

Naltrexone–Buprenorphine Interactions: Effects on Cocaine Self-Administration

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An opioid mixed agonist–antagonist analgesic, buprenorphine, significantly reduces cocaine self-administration by rhesus monkeys, but the relative contribution of buprenorphine's agonist and antagonist properties to this effect is unclear. This study examined the effects of concurrent treatment with naltrexone, a long-acting mu opioid antagonist, on buprenorphine's effects on cocaine and food self-administration by five rhesus monkeys. Cocaine (0.5 mg/kg per injection) and food self-administration (1 gm banana pellet) were maintained on a second order fixed ratio 4 (FR4) variable ratio (VR) 16:S schedule of reinforcement. Buprenorphine treatment alone (0.40 mg/kg/day) and in combination with ascending doses of naltrexone (0.05, 0.10, 0.20, and 0.40 mg/kg/day) was compared with naltrexone alone (0.40 mg/kg/day) and saline control treatment. Naltrexone was administered simultaneously or 20 minutes before buprenorphine administration. Each treatment condition was in effect for 10 days.

Buprenorphine alone significantly reduced cocaine self-administration by an average of 53% in comparison to the saline treatment baseline ($p < .01$). When saline

was substituted for buprenorphine, each monkey rapidly returned to its prebuprenorphine level of cocaine self-administration. Food self-administration in all conditions was equivalent to or significantly higher ($p < .05$) than food-maintained responding during the saline baseline. When buprenorphine and naltrexone were administered simultaneously, naltrexone significantly attenuated buprenorphine's suppressive effects on cocaine self-administration ($p < .05$ to $.01$). When naltrexone was administered 20 minutes before buprenorphine, there was a significant naltrexone dose-dependent ($p < .01$) decrease in buprenorphine's reduction of cocaine self-administration in comparison to the initial saline baseline. These data suggest that naltrexone antagonizes the partial mu agonist component of buprenorphine, which may be important for buprenorphine's effects on cocaine self-administration. Moreover, the addition of an opioid antagonist to reduce illicit diversion of buprenorphine might also compromise its effectiveness for treatment of dual dependence on cocaine and opiates.

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Buprenorphine, an opioid mixed agonist–antagonist analgesic, reduced cocaine self-administration by rhesus monkeys by 72% to 93% (Mello et al. 1989, 1990). This effect appeared to be selective for cocaine since food self-administration was initially reduced, but tolerance rapidly developed to buprenorphine's suppressive effects on food-maintained responding. In subsequent studies, we found that daily buprenorphine administration selectively reduced cocaine self-administration for as long as 120 days (Mello et al. 1992a). More recently, we found that daily buprenorphine treatment decreased the reinforcing potency of cocaine in rhesus

monkey and shifted the cocaine dose-response curve approximately one half to 1 log unit to the right (Drieze et al. 1993; Lukas et al. 1993). Acute administration of buprenorphine to rhesus monkey also reduced rates of cocaine-maintained responding and suppressed the peak response without altering its apparent potency (Winger et al. 1992). Cocaine-base smoking by rhesus monkeys and cocaine self-administration by rats were also reduced by buprenorphine treatment (Carroll et al. 1992; Carroll and Lac 1992). These preclinical data are concordant with clinical evaluations of buprenorphine's effects on cocaine abuse by polydrug abusers. Buprenorphine was significantly more effective than methadone in reducing cocaine self-administration by opiate abusers (Kosten et al. 1989a, 1989b; Rosen and Kosten 1991). Ongoing clinical trials indicate that buprenorphine also significantly decreases cocaine abuse by men who are dually dependent on cocaine and heroin, according to DSM-III-R criteria (Gastfriend et al. 1992, 1993a, 1993b; Mello and Mendelson 1993a, 1993b; Mello et al. 1993b).

Buprenorphine is usually classified as a low-efficacy μ agonist and has a complex profile of opioid partial agonist and antagonist activity (Jaffe and Martin 1990; Winger et al. 1992). The relative contribution of buprenorphine's agonist and antagonist properties to its effects on cocaine self-administration is unknown. The goal of this study was to determine if concurrent administration of a μ opioid antagonist, naltrexone, would change buprenorphine's effects on cocaine self-administration. Naltrexone was selected for study because it has a long duration of action comparable to that of buprenorphine (Lee et al. 1988; Lewis et al. 1983). In clinical studies, naltrexone antagonized the effects of opiate agonists for 24 to 48 hours (Martin et al. 1973; Mello et al. 1981; Verebey et al. 1976). In rhesus monkeys, naltrexone's apparent antagonist affinity for μ opioid receptors has been shown in operant behavioral studies (France et al. 1990; France and Woods 1989). If naltrexone reduced buprenorphine's effects on cocaine self-administration, this would suggest that buprenorphine's partial μ opioid agonist component is of critical importance in its interactions with cocaine. Alternatively, the antagonist component of buprenorphine may be important for its reduction of cocaine self-administration. Naltrexone, as well as buprenorphine, reduced cocaine self-administration by rhesus monkeys in our earlier studies (Mello et al. 1990). Naltrexone also was more effective than an opioid agonist, methadone, in reducing cocaine abuse by opiate-dependent patients (Kosten et al. 1989a; Rosen and Kosten 1991). If the addition of naltrexone enhanced buprenorphine's effects on cocaine self-administration, this would suggest that buprenorphine's interactions with cocaine are mediated by opioid antagonist activity.

We are unaware of any previous studies of the effects of naltrexone and buprenorphine combinations

on cocaine self-administration. There has been some interest in adding naloxone to buprenorphine formulations to reduce the possibility of illicit diversion of buprenorphine (Preston et al. 1988; Weinhold et al. 1992). Combinations of buprenorphine (0.4 or 0.8 mg/70 kg) and naloxone (0.4 or 0.8 mg/70 kg) reduced the subjective and physiologic effects of buprenorphine in men who were not opiate dependent (Strain et al. 1992). Buprenorphine (0.4 mg/70 kg) in combination with 0.8 mg per 70 kg of naloxone was never identified as an opiate (Strain et al. 1992). Yet, a lower dose of naloxone (0.2 mg) did not compromise the analgesic effectiveness of 0.3 mg buprenorphine in patients with postoperative pain (Rolly et al. 1986). When naloxone (0.2 mg, SC) was given in combination with buprenorphine (0.2 and 0.3 mg, SC) to methadone-maintained men (30 mg/day), the opioid abstinence signs induced were less severe than, but qualitatively similar to, those produced by naloxone alone (Preston et al. 1988). Despite its antagonist properties, buprenorphine produced minimal signs of opioid abstinence in patients maintained on methadone (25 to 45 mg/day) (Jasinski et al. 1983) and was not consistently identified as an agonist or an antagonist in patients maintained on 30 mg/day of methadone (Strain et al. 1992). Because buprenorphine does not precipitate severe withdrawal, it appears to be useful for opiate detoxification (Bickel et al. 1988; Kosten and Kleber 1988).

The effects of buprenorphine-naloxone combinations have been studied in rats and monkeys, and pretreatment with naloxone usually blocks buprenorphine's effects. In squirrel monkeys (*Saimiri sciureus*), simultaneous administration of naloxone (0.1 to 1.0 mg/kg, IM) and buprenorphine (0.01 to 0.10 mg/kg) resulted in an attenuation of the decreased rates of food-maintained responding induced by buprenorphine alone (Dykstra 1983). Naloxone (0.3 mg/kg) antagonism of buprenorphine's rate-reducing effects was equivalent when naloxone was given simultaneously with or 15 minutes before buprenorphine administration (Dykstra 1983). Simultaneous naloxone (1.0 mg/kg) and buprenorphine administration antagonized the discriminative stimulus effects of buprenorphine in rats (Shannon et al. 1984). Concurrent administration of naloxone (0.1 mg/kg and 1.0 mg/kg) also antagonized the rate-decreasing effects of buprenorphine (0.0001 to 0.1 mg/kg) on both punished and unpunished food-maintained responding in squirrel monkeys (DeRosett and Holtzman 1984). In rhesus monkeys that were not opioid dependent, combined administration of buprenorphine and naloxone maintained more avoidance-escape behavior than buprenorphine alone (Hoffmeister 1986).

In the present study, we compared the effects of *simultaneous* naltrexone and buprenorphine administration with the effects of pretreatment with the same ascending doses of naltrexone given 20 minutes before buprenorphine administration. The potential clinical

utility of a buprenorphine–naltrexone combination would be greatest in a simultaneous administration paradigm. However, the profile of buprenorphine's receptor binding in relation to its pharmacologic effects is not well understood and the kinetic and binding profile of buprenorphine in the presence of naltrexone is unknown. Buprenorphine's agonist and antagonist actions appear to have a bell-shaped dose–response curve on several measures (Cowan et al. 1977; Lizasoain et al. 1991; Pechnick et al. 1985). Kinetic studies indicate that buprenorphine reaches peak plasma levels within 2 minutes after intravenous administration in man (Bullingham et al. 1980), within 2 to 5 minutes in baboon (Lloyd-Jones et al. 1980), and rapidly reaches peak levels in rodent and baboon brain within 10 to 15 minutes after administration (Holland et al. 1989; Shiue et al. 1991). Brain uptake studies with tracer doses of a fluorinated analogue of naltrexone [6-deoxy-6 β -fluoronaltrexone; cyclofoxy] indicate that near maximal brain uptake occurs within 20 minutes after administration (Kawai et al. 1990; Ostrowski et al. 1987; Sawada et al. 1991).

We also studied the effects of naltrexone given 20 minutes before buprenorphine on cocaine and food-maintained responding. The 20-minute naltrexone pretreatment procedure was used to ensure that naltrexone binding to the opiate receptors occurred before buprenorphine administration. We postulated that if buprenorphine's opioid agonist effects were important in reducing cocaine self-administration, the administration of naltrexone 20 minutes before buprenorphine would antagonize the partial mu agonist activity of buprenorphine. Alternatively, if buprenorphine's antagonist effects were important in reducing cocaine self-administration, then simultaneous administration of naltrexone and buprenorphine might increase the antagonist effect of these compounds.

The effects of naltrexone given after buprenorphine were not studied because it is well established that opioid antagonists do not reverse buprenorphine's effects if buprenorphine is given first. For example, behavioral studies have shown that the discriminative stimulus effects of buprenorphine could not be reversed by naltrexone given 25 minutes after buprenorphine, but could be prevented by naltrexone pretreatment in pigeons (France et al. 1984). Similarly, administration of naloxone after buprenorphine did not antagonize buprenorphine's effects in a discrimination paradigm (Shannon et al. 1984) or on an analgesia measure in rats (Cowan et al. 1977). In clinical studies, naltrexone did not precipitate withdrawal signs or symptoms in buprenorphine-maintained patients as it did in methadone-maintained patients (Kosten et al. 1990).

METHODS

Five rhesus monkeys (*Macaca mulatta*) [one female and four males] were studied. Subjects weighed from 6.9

kg to 13.1 kg (average 10.3 ± 1.05 kg) and had a history of intravenous cocaine self-administration that averaged 599 days (range 44 to 1002 days) at the beginning of this study. Monkeys were maintained at ad libitum weight and given multiple vitamins, fresh fruit and vegetables, and Purina monkey chow to supplement a banana pellet diet. Food supplements were given between 5:00 PM and 5:30 PM. Water was continuously available. A 12-hour light–dark cycle was in effect from 7 AM to 7 PM, and the experimental chamber was dark during food and drug self-administration sessions.

Double-lumen silicone rubber catheters (inside diameter 0.028 inches, outside diameter 0.080 inches) were surgically implanted to facilitate pretreatment with saline, naltrexone, and buprenorphine (alone or in combination with naltrexone) and concurrent cocaine self-administration. Catheters were implanted in the jugular or femoral vein and exited in the midscapular region. All surgical procedures were performed under aseptic conditions, and monkeys were anesthetized with either pentobarbital (30 mg/kg, IV) or ketamine (25 mg/kg, IM). After surgery, monkeys were given 200,000 units of Combiotic Dihydrostreptomycin and Penicillin G intramuscular every other day for a total of five injections. The intravenous catheter was protected by a tether system consisting of a custom-fitted nylon vest connected to a flexible stainless-steel cable and fluid swivel (Spaulding Medical Products, Birmingham, AL). This flexible tether system permits monkeys to move freely. Catheter patency was evaluated periodically by administration of a short-acting barbiturate, methohexital sodium (3 mg/kg, IV), through the catheter.

Animal maintenance and research was conducted in accordance with the guidelines provided by the Committee on Laboratory Animal Resources. The facility is licensed by the U.S. Department of Agriculture, and protocols were approved by the Institutional Animal Care and Use Committee. The health of the monkeys was periodically monitored by consultant veterinarians trained in primate medicine. Operant food and drug acquisition procedures provided an opportunity for environmental manipulation and enrichment (Line 1987; Line et al. 1989). Monkeys had visual, auditory, and olfactory contact with other monkeys throughout the study.

Sequence of Treatment Conditions

Effects of Simultaneous Buprenorphine–Naltrexone Combinations on Cocaine and Food Self-Administration (Study I). The goal of this study was to examine the effects of concurrent treatment with buprenorphine and naltrexone on cocaine and food self-administration. Buprenorphine alone (0.40 mg/kg/day) and in combination with ascending doses of naltrexone (0.05, 0.10, 0.20, and 0.40 mg/kg/day) were compared with naltrexone alone (0.40 mg/kg/day) and saline control treat-

ment. The sequence of pretreatment conditions was as follows: (1) saline alone, (2) buprenorphine alone, (3) saline alone, (4 to 7) four combinations of buprenorphine and naltrexone, and (8) naltrexone alone. Each of the eight treatment conditions was in effect for 10 days. This buprenorphine dose (0.40 mg/kg/day) was within the range of doses that significantly reduced cocaine self-administration in our previous studies (Mello et al. 1989, 1990, 1992a).

Effects of Naltrexone Pretreatment on Buprenorphine's Effects on Cocaine and Food Self-Administration (Study II). Subsequently, the same four ascending doses of naltrexone (0.05 to 0.40 mg/kg/day) were administered 20 minutes before buprenorphine (0.40 mg/kg/day) and followed by a saline-only control treatment. Each of these five treatment conditions was in effect for 10 days. The 20-minute naltrexone pretreatment interval was used to ensure that there was sufficient time for naltrexone to bind to the opioid receptors before buprenorphine was administered (Kawai et al. 1990; Ostrowski et al. 1987; Sawada et al. 1991). Each treatment condition was in effect for 10 days.

Administration of Buprenorphine, Naltrexone or Saline Solutions

In Study I, buprenorphine, naltrexone, and buprenorphine-naltrexone combinations or an equal volume of saline control solution was administered as a slow injection between 9:30 and 10:30 AM. In Study II, ascending doses of naltrexone (0.05 to 0.40 mg/kg/day) were administered 20 minutes before buprenorphine (0.40 mg/kg/day) administration. Each solution was slowly injected at a rate of 1 ml of solution every 10 minutes over a 50-minute period and flushed through with sterile saline in a volume that exceeded the estimated catheter dead space. This buprenorphine, naltrexone, and saline administration procedure was identical to that used in each of our previous studies (Mello et al. 1989, 1990, 1992a). Each treatment solution was infused through the second lumen of the double-lumen catheter. Both catheter lumens remained patent throughout the study.

Operant Behavioral Procedures and Apparatus

Monkeys worked at an operant task for food and intravenous cocaine injections in a well-ventilated chamber equipped with an operant panel, a pellet feeder, and a water dispenser. Drug injections were delivered by a syringe pump in a single pulse that dispensed 0.1 ml of fluid over a 0.9-second period. The operation of the syringe pump (Model 981210; Harvard Apparatus, Inc., South Natick, MA) was audible to the monkey. Schedules of reinforcement were programmed by custom-

designed software and run on Apple IIGS microcomputers.

Cocaine self-administration was studied at the dose that maintained the highest response rates during training. All monkeys self-administered 0.05 mg/kg per injection of cocaine throughout this study. Food (1 gm banana pellet) and cocaine (0.05 mg/kg per injection) self-administration were maintained on a second-order schedule of reinforcement [fixed ratio 4 (FR 4) variable ratio (VR) 16:S]. An average of 16 responses on a VR 16 schedule produced a brief colored stimulus light (S+). However, a drug injection or a food pellet was delivered only after an FR 4 of the VR 16 response requirements had been completed; that is, each food pellet or drug injection required an average of 64 responses. These procedures were identical to those previously used in our studies of daily buprenorphine treatment (Mello et al. 1989, 1990, 1992a).

The conditions of food and cocaine availability were each associated with a different colored stimulus light (S+) projected on a translucent Plexiglas response key (2 inches in diameter) in the center of the operant panel. No stimulus lights (S+) were illuminated during time-out periods (when responses had no programmed consequence). When a food pellet or drug injection was delivered, the appropriate colored stimulus light (S+) (red or green) was illuminated for 1 second on 3 circles (3/4 inches in diameter) located in a vertical column below the response key. These 1-second colored stimulus light flashes (S+) also signaled the completion of each successive component of the second-order schedule response requirement.

Each experimental day began at 9:00 AM and consisted of four food and four drug availability sessions. Food sessions began at 11:00 AM, 3:00 PM, 7:00 PM, and 7:00 AM each day and drug sessions began 1 hour later at 12 noon, 4:00 PM, 8:00 PM, and 8:00 AM. Each food or drug session lasted for 1 hour or until 100 food pellets or 20 drug injections had been delivered. Cocaine injections were limited to 80 per day to minimize the possibility of adverse drug effects. A time-out period when responses have no programmed consequences occurs between successive drug and food sessions.

Drug Solution Preparation

Buprenorphine. Buprenorphine hydrochloride was obtained from the National Institute on Drug Abuse (NIDA). Buprenorphine was dissolved in sterile water at a concentration of 8.0 or 16.7 mg/ml. The stock solution was then filter sterilized using a 0.22- μ filter and stored in sterile, pyrogen-free vials. Solutions were checked daily to ensure that no precipitate had formed. Fresh solutions were prepared every 14 to 21 days. Doses were calculated on the basis of the monkeys' weights so that a final dilution of stock solution (with

sterile saline for injection, U.S.P.) resulted in a daily infusion of each buprenorphine dose in a volume of 5.0 ml per infusion.

Naltrexone. Naltrexone was obtained from NIDA. Stock solutions were prepared by dissolving naltrexone in sterile saline for injection, U.S.P. The solution was then filter sterilized using a 0.22- μ filter and stored in sterile, pyrogen-free vials. Doses were calculated on the basis of each monkey's weight so that a final dilution yielded a unit dose of 0.32 or 3.20 mg/kg per injection in a volume of 5.0 ml per injection per day.

Cocaine. Cocaine hydrochloride was obtained in crystalline form from NIDA. The purity was certified by Research Triangle Institute to be greater than 98%. Cocaine was dissolved in sterile saline for injection, U.S.P. to make a stock solution at a concentration of 50 mg/ml. The solution was then filter sterilized using a 0.22- μ Millipore filter and stored in sterile, pyrogen-free vials. Doses were calculated on the basis of monkeys' weights so that a final dilution of the stock solution (with sterile saline for injection, U.S.P.) resulted in a unit dose of 0.05 mg/kg per injection in a volume of 0.1 ml/injection.

Data Analysis

Buprenorphine's effects on cocaine- and food-maintained responding were evaluated with one-way analysis of variance (ANOVA) for repeated measures. The number of cocaine injections and food pellets acquired during the saline treatment baseline was compared with 10-day periods when buprenorphine only, naltrexone only, combinations were administered (Study I) and with 10-day periods when naltrexone was administered 20 minutes before buprenorphine (Study II). The effects of simultaneous buprenorphine and naltrexone treatment were also compared with conditions in which the same doses of naltrexone (0.05 to 0.40 mg/kg/day) were given 20 minutes before buprenorphine. If the ANOVA showed a significant main effect, Dunnett's Multiple Comparison Procedure was used to determine which conditions were significantly different from the saline treatment baseline or from the effects of buprenorphine alone. To determine if the effects of naltrexone on cocaine self-administration were naltrexone dose dependent, ANOVAs with naltrexone as a repeated measure were run for the simultaneous and for the 20-minute pretreatment conditions. Degrees of freedom were corrected using Geisser-Greenhouse Epsilon factors. When repeated-measures ANOVAs yielded significant effects, linear contrasts were evaluated comparing control conditions to all treatment conditions. Probability levels of $p < .05$ to $.0001$ are reported as statistically significant. In some instances, data are expressed as the average percent change from each subject's saline

treatment baseline to facilitate comparisons between monkeys.

RESULTS

Buprenorphine's Effects on Cocaine Self-Administration

Buprenorphine significantly reduced cocaine self-administration in comparison to saline treatment ($p < .01$). Group data for five monkeys are shown in Figure 1. During saline treatment, monkeys self-administered an average of $65.5 (\pm 5.8)$ cocaine injections per day. Cocaine self-administration fell to $27.9 (\pm 7.6)$ injections per day during buprenorphine treatment and then returned to baseline levels of $62.3 (\pm 3.6)$ injections per day when saline treatment was resumed (Fig. 1, left panel). This rapid increase in cocaine self-administration probably reflects the relatively short duration of buprenorphine treatment, because recovery was slower after 30 to 120 days of buprenorphine treatment (Mello et al. 1990, 1992a).

Simultaneous Naltrexone and Buprenorphine Administration: Effects on Cocaine Self-Administration (Study I)

When ascending doses of naltrexone (0.05 to 0.40 mg/kg/day) were given *simultaneously* with buprenorphine in a single solution, cocaine self-administration remained significantly below the saline treatment baseline ($p < .05$ to $.01$). Group data ($n = 5$) are shown in the center panel of Figure 1. The magnitude of the reduction in cocaine self-administration was significantly less ($p < .05$ to $.01$) during treatment with the four naltrexone and buprenorphine combinations than during treatment with buprenorphine alone. However, the effects of simultaneous buprenorphine and naltrexone administration were not naltrexone dose dependent. Naltrexone alone had no effect on cocaine-maintained responding. Average cocaine injections per day during naltrexone treatment were equivalent to cocaine self-administration during saline treatment (63.2 ± 5.3 vs. 65.5 ± 5.8).

Cocaine self-administration data for the group ($n = 5$) expressed as percent change from the initial saline treatment baseline are shown in Figure 2 (left panel). Buprenorphine alone reduced cocaine self-administration by 53% but ascending doses of naltrexone in combination with the same dose of buprenorphine reduced cocaine self-administration by only 30%, 30%, 23%, and 23%, respectively (Fig. 2, left). Cocaine self-administration during buprenorphine treatment alone was significantly less ($p < .05$ to $.01$) than during simultaneous buprenorphine plus naltrexone treatment.

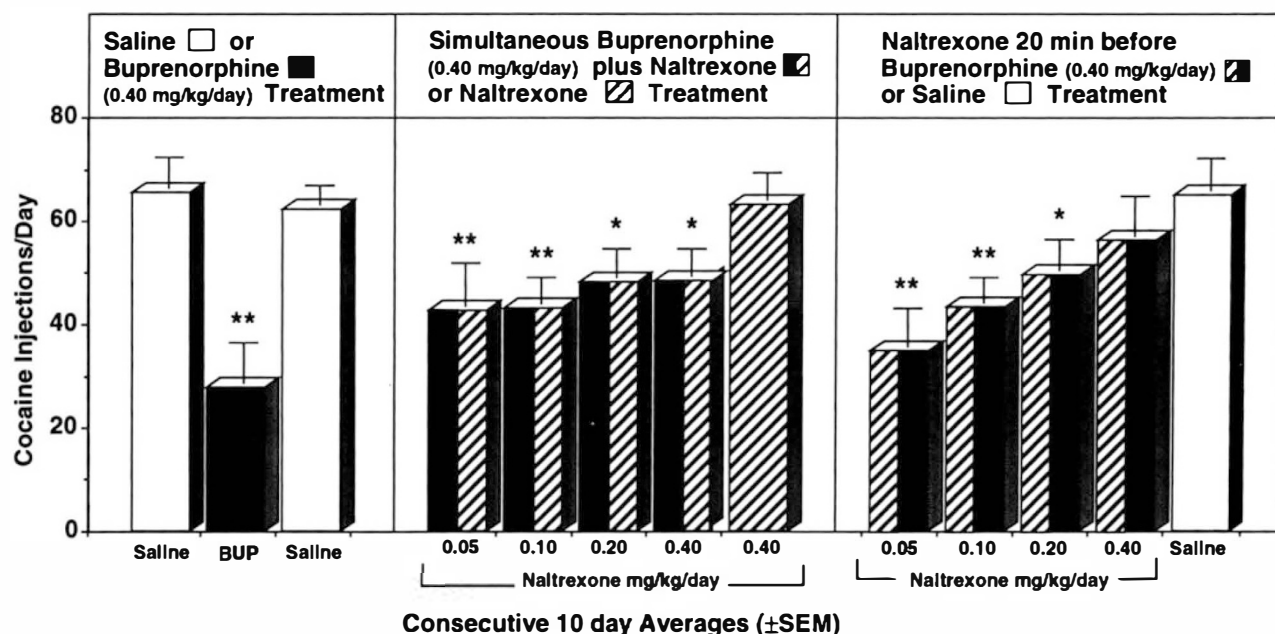


Figure 1. Effects of buprenorphine or naltrexone only, buprenorphine–naltrexone combinations, and saline control treatment on cocaine self-administration. Group data for five monkeys are shown in each 10-day treatment condition. Cocaine injections per day ($\bar{x} \pm \text{SE}$) are shown on the left ordinate. Cocaine self-administration during daily saline (open bar) and 0.40 mg/kg buprenorphine (black bar) treatment are shown in the left panel. Cocaine self-administration during simultaneous administration of buprenorphine and ascending doses of naltrexone (0.05 to 0.40 mg/kg) (black and striped bars) and naltrexone alone (striped bar) are shown in the middle panel. Cocaine self-administration during treatment with ascending doses of naltrexone (0.05 to 0.40 mg/kg/day) administered 20 minutes before buprenorphine (0.40 mg/kg/day) (striped and black bars) and during saline control treatment (open bar) are shown in the right panel. Asterisks indicate statistically significant changes from the prebuprenorphine saline baseline treatment as determined by ANOVA for repeated measures and Dunnett's follow-up tests (* $p < .05$; ** $p < .01$).

Effects of Naltrexone Pretreatment on Buprenorphine's Effects on Cocaine Self-Administration (Study II)

Administration of naltrexone 20 minutes before buprenorphine resulted in a significant naltrexone dose-dependent attenuation of buprenorphine's reduction of cocaine self-administration ($p < .01$). Cocaine self-administration remained significantly lower than the initial saline treatment baseline at naltrexone doses of 0.05 to 0.20 mg/kg/day in combination with buprenorphine (Fig. 1, right panel). But at the highest dose of naltrexone (0.40 mg/kg/day) and buprenorphine, cocaine self-administration was not significantly lower than during the first saline treatment baseline condition (Fig. 1). Cocaine self-administration during the third saline treatment condition also did not differ significantly from the initial saline baseline (Fig. 1).

In comparison to buprenorphine treatment alone (53% reduction), there was an orderly naltrexone dose-dependent decrease in buprenorphine's reduction of cocaine self-administration from 42% to 31% to 19% to 8%, respectively, below the saline treatment baseline. Cocaine self-administration was significantly higher during treatment with naltrexone doses of 0.10, 0.20, and 0.40 mg/kg in combination with buprenorphine

than during buprenorphine alone ($p < .05$ to $.01$) (Fig. 2, right panel). Cocaine self-administration during pretreatment with the lowest dose of naltrexone plus buprenorphine did not differ from buprenorphine alone (Fig. 2, right panel).

Buprenorphine's Effects on Food Self-Administration

Food self-administration decreased from 91.7 ± 14 to 67.2 ± 9 pellets per day during buprenorphine treatment, but this change (26.7%) was not statistically significant. When saline was substituted for buprenorphine, food self-administration returned to control levels of 95.7 ± 11 pellets per day. Food self-administration during saline and buprenorphine treatment is shown in Figure 3 (left panel).

Simultaneous Naltrexone and Buprenorphine Administration: Effects on Food Self-Administration (Study I)

Food self-administration during simultaneous buprenorphine and naltrexone administration did not differ significantly from either the saline treatment baseline

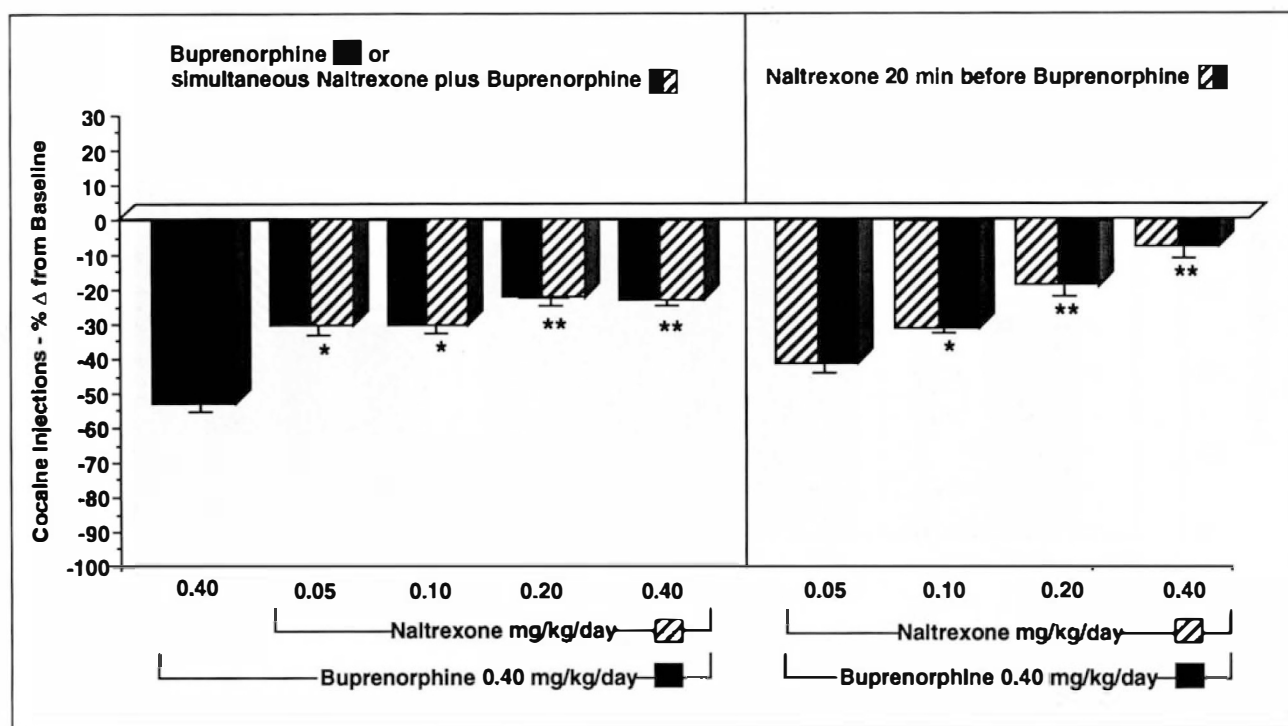


Figure 2. Comparison of the effects of buprenorphine only with buprenorphine–naltrexone combinations on cocaine self-administration. The average number of cocaine injections ($\bar{x} \pm \text{SE}$) self-administered by five monkeys during successive 10-day treatment conditions are shown as percent change from the prebuprenorphine saline treatment baseline. Percent change from baseline is shown on the left ordinate. Successive 10-day periods of buprenorphine treatment (black bar), buprenorphine and simultaneous administration of ascending doses of naltrexone (0.05 to 0.40 mg/kg/day) (black and striped bars) are shown in the left panel. Successive 10-day periods of ascending doses of naltrexone (0.05 to 0.40 mg/kg/day) administered 20 minutes before buprenorphine (striped and black bars) are shown in the right panel. The statistical significance of changes in cocaine self-administration during combined naltrexone–buprenorphine treatment in comparison to buprenorphine treatment alone are shown as asterisks (* $p < .05$; ** $p < .01$).

or buprenorphine treatment alone. Food self-administration was somewhat variable during this condition and showed no orderly relation to the ascending doses of naltrexone. Group data ($n = 5$) are shown in the center panel of Figure 3.

Effects of Naltrexone Pretreatment on Buprenorphine's Effects on Food Self-Administration (Study II)

Food self-administration did not differ significantly from the saline treatment baseline throughout the 20-minute naltrexone pretreatment plus buprenorphine condition (Fig. 3, right panel). However, there was a naltrexone dose-dependent increase in food self-administration that paralleled the increase in cocaine self-administration (Figs. 1 and 3, right panels). When cocaine self-administration increased further during the final saline treatment condition (Fig. 1), food self-administration returned to initial saline treatment levels (Fig. 3).

Individual Patterns of Cocaine Self-Administration During Buprenorphine and Naltrexone Treatment

Daily cocaine self-administration by individual monkeys during treatment with buprenorphine only, naltrexone only, and simultaneous administration of buprenorphine and naltrexone (0.40 mg/kg/day) are shown in figure 4. Data are shown as percent change from each monkey's saline treatment baseline to facilitate comparisons between subjects. The time course and degree of reduction in cocaine-maintained responding varied across individuals. Buprenorphine treatment was followed by an abrupt and sustained reduction in cocaine self-administration in four monkeys (Fig. 4, rows 1 to 4). Over the 10 days of buprenorphine treatment, their cocaine self-administration was reduced by an average of 96%, 75%, 42%, and 35%, respectively. One monkey was relatively insensitive to buprenorphine treatment, and cocaine self-administration averaged only 20% below baseline (Fig. 4, row 5).

In contrast to buprenorphine, naltrexone alone re-

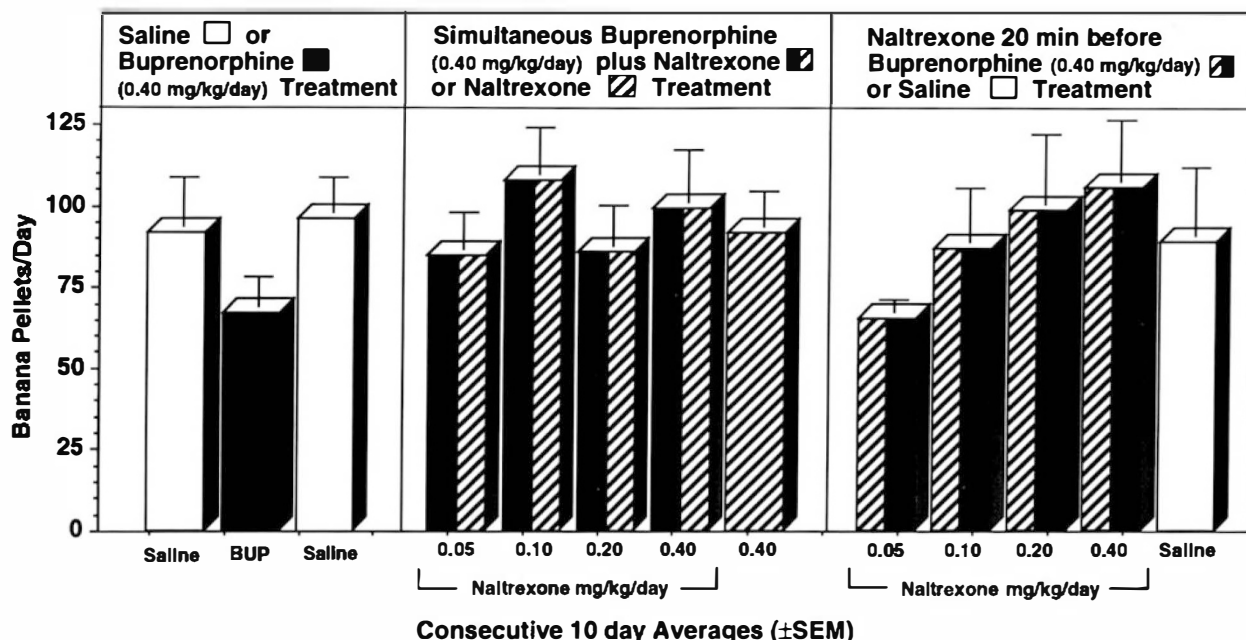


Figure 3. Effects of buprenorphine or naltrexone only, buprenorphine-naltrexone combinations, and saline control treatment on food self-administration. Group data for five monkeys are shown in each 10-day treatment condition. Food pellets per day ($\bar{x} \pm \text{SE}$) are shown on the left ordinate. Food self-administration during daily saline (open bar) and buprenorphine (0.40 mg/kg) (black bar) treatment are shown in the left panel. Food self-administration during simultaneous administration of buprenorphine and ascending doses of naltrexone (0.05 to 0.40 mg/kg) (black and striped bars), and naltrexone only (striped bar) are shown in the middle panel. Food self-administration during treatment with ascending doses of naltrexone (0.05 to 0.40 mg/kg/day) administered 20 minutes before buprenorphine (0.40 mg/kg/day) (striped and black bars) and during saline control treatment (open bar) are shown in the right panel.

duced cocaine self-administration by an average of 25% in only one monkey (Fig. 4, row 2). The other four monkeys' cocaine self-administration remained similar to their respective saline baselines during naltrexone treatment (range 7% to 10% below baseline). When the same doses of naltrexone and buprenorphine were administered simultaneously, cocaine self-administration was lower than during naltrexone treatment alone but higher than during buprenorphine treatment alone in all monkeys (Fig. 4, rows 1 to 4). The average reduction in cocaine self-administration over 10 days from the previous saline treatment baseline ranged from less than 1% (Fig. 4, row 3) to 59% (Fig. 4, row 2). The effectiveness of the buprenorphine-naltrexone combination in reducing cocaine self-administration increased over time in three monkeys (Fig. 4, rows 1, 2, and 4) and remained relatively stable in two monkeys (Fig. 4, rows 3 and 5).

DISCUSSION

Effects of Buprenorphine and Buprenorphine-Naltrexone Combinations on Cocaine Self-Administration

Buprenorphine alone (0.40 mg/kg/day) significantly reduced cocaine self-administration by rhesus mon-

keys by an average of 53% in comparison to saline control treatment ($p < 0.1$). These data confirm and extend previous findings in the primate and rodent drug self-administration model (Carroll et al. 1992; Carroll and Lac 1992; Mello et al. 1989, 1990, 1992a). However, concurrent administration of naltrexone and buprenorphine significantly reduced the effects of buprenorphine alone on cocaine self-administration (Figs. 1 and 2). Simultaneous administration of ascending doses of naltrexone (0.05 to 0.40 mg/kg/day) significantly reduced the suppressive effects of buprenorphine treatment on cocaine self-administration ($p < .05$ to $.01$), but this effect was equivalent across the naltrexone doses studied. Naltrexone alone had no effect on cocaine-maintained responding. When naltrexone was given 20 minutes before buprenorphine, there was a significant naltrexone dose-dependent attenuation of buprenorphine's effects on cocaine self-administration ($p < .05$ to $.01$) (Figs. 1 and 2).

Because the opioid antagonist, naltrexone, has selective activity at the mu receptor (France et al. 1990; Martin et al. 1973) and buprenorphine is a partial mu agonist (Jaffe and Martin, 1990), these data suggest that naltrexone antagonized the mu agonist component of buprenorphine and this, in turn, attenuated buprenorphine's effectiveness in reducing cocaine self-administration in monkey. These data are consis-

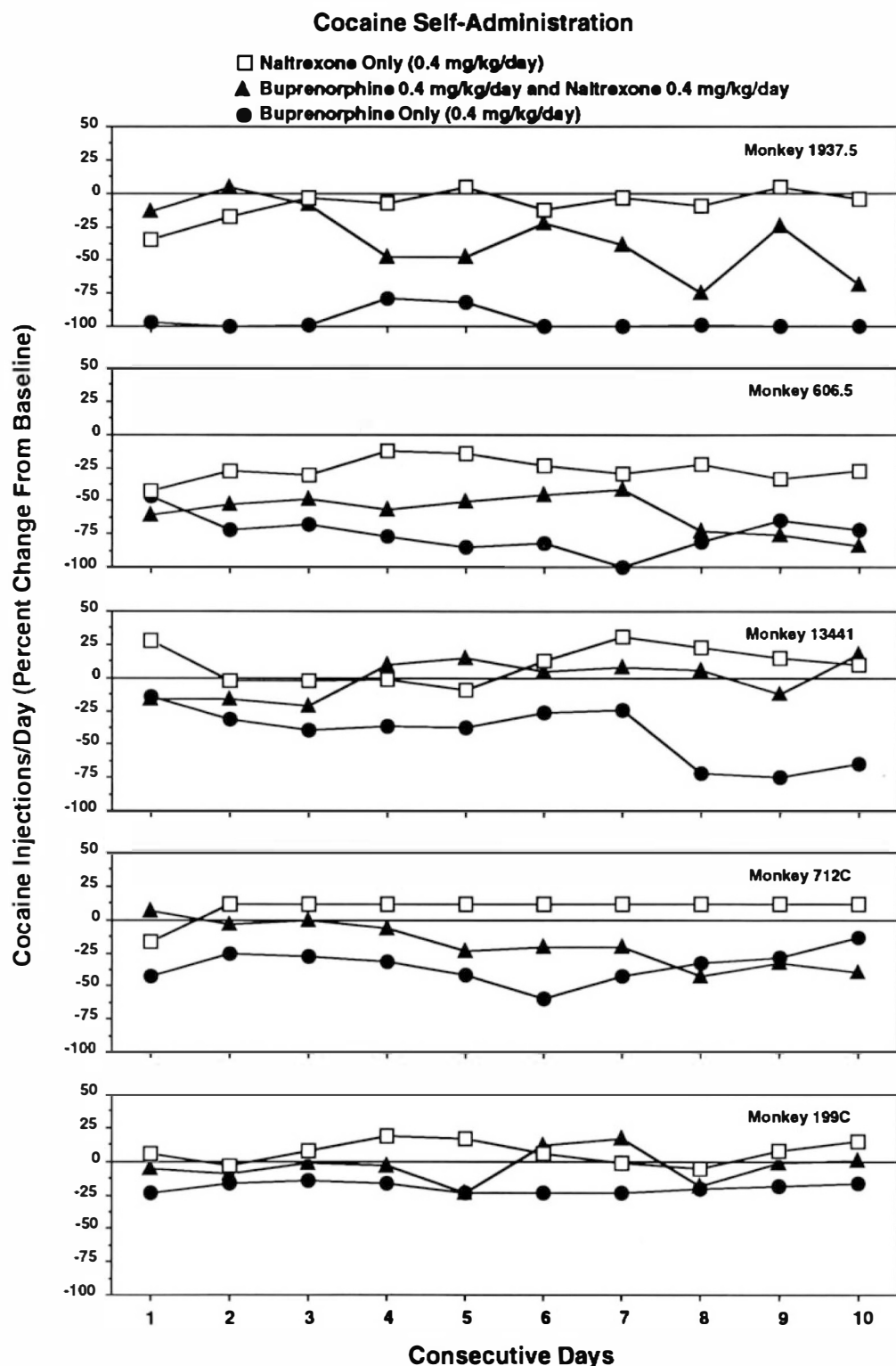


Figure 4. Time course of changes in cocaine self-administration during treatment with buprenorphine only (0.40 mg/kg/day), naltrexone only (0.40 mg/kg/day), and simultaneous administration of buprenorphine (0.40 mg/kg/day) and naltrexone (0.40 mg/kg/day). Daily cocaine self-administration during buprenorphine treatment (black circles), naltrexone treatment (open squares), and simultaneous administration of buprenorphine and naltrexone (0.40 mg/kg/day) (closed triangles) are shown for individual monkeys. Data are expressed as percent change in cocaine injections from the saline treatment baseline (left ordinate) over 10 consecutive days (abscissa).

tent with recent findings that naltrexone (0.3 to 1.0 mg/kg) antagonized the protective effects of buprenorphine in reducing lethality associated with cocaine-induced convulsions in mice (Witkin et al. 1991). The opioid agonists, morphine and methadone, also reduced cocaine-related lethality in mice, whereas naltrexone alone did not (Witkin et al. 1991). These data were interpreted to suggest that buprenorphine's protective effects were mediated by mu opioid receptors (Witkin et al. 1991).

In rhesus monkey, acute administration of either an opioid agonist, (heroin, 0.03 and 0.10 mg/kg) or buprenorphine (1.0 and 3.2 mg/kg) suppressed rates of cocaine-maintained responding over the dose range of 0.001 to 0.1 mg/kg per injection of cocaine (Winger et al. 1992). These data could be interpreted to suggest that buprenorphine was acting like a mu agonist in that paradigm. Yet, quadazocine, an opioid antagonist, produced equivalent suppression of cocaine-maintained responding at doses of 0.1 and 1.0 mg/kg, which was interpreted as probably not due to its opioid antagonist actions (Winger et al. 1992). Because the effects of heroin, buprenorphine, and quadazocine on concurrent food-maintained responding were not studied by Winger and coworkers, the selectivity of these drug effects for cocaine cannot be established with certainty.

If the mu opioid agonist component of buprenorphine is one important factor in its interactions with cocaine, then treatment with an opioid agonist such as methadone should also be effective in reducing cocaine self-administration. However, clinical reports indicate that methadone was less effective than buprenorphine or naltrexone in reducing cocaine abuse by opiate-dependent patients (Kosten et al. 1989a, 1989b). In other studies of opiate-dependent patients, intermittent cocaine use continued during treatment with either methadone or buprenorphine (Fudala et al. 1991; Johnson et al. 1992). Moreover, cocaine's acute subjective effects and heart rate increases were greater in polydrug users on methadone maintenance (50 mg/day) than in abstinent opioid abusers (Preston et al. 1993). Preclinical studies of the effects of opioid agonists on cocaine self-administration by monkeys are also inconsistent; both no effect (Stretch 1977) and decreased cocaine self-administration have been reported (Wilson and Schuster 1970; Winger et al. 1992).

Whatever the role of mu opioid agonist activity in buprenorphine-cocaine interactions, there is increasing evidence that cocaine per se directly affects mu opioid receptors in the brain. Chronic cocaine exposure increases opiate receptor density in rodent brain (Hammer 1989; Ishizuka et al. 1988; Unterwald et al. 1992). Increased opiate receptor density in brain areas associated with drug reinforcement was inferred

from observed changes in binding of [3 H]naloxone (Hammer 1989; Ishizuka et al. 1988) and a mu-selective opioid ligand [3 H]DSAMGO (Unterwald et al. 1992). Evidence of cocaine-induced increases in opioid receptor density in brain raises the intriguing possibility that the duration of cocaine exposure and/or the degree of cocaine dependence may influence buprenorphine's effectiveness in reducing cocaine self-administration. This notion is supported by the finding that although buprenorphine (4 mg/day) significantly reduced cocaine self-administration by patients who met DSM-III-R criteria for dependence on cocaine as well as opiates and had abused both drugs for over 10 years (Gastfriend et al. 1992, 1993a, 1993b), both buprenorphine and methadone were equally ineffective in reducing cocaine intake in nondependent, intermittent cocaine abusers (Fudala et al. 1991; Johnson et al. 1992). Because cocaine's reinforcing and discriminative stimulus properties appear to reflect inhibition of dopamine reuptake (Johanson and Fischman 1989; Kuhar et al. 1988), buprenorphine's interactions with both endogenous opioid and dopaminergic systems are probably important for its effects on cocaine self-administration. It was neuroendocrine evidence of dopamine-opioid interactions that originally prompted us to explore buprenorphine's effects on cocaine self-administration (Mello and Mendelson 1993a, 1993b; Mello et al. 1989). The complexity of these interactions is illustrated by reports that buprenorphine increases dopamine release in rat nucleus accumbens (Brown et al. 1991) and naltrexone (1.0 mg/kg) pretreatment prevents buprenorphine (0.1 mg/kg) induced dopamine release in the nucleus accumbens (Holman et al. 1993).

Effects of Naltrexone on Cocaine and Food Self-Administration

The failure of naltrexone (0.40 mg/kg) alone to affect cocaine self-administration is not consistent with previous clinical reports (Kosten et al. 1989a) or with our previous studies in rhesus monkey (Mello et al. 1990). Naltrexone significantly reduced cocaine-positive urines in heroin-dependent polydrug abusers (Kosten et al. 1989a) and reduced cocaine self-administration by rhesus monkeys by 25% to 27% (Mello et al. 1990). Our previous studies were conducted under identical behavioral conditions, and the doses of naltrexone (0.32 to 3.20 mg/kg/day) overlapped the dose used in the present study (0.40 mg/kg/day) (Mello et al. 1990). However, monkeys had a different sequence of exposure to treatment conditions. In our previous studies, naltrexone was administered after 15 days of saline treatment (Mello et al. 1990), whereas in this study, naltrexone treatment followed 40 days of treatment with buprenorphine and naltrexone combinations. Only one monkey

(199C) was a subject in both studies. Naltrexone (0.32 mg/kg/day) significantly decreased cocaine self-administration ($p < .01$) after 10 days of treatment (during days 11 to 15) in this monkey in our previous study (Mello et al. 1990), but cocaine self-administration was minimally affected by naltrexone (0.40 mg/kg/day) in the present study (see Fig. 4). The difference in naltrexone's effects in our two studies may be attributable, in part, to persistent effects of buprenorphine after 40 days of exposure. These data also underscore the importance of drug history and behavioral history in influencing responsivity to naltrexone (Warren and Morse 1989).

Naltrexone did not change food-maintained responding in comparison to the initial saline treatment baseline (Fig. 3). Naltrexone pretreatment was followed by a dose-dependent increase in food self-administration that paralleled an increase in cocaine-maintained responding (Figs. 1 and 3). In contrast to previous studies in squirrel monkeys (Goldberg et al. 1981), there was no evidence of excessive salivation or vomiting during 10 days of naltrexone treatment or 40 days of combined naltrexone and buprenorphine treatment in the present study or in our previous studies (Mello et al. 1990). In squirrel monkey, acute naltrexone administration (10 mg/kg) produced salivation and vomiting and after chronic daily naltrexone treatment for 38 to 39 days, supersensitivity to naltrexone developed and a lower dose (0.3 mg/kg) also produced vomiting (Goldberg et al. 1981). These discrepant findings may reflect differences in the naltrexone doses studied (10 mg/kg vs. 0.40 mg/kg) as well as unexplained species differences.

Buprenorphine-Cocaine Interactions

We have suggested that buprenorphine's unique combination of agonist and antagonist characteristics is essential for its selective effects on cocaine self-administration (Mello et al. 1993a; Mello and Mendelson 1993a, 1993b). Other opioid mixed agonist-antagonist analgesics such as nalbuphine and butorphanol also produce dose-dependent decreases in cocaine self-administration by rhesus monkeys (Mello et al. 1993b; Winger et al. 1992). However, these effects of chronic butorphanol and nalbuphine treatment over 10 days were not selective for cocaine because food-maintained responding also decreased in parallel with cocaine self-administration (Mello et al. 1993a).

Although data described in this study suggest that the mu agonist component of buprenorphine is important for its interactions with cocaine, the mechanisms by which buprenorphine reduces cocaine self-administration are unknown. There is also compelling behavioral and physiologic evidence that buprenorphine has kappa antagonist effects in addition to its partial

mu agonist properties. In behavioral studies, buprenorphine antagonized the effects of a selective kappa agonist, U50,488 (Negus and Dykstra 1988; Negus et al. 1990, 1991). Buprenorphine also precipitated withdrawal in kappa agonist-dependent monkeys (Gmerek et al. 1987) and antagonized the diuretic effects of a kappa agonist, brexazocine (Leander 1987; Richards and Sadee 1985). The extent to which buprenorphine's kappa antagonist effects may also contribute to its suppressive effects on cocaine self-administration remains to be determined once systemically active selective kappa antagonists become available.

Clinical Implications

Because the simultaneous administration of buprenorphine and naltrexone significantly reduced the suppression of cocaine self-administration achieved with buprenorphine alone (Figs. 1 and 2), the addition of an opioid antagonist to reduce illicit diversion of buprenorphine might compromise its effectiveness for treatment of cocaine and opiate dependence. The extent to which these findings with naltrexone, a long-acting mu opioid antagonist, are applicable to naloxone, a short-acting mu opioid antagonist is unknown. Naloxone-buprenorphine combinations attenuated the subjective and physiologic effects of buprenorphine alone but did not compromise buprenorphine's analgesic effectiveness in persons who were not opiate-dependent (Strain et al. 1992; Rolly et al. 1986). In methadone-dependent men, naloxone-buprenorphine combinations induced abstinence signs similar to the effects of naloxone alone (Preston et al. 1988). In preclinical studies, naloxone pretreatment antagonized buprenorphine's effects on a variety of behavioral measures (Dykstra, 1983; Shannon et al. 1984; DeRosett and Holtzman, 1984). There is considerable clinical evidence that buprenorphine reduces cocaine abuse in opiate-dependent patients (Kosten et al. 1989; Rosen and Kosten 1991) as well as in polydrug abusers dependent on both cocaine and opiates (Gastfriend et al. 1992, 1993a, 1993b). The concordance between preclinical and ongoing clinical evaluations of buprenorphine treatment suggests the value of animal models of drug self-administration for predicting the effectiveness of new pharmacotherapies for drug abuse treatment (Mello et al. 1993a, 1993b; Mello, 1992).

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