

Effects of Bremazocine on Self-Administration of Smoked Cocaine Base and Orally Delivered Ethanol, Phencyclidine, Saccharin, and Food in Rhesus Monkeys: A Behavioral Economic Analysis

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▶ Abstract

There is increasing evidence that κ -opioid receptor agonists modulate cocaine-maintained behavior, and limited findings implicate the involvement of κ -opioid receptors in ethanol-maintained behaviors. The purpose of the present study was to investigate the effects of bremazocine, a κ -opioid agonist, on the self-administration of smoked cocaine base and oral ethanol in rhesus monkeys (*Macaca mulatta*). To determine the selectivity of bremazocine, the effects of bremazocine pretreatment on the oral self-administration of phencyclidine (PCP), saccharin, and food were also examined. Adult male rhesus monkeys were trained to self-administer oral ethanol, PCP, saccharin ($n = 8$), food ($n = 6$), or smoked cocaine base ($n = 6$) and water during daily sessions. Bremazocine (0.00032-, 0.001-, and 0.0025-mg/kg i.m.) injections were given 15 min before session. The 4 days of stable behavior before pretreatment served as baseline. Demand curves (consumption \times fixed ratio; FR) were obtained for smoked cocaine base, ethanol, and PCP by varying the cost (FR) of drug deliveries and measuring consumption (deliveries). Bremazocine (0.001 mg/kg) was administered at each FR value in nonsystematic order. Results indicate that bremazocine dose dependently reduced cocaine, ethanol, PCP, and saccharin intake. Food intake was affected less by bremazocine than the other substances

in five of the six monkeys. Generally, bremazocine treatment reduced the demand for cocaine, ethanol, and PCP as well as other measures of response strength. These results extend the findings that κ -agonists reduce the self-administration of drug and nondrug reinforcers to smoked cocaine base and oral ethanol, PCP, and saccharin in rhesus monkeys.

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▶ Introduction

Cocaine and alcohol abuse are well recognized psychiatric disorders with high rates of recidivism. Currently, there are few effective pharmacotherapies for the treatment of these disorders. However, recently κ -opioid receptor agonists have shown potential for the treatment of cocaine abuse, and limited evidence suggests that κ -agonists modulate ethanol-maintained behaviors (Nestby et al., 1999*). It is increasingly evident that the mesolimbic dopamine system plays a role in mediating the reinforcing effects of psychostimulant drugs. It is well known that within this system, μ - and δ -agonists stimulate and κ -agonists suppress dopaminergic neurotransmission (Herz, 1998*), and it is likely that these opposing effects of μ - or δ - and κ -opioid receptors within this system modulate drug-maintained behaviors. For example, the κ -opioid agonists [U50488](#) and bremazocine reduced dopamine transmission in the mesolimbic dopamine system; whereas, μ -agonists stimulated dopamine transmission (Di Chiara and Imperato, 1988*).

It is generally accepted that κ -opioid receptors are involved in the neurobiological and behavioral effects of cocaine. κ -Agonists suppressed the increase in basal dopamine dialysate levels occurring during abstinence from cocaine (Heidbreder and Shippenberg, 1994*; Chefer et al., 2000*). The κ -agonist [U69593](#) decreased basal rates of dopamine uptake in rats, whereas acute administration transiently increased dopamine uptake (Thompson et al., 2000*). κ -Agonists may act as functional antagonists of cocaine by modulating dopamine neurotransmission.

In behavioral paradigms, the selective κ -opioid agonist [U69593](#) reduced the locomotor stimulant effects of cocaine (Vanderschuren et al., 2000*), blocked the development of sensitization to cocaine in a place preference paradigm (Shippenberg et al., 1996*), and prevented the acute locomotor-activating effects of cocaine and sensitization to its repeated administration (Heidbreder et al., 1995*). Additionally, the selective κ -opioid agonist [U50488](#) attenuated the locomotor stimulant effects of cocaine (Vanderschuren et al., 2000*), and low doses reduced the discriminative stimulus effects of cocaine (Kantak et al., 1999*). Also, [U50488](#) reduced i.v. self-administration of cocaine in rats (Glick et al., 1995*; Kuzmin et al., 1997*), and [U69593](#) attenuated i.v. cocaine self-administration and reinstatement in rats (Schenk et al., 1999*). Additionally, bremazocine and other κ -

agonists reduced i.v. cocaine-maintained behavior in rhesus monkeys (Mello and Negus, 1998⁺).

κ -Receptors may also modulate the effects of ethanol. Bremazocine, [U50488](#), and [U62066](#), a selective κ -agonist, increased ethanol-induced motor incoordination in the mouse (Dar, 1998⁺), and bremazocine has been reported to reduce ethanol self-administration, but not sucrose intake, in rats (Nestby et al., 1999⁺). Chronic administration of enadoline, a κ -agonist, was found to attenuate ethanol intake and preference in rats (Holter et al., 2000⁺). κ -Agonists may also modulate phencyclidine (PCP)-maintained behavior. A relationship between 6,7-benzomorphans and the *N*-methyl-D-aspartate receptor has been reported (Grauert et al., 1998⁺); however, the interaction is not fully understood. Additionally, dynorphin, an endogenous opioid, may act directly at the *N*-methyl-D-aspartate receptor without involving the κ -opioid receptor (Chen et al., 1995⁺).

Few studies have examined the effect of κ -agonists on drug self-administration, and no studies have examined the effect of κ -agonists on smoked cocaine base, which has become a prevalent route of cocaine abuse in humans. Additionally, it has been suggested that κ -opioid agonists that also possess antagonist activity at μ -receptors may be more effective in the treatment of cocaine abuse than selective κ -opioid agonists (Mello and Negus, 2000⁺; Neumeyer et al., 2000⁺) due to the additional inhibition of dopamine release. Bremazocine, a benzomorphan analog, acts as a potent κ -opioid agonist (Romer et al., 1980⁺), has a high binding affinity for μ - and δ -opioid receptors (Emmerson et al., 1994⁺), and acts as a strong antagonist at the μ -opioid receptor (Von Voigtlander and Lewis, 1982⁺; Mulder et al., 1991⁺). Bremazocine may also have an agonist effect at a subtype of the δ -opioid receptor, resulting in antagonism of the dopamine D₁ receptor (Heijna et al., 1989⁺; Vanderschuren et al., 2000⁺).

The purpose of the present study was to extend the findings on κ -agonists by investigating the effects of bremazocine on smoked cocaine base and oral intake of ethanol and PCP in rhesus monkeys. Additionally, it was important to evaluate the selectivity of effects of bremazocine on cocaine- and ethanol-maintained behavior by examining the effects of bremazocine on behaviors maintained by other nondrug reinforcers (saccharin and food). A second purpose of the study was to examine the effects of bremazocine on the demand for cocaine-, ethanol-, and PCP-using behavioral economic measures. Demand curves were obtained by varying the price or number of responses required for each drug delivery or fixed ratio (FR), and measuring the number of drug deliveries (consumption) at each FR.



Materials and Methods

Animals

Sixteen adult male rhesus monkeys (*Macaca mulatta*) served as experimental subjects. Eight monkeys (M-A1, M-B4, M-E, M-G2, M-I, M-J1, M-J2, and M-X) self-administered orally delivered ethanol, PCP, or saccharin concurrently with water under an FR schedule. These monkeys had previous experience orally self-administering these substances. Six monkeys (M-B4, M-C2, M-G2, M-I, M-J2, and M-Y) that had previously self-administered food were assigned to the group that self-administered food pellets. Six monkeys that had previously self-administered smoked cocaine base (M-L, M-L2, M-O, M-M3, M-S, and M-S4) were assigned to the cocaine group. Monkeys were maintained at 85% of their free feeding weights, and the 85% weights ranged from 9.0 to 13.0 kg across monkeys. The animals were weighed every 2 weeks to monitor body weight, and food allotments were adjusted to maintain them at their 85% weights. The monkeys' diet consisted of Teklad monkey chow (Bartonville, IL), fresh fruit on a daily basis, and trail mix or other small snacks were provided several times per week for enrichment at least 1 h after the daily session. Other forms of enrichment (television, Kong toys) were provided nonsystematically, several times per week, and they did not interfere with the daily session responding for food or liquids. Animals had visual, auditory, and olfactory contact with each other throughout the study. They were monitored at least every other day by the veterinary staff. Animals were individually housed in temperature- and humidity-controlled colony rooms on a 12-h light/dark cycle with lights on at 7:00 AM. Use of the animals for this protocol was approved by the University of Minnesota Institutional Animal Care and Use Committee (protocol number 0112A14081). Laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care, and principles of laboratory animal care (National Research Council, 1996) were followed.

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Apparatus

Monkeys were housed in individual, custom-made stainless steel cages (83 cm in width × 76 cm in height × 100 cm in depth) (Lab Products, Maywood, NJ) consisting of three solid walls, a barred front door, a grid floor, and a primate perch. One side wall was modified to allow for attachment of an operant panel from the exterior of the cage. Through cutouts in the side wall, response devices on the panel were inserted into the cage. These included two solenoid-operated brass drinking spouts, a primate lever, and stimulus lights above the spouts and lever. The two brass drinking spouts (1.2 cm in diameter) extended 2.7 cm into the cage and were located at the level of the monkey's mouth (45 cm above the cage floor). The drinking spouts were activated by lip contact responses. Upon completion of the required number of lip contact responses, under an FR schedule, a solenoid valve opened allowing 0.6 ml of liquid to flow through Tygon tubing from a 2000-ml Nalgene reservoir suspended above the cage panel through the drinking spout. Lip removal closed the solenoid valve and terminated the liquid delivery. A primate lever was located in the middle of the panel approximately 20 cm above the cage floor. A recessed food receptacle was located directly underneath the primate lever. Upon completion of lever FR requirements, one primate chow biscuit (7.0 g) was released into

the food receptacle from a primate universal magazine feeder (Gerbrands Inc., Arlington, MA) that was mounted on the exterior of the cage and connected by a chute to the food receptacle.

Colored stimulus lights (3-cm LED) were located directly above the primate lever (red) and above the two drinking spouts (green) mounted on either side of the lever. During daily sessions, a green LED flashed to signal ethanol, PCP, or saccharin availability at that spout. The other green LED remained solid to signal water availability at the spout. During food-maintained responding sessions, a red LED above the lever remained solid on to signal food availability, and the green LEDs remained illuminated to signal water availability at both drinking spouts. Each drinking spout was circumscribed by four small white and green cue lights, visible through a clear Plexiglas mounting plate that provided visual feedback when a lip contact was made. These lights remained illuminated during a lip contact, and they served as feedback to acknowledge that a lip contact was made, since no auditory stimuli occurred during the response. The two green lights indicated lip contacts when ethanol, PCP, or saccharin was available, and the two white lights indicated lip contacts when water was available.

The panel was slightly modified for the smoked cocaine base condition. The right drinking device was replaced with a smoking device that had a stainless steel spout similar in size to the drinking spouts. The panels had colored stimulus lights (3-cm LED) above the response lever (red) and both spouts (green). A solid green light was continuously illuminated over the drinking spout to indicate water access during the session and intersession periods. A solid red light was illuminated above the lever to indicate cocaine access. Upon completion of lever responses, the red light was extinguished, and a flashing green light was illuminated over the smoking spout to indicate availability of smoked cocaine. Each inhalation response was recorded by a vacuum sensor and resulted in the illumination of two white stimulus lights positioned around the spout and visible through a clear Plexiglas mounting plate. During the fifth inhalation response, a cocaine-coated nichrome wire coil was heated, the cocaine was volatilized, and smoke was drawn through the spout by the monkey into the lungs during the inhalation response. The fifth inhalation was used to trigger the heating of the cocaine-coated coil to ensure that the monkey was well engaged in a bout of inhalation responses and would have its mouth in a position on the spout to receive the volatilized cocaine base. Subsequently, the flashing green light over the smoking spout was extinguished, and a 15-min time-out followed during which stimulus lights were extinguished and responding had no consequences. The smoking device apparatus has been explained in detail previously (Carroll et al., 1990*). Data collection and programming of the equipment were controlled by IBM-compatible computers in an adjacent room running MED-PC software (MED Associates, St. Albans, VT).

Drugs

Ethanol (95% w/v) was obtained from the University of Minnesota Chemical Storehouse and was diluted with tap water to an 8% w/v concentration. Cocaine base (National Institute on Drug Abuse, Research Triangle Institute, Research Triangle Park, NC) was

dissolved in 95% ethanol to a concentration of 100 mg/ml and stored in an airtight volumetric flask. An exact amount of cocaine was dripped onto nichrome wire coils and allowed to air dry for at least 24 h before use. Coils were weighed before and after loading to verify that the predetermined amounts of cocaine had evaporated on them. Phencyclidine HCl was obtained from the National Institute on Drug Abuse. Stock concentrations of 1.0 mg/ml PCP were mixed with tap water, and a 0.25-mg/ml concentration was diluted from the stock solution. Solutions were mixed at least 18 h before each session, and they were stored at room temperature. Sodium saccharin was obtained from Sigma-Aldrich (St. Louis, MO) and it was mixed with tap water to form a 0.03% w/v concentration. Bremazocine HCl was obtained from Sigma/RBI (Natick, MA) and it was diluted with saline and stored at room temperature.

Procedure

General Procedure. Three groups of monkeys were involved in the study. One group ($n = 6$) self-administered only smoked cocaine base. A second group ($n = 8$) self-administered orally delivered ethanol, PCP, and saccharin solutions. A third group ($n = 6$) self-administered food pellets. This group consisted of some monkeys from the second group, and other monkeys with a history of lever pressing for food pellets. These animals were all chosen for each part of the experiment based on having previous experience self-administering these substances; therefore, no animal had to be trained to reliably consume the drug, or to lever press. The presentation of the drugs for the second group of monkeys was random to prevent order effects. The monkeys typically self-administered each drug in the dose-response condition for 2 months or until the injection series was completed. They were then switched to a different drug and bremazocine testing began when their behavior stabilized. This typically took no longer than 2 weeks. The monkeys self-administered each orally delivered drug in the behavioral economics condition for a longer period of time, a minimum of 3 to 4 months, due to the lengthier procedure. The behavioral economics condition for the animals self-administering smoked cocaine base took a minimum of 4 to 5 months. The length of time any given monkey self-administered a drug varied according to stability and reliability of drug-taking behavior and equipment malfunctions.

Dose-Response Conditions. One group of animals ($n = 6$) self-administered smoked cocaine base (1 mg/kg/delivery) during daily 4-h sessions beginning at 8:30 AM. Before each session there was a 60-min time-out during which all stimulus lights were extinguished and responding had no consequences. During this time, water intake from the previous day was measured, reservoirs were filled with fresh water, and fresh coils were placed in the smoking spouts. Daily sessions were followed by a 30-min time-out during which animals were fed, water intake was measured, reservoirs were refilled with water, and the smoking spouts were cleaned with alcohol. Animals did not have access to food during the smoked cocaine base daily sessions. During each session animals had the opportunity to receive a maximum of 10 deliveries of cocaine, each delivery was available in consecutive trials. During a trial, animals had 30 min to respond on a lever under FR schedules. Each monkey performed on an FR schedule that produced high rates of responding. Upon completion of the ratio requirements, five inhalation responses were

required to obtain the delivery of cocaine. Five inhalation responses were required to instigate a bout of inhalation responses that ensured that the monkeys' mouth was in contact with the spout and the monkey was ready to receive the smoke. Each completed trial was followed by a 15-min time-out. If response requirements were not completed within the 30 min, the trial was terminated. Two terminated trials ended the session for the subject for that day. During the 15-min time-out, the experimenter entered the room and replaced the used coils with fresh coils. Water was available via lip contact responses on the drinking spout during the session and intersession under an FR 1 schedule.

A second group of monkeys self-administered ethanol, PCP, or saccharin ($n = 8$) concurrently with water during daily 3-h sessions, beginning at 10:00 AM. A third group of monkeys self-administered food pellets during daily 3-h sessions; however, to avoid bloating, water was not available from the two drinking spouts under an FR 1 schedule until 1 h after the animal had terminated access to further food deliveries. Sessions were preceded by a 1-h time-out, during which all stimulus lights were extinguished and responding had no consequences. During this time, water consumption from the previous intersession was measured and recorded, and liquids were prepared for the upcoming session. Daily sessions were followed by a 1.5-h time-out, during which liquid and food consumption were measured, the monkeys were fed, reservoirs were filled with water, and liquids were prepared for the next day. During sessions, monkeys had access to the drug solutions and water under an FR 16 schedule, and food was available contingent on a lever press response under an FR 356 schedule. These FR values were chosen to produce high, stable rates of responding. During the intersession period, from 2:30 PM to 8:00 AM, the monkeys had access to water from both drinking spouts under an FR 1 schedule.

Water was available concurrently with the orally self-administered drugs and saccharin to establish that the animals were reliably choosing the drug or saccharin versus liquid, in general. That drug or saccharin is chosen over water assumes that these substances are functioning as reinforcers. Typically, the selection of drug or saccharin over water becomes more reliable under at least an FR 8 schedule (Carroll, 1982*).

Bremazocine (0.00032, 0.001, 0.0025 mg/kg i.m.) was administered in equal volumes in nonsystematic order for seven consecutive days 15 min before the session. The monkeys were allowed at least 4 days between each injection series to return to baseline levels of behavior. Four days of stable behavior immediately preceding the bremazocine pretreatment days were used as a comparison for the bremazocine administration instead of a vehicle administration because a previous study established that there was no significant difference in drug-maintained responding between these two conditions (Carroll et al., 1992*).

Behavioral Economic Conditions. Animals and general procedure were identical to the dose-response study described above except that monkey M-S4 was not included in the smoked cocaine group due to adverse reactions to the bremazocine that did not dissipate. The effect of 0.001 mg/kg bremazocine on the demand for cocaine, ethanol, and PCP was examined by nonsystematically presenting each subject with a series of FR values. After 4 days of stable behavior at each FR, bremazocine was injected 15 min before session for five consecutive days. During the dose-response conditions, no significant tolerance to

the suppressive effects of bremazocine was observed over the 7-day treatment period; thus, for the behavioral economic analysis bremazocine was administered for five consecutive days. The FR for ethanol and PCP deliveries varied in nonsystematic order, and the FR values were 4, 8, 16, 32, 64, and 128. The FR for smoked cocaine deliveries also varied in nonsystematic order, and the FR values were 16, 32, 64, 128, 256, 512, 1024, and 2056.

Data Analysis

Dose Analysis. Mean numbers of smoke, food, and oral deliveries and responses were calculated for each monkey for the seven consecutive days of bremazocine treatment and for the four preceding baseline days. Repeated measures analyses of variance (ANOVA) were performed separately for smoke, food, and oral responses and deliveries to assess main effects. Post hoc comparisons were made with Fisher's least significant difference-corrected t tests. Significance levels were set a priori at $P < 0.05$.

Behavioral Economic Analysis. Mean numbers of smoke and oral deliveries and responses were calculated for each monkey for the five consecutive days of bremazocine treatment and for the four preceding baseline days. Individual means were averaged across monkeys to determine the S.E.M. Demand curves were obtained by graphing deliveries as a function of unit price (FR value) on a log-log scale. The slope of each demand curve was determined by using simple linear regression analysis. P_{\max} values were obtained with the use of SuperANOVA (Abacus Concepts, Berkeley, CA) according to procedures described by Hursh (1991)*. P_{\max} is a statistical estimate of the unit price (FR) at which maximum responding occurred (Hursh, 1991*). Nonoverlapping 95% confidence intervals were used to establish differences in P_{\max} values. An ANOVA was used to analyze the effects of FR value and bremazocine treatment on cocaine, ethanol, and PCP self-administration (GB Stat, Silver Spring, MD). Post hoc comparisons were made with Fisher's least significant difference-corrected t tests. Significance levels were set a priori at $P < 0.05$.

Other Measures of Reinforcer Strength. Behavior under the increasing FR values that were tested was also analyzed as performance under a progressive ratio (PR) schedule, and break points were defined as the highest ratio completed under each condition for each monkey. In addition, a persistence ratio (Meisch, 2000*) was calculated by the amount consumed at a higher FR (64 or 256 for liquid reinforcers or smoked cocaine, respectively) divided by the amount consumed at a lower FR (4 or 16, respectively) and multiplied by 100.

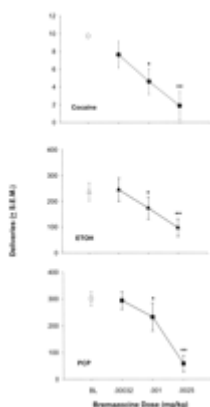
Results

Dose-Response Analyses

There were findings that were similar across the experimental conditions. First, bremazocine was found to dose dependently suppress responses and deliveries across all forms of drug- and nondrug-maintained behavior; however, there was high intersubject variability within each condition. The monkeys self-administering smoked cocaine base initially exhibited more severe behavioral sedation after bremazocine than the other groups, and bremazocine administration at the 0.001- and 0.0025-mg/kg dose produced vomiting in three of the six subjects. These behaviors dissipated after the first or second day of treatment in all but one monkey. A second commonality is that the monkeys consumed all of their daily food allotment postsession during the conditions in which they were not required to lever press for food. Thus, they seemed healthy and side effects were minimal on the days used in the data analysis. Third, these animals had a history of reliably consuming drug versus water during session, and they consumed only minimal amounts of water. The majority of their water intake occurred during the 17.5-h intersession period when food and water but not drug were available. Due to the low volume of water consumption, there was a floor effect, and the comparison of water intake before and during bremazocine administration revealed no differences.

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Smoked Cocaine Base Self-Administration. Figure 1 depicts the effect of bremazocine on deliveries of smoked cocaine base, ethanol, and PCP. Bremazocine significantly reduced responding for smoked cocaine base [$F_{(3,23)} = 3.65, P < 0.05$] at the 0.001-mg/kg [$t_{(5)} = 2.21, P < 0.05$] and 0.0025-mg/kg [$t_{(5)} = 3.22, P < 0.01$] dose. A repeated measures ANOVA revealed a significant main effect of bremazocine [$F_{(3,23)} = 9.34, P < 0.01$] on cocaine consumption. Post hoc analyses revealed a significant decrease at the 0.001-mg/kg [$t_{(5)} = 3.21, P < 0.01$] and 0.0025-mg/kg [$t_{(5)} = 4.93, P < 0.01$] doses, but not at the 0.00032-mg/kg dose. The number of responses and deliveries within all conditions were similarly affected by bremazocine; therefore, only the effect of bremazocine on deliveries are shown.



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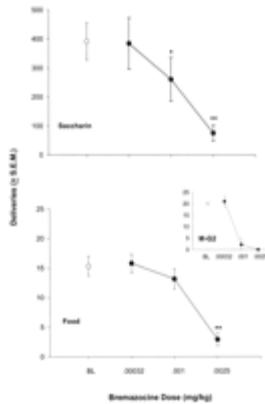
Fig. 1. Mean (\pm S.E.M.) number of deliveries for smoked cocaine base (circles), ethanol (triangles), and PCP (squares) during 3-h sessions of the 4-day baseline period (BL) and 7 days of bremazocine (0.00032-0.0025-mg/kg) pretreatment. Baseline points (open circles) represent a mean for eight monkeys (six for smoked cocaine base) over four consecutive stable days of behavior. Filled circles represent a mean for eight monkeys (six for smoked cocaine base) over seven consecutive days of bremazocine treatment. Asterisks indicate significantly different from BL at the $P < 0.05$ (*) and $P < 0.01$ (**) level.

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Ethanol Self-Administration. Bremazocine dose dependently decreased responses and intake of ethanol. There was a main effect of bremazocine on the number of responses for ethanol [$F_{(3,31)} = 16.44, P < 0.01$] with significant decreases at the 0.001-mg/kg [$t_{(7)} = 2.57, P < 0.05$] and at the 0.0025-mg/kg [$t_{(7)} = 5.79, P < 0.01$] dose. Similarly, there was a main effect of bremazocine on the number of ethanol deliveries consumed [$F_{(3,31)} = 17.06, P < 0.05$] with significant decreases at the 0.001-mg/kg [$t_{(7)} = 2.68, P < 0.05$] and at the 0.0025-mg/kg [$t_{(7)} = 5.94, P < 0.01$] dose.

PCP Self-Administration. There was a main effect of bremazocine treatment on responding for PCP [$F_{(3,31)} = 31.59, P < 0.01$], and responses were significantly reduced at the 0.001-mg/kg [$t_{(7)} = 2.44, P < 0.05$] and 0.0025-mg/kg [$t_{(7)} = 8.55, P < 0.01$] dose. Bremazocine treatment also significantly decreased deliveries of PCP [$F_{(3,31)} = 32.41, P < 0.05$] at the 0.001-mg/kg [$t_{(7)} = 2.42, P < 0.05$] and 0.0025-mg/kg [$t_{(7)} = 8.63, P < 0.01$] dose.

Food-Maintained Behavior. Figure 2 depicts the group data for food deliveries, with monkey G-2 removed. The data were separated in this way because one monkey (M-G2) showed a much greater reduction in responding and intake of food at the 0.001-mg/kg dose, approximately an 89% drop from baseline, than the other monkeys, which, on average, showed only a 16% reduction at this dose. Therefore, the data for this condition were analyzed and are reported for both the entire group ($n = 6$) and for the group excluding monkey M-G2 ($n = 5$). The individual data for M-G2 are shown inset in the group data in Fig. 2. For the entire group ($n = 6$), there was a main effect of bremazocine on food-maintained responses [$F_{(3,23)} = 17.68, P < 0.01$] and deliveries [$F_{(3,23)} = 17.88, P < 0.05$]. Responses were significantly decreased at the 0.001-mg/kg [$t_{(5)} = 2.19, P < 0.05$] and at the 0.0025-mg/kg [$t_{(5)} = 6.23, P < 0.01$] dose of bremazocine. Similarly, food deliveries were reduced at the 0.001-mg/kg [$t_{(5)} = 2.19, P < 0.05$] and 0.0025-mg/kg [$t_{(5)} = 6.25, P < 0.01$] doses. Analysis of the data with monkey M-G2 removed indicate a main effect of bremazocine on responses [$F_{(3,19)} = 26.72, P < 0.01$] and deliveries [$F_{(3,19)} = 28.17, P < 0.01$]. However, bremazocine significantly reduced responses [$t_{(4)} = 7.52, P < 0.01$] and deliveries [$t_{(4)} = 7.67, P < 0.01$] only at the 0.0025-mg/kg dose.

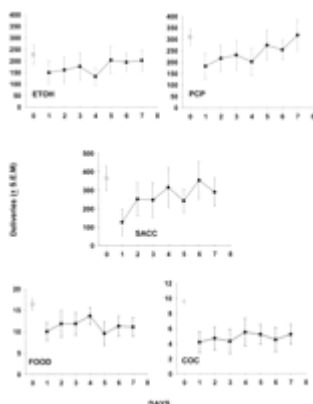


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Fig. 2. Mean (\pm S.E.M.) number of deliveries for saccharin (top) and food (bottom) during 3-h sessions of the 4-day baseline period (BL) and 7 days of bremazocine (0.00032-0.0025-mg/kg) pretreatment. Open circles (baseline points) and filled circles (bremazocine pretreatment) represent a mean for eight monkeys (saccharin) and for five monkeys (food). The food data for monkey M-G2 are unlike that of the other five monkeys and it is presented inset in the bottom figure. Asterisks indicate significantly different from BL at the $P < 0.05$ (*) and $P < 0.01$ (**) level.

Saccharin-Maintained Behavior. Deliveries of saccharin are shown in Fig. 2. Saccharin responses and deliveries were dose dependently reduced by bremazocine treatment. Responses for saccharin were significantly decreased [$F_{(3,31)} = 15.61$, $P < 0.01$] at the 0.001-mg/kg [$t_{(7)} = 2.73$, $P < 0.05$] and 0.0025-mg/kg [$t_{(7)} = 6.05$, $P < 0.01$] doses. There was also a main effect of bremazocine on saccharin intake [$F_{(3,31)} = 14.76$, $P < 0.05$], which was significantly reduced at the 0.001-mg/kg [$t_{(7)} = 2.39$, $P < 0.05$] and 0.0025-mg/kg [$t_{(7)} = 5.80$, $P < 0.01$] doses.

Figure 3 illustrates the effect of bremazocine over time for ethanol, PCP, saccharin, food, and smoked cocaine base. The adverse behavioral effects of bremazocine were generally noted during the first days of administration. An ANOVA was conducted to determine whether the effects of bremazocine differed as a function of treatment day. There were not significant differences among the 7 days of treatment.



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Fig. 3. Mean (\pm S.E.M.) number of deliveries for ethanol, PCP, saccharin, food, and smoked cocaine base during 3-h sessions of the 4-day baseline period (0) and over the 7 days of bremazocine (0.001-mg/kg) pretreatment. Open circles (baseline points) and filled circles (bremazocine pretreatment) represent a mean for eight monkeys (ethanol, PCP, and saccharin) and for six monkeys (food and smoked cocaine).

Behavioral Economic Analyses

Demand for Smoked Cocaine Base, Ethanol, and PCP. The behavioral economic analysis of demand consists of several measures, including demand intensity and elasticity, and P_{\max} , which can be used to estimate the reinforcing efficacy of drugs. Demand for a drug refers to the relationship between drug consumption and unit price. Demand curves are obtained by plotting drug consumption as a function of unit price in log-log coordinates. The demand curves for smoked cocaine base, ethanol, and PCP are shown in Fig. 4. Elasticity of demand is denoted by the slope of the function and indicates the sensitivity of consumption to changes in unit price. Inelastic demand is defined by a slope between 0 and 1 (absolute value), indicating that consumption of the drug is resistant to change, and that changes in price are proportionally greater than decreases in consumption. Elastic demand, defined by a slope greater than 1 (absolute value), indicates that the decreases in consumption are proportionally greater than the increases in price. Table 1 shows the slopes of the demand curves before and during bremazocine pretreatment for the smoked cocaine base, ethanol, and PCP conditions. The absolute values for the slopes of the demand curves for baseline cocaine and cocaine during bremazocine pretreatment were both less than 1, indicating inelastic demand for cocaine. The absolute values of the baseline ethanol and PCP demand curve slopes were less than 1, indicating inelastic demand; however, the absolute value of the slopes of the demand curves during bremazocine pretreatment were greater than 1, indicating elastic demand.

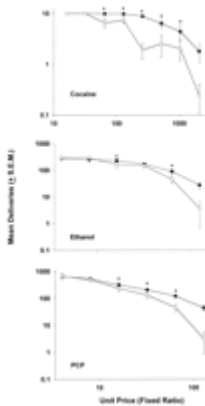


Fig. 4. Cocaine (top), ethanol (middle), and PCP (bottom) deliveries are plotted as a function of unit price (FR) for four baseline (filled circles) days and five bremazocine (0.001-mg/kg) treatment days (open circles) at each FR. Each point represents a mean of eight monkeys (five for smoked cocaine base). Asterisks indicate significantly different from baseline days at the $P < 0.05$ (*) level.

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TABLE 1

Measures of response strength for demand curves before and during 0.001 mg/kg bremazocine administration

Figure 4 shows the mean number of deliveries of smoked cocaine base, ethanol, and PCP as a function of FR value for baseline days and during pretreatment with 0.001 mg/kg bremazocine. Generally, pretreatment with bremazocine reduced the number of smoked cocaine base, ethanol, and PCP deliveries as the FR value increased. As the FR value increased, smoked cocaine deliveries decreased [$F_{(7,79)} = 17.42, P < 0.01$]. There was a significant main effect of bremazocine [$F_{(1,79)} = 46.86, P < 0.01$], and there was a significant interaction between FR value and bremazocine pretreatment [$F_{(7,79)} = 4.54, P < 0.01$]. Post hoc analyses indicate that bremazocine pretreatment significantly reduced the number of smoked cocaine deliveries from baseline at FR values 64 to 1024 ($P < 0.05$). Baseline was defined as no increasing or decreasing trend in behavior for the 4 days before bremazocine treatment. In the ethanol condition, there was a significant main effect of FR value [$F_{(5,95)} = 11.04, P < 0.01$], a significant main effect of bremazocine pretreatment [$F_{(1,95)} = 7.13, P < 0.05$], and a significant interaction between FR value and bremazocine pretreatment [$F_{(5,95)} = 5.22, P < 0.01$]. Post hoc analyses indicated that bremazocine pretreatment significantly decreased deliveries of ethanol from baseline at FR 16 and 64 ($P < 0.05$). In the PCP condition there was a significant main effect of FR value [$F_{(5,95)} = 14.59, P < 0.01$] and bremazocine pretreatment [$F_{(1,95)} = 15.66, P < 0.01$] but there was not a significant interaction. Bremazocine pretreatment significantly reduced PCP deliveries from baseline at FR 16, 32, and 64 ($P < 0.05$).

The change in behavior as a function of increased price can also be plotted as the number of responses emitted for a drug delivery as a function of unit price (FR), resulting in an inverted U-shaped curve. Curves of the responses for smoked cocaine base, ethanol, and PCP are shown in Fig. 5. Generally, pretreatment with bremazocine reduced the number of responses for smoked cocaine base, ethanol, and PCP as the FR value increased. As the FR value increased, smoked cocaine responses decreased [$F_{(7,79)} = 2.89, P < 0.05$], and there was a significant main effect of bremazocine [$F_{(1,79)} = 15.84, P < 0.01$]. There was not a significant interaction between FR value and bremazocine pretreatment. Post hoc analyses indicate that bremazocine pretreatment significantly reduced the number of responses for smoked cocaine from baseline at FR values 512, 1024, and 2048 ($P < 0.05$). In the ethanol condition there was a significant main effect of FR value [$F_{(5,95)} = 5.63, P < 0.01$], a significant main effect of bremazocine pretreatment [$F_{(1,95)} = 35.35, P < 0.01$], and a significant interaction between FR value and bremazocine pretreatment [$F_{(5,95)} = 8.74, P < 0.01$]. Post hoc analyses indicate that bremazocine pretreatment significantly decreased responding for ethanol from baseline at FR 64 and 128 ($P < 0.01$). In the PCP condition there was a significant main effect of FR value [$F_{(5,95)} = 3.03, P < 0.05$] and bremazocine pretreatment [$F_{(1,95)} = 47.36, P < 0.01$], and there was a significant interaction between FR and bremazocine dose [$F_{(5,95)} = 7.49, P < 0.01$]. Bremazocine pretreatment significantly reduced PCP responses

from baseline at FR 32, 64, and 128 ($P < 0.05$).

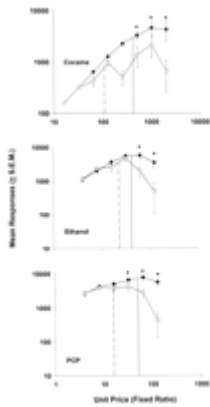


Fig. 5. Cocaine (top), ethanol (middle), and PCP (bottom) responses are plotted as a function of unit price (FR) for four baseline (filled circles) days and five breamazocine (0.001-mg/kg) treatment days (open circles) at each FR. Each point represents a mean of eight monkeys (five for smoked cocaine base). Solid vertical lines indicate baseline P_{max} values and dashed vertical lines indicate P_{max} values during breamazocine treatment. Asterisks indicate significantly different from baseline days at the $P < 0.05$ (*) level.

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The peak of this demand curve is estimated by statistical methods and is represented by a P_{max} value, which refers to the unit price (FR) at which maximum responding occurred (Hursh, 1991*). P_{max} also represents the point on the curve where the slope changes from inelastic to elastic; that is, at that unit price, the demand for the drug begins to decrease. Figure 5 depicts the mean number of responses plotted as a function of unit price. As unit price increased, responding increased and then decreased under all conditions. The P_{max} values for the conditions are shown by the vertical lines on Fig. 5 and are also presented in Table 1. P_{max} values were reduced for smoked cocaine base, ethanol, and PCP after pretreatment with breamazocine, indicating a reduction in reinforcing efficacy. Differences in P_{max} were significant based on nonoverlapping 95% confidence intervals.

Several other measures of reinforcing efficacy related to P_{max} have been used as indicators of response strength. These include break point, or the last completed ratio, under a PR schedule (Stafford et al., 1998*) and a persistence ratio or ratio of deliveries earned at a high ratio to those earned at a lower ratio (Meisch, 2000*). These measures were also evaluated to determine the effect of breamazocine pretreatment on smoked cocaine base, ethanol, and PCP. In this study, the break point was defined as the last completed FR; like P_{max} , this is also a measure of the conditions under which maximal responding occurs and then behavior declines. The break points for baseline smoked cocaine base, ethanol, and PCP responses and the break points for the drug responses during breamazocine administration are shown in Table 1. Typically, FRs are presented in ascending order to obtain a break point either within a session or on different days (Stafford et al., 1998*); however, the FR values were presented in nonsystematic order in the present study. It has been reported in similar experiments with rhesus monkeys that the same break points are obtained when the order of FR values is random or ascending (Rodefer, 1998*). Table 1 shows that breamazocine treatment reduced the breakpoints under the PR schedule for all drugs.

An additional measure of reinforcing efficacy is the persistence ratio (Meisch, 2000*), which evaluates the tenacity of drug-maintained behavior. Specifically, the ratio is the amount consumed at a higher FR, divided by the amount consumed at a lower FR, multiplied by 100. Higher values indicate greater reinforcer strength. Table 1 shows the persistence ratios for smoked cocaine base, ethanol, and PCP at FRs that were a 1:16 ratio. For smoked cocaine base the persistence ratio was FR 16 versus 256, and for ethanol and PCP it was FR 4 versus 64. Across the conditions, bremazocine treatment reduced the persistence ratios.

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► Discussion

Bremazocine dose dependently reduced self-administration of smoked cocaine base, and orally delivered ethanol and PCP. Behavior maintained by nondrug reinforcers (saccharin and food) was also reduced by bremazocine pretreatment; however, food intake was less affected by bremazocine than were the drugs and saccharin. This effect was significant at the middle and high doses of bremazocine, but not the low dose. These results are consistent with reports that higher doses of bremazocine significantly attenuated i.v. cocaine self-administration in rhesus monkeys (Mello and Negus, 1998*) and oral ethanol self-administration in rats (Nestby et al., 1999*). Although one monkey showed a reduction in food intake at the 0.001-mg/kg dose of bremazocine, five of the six did not. This decrease in food-maintained behavior is consistent with a study (Mello and Negus, 1998*) in which κ -agonists reduced food-maintained behavior at higher doses than those that decreased cocaine-maintained behavior. As in the previous study, although bremazocine significantly reduced food-maintained behavior, responding for food tended to increase after day 4 of treatment (Mello and Negus, 1998*). Although food was less affected by bremazocine, these results should be interpreted with caution due to the small sample size. In contrast to the mostly nonselective effects of bremazocine in this and previous studies, Nestby et al. (1999)* reported that bremazocine selectively reduced oral ethanol intake in rats without affecting sucrose intake. The discrepancy between Nestby et al. (1999)* and the present study may be due to the caloric value of sucrose, species differences, or differences in the paradigms. Nestby et al. (1999)* used a free-choice drinking paradigm, whereas the present study required animals to work under FR schedules. Also, food is an essential commodity; whereas, sucrose or saccharin is not, and food-maintained responding may be more resistant to suppression by medication treatment. An analysis of food versus saccharin as nondrug controls supports this hypothesis (Carroll et al., 2000*). These findings indicate that bremazocine nonselectively attenuates drug- and nondrug-maintained behaviors in rhesus monkeys.

A number of behavioral economic measures were analyzed in this study as indicators of response strength. These measures are important because treatment effects can vary

dramatically depending upon the economic context (e.g., price of drug, availability of nondrug substitutes) of drug self-administration (Comer et al., 1994*; Carroll et al., 2000*). For example, demand for a drug refers to the relationship between consumption of a drug and unit price (FR), or number of responses per milligram consumed. In this study, bremazocine pretreatment reduced the demand for cocaine, ethanol, and PCP by reducing the number of deliveries consumed at each unit price (FR). Additionally, bremazocine consistently shifted the P_{max} , the estimate of the unit price at which maximum responding for a drug occurred, for these drugs to the left, indicating a reduction in the unit price at which animals emitted peak response output for the drug. The reduction in P_{max} suggests that bremazocine reduced the reinforcing strength of the drugs. The baseline demand curves for smoked cocaine base, ethanol, and PCP had slopes of less than 1 (absolute value), indicating inelastic demand. Inelasticity of demand indicates that behavior is resistant to change when price of drug is increased. However, the slopes of the curves for ethanol and PCP during bremazocine pretreatment were greater than 1 (absolute value), indicating bremazocine altered the demand for ethanol and PCP by increasing elasticity of these drugs and making them less resistant to change. Conversely, bremazocine pretreatment did not alter the elasticity of smoked cocaine base. It remained inelastic as it has with other pharmacological and behavioral (Comer et al., 1994*) treatments. The elasticity of ethanol and PCP may have been reduced more than smoked cocaine due to the difference in route of administration or the higher relative dose of smoked cocaine. Demand can also be described by intensity, which is defined as a parallel shift upward or downward across a range of unit prices. In this study, the demand curves for smoked cocaine, ethanol, and PCP were shifted downward during bremazocine pretreatment, indicating that decreased effort was expended to obtain drugs at all prices. Therefore, bremazocine reduced the reinforcing effects, intensity, and elasticity of ethanol and PCP. This is consistent with a study reporting the effects of dopamine antagonists on self-administration of smoked cocaine base in rhesus monkeys (Campbell et al., 1999*). There are many other economic variables affecting cocaine abuse in humans such as supply of the drug, dose, and availability of concurrent nondrug reinforcers.

In this study there was an interaction between the 0.001-mg/kg dose of bremazocine and FR value on consumption of smoked cocaine base and ethanol, indicating bremazocine was more effective in reducing intake of these drugs as the FR value increased. This indicates that bremazocine had a greater effect at higher unit prices, which occurs when the dose is low and/or the response requirement is high. This effect is consistent with findings reported in other studies that medications [e.g., buprenorphine, SCH 23390, raclopride] were more effective at reducing smoked cocaine self-administration at higher FR values (Comer et al., 1994*; Campbell et al., 1999*). This finding suggests that the combination of pharmacological treatments and high prices is optimal for attenuating drug-maintained behavior.

The present data were also evaluated using other measures of response strength such as break point under a PR schedule and a persistence ratio (Meisch, 2000*). These measures were reduced after bremazocine administration, indicating that bremazocine decreased the reinforcing strength and persistence of smoked cocaine-, ethanol-, and PCP-maintained behavior. The effect of bremazocine on persistence of drug-maintained behavior in this

study is consistent with an analysis indicating that SCH 23390 and raclopride (dopamine D₁ and D₂ antagonists, respectively), and buprenorphine (a partial μ -agonist) reduced the persistence of smoked cocaine base and PCP, respectively, in rhesus monkeys (Carroll, 2000*). It is important to evaluate the effect of treatments on persistence of drug-taking behavior, because it is a core feature of the problem in individuals who abuse alcohol and drugs.

In humans, the side effects of pharmacological treatments (e.g., naltrexone for alcohol abuse) can significantly impact medication compliance and treatment outcome (Rohsenhow et al., 2000*). Bremazocine, at the 0.001- and 0.0025-mg/kg doses, was associated with emesis and behavioral sedation. These adverse behaviors were reported in another study (Mello and Negus, 1998*) using higher doses of κ -agonists, but in both studies these effects were reported to be transient. In this study these behaviors dissipated in all but one monkey over the first few days of treatment. When monkeys were working for drug during sessions, their postsession food consumption was not affected by bremazocine pretreatment at any dose, indicating that bremazocine was not affecting normal behavior. The effective doses of bremazocine used in this study, were relatively lower than those in other studies (Mello and Negus, 1998*; Nestby et al., 1999*), suggesting that low doses of κ -agonists may elicit some transient side effects while remaining clinically effective. Although side effects of other treatment drugs influence medication compliance for alcohol abuse, the medications still possess clinical efficacy. It is not known whether a similar problem will generalize to cocaine abuse, and it is hopeful that as additional benzomorphan derivatives are synthesized one or more will prove useful and have fewer adverse side effects than bremazocine.

A limitation of the present study is that the effects of bremazocine were examined only in males. It is possible that κ -agonists differentially affect males versus females. κ -Agonists produced a significantly greater analgesic response in female versus male patients (Gear et al., 1996*), and a high dose of bremazocine produced a greater antinociceptive response in female versus male rats (Craft and Bernal, 2001*). The potential for sex differences in the effects of κ -agonists on drug-maintained behavior is being investigated in this laboratory in rhesus monkeys. Another limitation is that several doses or concentrations of the self-administered drugs were not examined, and this may explain some of the difference in elasticity between smoked cocaine, and ethanol and PCP. Determination of the dose range of the self-administered drugs that is sensitive to bremazocine's effects awaits further parametric analysis. Generally, treatment drugs are more effective at low doses of the self-administered drug and doses of cocaine base, PCP, and ethanol were selected based on those that were sensitive to medication effects in previous studies (Carroll et al., 1992*). Importantly, the preclinical findings that many κ -agonists attenuate cocaine-maintained behaviors warrant further evaluation of whether a treatment strategy for cocaine abuse may be developed.

In conclusion, bremazocine pretreatment dose dependently decreased self-administration of cocaine, ethanol, and PCP. This effect generalized to nondrug reinforcers (saccharin and food), indicating bremazocine did not selectively decrease drug-maintained behavior. Bremazocine treatment was also effective in reducing the demand and response strength

of smoked cocaine base, and oral ethanol and PCP. Bremazocine treatment elicited some aversive side effects, which rapidly dissipated. These results extend previous findings on the effects of κ -agonists to smoked cocaine base and orally delivered ethanol in rhesus monkeys. The results of this study suggest that κ -agonists possessing μ -antagonist activity may prove useful in the future for the treatment of cocaine abuse.

Acknowledgments

We gratefully acknowledge Jennifer Mickelberg and Megan Roth for assistance in collecting the data and Andy Morgan, Tina Gremel, and Megan Roth for helpful comments on the manuscript.

Footnotes

Accepted for publication February 16, 2002.

Received for publication November 14, 2001.

This research was supported by National Institute on Drug Abuse Grant R01-DA02486-21 and National Institute on Alcohol Abuse and Alcoholism Grant F31-AA005575-02. Portions of this work were previously presented at The College of Problems of Drug Dependence, 2000.

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Abbreviations

PCP, phencyclidine; FR, fixed ratio; LED, light-emitting diode; ANOVA, analysis of variance; PR, progressive ratio; SCH 23390, *R*-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; [U50488](#), *trans*-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidiny)-cyclohexyl]benzeneacetamide; [U69593](#), (5*a*,7*a*,8*b*)-(–)-*N*-methyl-*N*-(7-(1-pyrrolidinyl)-1-oxaspiro-(4,5)-dec-8-yl)-benzeneacetamide; [U62066](#), spiradoline mesylate.

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