Available online at www.sciencedirect.com

SCIENCE DIRECT®

European Journal of Pharmacology 506 (2004) 133–141

www.elsevier.com/locate/ejphar

Effects of the mixed-action κ/μ opioid agonist 8-carboxamidocyclazocine on cocaine- and food-maintained responding in rhesus monkeys

Glenn W. Stevenson[a], Mark P. Wentland[b], Jean M. Bidlack[c], Nancy K. Mello[a], S. Stevens Negus[a,*]

[a]*Alcohol and Drug Abuse Research Center, McLean Hospital-Harvard Medical School, 115 Mill Street, Belmont, MA 02478, USA*
[b]*Department of Chemistry, Cogswell Laboratory, Rensselaer Polytechnic Institute, Troy, NY, USA*
[c]*Department of Pharmacology and Physiology, University of Rochester, Rochester, NY, USA*

Received 18 October 2004; accepted 28 October 2004

Abstract

The present study evaluated the effects of 8-carboxamidocyclazocine (8-CAC), a novel mixed-action κ/μ agonist with a long duration of action, on food- and cocaine-maintained responding in rhesus monkeys to assess the potential utility of 8-CAC as a medication for the treatment of cocaine dependence. The effects of acute and chronic (10 days) 8-CAC were examined in rhesus monkeys responding under a multiple schedule for both cocaine and food reinforcement. Acute 8-CAC (0.032–0.56 mg/kg, i.m.) dose-dependently eliminated cocaine-maintained responding in all three monkeys. However, doses of 8-CAC that decreased cocaine self-administration typically also decreased food-maintained responding, and 8-CAC-induced decreases in cocaine self-administration diminished during chronic 8-CAC treatment. These results confirm that 8-CAC acutely decreases cocaine self-administration. However, non-selective effects of 8-CAC on food-maintained responding and tolerance to 8-CAC effects on cocaine self-administration may limit its potential for the treatment of cocaine dependence.

Keywords: 8-Carboxamidocyclazocine; Kappa agonist; Cocaine; Drug self-administration; Monkey, rhesus

1. Introduction

Cocaine abuse continues to be a persistent public health problem (NIDA, 2000) and as yet, no consistently effective pharmacotherapies are available (Kleber, 2003; Mendelson and Mello, 1996). Kappa agonists may oppose abuse-related neurochemical effects of cocaine and decrease cocaine's reinforcing effects. (Devine et al., 1993; Di Chiara and Imperato, 1988; Maisonneuve et al., 1994). Consistent with this possibility, selective kappa agonists such as the arylacetamides U50,488, U69,593 and spiradoline attenuated cocaine self-administration in rats (Glick et al., 1995) and rhesus monkeys (Bowen et al., 2003; Mello and Negus, 1998; Negus et al., 1997). However, these selective kappa agonists decreased cocaine self-administration at doses similar to those that also decreased responding maintained by other reinforcers, such as food or water. In addition, selective kappa agonists produced transient sedation and emesis in rhesus monkeys, although tolerance developed to these effects during chronic kappa agonist treatment (Bowen et al., 2003; Mello and Negus, 1998; 2000; Negus et al., 1997). Taken together, these findings suggest that selective kappa agonists may decrease cocaine self-administration by producing a general disruption of behavior rather than a selective decrease in the reinforcing effects of cocaine.

Mixed-action κ/μ agonists such as the benzomorphans ethylketocyclazocine (EKC) and (S) tetrahydrofurfurylbenzomorphan (MR2033), or the morphinan (−)-3-hydroxy-*N*-cyclobutylmethylmorphinan *S*(+)-mandelate (MCL-101),

* Corresponding author. Tel.: +1 617 855 3324; fax: +1 617 855 2519.
E-mail address: negus@mclean.harvard.edu (S.S. Negus).

0014-2999/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2004.10.051

also decreased cocaine-maintained responding in rhesus monkeys (Bowen et al., 2003; Mello and Negus, 1998; 2000; Negus et al., 1997). However, in comparison to the highly selective kappa agonists, doses of mixed-action κ/μ agonists that decreased cocaine-maintained responding usually produced smaller decreases in food-maintained responding, less sedation and emesis, and only mild salivation. These findings suggest that kappa agonists with mixed activity at kappa and mu receptors may be more promising candidate pharmacotherapies for cocaine abuse than highly selective kappa agonists (Mello and Negus, 2000).

Given the usefulness of long-acting compounds in treating opioid and nicotine addiction (Greenstein et al., 1997; Lowinson et al., 1997; Richmond et al., 1994), optimal pharmacotherapies for cocaine abuse might also be expected to include drugs that have long durations of action. From this perspective, one limitation to existing mixed-action κ/μ agonists is that they have relatively short durations of action. For example, following systemic administration in non-human primates, the benzomorphan EKC has a duration of action of approximately 1 h (Heath et al., 1984; Katz and Goldberg, 1986). Accordingly, the identification of longer-acting compounds might represent a significant advance in the development of mixed-action κ/μ agonists as candidate pharmacotherapies for the treatment of cocaine dependence.

Recently, a long-acting congener of the nonselective kappa agonist cyclazocine, 8-carboxamidocyclazocine (8-CAC), has been synthesized (Bidlack et al., 2002; Wentland et al., 2001). The 8-OH group of cyclazocine was replaced with an 8-$CONH_2$ group in an effort to retard metabolism and increase duration of action. In binding studies, 8-CAC had similar high affinities for both kappa and mu receptors and approximately 10-fold lower affinity for delta receptors. In vitro, 8-CAC acted as a partial agonist in stimulating GTPγS binding in Chinese hamster ovary cells stably expressing kappa or mu receptors. In vivo, 8-CAC produced dose-dependent antinociception in mice. These effects were attenuated by both kappa- and mu-selective antagonists, suggesting that 8-CAC-induced antinociception resulted from both kappa and mu agonist effects. 8-CAC also had an extremely long duration of action in mice. The parent compound cyclazocine produced antinociception for only 2 h, whereas an equieffective dose of 8-CAC produced antinociception for up to 15 h. Taken together, these results suggest that 8-CAC is a mixed-action κ/μ agonist with a very long duration of action. Given the potential promise of long-acting, mixed-action κ/μ agonists for the treatment of cocaine abuse, the present study assessed the effects of 8-CAC in rhesus monkeys using two procedures. First, the time course of 8-CAC was compared to the time course of EKC in an assay of food-maintained responding. Second, the acute and chronic effects of 8-CAC were examined in monkeys responding under a multiple schedule for food and cocaine reinforcement.

2. Materials and methods

2.1. Subjects

Five rhesus monkeys (2 male and 3 female) were used in the assay of food-maintained responding for preliminary time course studies, and three monkeys (1 male and 2 female) were used in studies to compare acute and chronic effects of 8-CAC on cocaine- and food-maintained responding. All monkeys had prior exposure to drugs (primarily dopaminergic and opioid compounds) and operant behavioral procedures. The subjects were individually housed, and water was freely available. Their diet consisted of PMI Feeds Jumbo monkey diet (2–6 biscuits/day) and was supplemented with fresh fruit twice daily. A 12 h light/12 h dark cycle was in effect (lights on from 7 AM–7 PM). All housing and procedures were in compliance with NIH guidelines on care and use of animal subjects in research, and were approved by the McLean Hospital Institutional Animal Care and Use Committee.

2.2. Apparatus

Experimental sessions were conducted in each monkey's home cage. The front wall was equipped with an operant panel (28×28 cm^2) that included three circular response keys (5.1 cm in diameter) arranged 2.5 cm apart horizontally. Each key could be transilluminated by red, green, or yellow stimulus lights (Superbright LEDs, St. Louis MO). A food-pellet dispenser (Model G5210, Ralph Gerbrands, Arlington, MA) was mounted above each cage to deliver 1 g banana-flavored food pellets to a receptacle located below the operant panel. In addition, cages used for drug self-administration studies were also equipped with two infusion pumps (Model B5P-1E, Braintree Scientific, Braintree, MA; or Model 98021, Harvard Apparatus, South Natick, MA) for delivery of saline or drug solutions through the two lumen of the intravenous catheters. The schedules of reinforcement were controlled and data were collected with a computer and interface (MED Associates, Georgia, VT) located in a separate room.

For intravenous drug administration, a chronic double-lumen catheter was implanted into a jugular or femoral vein under aseptic conditions as described previously (Negus et al., 1997). One lumen of the double-lumen catheter was used for i.v. cocaine self-administration, and the second lumen was used for continuous saline administration to maintain catheter patency. Each monkey was fitted with a nylon vest attached to a flexible stainless-steel cable through which the catheter was threaded. The distal end of the catheter and cable were attached to a fluid swivel (Lomir Biomedical, Montreal, Canada), which in turn was connected to the syringe pumps.

2.3. Assay of food-maintained responding

The relative time courses of 8-CAC and EKC in rhesus monkeys were determined using an assay of food-maintained responding that has been used to evaluate a wide range of opioid compounds (Gatch et al., 1996; Mello and Negus, 1998; Negus et al., 1993) Training sessions lasted 75 min and consisted of five consecutive components. Each component was 15 min long and consisted of a 10-min pretreatment period followed by a 5-min response period. During the pretreatment period, no stimulus lights were illuminated, and responding had no scheduled consequences. During the response period, the center key was illuminated yellow, and the subjects could respond for up to 10 food pellets under a fixed-ratio 30 (FR 30) schedule of reinforcement. If all 10 food pellets were earned before 5 min had elapsed, the lights were turned off, and responding had no scheduled consequences for the remainder of that response period. All monkeys were trained until they responded at rates greater than 0.5 responses/s during all five response periods for 10 consecutive days.

Test sessions were conducted only after a training session during which the monkeys responded at rates greater than 0.5 responses/s for all five response periods. Saline, 8-CAC (0.1–0.56 mg/kg) or EKC (0.01 mg/kg) was administered intramuscularly at the start of the test session, and 5-min response periods identical to those described above were scheduled to begin after 3, 10, 30, 100 and 300 min and after 24 h. The range of 8-CAC doses was selected to cover a range from a relatively inactive dose to a dose that eliminated responding in all monkeys. The EKC dose was selected as the lowest dose to eliminate responding in all monkeys (Mello and Negus, 1998). Data from saline sessions were used to establish control rates of responding at each time point in each monkey. Data from test sessions with 8-CAC and EKC were expressed as the % control response rate using the formula (rate after 8-CAC/EKC÷ Rate after Saline)×100. The effects of 8-CAC and EKC were each evaluated in three monkeys.

2.4. Assay of cocaine- and food-maintained responding

2.4.1. Behavioral procedure

Once the time course of 8-CAC had been established, the acute and chronic effects of 8-CAC on responding maintained by cocaine and food were compared in three monkeys responding under a multiple schedule of cocaine and food reinforcement. Sessions were conducted seven days per week, and each 2-h session consisted of three components. During the first and third components, food pellets were available under a FR 30 schedule for 5 min, and the center response key was transilluminated with a red stimulus light. During the second component, i.v. injections of saline or cocaine were available under a FR 30 schedule for 100 min, and the center response key was transilluminated with a green stimulus light. Session components were separated by 5-min time-out periods, during which all stimulus lights were off and responding had no scheduled consequences. The unit dose of cocaine available during the drug component of each session was determined by the concentration of drug in the syringe, and the syringe pumps were programmed to deliver 100 μl in 1 s. A 10-s time-out followed the completion of the ratio requirement for each food pellet or injection, and this time-out was signaled by the transillumination of the center response key with a yellow stimulus light. The second component (i.e., the drug component) was initiated by a 10-s transillumination of the center response key with a yellow stimulus light and the noncontingent delivery of a single 'priming' injection of the solution available for self-administration.

2.4.2. Testing procedures

Test sessions were conducted no more than twice each week and were separated by at least 48 h (with the exception of chronic 8-CAC studies; see below). On intervening days, the solution available for self-administration during the drug component was either saline or the maintenance dose of cocaine (0.032 mg/kg/inj). Initially, a cocaine self-administration dose–effect curve was determined by substituting various cocaine doses (0.001–0.1 mg/kg/inj) for the maintenance dose of 0.032 mg/kg/inj cocaine. Each cocaine dose was made available during the drug component for a single session, and each dose was tested at least twice in each monkey.

Following determination of the cocaine self-administration dose–effect curve, the acute effects of 8-CAC treatment were examined. A single dose of 8-CAC (0.032–0.56 mg/kg) was administered i.m. 30 min before the beginning of a test session, during which the available cocaine dose was 0.01, 0.032 or 0.1 mg/kg/inj cocaine. The doses and pretreatment times for 8-CAC were based on time course studies in the assay of food-maintained responding as described above. Unit doses of 0.01, 0.032 and 0.1 mg/kg/inj cocaine were used, because these doses maintained self-administration in all monkeys and comprised the peak and descending limb of the cocaine self-administration dose–effect curve.

The effects of chronic 8-CAC treatment were examined over a period of 20 days. A dose of 0.56 mg/kg 8-CAC was used for this chronic study, because this dose reliably decreased cocaine self-administration in all monkeys during the acute studies. A cocaine unit dose of 0.01 mg/kg/inj was used, because this was the lowest cocaine dose to reliably maintain self-administration in all monkeys. Saline or 8-CAC was administered 30 min before each daily session. Saline was administered during days 1–5 to establish baseline levels of cocaine- and food-maintained responding. 8-CAC was administered on days 6–15. After 8-CAC treatment was terminated, saline treatment was resumed on days 16–20 to assess recovery from chronic 8-CAC treatment.

2.5. Data analysis

The principal dependent variables were the number of reinforcers delivered during the drug component (when cocaine was available), the first food component (designated Food 1, which occurred before the drug component) and the second food component (designated Food 2, which occurred after the drug component). For analysis of 8-CAC effects on cocaine- and food-maintained responding, data for each monkey were converted to percent control values, with "control" defined as the data obtained during the initial determination of the cocaine self-administration dose–effect curve in that monkey. Because of the small number of monkeys tested, effects of 8-CAC are shown for each individual monkey, and statistical analyses were not conducted. Data from acute studies were also used to determine ED50 values for 8-CAC-induced decreases in cocaine- and food-maintained responding. The ED50 value was defined as the dose of 8-CAC that decreased rates of cocaine- or food-maintained responding to 50% of control. For each monkey, ED50 values were calculated by interpolation when only two data points were available (one below and one above 50% control) or by linear regression when at least three data points were available on the linear portion of the dose–effect curve. For analysis of chronic 8-CAC effects on cocaine- and food-maintained responding, data for each monkey were converted to percent control values, with "control" defined as the mean number of reinforcers delivered during each component during five consecutive days of saline pretreatment. As with acute studies, effects of chronic 8-CAC are shown for each monkey.

2.6. Drugs

Cocaine HCl (supplied by the National Institute on Drug Abuse, NIH, Bethesda, MD) was dissolved in sterile saline and filter-sterilized using a 0.22-μm Millipore filter. 8-Carboxamidocyclazocine HCl (8-CAC; synthesized and provided by Mark P. Wentland) and ethylketocyclazocine (EKC; kindly provided by Sanofi-Synthelabo Research, Malvern, PA) were dissolved in distilled water. Cocaine was delivered intravenously in a volume of 0.10 ml/inj. 8-CAC and EKC were administered intramuscularly into the thigh in a volume of 0.10–1 ml.

3. Results

3.1. Time course of 8-CAC and EKC in the assay of food-maintained responding

Rates of food-maintained responding were relatively stable at various times after saline administration. For the three monkeys used to test 8-CAC, mean response rates (±S.E.M.) after saline administration varied from 1.36 (±0.75) to 1.72 (±0.77) responses/s. For the three monkeys used to test EKC, response rates varied from 2.18 (±0.53) to 2.35 (±0.55) responses/s. Fig. 1 shows the time course of effects produced by 8-CAC (0.1–0.56 mg/kg) and EKC (0.01 mg/kg). 8-CAC produced a dose- and time-dependent decrease in response rates. The highest dose of 8-CAC eliminated responding in all monkeys after 10–30 min, and responding remain suppressed for up to 300 min. Response rates recovered to control levels after 24 h. In contrast, EKC eliminated responding in 3–10 min, and the effects of EKC dissipated after 30–100 min. Thus, in comparison to EKC, 8-CAC had a slower onset and a much longer duration of action.

3.2. Control levels of cocaine- and food-maintained responding under the multiple schedule of cocaine and food reinforcement

Fig. 2 (top panel) shows that the cocaine self-administration dose–effect curve under the multiple schedule exhibited a characteristic inverted "U" shape (top panel).

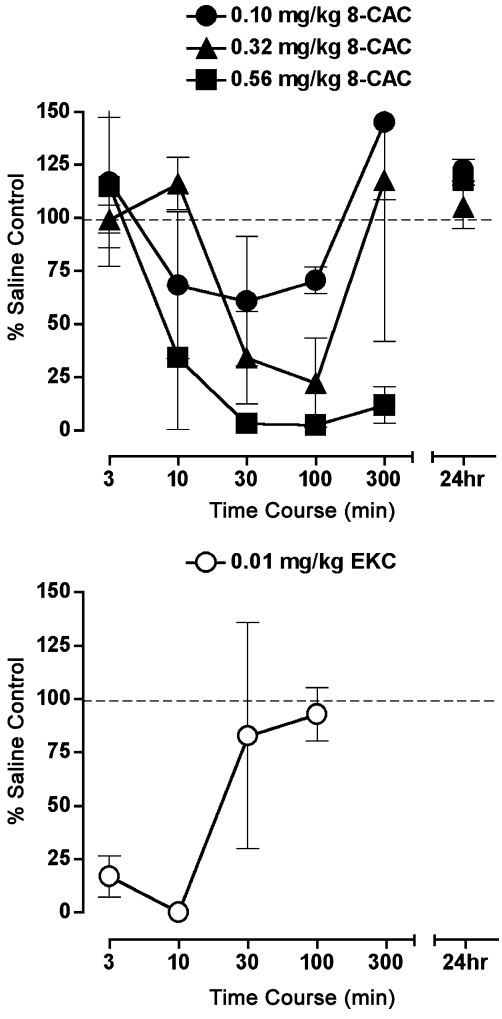

Fig. 1. Time course of effects of 8-CAC (top panel) and EKC (bottom panel) in an assay of food-maintained responding. Abscissae: Time after drug injection. Ordinates: Percent control rates of responding. All points shows mean data (±S.E.M.) in three monkeys.

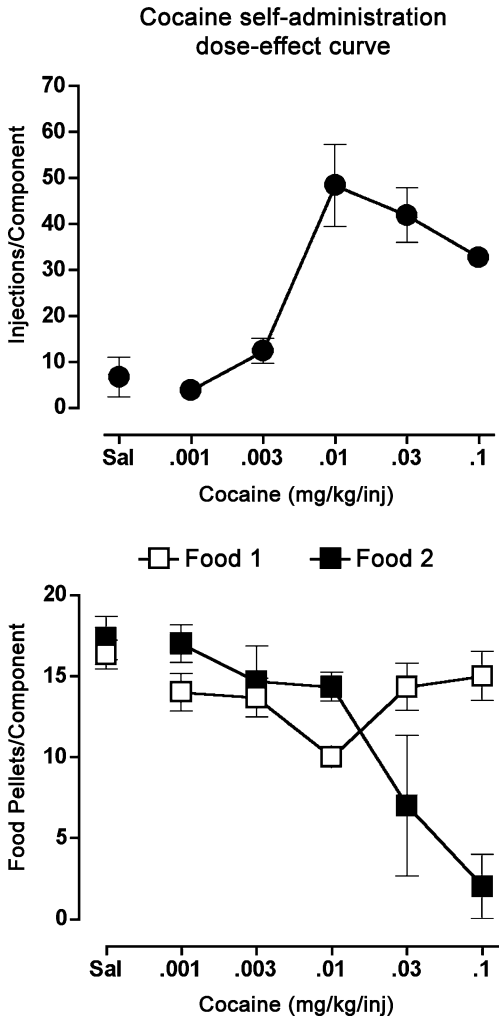

Fig. 2. Mean control levels of cocaine- and food-maintained responding. Abscissae: Unit dose of cocaine available during the drug component of each session (mg/kg/inj; log scale). "Sal" indicates saline availability. Top ordinate: total number of injections delivered during the drug component of each session. Bottom ordinate: total number of food pellets delivered during the first food component (Food 1, open squares) which preceded the drug component, and during the second food component (Food 2, filled squares), which followed the drug component. All points show mean data±S.E.M. from at least two determinations in each of three monkeys.

The peak of the curve occurred at 0.01 mg/kg/inj cocaine, and doses of 0.032 and 0.1 mg/kg/inj cocaine were located on the descending limb of the cocaine dose–effect curve. Fig. 2 (bottom panel) shows the numbers of food pellets earned during the Food 1 and Food 2 components. When saline was available during the drug component, the mean control numbers of food pellets earned during the Food 1 and Food 2 components were 16.3 and 17.3, respectively. As the available dose of cocaine increased, the mean number of pellets earned during the Food 1 component ranged from 10 to 14 pellets and remained relatively stable. However, the mean number of pellets earned during the Food 2 component decreased as the cocaine dose increased.

Table 1 shows the mean control response rates (responses/s) during the Drug, Food 1 and Food 2 components. Response rates during the drug component were usually lower than rates during either of the food components. The only exception to this general finding was that response rates during the Drug component and the Food 2 component were similar during sessions when the highest cocaine dose was available (0.1 mg/kg/inj).

3.3. Effects of acute 8-CAC treatment

Fig. 3 shows the acute effects of 8-CAC on cocaine self-administration in individual monkeys. In general, 8-CAC produced a dose-dependent decrease in cocaine self-administration in all three monkeys at all three cocaine unit doses. The low dose of 0.032 mg/kg 8-CAC usually had no effect on or increased cocaine self-administration, whereas higher doses of 0.32 or 0.56 mg/kg 8-CAC tended to eliminate cocaine self-administration. One exception to this general finding was that all doses of 8-CAC eliminated responding for the low dose of 0.01 mg/kg/inj cocaine in monkey RQ1731 (see Fig. 3, top right panel). Table 2 shows the ED50 values for 8-CAC-induced decreases in self-administration of each cocaine dose. There was no clear relationship between the unit dose of cocaine and the potency of 8-CAC to decrease cocaine self-administration.

Fig. 3 also shows that doses of 8-CAC that decreased cocaine self-administration had mixed effects on responding during the Food 1 component. In monkey RQ2199, responding during Food 1 was decreased at doses similar to or lower than those that decreased cocaine self-administration. Conversely, in monkey 96C134, doses of 0.32 or 0.56 mg/kg 8-CAC eliminated cocaine self-administration but had little effect on food-maintained responding except during the availability of the highest cocaine dose (0.1 mg/kg/inj), when 8-CAC produced greater decreases in cocaine-maintained responding than in food-maintained responding. In monkey RQ1731, 8-CAC had more variable effects on food-maintained responding. Table 2 shows the ED50 values for 8-CAC to decrease responding during the Food

Table 1
Mean control response rates (responses/s; ±S.E.M.) for Drug, Food 1 and Food 2 components during availability of saline or different unit doses of cocaine (0.001–0.1 mg/kg/inj)

	Response rates					
	Saline	0.001	0.0032	0.01	0.032	0.1
Drug	0.05 (±0.02)	0.03 (±0.02)	0.16 (±0.14)	0.66 (±0.31)	0.51 (±0.04)	0.38 (±0.18)
F 1	3.73 (±0.66)	2.81 (±0.40)	3.06 (±0.36)	2.85 (±0.62)	2.28 (±1.00)	2.33 (±0.98)
F 2	4.36 (±1.26)	4.43 (±0.41)	3.95 (±1.03)	2.57 (±0.70)	1.95 (±2.04)	0.37 (±0.28)

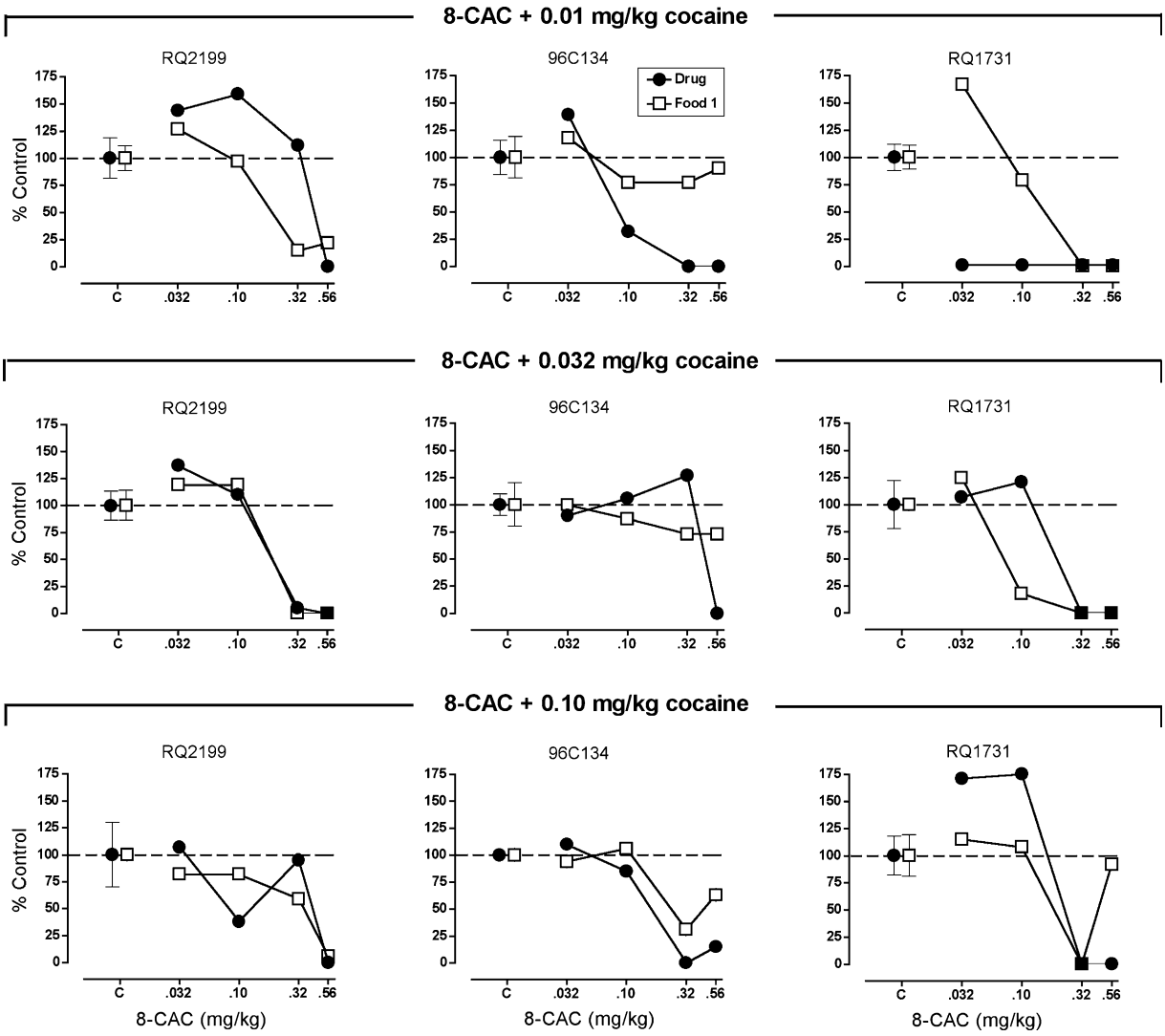

Fig. 3. Acute effects of 8-CAC on cocaine self-administration (filled circles) and food-maintained responding (open squares) in individual monkeys. The unit dose of cocaine available during the drug component is shown above each row of panels (0.01, 0.032 and 0.10 mg/kg/inj cocaine for top, middle and bottom panels, respectively). Data for food-maintained responding show data from the first food component (Food 1), which preceded the drug component. Each panel shows data for an individual monkey (monkey identification numbers shown above each panel). Abscissae: Dose of 8-CAC in mg/kg (log scale). Ordinates: Percent control number of cocaine injections or food pellets delivered in the absence of 8-CAC treatment. Each point shows data from a single determination in each monkey.

1 component in individual monkeys. There was no clear relationship between the unit dose of cocaine available during the drug component and the potency of 8-CAC to decrease food-maintained responding during the Food 1 component. Also, there were no reliable differences in the potency of 8-CAC to decrease cocaine self-administration during the drug component and its potency to decrease food-maintained responding during the Food 1 component.

Table 2
ED50 values (mg/kg) for 8-CAC-induced decreases in cocaine- and food-maintained responding in individual monkeys during availability of different cocaine unit doses (0.01, 0.032 and 0.1 mg/kg/inj)

Unit Dose Cocaine	Cocaine-maintained responding			Food-maintained responding		
	2199	C134	1731	2199	C134	1731
0.01	0.44	0.08	<0.032[a]	0.19	>0.56[b]	0.15
0.032	0.27	0.45	0.20	0.20	>0.56[b]	0.07
0.1	0.12	0.16	0.23	0.35	0.24	0.19

Data for food-maintained responding show results from the first food component of each daily session (Food 1).

[a] ED50 not determined because all doses produced <50% control responding.

[b] ED50 not determined because all doses produced >50% control responding.

Table 3
Effects of 8-CAC on percent control responding during the Food 2 component

Dose 8-CAC	Dose cocaine		
	0.01	0.032	0.1
0.032	79 (±14.15)	100 (±9.52)	33 (±11.17)
0.1	79 (±13.12)	0 (±0.00)	133 (±44.5)
0.32	33 (±11.12)	0 (±0.00)	184 (±33.83)
0.56	0 (±0.00)	19 (±4.19)	300 (±75.17)

The mean number of pellets (±S.E.M.) delivered during Food 2 was 11±3.6 during availability of 0.01 mg/kg cocaine, 7.0±4.4 during availability of 0.032 mg/kg cocaine and 2.0±2.0 during availability of 0.1 mg/kg cocaine.

Table 3 shows the mean effects of 8-CAC during the Food 2 component. Baseline responding during the Food 2 component was variable across monkeys and was influenced by the self-administered cocaine dose. When the low dose of 0.01 mg/kg/inj cocaine was available, the control number of pellets (mean±S.E.M.) delivered during Food 2 was 11±3.6, and 8-CAC dose-dependently decreased Food 2 responding. When the intermediate dose of 0.032 mg/kg/inj cocaine was available, the control number of pellets earned during Food 2 decreased and became more variable across monkeys (7.0±4.4), but 8-CAC again had the general effect of decreasing food-maintained responding. When the high dose of 0.1 mg/kg/inj cocaine was available, the control number of pellets delivered during Food 2 decreased further to 2.0±2.0, and 8-CAC pretreatment slightly increased responding relative to this low baseline.

3.4. Effects of chronic 8-CAC treatment

Fig. 4 shows the effects of chronic treatment with 0.56 mg/kg/day 8-CAC. The 10-day period of 8-CAC treatment was preceded and followed by 5 days of saline treatment. During the first 5 days of saline treatment, cocaine maintained responding varied between 74% and 125% of control values for monkeys RQ2199 and 96C134, whereas food-maintained responding for these two monkeys was more stable. Cocaine maintained responding for monkey RQ1731 was stable during the first 5 days of saline treatment, whereas food-maintained responding for this monkey varied between 67% and 122% of control values. Cocaine-maintained responding was completely eliminated for all three monkeys during the first day of the 10-day period of 8-CAC treatment. Rates of cocaine self-administration recovered partially in monkey RQ2199 and completely in monkey 96C134 by the end of the 10-day treatment. In monkey RQ1731, cocaine self-administration remained suppressed throughout the 10-day treatment period. Cocaine self-administration recovered to control levels within five days after 8-CAC treatment in all monkeys.

Fig. 4 also shows that the effects of chronic 8-CAC treatment on responding during the Food 1 component varied across monkeys. In monkey RQ2199, food-maintained responding remained suppressed throughout the 10-day treatment, then recovered when 8-CAC treatment was terminated. Conversely, in monkey 96C134, chronic 8-CAC treatment had little effect on responding during the Food 1 component, and food-maintained responding was also unaffected by termination of 8-CAC treatment. Finally, in monkey RQ1731, responding during the Food 1 component was initially suppressed, then recovered almost completely by the end of the 10-day treatment. In this monkey, rates of food-maintained responding decreased again on the first day after termination of 8-CAC treatment then recovered back to baseline levels by the fifth day after termination of 8-CAC treatment.

Table 4 shows the effects of chronic 8-CAC treatment on responding during the Food 2 component. Baseline measures during saline treatment were highly variable across time and monkeys. In general though, 8-CAC effects on

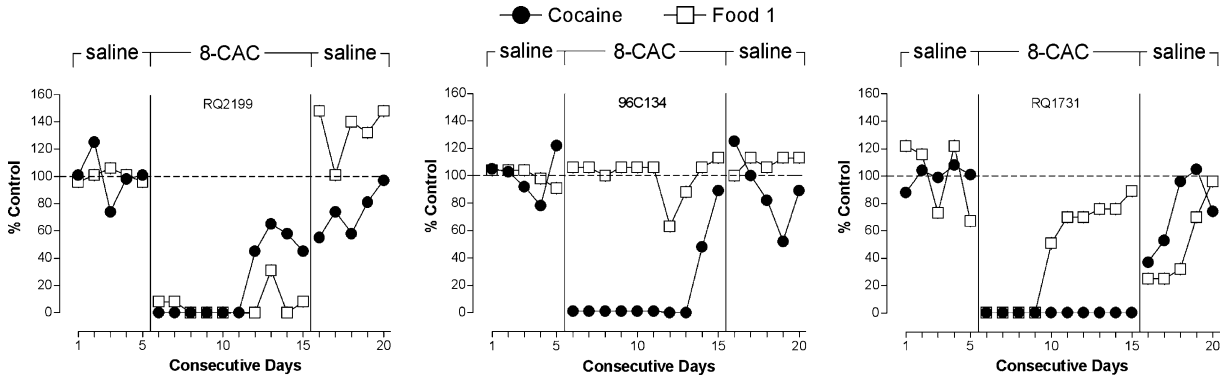

Fig. 4. Chronic effects of 8-CAC on responding maintained by cocaine (0.01 mg/kg/inj; filled circles) or by food pellets (Food 1; open squares). Each panel shows data for an individual monkey (monkey identification numbers shown above the panel). Abscissae: Consecutive days of treatment. Monkeys were treated with saline during days 1–5, with 0.56 mg/kg/day 8-CAC during days 6–15, and with saline during days 16–20. Ordinates: Percent control number of cocaine injections or food pellets delivered during each session. The mean numbers of cocaine injections and food pellets delivered during the first 5 days of saline treatment (i.e., Days 1–5) served as the control values for cocaine- and food-maintained responding. Each point shows individual data from a single determination in each monkey.

Table 4
Mean number of food pellets (±S.E.M.) earned in the Food 2 component during saline pretreatment (Days 1–5), 0.56 mg/kg/day chronic 8-CAC treatment (Days 6–15) and saline recovery (Days 16–20) when 0.01 mg/kg/inj cocaine was available

Monkey #	Sal 1–5	8-CAC 6–10	8-CAC 11–15	Sal 16–20
RQ2199	8.2 (±3.35)	0.20 (±0.20)	5.8 (±3.58)	3.4 (±3.40)
96C134	5.8 (±3.53)	11.6 (±3.31)	13.8 (±0.66)	12.2 (±3.17)
RQ1731	6.4 (±3.50)	3.8 (±2.38)	12.2 (±0.86)	0.20 (±0.20)

food-maintained responding during Food 2 were similar to those described above for Food 1.

3.5. Emetic and sedative effects of 8-CAC

Observation of monkeys in both the food-maintained responding procedure and the multiple-schedule procedure indicated that 8-CAC produced only mild sedation across the dose-range tested in acute studies, and only one episode of emesis was observed in one monkey in the multiple-schedule procedure. During chronic studies, tolerance developed to the sedative effects of 8-CAC, and emesis was not observed.

4. Discussion

The present study assessed the acute and chronic effects of 8-CAC, a long-acting mixed-action κ/μ opioid agonist, on cocaine- and food-maintained responding in rhesus monkeys. Time course studies in an assay of food-maintained responding confirmed that 8-CAC has a very long duration of action in rhesus monkeys in comparison to other mixed-action κ/μ agonists such as EKC. Acute administration of 8-CAC reduced cocaine-maintained responding across a 10-fold range of cocaine unit doses. However, doses of 8-CAC that decreased cocaine self-administration were similar to doses that decreased food-maintained responding. In addition, 8-CAC-induced decreases in cocaine self-administration diminished during chronic 8-CAC treatment. Taken together, these results agree with previous findings to indicate that mixed-action κ/μ agonists decrease rates of cocaine self-administration in rhesus monkeys. However, the utility of 8-CAC as a treatment for cocaine dependence may be limited by its non-selective effects on food-maintained responding and tolerance to its effects on cocaine self-administration during chronic treatment.

The reduction of cocaine-maintained responding by acute administration of 8-CAC agrees with previous studies of acute kappa agonist effects on cocaine self-administration in rats (Glick et al., 1995; Schenk et al., 1999) and rhesus monkeys (Bowen et al., 2003). For example, acute administration of the kappa agonist enadoline, the mixed-action κ/μ agonists (RS) tetrahydrofurfurylbenzomorphan (MR 2034) and MCL-101, and the κ agonist-μ antagonist (−)cyclorphan decreased cocaine-maintained responding in rhesus monkeys (Bowen et al., 2003). One advantage of 8-CAC in comparison to these other kappa agonists is its long duration of action. Time course studies in the assay of food-maintained responding indicated that effects of 0.56 mg/kg 8-CAC lasted at least 5 h, and this agrees with the long duration of action of 8-CAC in mice (Bidlack et al., 2002).

Drug-induced decreases in cocaine self-administration could reflect either a selective decrease in the reinforcing effects of cocaine or a non-selective decrease in the ability of the subject to respond (Mello and Negus, 1996). To address this issue, the effects of 8-CAC were examined on both cocaine- and food-maintained responding in monkeys responding under a multiple schedule of cocaine and food reinforcement. Acute administration of 8-CAC selectively decreased cocaine-maintained responding in one of three monkeys, but in the other two monkeys, doses of 8-CAC that decreased cocaine self-administration also decreased food-maintained responding. Similarly, the other mixed-action κ/μ agonists MR-2034 and MCL-101 selectively decreased cocaine-maintained responding in some but not all monkeys responding for both cocaine and food (Bowen et al., 2003). These results suggest that mixed-action κ/μ agonists may attenuate the reinforcing effects of cocaine but also appear to produce more global effects that non-selectively suppress responding in some monkeys. In contrast, the highly selective kappa agonist enadoline decreased cocaine- and food-maintained responding at similar doses in all monkeys tested (Bowen et al., 2003).

Medications used to treat drug dependence are usually administered chronically (Greenstein et al., 1997; Lowinson et al., 1997; Richmond et al., 1994). Consequently, it has been argued that preclinical evaluation of candidate pharmacotherapies should include chronic treatment studies, and optimal medications should produce sustained decreases in cocaine self-administration (Mello and Negus, 1996). In the present study, chronic treatment with 8-CAC for 10 days produced a sustained decrease in cocaine self-administration in only one monkey. Tolerance developed to the effects of 8-CAC on cocaine self-administration in the other two monkeys tested. Similarly, tolerance also developed in some monkeys to the effects of other mixed-action and selective kappa agonists on cocaine self-administration (Bowen et al., 2003; Mello and Negus, 1998; 2000; Negus et al., 1997). Taken together, these results suggest that tolerance to kappa agonist effects on cocaine self-administration may limit the utility of kappa agonists for the treatment of cocaine dependence.

8-CAC produced grossly observable behavioral effects (e.g. sedation, emesis) similar to those produced by other mixed-action κ/μ agonists such as MR-2033, MR-2034, MCL-101 and EKC (Bowen et al., 2003; Mello and Negus, 1998; Negus et al., 1997). These effects of mixed-action κ/μ agonists are generally less severe than effects produced by highly selective kappa agonists administered at doses that decrease cocaine self-administration (Bowen et al., 2003; Mello and Negus, 1998; Negus et al., 1997). It has also been found that selective and mixed-action kappa agonists produce dysphoric and psychotomimetic effects in humans (Pfeiffer et al., 1986; Walsh et al., 2001), and these subjective effects may also limit the clinical utility of kappa agonists for drug abuse treatment. Overall, results obtained in monkeys suggest that mixed-action κ/μ agonists might decrease cocaine self-administration with a lower incidence of other, potentially undesirable effects than highly selective kappa agonists.

Acknowledgements

This work was supported by Grants RO1-DA02519, T32-DA07252, DA012180 K05-DA00360 and K05-DA00101 from the National Institute on Drug Abuse. The authors would like to thank Peter Fivel, Sam McWilliams and Kyle Rheaume for excellent technical assistance.

References

Bidlack, J.M., Cohen, D.J., McLaughlin, J.P., Lou, R., Ye, Y., Wentland, M.P., 2002. 8-Carboxamidocyclazocine: a long-acting, novel benzomorphan. J. Pharmacol. Exp. Ther. 302, 374–380.

Bowen, C.A., Negus, S.S., Zong, R., Neumeyer, J.L., Bidlack, J.M., Mello, N.K., 2003. Effects of mixed-action kappa/mu opioids on cocaine self-administration and cocaine discrimination by rhesus monkeys. Neuropsychopharmacology 28, 1125–1139.

Devine, D.P., Leone, P., Pocock, D., Wise, R.A., 1993. Differential involvement of ventral tegmental mu, delta and kappa opioid receptors in modulation of basal mesolimbic dopamine release: in vivo microdialysis studies. J. Pharmacol. Exp. Ther. 266, 1236–1246.

Di Chiara, G., Imperato, A., 1988. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. U. S. A. 85, 5274–5278.

Gatch, M.B., Negus, S.S., Mello, N.K., Archer, S., Bidlack, J.M., 1996. Effects of the structurally novel opioid 14 alpha, 14′ beta-[dithiobis [(2-oxo-2,1-ethanediyl)imino]]bis(7,8-dihydromorphinone) on schedule-controlled behavior and thermal nociception in rhesus monkeys. J. Pharmacol. Exp. Ther. 278, 1282–1289.

Glick, S.D., Maisonneuve, I.M., Raucci, J., Archer, S., 1995. Kappa opioid inhibition of morphine and cocaine self-administration in rats. Brain Res. 681, 147–152.

Greenstein, R.A., Fudala, P.J., Obrien, P., 1997. Alternative pharmacotherapies for opiate addiction. In: Lowinson, J., Ruiz, P., Millman, R.B., Langrod, J.G. (Eds.), Substance Abuse: A Comprehensive Textbook. Williams and Wilkins, Baltimore, pp. 415–425.

Heath, R.G., Fitzjarrell, A.T., Walker, C.F., 1984. Kappa opiate receptor agonists: effects on behavior and on brain function and structure in rhesus monkeys. Biol. Psychiatry 19, 1045–1074.

Katz, J.L., Goldberg, S.R., 1986. Effects of ethylketazocine and morphine on schedule-controlled behavior in pigeons and squirrel monkeys. J. Pharmacol. Exp. Ther. 239, 433–441.

Kleber, H.D., 2003. Pharmacologic treatments for heroin and cocaine dependence. Am. J. Addict. 12 (Suppl. 2), S5–S18.

Lowinson, J.H., Payte, J.T., Salsitz, E., Joseph, H., Marion, I.J., Dole, V.P., 1997. Methadone maintenance. In: Lowinson, J., Ruiz, P., Millman, R.B., Langrod, J.G. (Eds.), Substance Abuse: A Comprehensive Textbook. Williams and Wilkins, Baltimore, pp. 405–415.

Maisonneuve, I.M., Archer, S., Glick, S.D., 1994. U50,488, a kappa opioid receptor agonist, attenuates cocaine-induced increases in extracellular dopamine in the nucleus accumbens of rats. Neurosci. Lett. 181, 57–60.

Mello, N.K., Negus, S.S., 1996. Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. Neuropsychopharmacology 14, 375–424.

Mello, N.K., Negus, S.S., 1998. Effects of kappa opioid agonists on cocaine- and food-maintained responding by rhesus monkeys. J. Pharmacol. Exp. Ther. 286, 812–824.

Mello, N.K., Negus, S.S., 2000. Interactions between kappa opioid agonists and cocaine. Preclinical studies. Ann. N.Y. Acad. Sci. 909, 104–132.

Mendelson, J.H., Mello, N.K., 1996. Management of cocaine abuse and dependence. N. Engl. J. Med. 334, 965–972.

Negus, S.S., Burke, T.F., Medzihradsky, F., Woods, J.H., 1993. Effects of opioid agonists selective for mu, kappa and delta opioid receptors on schedule-controlled responding in rhesus monkeys: antagonism by quadazocine. J. Pharmacol. Exp. Ther. 267, 896–903.

Negus, S.S., Mello, N.K., Portoghese, P.S., Lin, C.E., 1997. Effects of kappa opioids on cocaine self-administration by rhesus monkeys. J. Pharmacol. Exp. Ther. 282, 44–55.

NIDA, 2000. Epidemiologic trends in drug abuse. NIH Publication No. 00-4739A. National Institute on Drug Abuse, pp. 99.

Pfeiffer, A., Brantl, V., Herz, A., Emrich, H.M., 1986. Psychotomimesis mediated by kappa opiate receptors. Science 233, 774–776.

Richmond, R.L., Harris, K., de Almeida Neto, A., 1994. The transdermal nicotine patch: results of a randomised placebo-controlled trial. Med. J. Aust. 161, 130–135.

Schenk, S., Partridge, B., Shippenberg, T.S., 1999. U69593, a kappa-opioid agonist, decreases cocaine self-administration and decreases cocaine-produced drug-seeking. Psychopharmacology (Berl.) 144, 339–346.

Walsh, S.L., Strain, E.C., Abreu, M.E., Bigelow, G.E., 2001. Enadoline, a selective kappa opioid agonist: comparison with butorphanol and hydromorphone in humans. Psychopharmacology (Berl.) 157, 151–162.

Wentland, M.P., Lou, R., Ye, Y., Cohen, D.J., Richardson, G.P., Bidlack, J.M., 2001. 8-Carboxamidocyclazocine analogues: redefining the structure-activity relationships of 2,6-methano-3-benzazocines. Bioorg. Med. Chem. Lett. 11, 623–626.