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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Running title: Cocaine-Heroin Combinations

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Abbreviations: $BP_{\text{max}}$, maximum break point irrespective of dose; $I_{\text{max}}$, maximum injections/session irrespective of dose; IRR, initial response requirement

Section assignment: Behavioral Pharmacology
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 (IRR) was varied. Combination of cocaine with heroin enhanced self-administration compared to 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, as well as the 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/session (“income”) and total responses per session (“labor”). In addition, combination of a relatively high dose of cocaine with either heroin or alfentanil, but not nalbuphine, 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 neuropharmacological 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 (e.g., 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 the mu opioid receptor subtype primarily. For example, under 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 pA2 analysis of these results showed apparent affinity estimates consistent with blockade at the mu receptor subtype. Similar findings have been found by others using different procedures and species (e.g., Hemby et al., 1996). In other studies, however, the opioid antagonist quazacine 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 clearly is warranted.

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.,
A well-documented observation is that mu 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 mu agonists with relatively high intrinsic efficacy (e.g., Walker et al., 1993; Gerak et al., 1994). In particular, direct comparisons of the high-efficacy mu agonist alfentanil and the 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 mu 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 mu 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 6.0 – 11 kg, were studied in daily experimental sessions (Mon – Fri). Four monkeys were experimentally naïve 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 hr light/dark cycle (lights on at 0630 hr), had unrestricted access to water, and were fed (Teklad Monkey Diet, supplemented by fresh fruit) each morning between 0800 and 0900. Monkeys periodically were anesthetized (ketamine, 10 mg/kg, i.v.) to assess catheter patency and general health, and to transfer to sanitized cages. All procedures were conducted with the approval and under the supervision of the Harvard University Institutional Animal Care and Use Committee. The monkeys were cared for according to the Guide for Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, 1996).

Each monkey was prepared with a chronic indwelling venous catheter according to the general procedures described by Carey and Spealman (1998). A polyvinyl chloride catheter (Tygon®, inner diameter: 0.025 cm; outer diameter: 0.052 cm) was implanted in a jugular (internal or external), femoral, or brachial vein under isoflurane anesthesia and aseptic conditions. The proximal end of the catheter terminated above the right atrium, and the distal end was passed subcutaneously to exit in the midscapular region. Monkeys were treated postoperatively with antibiotics for 10 days and with an analgesic (butorphanol, 0.1 mg/kg, twice a day) for 3 days. Experimental sessions began 3 – 5 days following surgery.

Apparatus. 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 (two red and two white; 3 cm, 1.1 W; Med Associates, Georgia, VT) 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, which 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 1100 hr. At the beginning of the session, the white stimulus lights above the lever were illuminated to signal the start of a trial. Upon completion of the response requirement, the white lights were extinguished and the red stimulus lights were illuminated for 1 sec, coinciding with a 1-sec 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 lights were extinguished and responding had no programmed consequences.

Experimental sessions consisted of 5 components made up of 4 trials each, for a possible maximum of 20 trials per session. The response requirement remained constant during each of the 4 trials within a component, and doubled across successive components of the session. For example, a session with an initial response requirement (IRR) of 100 consisted of the following five components with increasing response requirements (4 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 hours or less each day.
Under 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/session maintained by cocaine was greater than or equal to 11 for at least three sessions of cocaine availability, and the number of injections/session maintained by saline was less than or equal to 5 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, etc.

Test sessions were identical to training sessions except that the drug, dose, and/or IRR were 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 drugs, drug combinations, and IRRs were tested in an irregular order across subjects, with the restriction that all doses of a particular drug or drug combination were studied at each IRR prior to testing the next drug or drug combinations. 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 4 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-RBI, Sigma-Aldrich, St. Louis, MO) and alfentanil HCl was obtained from the National Institute on Drug Abuse (Bethesda, MD). All drugs were dissolved in 0.9% saline.
solution and filter-sterilized (0.2 μm) prior to administration. Doses were expressed as the salt form of the drugs.

**Data Analysis.** The number of injections/session and the break points were determined for individual monkeys under each test condition. The mean number of injections/session for each drug combination was analyzed by two-within, repeated measures analysis of variance (ANOVA) and planned multiple comparisons using Bonferroni t-tests (alpha 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 (BPmax), a measure of the effects of drug combinations on maximum performance. In addition to BPmax, the maximum number of injections/session irrespective of dose (I_max) was calculated as a measure of maximum performance. Because break point data characteristically violate assumptions of homogeneity of variance and normality, the BPmax data were transformed to log10 values. The log10(BPmax) and I_max 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/session and was plotted as a function of “labor”, defined as total responses/session (Allison, 1993; Rowlett, 2000). Labor supply theory postulates that income declines 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/session; “Y” is the y-intercept; “L”, labor, is the total responses/session; and “a”, the slope of the labor supply function, is defined as \( \Delta I / \Delta L \). The slope, \( \Delta I / \Delta L \), provides an estimate of the elasticity in the relationship between I and L: As the value of \( \Delta I / \Delta L \) 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 since this data set consisted of three IRRs (cf. Rowlett et al., 2002).

Performance under progressive-ratio schedules typically is evaluated using income and break point measures, while 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 was 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; cf. Rowlett et al., 1996). Therefore, labor values were transformed to \( \log_{10}(\text{labor}) \) prior to 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/session increased as a function of dose for both heroin (Figure 1, points above “heroin”) and cocaine (Figure 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/session maintained by the two lower cocaine doses under all IRR conditions [Figure 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/session that were significantly greater than the number of injections/session maintained by saline [Figure 1, points with both asterisks (*) and daggers (†); Bonferroni t-tests, p<0.05]. Moreover, combinations of these doses of heroin and cocaine maintained injections/session that were significantly greater than the number of injections/session maintained by either drug individually (points with both 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/session increased as a function of dose for both alfentanil (Figure 2, points above “alfentanil”) and cocaine (Figure 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 cocaine produced a reliable increase in the number of injections/session maintained by the two lower cocaine doses under both IRR
conditions [Figure 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/session that were significantly greater than the number of injections/session maintained by saline [Figure 2, points with both asterisks (*) and daggers (†); Bonferroni t-tests, p<0.05]. Moreover, combinations of these doses of alfentanil and cocaine maintained injections/session that were significantly greater than the number of injections/session maintained by either drug individually (points with both 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 (Figure 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/session under the IRR 25 conditions [Figure 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 that combination of 0.001 mg/kg/injection of nalbuphine with 0.003 and 0.01 mg/kg/injection of cocaine maintained injections/session that were significantly greater than either drug individually [Figure 3, top panel, points with both asterisks (*) and daggers (†); Bonferroni t-tests, p<0.05]. Despite the
fact that nalbuphine failed to maintain self-administration under the IRR 400 condition when studied alone, it did reliably increase the number of injections/session maintained by the lowest dose of cocaine; and 0.001 mg/kg/injection of nalbuphine also reliably increased the number of injections/session maintained by 0.03 mg/kg/injection [Figure 3, bottom panel, points with asterisks (*), Bonferroni t-test, p<0.05]. Repeated measures ANOVA showed no significant nalbuphine x cocaine dose interaction under this IRR condition, however.

**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.** The top panels of Figure 4 show labor-income plots for combinations of the lowest and highest doses of 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/session, or income, which are the same as the y-axes shown in Figure 1. Income is plotted as a function of IRR (represented by dashed curves) and labor (total responses/session, represented on the x-axis). As the IRR was increased, the lowest dose of cocaine alone (Figure 4, top left panel, filled circles) as well as 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 (Figure 4, top left panel, solid lines). Combination of heroin with cocaine shifted the cocaine labor supply function upwards and to the right; and for the highest dose of cocaine, tended to flatten the labor supply function. 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 also were observed at the highest cocaine dose (0.1 mg/kg/injection; Figure 4, top right panel), the apparent differences in slope were more pronounced at this dose. Thus, the slope for cocaine alone (-0.0014) was increased by approximately ½ 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). Altogether, 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 the bottom panels of Figure 4. Under 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 (Figure 4, left bottom panel). 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 x IRR interaction. In contrast, at the higher cocaine dose (Figure 4, right bottom panel), a significant heroin dose x 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 [Figure 4, point with asterisk (*) compared to cocaine alone; planned Bonferroni t-test, 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 (Figure 5). Regression analysis was
not possible for the labor-income plots shown in the top panels of Figure 5, 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 (Figure 5, top left and right panels). Moreover, the labor supply function for cocaine was shifted upwards 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 (Figure 5, bottom left panel). 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 x IRR interaction. At 0.1 mg/kg/injection of cocaine, however, a significant alfentanil dose x 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 [Figure 5, bottom right panel, points with asterisks (*) compared to 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 (Figure 6, top panels). 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 appeared to be more variable and less dose-dependent. Analysis of labor alone (Figure 6, bottom panels) 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 were significant for the higher dose of cocaine.
Discussion

Cocaine-heroin combinations. Consistent with previous findings using related procedures, self-administration of cocaine-heroin combinations was enhanced compared to that of either cocaine or heroin alone in rhesus monkeys responding under a progressive-ratio schedule of cocaine injection (cf. 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 to 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 to 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 to 400), suggesting that this phenomenon may be evident over a broad range of response requirements. Increasing the IRR to 400, however, eliminated self-administration of the specific combinations of ineffective cocaine and heroin doses. Another condition under 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, $I_{max}$ and $BP_{max}$, 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 alfentanil’s and nalbuphine’s differences 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 unsurmountable antagonist clocinnamox (Zernig et al., 1997). In addition, self-administration of alfentanil 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 is a determinant of enhanced reinforcing effects of cocaine-opioid combinations, then nalbuphine should 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, both alfentanil and nalbuphine combined with cocaine increased self-administration to a degree similar to the effect of heroin. In addition, ineffective doses of either alfentanil or nalbuphine combined with ineffective doses of cocaine resulted in significant self-administration, an effect that was eliminated by increasing the IRR to 400. Maximum performance engendered by cocaine (measured by 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 at this IRR (Rowlett et al., 2002; present results). Thus, enhancement of cocaine self-administration by combination with a mu agonist may occur under at least two conditions in
which the mu agonist lacks reinforcing effects: At doses of the mu agonist too low to maintain self-administration and under conditions in which mu agonist efficacy is insufficient to maintain self-administration. An implication of the latter finding is that while opioid partial agonists may have reduced abuse potential compared to full agonists, partial agonists still might 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, approximately 30% of the study participants reported past use of cocaine (Wines et al., 1999).

**Labor supply analysis.** In order to explore the interactions between cocaine and opioid agonist self-administration further, we employed 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 are increased, 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 over 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 in order 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 mu 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 mu agonists that were not evident with more traditional measures, such as injections/session and break point.

The behavioral economic model we employed suggests that increasing response costs, though usually resulting in a decrease in income, also can increase labor, the net result of which is minimization of loss of income. For speedballs consisting of relatively high doses of cocaine
and heroin, increasing response costs may have very little effect on drug consumption, due to a large compensatory increase in the amount of labor. The relatively inelastic relationship between labor and income we observed might, in part, contribute to the relatively poor success rate in treating speedball abusers (cf. 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.
Acknowledgements

The authors thank Dr. Donna M. Platt for helpful comments on this manuscript. We thank Elizabeth Lipman, Brian Platt, and Emily Walker for technical assistance.
References


Footnotes:

a) Unnumbered footnote:

This research was supported by U.S.P.H.S. grants DA11928 and RR00168.

b) Corresponding author:

Please send request for reprints to James K. Rowlett, Ph.D., Harvard Medical School, New England Primate Research Center, Box 9102, One Pine Hill Drive, Southborough, MA 01772-9102, USA.

c) Numbered footnote:

1Current address for J.S. Rodefer: Department of Psychology, University of Iowa, Iowa City, IA 52242
Figure Captions

Figure 1. Self-administration of cocaine and heroin, alone and combined, in rhesus monkeys responding under progressive-ratio schedules of i.v. cocaine injection. Data are mean number of injections/session ± SEM for N=4 monkeys. Each panel represents progressive-ratio schedules with different initial response requirements (IRRs). Points above “heroin” represent data from sessions in which heroin was available alone. Dashed horizontal lines represent the upper and lower SEMs obtained from sessions of saline availability. These values were obtained from the number of injections/session during saline availability for the four monkeys, determined prior to and after tests with drugs and drug combinations. Note that *p<0.05, combination vs. corresponding dose of cocaine alone; †p<0.05, combination vs. corresponding dose of opioid alone; Bonferroni t-tests.

Figure 2. Self-administration of cocaine and alfentanil, alone and combined, in rhesus monkeys responding under progressive-ratio schedules of i.v. cocaine injection. Points above “alfentanil” represent data from sessions in which alfentanil was available alone. Other details as in Figure 1.

Figure 3. Self-administration of cocaine and nalbuphine, alone and combined, in rhesus monkeys responding under progressive-ratio schedules of i.v. cocaine injection. Points above “nalbuphine” represent data from sessions in which nalbuphine was available alone. Other details as in Figure 1.

Figure 4. Labor supply analysis of cocaine-heroin self-administration by rhesus monkeys responding under a progressive-ratio schedule of i.v. cocaine delivery. Top panels: Labor income relationships for 0.01 mg/kg/injection (left panel) and 0.1 mg/kg/injection (right panel) of cocaine, alone and combined with 0.001 and 0.01 mg/kg/injection of heroin. Curvilinear plots represent the
response requirements of the progressive-ratio schedule, identified by the three initial response requirement (IRR) conditions. Data are means for N=4 monkeys, bidirectional error bars represent SEMs. **Bottom panels:** Effects of combining heroin and cocaine on labor (total responses/session). Values are mean log\(_{10}\)(total responses/session) ± SEM. Note that *p<0.05 vs. cocaine alone, Bonferroni t-test.

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

**Figure 6.** Labor supply analysis of cocaine-nalbuphine self-administration by rhesus monkeys responding under a progressive-ratio schedule of i.v. cocaine delivery. **Top panels:** Labor income relationships for 0.01 mg/kg/injection (left panel) and 0.1 mg/kg/injection (right panel) of cocaine, alone and combined with 0.001 and 0.01 mg/kg/injection of nalbuphine. **Bottom panels:** Effects of combining nalbuphine and cocaine on labor. Other details as in Figure 4.
Table 1. BP$_{\text{max}}$ (maximum break point irrespective of dose) and I$_{\text{max}}$ (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$_{\text{max}}$ (mean ± SEM)</th>
<th>log$<em>{10}$(BP$</em>{\text{max}}$) (mean ± SEM)</th>
<th>I$_{\text{max}}$ (mean ± SEM)</th>
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<tbody>
<tr>
<td><strong>heroin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRR 25</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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<td>+ 0.001</td>
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<td>+ 0.01</td>
<td>300 ± 58</td>
<td>2.45 ± 0.09</td>
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<td>IRR 100</td>
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<tr>
<td>cocaine alone</td>
<td>1000 ± 346</td>
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<td>+ 0.001</td>
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<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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<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 ± 0.7</td>
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<tr>
<td>+ 0.01</td>
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<td>3.35 ± 0.09</td>
<td>12.8 ± 1.1</td>
</tr>
<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>
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<td>17.3 ± 1.0</td>
</tr>
<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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<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>
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<td>+ 0.0001</td>
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<td>2.38 ± 0.08</td>
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<tr>
<td>+ 0.01</td>
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</tr>
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<td>1600 ± 566</td>
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<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>
</tr>
</tbody>
</table>

*p<0.05 vs. cocaine alone at IRR 25, Bonferroni t-test.
Figure 1

**IRR 25**

- **Cocaine**
- **+ 0.001 heroin**
- **+ 0.01 heroin**

**IRR 100**

**IRR 400**

Injections/Session vs. Cocaine (mg/kg/injection) for different IRRs and heroin doses.
Figure 2

- **IRR 25**
  - Cocaine
  - 0.0001 alfentanil
  - 0.001 alfentanil

- **IRR 400**
  - Cocaine
  - 0.0001 alfentanil
  - 0.001 alfentanil

Cocaine Dose (mg/kg/injection) vs. Injections/Session for different doses of alfentanil and cocaine.
Figure 4

Labor (Total Responses/Session)

Income (Injections/Session)

IRR 25
IRR 100
IRR 400

0.01 cocaine

0.1 cocaine

log_{10}(Labor)

Initial Response Requirement

○ cocaine alone △ + 0.001 heroin □ + 0.01 heroin
Figure 5

- **0.01 cocaine**
  - **Income (injections/session)**
  - **Labor (total responses/session)**
  - IRR 25
  - IRR 400

- **0.1 cocaine**
  - **Income (injections/session)**
  - **Labor (total responses/session)**
  - IRR 25
  - IRR 400

- **log$_{10}$(Labor)**
  - **Initial Response Requirement**
  - * + 0.0001 alfentanil
  - * + 0.001 alfentanil
  - * cocaine alone

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**Figure 6**

- Initial Response Requirement

<table>
<thead>
<tr>
<th>Income (injections/session)</th>
</tr>
</thead>
<tbody>
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</table>

- Labor (total responses/session)

- 0.01 cocaine

- 0.1 cocaine

- * + 0.001 nalbuphine

- ** + 0.01 nalbuphine

- log10(Labor)

- 25  | 400  |

- Initial Response Requirement

- 25  | 400

- 2.0  | 2.5  | 3.0  | 3.5  | 4.0  |

- ** + sign indicates significance.