding are less effective in producing characteristic opioid agonist effects than are μ agonists with relatively high intrinsic efficacy (Walker et al., 1993; Gerak et al., 1994). In particular, direct comparisons of the high-efficacy μ agonist alfentanil and low-efficacy agonist nalbuphine have revealed quantitative differences in their ability to maintain i.v. self-administration in monkeys, suggesting that intrinsic efficacy may be an important determinant of the reinforcing effects of opioid agonists (Winger et al., 1996; Zernig et al., 1997; Rowlett et al., 2002).

Although information is available about the role of intrinsic efficacy in the self-administration of μ-opioid agonists, considerably less is known regarding the role of intrinsic efficacy in the enhanced reinforcing effects of opioids combined with cocaine. Therefore, a goal of the present study was to compare self-administration of cocaine-heroin combinations with cocaine-alfentanil and cocaine-nalbuphine combinations. To evaluate the interactions of cocaine with the μ agonists quantitatively, we used progressive-ratio schedules of i.v. cocaine injection in which the initial response requirement (IRR) was varied systematically. This approach allowed the use of a quantitative economic model termed labor supply analysis (Allison, 1993; Rowlett, 2000) to determine the extent to which heroin, alfentanil, and nalbuphine differed in their ability to augment the reinforcing effects of cocaine. This approach has been used previously to evaluate the relative reinforcing effectiveness of alfentanil and nalbuphine individually under a similar progressive-ratio schedule (Rowlett et al., 2002).

Materials and Methods

Subjects. Two male and six female adult rhesus monkeys (Macaca mulatta), weighing 6 to 11 kg, were studied in daily experimental sessions (Monday through Friday). Four monkeys were experimentally naive at the beginning of the study, and the remaining monkeys had self-administered cocaine, alfentanil, and nalbuphine previously under a progressive-ratio schedule of i.v. drug injection as described by Rowlett et al. (2002). Monkeys were housed in colony rooms with a 12-h light/dark cycle (lights on at 6:30 AM), had unrestricted access to water, and were fed (Teklad Monkey Diet, Harlan, 0.1 mg/kg, twice a day) for 3 days. Experimental sessions began 3 days after surgery. Monkeys were housed individually in stainless steel primate cages that also served as the experimental chambers. A removable panel was placed on the front of each cage and contained four stimulus lights (MED Associates, St. Albans, VT; two red and two white; 3 cm, 1.1 W) and a response lever (MED Associates). Each monkey was fitted with a nylon mesh jacket (Lomir Biomedical Inc., Malone, NY) that was connected to a 1-m stainless steel flexible tether (Lomir Biomedical). The monkey’s catheter was routed through the tether and attached to a fluid swivel (Lomir Biomedical) on top of the cage. The swivel was attached to an injection pump (MED Associates) located on top of the cage that could infuse drug solutions at a rate of 0.2 ml/s. The stimulus lights, response levers, and infusion pump were connected to interfaces (MED Associates) and PC-compatible computers located in an adjacent room.

Procedure. Monkeys were trained to self-administer cocaine under a progressive-ratio schedule of i.v. drug injection according to the schedule parameters described by Rowlett et al. (2002). Experimental sessions began daily at 12:00 noon. At the beginning of the session, the white stimulus lights above the lever were illuminated to signal the start of a trial. The white lights were extinguished upon completion of the response requirement, and the red stimulus lights were illuminated for 1 s, coinciding with a 1-s infusion of drug or saline. Each trial ended with either an injection or the expiration of a 30-min limited hold. Trials were separated by a 30-min timeout period, during which all the lights were extinguished and responding had no programmed consequences. Experimental sessions consisted of five components made up of four trials each, for a possible maximum of 20 trials per session. The response requirement remained constant during each of the four trials within a component and doubled across successive components of the session. For example, a session with an IRR of 100 consisted of the following five components with increasing response requirements (four trials each): 100, 200, 400, 800, and 1600. The session ended when a monkey self-administered a maximum of 20 injections or when the response requirement was not completed for two consecutive trials. The number of trials per response requirement was chosen so that completing the maximum number of injections could be delivered in 10 h or less each day.

During the initial training conditions, cocaine (0.1 or 0.18 mg/kg injection, depending on the monkey) or an equivalent volume of 0.9% saline solution was available for self-administration on alternate days. Stable self-administration was defined by the following criteria: 1) the number of injections per session maintained by cocaine was greater or equal to 11 for at least three sessions of cocaine availability, and the number of injections per session maintained by saline was less or equal to five for at least three sessions of saline availability; and 2) no upward or downward trends in the number of injections were observed across either type of session. Once self-administration was stable, test sessions (T) were added to the alternating sequence of cocaine (C) and saline (S) sessions according to the following sequence: STSCTCTCST, and so on.

Test sessions were identical to training sessions except that the drug, dose, and/or IRR was manipulated. Cocaine (0.01–0.1 mg/kg injection), heroin (0.001 and 0.01 mg/kg injection), and cocaine + heroin combinations were tested under the progressive-ratio schedule with IRRs of 25, 100, and 400. Cocaine (0.003–0.1 mg/kg injection), alfentanil (0.0001 and 0.001 mg/kg injection), nalbuphine (0.001 and 0.01 mg/kg injection), and combinations of cocaine + alfentanil and cocaine + nalbuphine were then tested with IRRs of 25 and 400. All the drugs, drug combinations, and IRRs were tested in an irregular order across subjects, with the restriction that all the doses of a particular drug or drug combination were studied at each IRR before testing the next drug or drug combination. Each test condition was determined twice in individual monkeys (once after a cocaine training session and once after a saline training session), and...
groups of four monkeys were used in experiments with each opioid agonist and corresponding cocaine-opioid combination.

**Drug Preparation.** Cocaine HCl and nalbuphine HCl were obtained from commercial sources (Sigma-Aldrich, St. Louis, MO), and alfentanil HCl was obtained from the National Institute on Drug Abuse (Bethesda, MD). All the drugs were dissolved in 0.9% saline solution and filter-sterilized (0.2 µm) before administration. Doses were expressed as the salt form of the drugs.

**Data Analysis.** The number of injections per session and break points were determined for individual monkeys for each test condition. The mean number of injections per session for each drug combination was analyzed by two-within, repeated measures analysis of variance (ANOVA) and planned multiple comparisons using Bonferroni t tests (α level equal to P < 0.05). Break point, defined as the highest response requirement completed during a test session, was used to calculate the maximum break point irrespective of dose (BP<sub>max</sub>), a measure of the effects of drug combinations on maximum performance. In addition to BP<sub>max</sub>, the maximum number of injections per session irrespective of dose (I<sub>max</sub>) was calculated as a measure of maximum performance. Because break point data characteristically violate assumptions of homogeneity of variance and normality, the BP<sub>max</sub> data were transformed to log<sub>10</sub> values. The log<sub>10</sub>(BP<sub>max</sub>) and I<sub>max</sub> data were analyzed within IRR conditions using repeated measures ANOVA and Bonferroni t tests.

For labor supply analysis, income was defined as the mean number of injections per session and plotted as a function of labor, defined as total responses per session (Allison, 1993; Rowlett, 2000). Labor supply theory postulates that income decreases according to a negative linear relationship between income and labor (Rowlett et al., 2002): I = Y - a(L). In the equation, the variable I, income, is the mean injections per session; Y is the y-intercept; L, labor, is the total responses per session; and a, the slope of the labor supply function, is defined as ΔI/ΔL. The slope, ΔI/ΔL, provides an estimate of the elasticity in the relationship between I and L; as the value of ΔI/ΔL approaches zero, the relationship between labor and income becomes progressively inelastic (Rowlett, 2000). Linear regression analysis was used to calculate slopes, but this analysis was used for cocaine-heroin combinations only because this data set consisted of three IRRs (Rowlett et al., 2002).

Performance under progressive-ratio schedules typically is evaluated using income and break point measures, whereas labor supply analysis provides labor as a third variable. In the present study, the effects of the three opioid agonists on labor maintained by cocaine were analyzed separately using two-within, repeated measures ANOVA and planned Bonferroni t tests. Similar to break point data, labor data violate the assumption of homogeneity of variance, with mean labor values showing a strong positive correlation with corresponding variance (preliminary observations; Rowlett et al., 1996). Therefore, labor values were transformed to log<sub>10</sub>(labor) before the analyses. Because of the large number of data points generated for these analyses, for clarity only the highest and lowest doses of cocaine were selected for presentation.

**Results**

**Combinations of Cocaine and Heroin.** When cocaine and heroin were available individually for self-administration, the mean number of injections per session increased as a function of dose for heroin (Fig. 1, points above heroin) and cocaine (Fig. 1, filled circles) at all IRRs. Combined self-administration of heroin (0.001 and 0.01 mg/kg/injection) and cocaine produced a reliable increase in the number of injections per session maintained by the two lower cocaine doses at all the IRR conditions (Fig. 1, points with asterisks; Bonferroni t tests, P < 0.05) and resulted in an overall upward shift and flattening of the cocaine dose-response function. Repeated measures ANOVA revealed a reliable interaction between heroin dose and cocaine dose at IRR 25 [F(6,18) = 14.3, P < 0.05] and IRR 100 [F(6,18) = 6.7, P < 0.05] but not at IRR 400. The significant interactions at the two lower IRRs reflect the finding that combinations of the lowest dose of heroin (0.001 mg/kg/injection) and cocaine (0.01 mg/kg/injection), which individually were not reliably self-administered, maintained injections per session that were significantly greater than the number of injections per session maintained by saline (Fig. 1, Bonferroni t tests, P < 0.05). Moreover, combinations of these doses of heroin and cocaine maintained injections per session that were significantly greater than the number of injections per session maintained by either drug individually (points with asterisks and daggers; Bonferroni t tests, P < 0.05).

**Combinations of Cocaine and Alfentanil.** When cocaine and alfentanil were available individually for self-administration, the mean number of injections per session increased as a function of dose for alfentanil (Fig. 2, points above alfentanil) and cocaine (Fig. 2, filled circles) at both IRRs. As with cocaine and heroin, combined self-administration of alfentanil (0.0001 and 0.001 mg/kg/injection) and co-
Cocaine produced a reliable increase in the number of injections per session maintained by the two lower cocaine doses under both IRR conditions (Fig. 2, points with asterisks; Bonferroni t tests, \( P < 0.05 \)) and resulted in an overall upward shift and flattening of the cocaine dose-response function. Repeated measures ANOVA revealed a reliable alfentanil dose x cocaine dose interaction at IRR 25 \([F(8,24) = 5.0, P < 0.05]\) but not at IRR 400. The significant interaction at IRR 25 reflects the finding that combinations of the lowest dose of alfentanil (0.0001 mg/kg/injection) and cocaine (0.01 mg/kg/injection), which individually were not reliably self-administered, maintained injections per session that were significantly greater than the number of injections per session maintained by saline (Fig. 2, Bonferroni t tests, \( P < 0.05 \)). Moreover, combinations of these doses of alfentanil and cocaine maintained injections per session that were significantly greater than the number of injections per session maintained by either drug individually (points with asterisks and daggers; Bonferroni t tests, \( P < 0.05 \)).

**Combinations of Cocaine and Nalbuphine.** Unlike heroin, alfentanil, and cocaine, nalbuphine maintained reliable self-administration only under the progressive-ratio schedule with an IRR of 25 (Fig. 3, points above nalbuphine). Planned comparisons showed that combined self-administration of nalbuphine (0.001 and 0.01 mg/kg/injection) with the two lowest doses of cocaine (0.003 and 0.01 mg/kg/injection) produced a significant increase in the number of injections per session during the IRR 25 conditions (Fig. 3, points with asterisks; Bonferroni t tests, \( P < 0.05 \)), resulting in an overall upward shift and flattening of the cocaine dose-response function. Repeated measures ANOVA revealed a significant interaction between nalbuphine and cocaine doses at IRR 25 \([F(8,24) = 6.3, P < 0.05]\). As with cocaine combined with heroin or alfentanil, the reliable interaction at IRR 25 likely reflects the fact that the combination of 0.001 mg/kg/injection of nalbuphine with 0.003 and 0.01 mg/kg/injection of cocaine maintained injections per session that were significantly greater than either drug individually (Fig. 3, top, points with asterisks and daggers; Bonferroni t tests, \( P < 0.05 \)). Despite the fact that nalbuphine failed to maintain self-administration during the IRR 400 condition when studied alone, it did reliably increase the number of injections per session maintained by the lowest dose of cocaine, and 0.001 mg/kg/injection of nalbuphine also reliably increased the number of injections per session maintained by 0.03 mg/kg/injection of cocaine (Fig. 3, bottom, points with asterisks; Bonferroni t test, \( P < 0.05 \)). However, repeated measures ANOVA showed no significant nalbuphine x cocaine dose interaction at this IRR condition.

**BP\textsubscript{max} and I\textsubscript{max} Analysis.** Increasing the response requirements of the progressive-ratio schedule from IRR 25 to IRR 400 resulted in a reliable increase in mean log\textsubscript{10}(BP\textsubscript{max}) values for cocaine alone, despite a corresponding reliable decrease in the mean I\textsubscript{max} (Bonferroni t tests, \( P < 0.05 \); see Table 1). Within each IRR condition, combination of cocaine with heroin, alfentanil, or nalbuphine had no significant effect on either BP\textsubscript{max} or I\textsubscript{max} (Bonferroni t tests, \( P > 0.05 \)).

**Labor Supply Analysis.** Figure 4, top, shows labor-income plots for combinations of the lowest and highest doses of
TABLE 1

BP_{max} (maximum break point irrespective of dose) and I_{max} (maximum number of injections/session irrespective of dose) for cocaine, alone and combined with opioid agonists, in rhesus monkeys (n = 4) responding under a progressive-ratio schedule of i.v. cocaine injection.

<table>
<thead>
<tr>
<th></th>
<th>BP_{max}</th>
<th>log_{10}(BP_{max})</th>
<th>I_{max}</th>
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<tbody>
<tr>
<td></td>
<td>mean ± S.E.M.</td>
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<tr>
<td><strong>Heroin</strong></td>
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<tr>
<td>IRR 25</td>
<td></td>
<td></td>
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<tr>
<td>Cocaine alone</td>
<td>350 ± 50</td>
<td>2.53 ± 0.08</td>
<td>18.0 ± 1.7</td>
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<tr>
<td>+0.001</td>
<td>350 ± 50</td>
<td>2.53 ± 0.08</td>
<td>18.8 ± 1.3</td>
</tr>
<tr>
<td>+0.01</td>
<td>300 ± 58</td>
<td>2.45 ± 0.09</td>
<td>17.8 ± 1.3</td>
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<tr>
<td>IRR 100</td>
<td></td>
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<tr>
<td>Cocaine alone</td>
<td>1000 ± 346</td>
<td>3.00 ± 0.17</td>
<td>14.5 ± 1.4</td>
</tr>
<tr>
<td>+0.001</td>
<td>900 ± 252</td>
<td>2.90 ± 0.12</td>
<td>14.3 ± 0.9</td>
</tr>
<tr>
<td>+0.01</td>
<td>900 ± 252</td>
<td>2.90 ± 0.12</td>
<td>12.8 ± 1.6</td>
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<tr>
<td>IRR 400</td>
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<td></td>
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<tr>
<td>Cocaine alone</td>
<td>1600 ± 0.0</td>
<td>3.20 ± 0.00*</td>
<td>11.5 ± 0.3*</td>
</tr>
<tr>
<td>+0.001</td>
<td>2400 ± 462</td>
<td>3.35 ± 0.09</td>
<td>12.7 ± 0.7</td>
</tr>
<tr>
<td>+0.01</td>
<td>2400 ± 462</td>
<td>3.35 ± 0.09</td>
<td>12.8 ± 1.1</td>
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<tr>
<td><strong>Alfentanil</strong></td>
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<tr>
<td>IRR 25</td>
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<td></td>
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<tr>
<td>Cocaine alone</td>
<td>250 ± 50</td>
<td>2.38 ± 0.08</td>
<td>15.8 ± 0.5</td>
</tr>
<tr>
<td>+0.0001</td>
<td>350 ± 50</td>
<td>2.53 ± 0.08</td>
<td>17.3 ± 1.0</td>
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<tr>
<td>+0.001</td>
<td>400 ± 0</td>
<td>2.60 ± 0.00</td>
<td>17.8 ± 0.8</td>
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<tr>
<td>IRR 400</td>
<td></td>
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<tr>
<td>Cocaine alone</td>
<td>1400 ± 600</td>
<td>3.05 ± 0.15*</td>
<td>9.0 ± 2.0*</td>
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<tr>
<td>+0.0001</td>
<td>1800 ± 503</td>
<td>3.20 ± 0.12</td>
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<td>Cocaine alone</td>
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<td>+0.001</td>
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<td>IRR 400</td>
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<tr>
<td>Cocaine alone</td>
<td>1400 ± 600</td>
<td>3.05 ± 0.15*</td>
<td>9.0 ± 2.0*</td>
</tr>
<tr>
<td>+0.001</td>
<td>1600 ± 566</td>
<td>3.13 ± 0.14</td>
<td>10.0 ± 2.4</td>
</tr>
<tr>
<td>+0.01</td>
<td>1600 ± 566</td>
<td>3.13 ± 0.14</td>
<td>10.0 ± 1.5</td>
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*p < 0.05 vs. cocaine alone at IRR 25, Bonferroni t test.

cocaine (0.01 and 0.1 mg/kg/injection) and heroin (0.001 and 0.01 mg/kg/injection). The y-axes of the plots show the mean number of injections per session, or income, which are the same as the y-axes shown in Fig. 1. Income is plotted as a function of IRR (represented by dashed curves) and labor (total responses per session, represented on the x-axis). As the IRR was increased, the lowest dose of cocaine alone (Fig. 4, top left, filled circles) and this dose of cocaine combined with the two heroin doses (open triangles and squares) showed an overall decrease in income and an increase in labor. Thus, for cocaine alone and combined with heroin, there was a negative relationship between income and labor as IRR was increased, as illustrated by the regression lines (Fig. 4, top left, solid lines). Combination of heroin with cocaine shifted the cocaine labor supply function upward and to the right, and for the highest dose of cocaine, it tended to flatten the labor supply function. The calculation of slopes for these labor supply functions generally revealed values close to zero, with the slopes for cocaine alone (−0.0052) and cocaine + 0.001 mg/kg/injection of heroin (−0.0048) being...
similar, whereas the slope for cocaine + 0.01 mg/kg/injection of heroin (−0.0022) was closer to zero than the other two slopes. Although negative relationships between income and labor were also observed at the highest cocaine dose (0.1 mg/kg/injection; Fig. 4, top right), the apparent differences in slope were more pronounced at this dose. Thus, the slope for cocaine alone (−0.0014) was increased by approximately one-half by combination with 0.001 mg/kg/injection of heroin (−0.00067) and increased further by combination with the dose of 0.01 mg/kg/injection of heroin (−0.00032). Collectively, the apparent changes in slope suggested that combination of heroin with the highest cocaine dose resulted in slope values that were closer to zero than cocaine alone (i.e., combination of heroin made the labor-income relationship for cocaine increasingly inelastic at the higher dose).

The effects of combining cocaine and heroin on labor are shown in Fig. 4, bottom. At each IRR condition, combining 0.01 mg/kg/injection of cocaine with 0.001 and 0.01 mg/kg/injection of heroin resulted in a significant increase in labor (Fig. 4, left bottom). The magnitude of the increase in labor was approximately the same across IRRs, as shown by repeated measures ANOVA, in which main effects for heroin dose \( F(2,6) = 48.2, P < 0.05 \) and IRR \( F(2,6) = 28.5, P < 0.05 \) were found but without a reliable heroin dose × IRR interaction. In contrast, at the higher cocaine dose (Fig. 4, right bottom), a significant heroin dose × IRR interaction was observed \( F(4,12) = 13.1, P < 0.01 \), likely reflecting the finding that the only increase in labor was by cocaine combined with 0.01 mg/kg/injection of heroin at IRR 400 (Fig. 4, point with asterisk compared with cocaine alone; planned Bonferroni \( t \) tests, \( P < 0.05 \)). Finally, a similar analysis of the intermediate dose of cocaine (0.03 mg/kg/injection) resulted in a pattern of effects that generally resembled the pattern observed with the lower cocaine dose (data not shown).

Labor supply analysis for cocaine-alfentanil combinations showed a pattern of effects similar to that observed for cocaine-heroin combinations (Fig. 5). Regression analysis was not possible for the labor-income plots shown in Fig. 5, top, although it is apparent that the increase in IRR from 25 to 400 resulted in a reduction in income along with an increase in labor for both cocaine doses (Fig. 5, top left and right). Moreover, the labor supply function for cocaine was shifted upward and to the right by combination with alfentanil, with a flattening of the function at the highest dose of cocaine. As with cocaine-heroin combinations, analysis of labor alone revealed that this measure was enhanced by combination of 0.01 mg/kg/injection of cocaine with both doses of alfentanil (Fig. 5, bottom left). The magnitude of this increase in labor was approximately the same across the two IRRs, as shown by repeated measures ANOVA, in which main effects for alfentanil dose \( F(2,6) = 14.3, P < 0.05 \) and IRR \( F(1,3) = 51.3, P < 0.05 \) were found but no reliable alfentanil dose × IRR interaction. At 0.1 mg/kg/injection of cocaine, however, a significant alfentanil dose × IRR interaction was revealed \( F(2,6) = 9.4, P < 0.05 \). This interaction likely reflects that labor was enhanced only by combination of the highest doses of cocaine and alfentanil at IRR 400 (Fig. 5, bottom right, points with asterisks compared with cocaine alone; planned Bonferroni \( t \) tests, \( P < 0.05 \)).

The labor-income plots for nalbuphine revealed that combinations of this partial agonist with cocaine, as with cocaine alone, resulted in an overall decrease in income and an increase in labor (Fig. 6, top). As with cocaine-heroin and cocaine-alfentanil combinations, nalbuphine combined with cocaine resulted in upward and rightward shifts in the labor supply functions; however, the effects of nalbuphine seemed to be more variable and less dose-dependent. An analysis of labor alone (Fig. 6, bottom) revealed main effects of nalbuphine dose and IRR \( F(2,6) = 6.6, P < 0.05 \) and \( F(1,3) = 39.1, P < 0.05 \), respectively, with no interaction of the two factors, a finding that parallels the results with cocaine combined with the other opioids. However, in contrast to heroin and alfentanil, neither the main effects nor the interaction of nalbuphine dose and IRR was significant for the higher dose of cocaine.

Fig. 5. Labor supply analysis of cocaine-alfentanil self-administration by rhesus monkeys responding under a progressive-ratio schedule of i.v. cocaine delivery. Top, labor-income relationships for 0.01 mg/kg/injection (left) and 0.1 mg/kg/injection (right) of cocaine, alone and combined with 0.0001 and 0.001 mg/kg/injection of alfentanil. Bottom, effects of combining alfentanil and cocaine on labor. Other details as in Fig. 4.
Discussion

Cocaine-Heroin Combinations. Consistent with previous findings using related procedures, self-administration of cocaine-heroin combinations was enhanced compared with that of either cocaine or heroin alone in rhesus monkeys responding under a progressive-ratio schedule of cocaine injection (Rowlett and Woolverton, 1997; Rowlett et al., 1998b). A consistent finding across the present and previous studies is that doses of cocaine and heroin that did not maintain self-administration above saline levels when tested alone resulted in significant self-administration when available in combination. The relationship of this enhancement by combining ineffective doses of the constituent drugs with the doses of cocaine and heroin typically used by speedball abusers is, at present, unknown. Nevertheless, these results suggest that an important factor to speedball abuse may be an increase in the reinforcing effects of cocaine and heroin compared with either drug alone.

In the present study, enhanced self-administration of cocaine by combination with heroin was observed at IRRs spanning a 15-fold range (IRR 25–400), suggesting that this phenomenon might be evident for a broad range of response requirements. However, increasing the IRR to 400 eliminated self-administration of the specific combinations of ineffective cocaine and heroin doses. Another condition during which enhanced cocaine-heroin self-administration generally was not observed was at combinations of relatively high doses of the two drugs. Consistent with this observation, the two measures of maximum performance, $I_{\text{max}}$ and $\text{BP}_{\text{max}}$, were not altered by combining cocaine and heroin. This finding is consistent with previous results (Rowlett and Woolverton, 1997; Rowlett et al., 1998b) and suggests that an enhanced intake of cocaine-heroin combinations may occur primarily at relatively low-dose combinations.

Cocaine Combined with Alfentanil or Nalbuphine: Role of Efficacy at $\mu$ Receptors. Previous research has shown that the differences of alfentanil and nalbuphine in efficacy at $\mu$-opioid receptors correlates with differences in the behavioral effects of these opioid agonists. For example, self-administration of alfentanil is less sensitive than nalbuphine to inactivation of $\mu$ receptors by the insurmountable antagonist clocinnamox (Zernig et al., 1997). Self-administration of alfentanil also was less sensitive to increasing response requirements than nalbuphine (Winger et al., 1996; Rowlett et al., 2002).

Because the sensitivity of alfentanil and nalbuphine self-administration to increasing response requirements closely parallels the intrinsic efficacy of these agonists at the $\mu$-opioid receptor, we sought to determine the degree to which combining cocaine with either alfentanil or nalbuphine resulted in enhanced reinforcing effects similar to cocaine-heroin combinations. We postulated that if agonist efficacy at $\mu$-opioid receptors were a determinant of enhanced reinforcing effects of cocaine-opioid combinations, nalbuphine then would be less likely to enhance the reinforcing effects of cocaine compared with alfentanil. In most cases, however, this hypothesis was not supported by the present results. That is, alfentanil and nalbuphine combined with cocaine increased self-administration to a degree similar to the effect of heroin. Ineffective doses of either alfentanil or nalbuphine combined with ineffective doses of cocaine also resulted in significant self-administration, an effect that was eliminated by increasing the IRR to 400. Maximum performance engendered by cocaine (measured by $\text{BP}_{\text{max}}$ and $I_{\text{max}}$ values) was not altered by alfentanil or nalbuphine at either IRR, suggesting that, as with heroin, the enhancement of cocaine self-administration by $\mu$ agonists was evident mostly at relatively low dose combinations. The finding that efficacy at $\mu$-opioid receptors is not a key determinant of the interaction between opioids and cocaine also has been shown for other behavioral effects (e.g., stimulation of locomotor activity; Smith et al., 2003).

The ability of nalbuphine to enhance self-administration of cocaine at IRR 400 is particularly noteworthy because nalbuphine does not function as a reinforcer when tested alone.

Fig. 6. Labor supply analysis of cocaine-nalbuphine self-administration by rhesus monkeys responding under a progressive-ratio schedule of i.v. cocaine delivery. Top, labor-income relationships for 0.01 mg/kg/injection (left) and 0.1 mg/kg/injection (right) of cocaine, alone and combined with 0.001 and 0.01 mg/kg/injection of nalbuphine. Bottom, effects of combining nalbuphine and cocaine on labor. Other details as in Fig. 4.
at this IRR (Rowlett et al., 2002; present results). Thus, enhancement of cocaine self-administration by combination with the μ agonist may occur during at least two conditions in which the μ agonist lacks reinforcing effects: at doses of the μ agonist too low to maintain self-administration and during conditions in which μ agonist efficacy is insufficient to maintain self-administration. An implication of the latter finding is that whereas opioid partial agonists may have reduced abuse potential compared with full agonists, partial agonists still may have the potential to be combined with cocaine and abused in the form of a speedball. To our knowledge, virtually no information is available regarding the prevalence of cocaine use in subjects reporting abuse of opioid partial agonists, although in a relatively small sample of nalbuphine abusers, ~30% of the study participants reported past use of cocaine (Wines et al., 1999).

Labor Supply Analysis. To further explore the interactions between cocaine and opioid agonist self-administration, we used a behavioral economic model termed labor supply (for review, see Rowlett, 2000). According to the labor supply model, increasing response costs will decrease consumption in a predictable manner; as response costs increase, the amount of drug consumed, or income, initially will decrease according to a negative linear function of the total number of responses maintained by the drug, or labor. This effect is referred to as an “income effect” and presumably reflects the tendency of an organism to keep income at an optimal level (Allison, 1983; Rowlett et al., 2002). Similar to our previous study (Rowlett et al., 2002), the income-labor relationship observed with self-administration of cocaine alone and cocaine combined with opioid agonists was consistent with an income effect for a relatively broad range of response requirements (i.e., response requirements as low as 25, up to a possible of 6400). In economic terms, these data suggest that the monkeys tended to increase labor to maintain optimal levels of income when either cocaine or speedball combinations were available.

For cocaine-heroin combinations, comparison of the slopes of the labor supply functions suggests that the relative change in income and labor for cocaine across IRR conditions was altered by combination with heroin. In this regard, the slope values tended to approach zero when combined with heroin (i.e., the labor-income relationship became less elastic). Elasticity in this context refers to the extent to which income is resistant to increases in response cost or alternatively the extent to which increases in response cost are countered by increases in labor. Consistent with a reduction in elasticity, the analysis of labor alone revealed several instances in which this measure was increased reliably by combining cocaine with heroin. Moreover, the effects of combining cocaine and heroin on labor differed between the relatively low and high doses of cocaine. In this regard, combination of the lower dose of cocaine with heroin enhanced labor at both heroin doses, and the magnitude of the enhancement was approximately the same. In contrast, at the higher dose of cocaine, labor was increased at the highest IRR only, and this effect occurred with no reliable increases in income. These latter results suggest that combining relatively high doses of heroin with relatively high doses of cocaine results in an interaction that is markedly inelastic (i.e., more resistant to increases in response cost), even in the absence of reliable changes in drug intake.

Labor supply analysis of the effects of cocaine combined with alfentanil showed a pattern of results strikingly similar to that observed with heroin. For nalbuphine, however, labor supply analysis revealed that at the highest dose of cocaine, no effects of combination with cocaine were evident with respect to labor. This finding raises the possibility that an increase in inelasticity of the labor-income relationship at high doses of cocaine and the opioid requires a μ agonist with relatively high intrinsic efficacy. Moreover, these findings demonstrate the potential utility of labor supply analysis in revealing quantitative differences in the cocaine-modulating effects of different μ agonists that were not evident with more traditional measures, such as injections per session and break point.

The behavioral economic model we used suggests that increasing response costs, although usually resulting in a decrease in income, also can increase labor, the net result of which is minimization of the loss of income. For speedballs consisting of relatively high doses of cocaine and heroin, increasing response costs may have little effect on drug consumption because of a large compensatory increase in the amount of labor. The relatively inelastic relationship between labor and income we observed might partly contribute to the relatively poor success rate in treating speedball abusers (Kosten et al., 1986; Brooner et al., 1997). Moreover, our findings suggest that approaches to treat speedball abuse based primarily on decreasing income could, in some circumstances, actually increase efforts devoted to drug procurement, resulting in little or no change in overall drug consumption. Novel therapeutic approaches aimed at breaking the inelastic relationship between labor and income for speedball self-administration may, when applied with other treatment modalities, hold promise for effective management of dual cocaine-heroin abuse.

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