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ORIGINAL INVESTIGATION

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Repeated administration of the $D_{1/5}$ antagonist ecopipam fails to attenuate the subjective effects of cocaine

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Abstract *Rationale:* Dopaminergic compounds have been targeted as potential treatments for cocaine abuse because of the known role of dopamine systems in drug reinforcement. Recent preclinical and human data have focused on the $D_{1/5}$ antagonist, SCH 39166 (ecopipam), as a potential therapeutic agent. *Objectives:* The objective of the present study was to determine whether treatment with chronic ecopipam can blunt or block the subjective effects of cocaine in the absence of significant behavioral impairment or toxic physiological effects. *Methods:* Four doses of ecopipam (0, 10, 25, and 100 mg p.o.) were administered daily for 1 week each in double-blind, random order to inpatient cocaine-dependent volunteers (n=10). Cocaine challenge doses (0, 25, and 50 mg/70 kg i.v.) were administered on the 7th day in ascending order, 1 h apart. *Results:* Ecopipam alone produced reliable dose-dependent deficits in performance on the digit symbol substitution task (DSST) and the circular lights task, but not a balance task. Impairment on the DSST waned with repeated dosing suggesting the development of tolerance. Ecopipam resulted in few direct subjective effects. Cocaine alone produced dose-dependent changes in prototypic subjective and physiological measures, however, ecopipam largely failed to alter either cocaine's direct effects or the desire for cocaine. *Conclusions:* Although the performance effects verify that these doses of ecopipam were behaviorally active, the absence of an attenuation of cocaine's effects or craving for cocaine in this chronic dosing paradigm suggests this compound is unlikely to be an effective pharmacotherapy for cocaine abuse.

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Introduction

Cocaine-induced activation of the dopaminergic system is believed to be the primary mediator of its reinforcing effects. Therefore, it is not surprising that several medications which interact with dopamine receptors have been evaluated as cocaine pharmacotherapies (see, for example, Rothman and Glowa 1995; Mello and Negus 1996; Bigelow and Walsh 1998; Winger 1998). Despite this effort, no compound tested to date has proven to be efficacious in the treatment of cocaine dependence. Development of an effective pharmacotherapy may depend in part on the compound's specificity for the five known subtypes of dopamine receptors, D_1, D_2, D_3, D_4, and D_5. These receptors have been grouped into two major categories, $D_{1/5}$ (D_1 and D_5) and $D_{2/3/4}$ (D_2, D_3, D_4), which are distinguished by their structural, pharmacological, and functional characteristics (see Sibley and Monsma 1992; Sibley et al. 1993).

The extrapyramidal side effects associated with the use of traditional antipsychotics is believed to be mediated by antagonism of the $D_{2/3/4}$ family of receptors (Kapur et al. 2000). Early evaluations of haloperidol confirmed that these side effects likely prohibit the use of $D_{2/3/4}$ antagonists for cocaine dependence since even large doses that result in extrapyramidal effects produce only minor changes in cocaine's effects (see, for example, Sherer et al. 1989). Targeting $D_{2/3/4}$ agonists has also had limited success. The $D_{2/3/4}$ agonist, bromocriptine failed to block the subjective effects of cocaine in a human laboratory study (Preston et al. 1992) and had no reported effect on cocaine use or cocaine withdrawal in controlled clinical trials (Eiler et al. 1995; Handelsman et al. 1997). Pergolide, a dopamine agonist with greater affinity for the $D_{2/3/4}$ receptor subtypes, has been shown to attenuate cocaine's subjective effect in humans; however, it did not decrease cocaine self-administration in

the laboratory setting (Haney et al. 1998) and failed to reduce cocaine use in cocaine-dependent outpatients (Malcolm et al. 2000).

Preclinical data have supported a role of $D_{1/5}$ receptors in the behavioral and subjective effects of cocaine. $D_{1/5}$ antagonists attenuate cocaine-induced locomotor activity (Cabib et al. 1991; Katz et al. 1999) and cocaine's discriminative stimulus effects (Katz et al. 1999). Importantly, $D_{1/5}$ antagonists blunt the reinforcing effects of cocaine in animals (Corrigall and Coen 1991a; Grech et al. 1996; Caine et al. 1999; Campbell et al. 1999) and $D_{1/5}$ agonists are self-administered by both rodents and primates (Self and Stein 1992; Weed and Woolverton 1995; Grech et al. 1996). These data indicate that cocaine's reinforcing properties are mediated, in part, through the $D_{1/5}$ subtype. Ecopipam (SCH 39166) is a highly selective $D_{1/5}$ receptor antagonist (Tice et al. 1994). Similar to other $D_{1/5}$ antagonists, ecopipam attenuates cocaine-induced locomotor effects (Katz et al. 1999), produces a rightward shift in the dose-effect curve for cocaine discrimination (Spealman et al. 1997), and attenuates the reinforcing effects of cocaine as measured by self-administration in both rodents (Caine and Koob 1994) and primates (Bergman et al. 1990). Furthermore, cocaine-induced reinstatement of cocaine self-administration following extinction is attenuated by ecopipam (Spealman et al. 1999), suggesting it may be effective in preventing relapse.

Because of these promising preclinical data, the pharmaceutical sponsor and the National Institute on Drug Abuse launched a systematic development effort aimed toward evaluating the safety and efficacy of ecopipam for the treatment of cocaine dependence. To date, three inpatient laboratory evaluations of ecopipam, including the present study, and one large multisite clinical trial have been conducted in cocaine-dependent humans as part of this effort. The first study (Romach et al. 1999) examined the safety and pharmacodynamic interaction between acute doses of ecopipam and cocaine in inpatient volunteers. Single doses of ecopipam (10, 25, and 100 mg) and placebo were administered in ascending order approximately 3 days apart and followed by challenge with a single dose of intravenous cocaine (30 mg). Ecopipam was safely tolerated in the presence of cocaine and appeared to attenuate ratings on an array of subjective measures sensitive to cocaine's effects, including ratings of high, good drug effects, and stimulation. Haney and colleagues (2001) recently completed the second within-subject study in which the effects of repeated daily dosing with either placebo or 100 mg ecopipam on the subjective, physiological, and reinforcing effects of smoked cocaine were examined. In contrast to the acute interaction findings of Romach and colleagues (1999), repeated daily treatment with 100 mg ecopipam for 5 days increased the positive subjective effects of cocaine, including ratings of good drug effects, high, and stimulated, and significantly increased self-administration at the lowest dose of cocaine.

The present study was designed to examine the effects of repeated dosing with ecopipam on the response to intravenous cocaine. This within-subject study incorporates a broad dose-effect evaluation of both ecopipam (0, 10, 25, and 100 mg) and cocaine (0, 25, and 50 mg), and assesses the safety and pharmacodynamic interaction using multidimensional measurements including subjective, behavioral, and physiological responses. Cocaine challenge testing was performed 20 h after the 7th day of daily ecopipam dosing at each dose level. This chronic dosing procedure was used to assess the potential therapeutic value of ecopipam when evaluated at steady state concentrations. Cocaine was administered 20 h after ecopipam to determine its likely clinical efficacy throughout the dosing period. In addition, given the putative role of dopaminergic systems in nicotine reinforcement (Corrigall and Coen 1991b), we incorporated preliminary measurements of smoking behavior to determine if the doses of ecopipam used here would alter cigarette consumption or the subjective effects of smoking.

Materials and methods

Subjects

Ten participants (nine male, one female) with a mean age of 38.2 years (±1.16, SEM) were recruited through local newspaper advertisements and word-of-mouth, and paid for their participation. All subjects gave informed consent and were not seeking treatment for drug dependence. Exclusion criteria included any history of seizures, cardiovascular disorders, diabetes, any current medical condition requiring medication, or abnormal laboratory values judged clinically significant. All subjects were determined to be healthy by physical examination, ECG, laboratory tests, and structured psychiatric interview (structured clinical interview; Spitzer and Williams 1986). Female subjects were tested for pregnancy prior to admission and every week while residing on the research unit; all results were negative. All subjects were within the normal weight range with a mean weight of 163.2 lb (±8.7) or 74.18 kg (±3.95).

All participants met DSM-IV criteria for cocaine dependence and reported spending an average of $23 (±3.59) per day on cocaine. The average reported age of first cocaine use was 21.9 (±1.33) years. All participants had experience using either smoked or intravenous cocaine. Other drugs used during the 30 days prior to admission included heroin (3.7±1.21 days) and alcohol (9.3±2.06 days). Urine samples were collected daily throughout the inpatient stay and were randomly analyzed for the presence of illicit drugs; no illicit drug use was detected in any volunteer during participation.

Of the ten volunteers, two did not smoke more than 10 cigarettes/day and a complete set of smoking data was not collected on a third. All smoking data, therefore, refers to the subset of seven volunteers. These seven volunteers smoked on average 12.9 (±0.29) cigarettes/day with a mean baseline score of 5.3 (±0.61) on the Fagerstrom tolerance questionnaire (Fagerstrom 1978; Fagerstrom and Schneider 1989), indicating they were light to moderate smokers. Subjects were not physically dependent on any substances other than nicotine and caffeine. Subjects were maintained on a caffeine-free diet, but were permitted to smoke cigarettes during their stay on the residential unit, except for 1 h before and throughout each experimental session. No assessment of caffeine withdrawal was made.

Study design

This inpatient study used a placebo-controlled, double-blind, within-subject, multidose, cross-over design. The study design and experimental procedures were approved by the local institutional review board and were in accordance with the 1964 Declaration of Helsinki. The subjects resided on a residential research unit for approximately 5 weeks. For 3 days prior to initiating the study, subjects habituated to the residential unit, were observed for signs of withdrawal, and practiced computer tasks. The day before the first dose of ecopipam all volunteers participated in a safety screening session to evaluate their cardiovascular response to cocaine. Three intravenous cocaine injections were given in ascending order (0, 25, and 50 mg/70 kg) separated by 1 h. Two volunteers were excluded from further participation after exceeding our cardiovascular safety parameters (see below), one due to elevated systolic blood pressure and the other due to premature ventricular contractions following cocaine administration.

For the remainder of the study, subjects received oral capsules of ecopipam (or placebo) every evening at 5:45 p.m. Four doses of ecopipam (0, 10, 25, and 100 mg/day) were administered for 7 consecutive days at each dose in random order. Oral medication was dispensed by nursing staff. Vital signs, subjective measures, and performance measures were monitored at 25 min before and 1, 2, and 4 h after each oral medication. On the 7th day at each dose of ecopipam, intravenous cocaine challenge sessions (see below for details) were conducted. As in the safety session, volunteers were given three intravenous cocaine injections during each session in ascending order (0, 25, and 50 mg/70 kg), separated by 1 h.

Daily measures

Vital signs (heart rate, blood pressure, respiration, and body temperature) were recorded on the residential unit to monitor safety every morning (8:00 a.m.). Subjective and performance measures and a smoking questionnaire were also presented on the residential unit to assess the direct effects of ecopipam. Subjective effects were assessed with a 34-item adjective checklist, the Addiction Research Center Inventory (ARCI), and the profile of mood states (POMS; McNair et al. 1971). Performance effects were evaluated with the digit symbol substitution test (DSST; McLeod et al. 1982; a measure of information processing and reaction time), a balance task (a measure of gross motor coordination), and the circular lights task (Roache and Griffiths 1985; a measure of visual perception and hand–eye coordination). All performance measures were practiced a minimum of eight times prior to dosing in order to minimize changes in performance related to acquisition. The DSST, balance task, circular lights, and subjective questionnaire were administered 25 min before and 1, 2, and 4 h after each oral 5:45 p.m. medication (6:45 p.m., 7:45 p.m., and 9:45 p.m.). The POMS was administered 25 min prior to oral dosing (5:20 p.m.) and the smoking questionnaires were administered after the first and last cigarette of the day. The subjective questionnaire, POMS, ARCI, and DSST were presented on a personal computer (Apple IIGS; Apple Computer, Cupertino, Calif., USA). The subjects responded using a joystick (adjectives and POMS) and/or keyboard (DSST) while in a quiet test room located within the residential unit.

Subjective measures

The adjectives on the 34-item subjective questionnaire designed to detect the direct acute and chronic effects of ecopipam were rated from 0 (indicating "not at all") to 4 (indicating "extremely"). These items included "do you feel... a drug effect?,...an arousing or stimulant drug effect?,...a sedating or depressant drug effect?,...limp or loose?,...light-headed or dizzy?,...queasy or sick to your stomach?,...fatigued or weak?,...unsteady?, ...hot or flushed?,...confused or disoriented?,...sleepy?,...mentally slowed down?,...your limbs are heavy or rigid?,...tired or lazy?,...easy going or mellow?,...forgetful?,...talkative?,...excited?,...comfortable?,...relaxed?,...nervous or anxious?,...any numbness or tingling?,...restless like you have to keep moving?,...energetic?,...shaky or jittery?,...irritable or grumpy?," "do you like the drug effect?," "does the drug have any good effects?," "does the drug have any bad effects?," "do you have a headache?," "do you have blurred vision?," "is your mouth dry?," "do you have difficulty concentrating?," and "is your speech slurred?." The POMS consists of 65 items which are rated from zero (indicating "not at all") to four (indicating "extremely") and constitute subscales for tension-anxiety, depression-dejection, anger-hostility, vigor, fatigue, confusion-bewilderment, friendliness, and total mood disturbance.

Performance measures

The DSST presents a 90-s series of patterns of squares on a computer screen that the subjects attempt to replicate as quickly as possible by duplicating the pattern on the keyboard. For the balance task, participants were instructed to close their eyes and stand on either their left or right foot. Latency to fall or hop was measured for a maximum of 30 s for each foot. Psychomotor performance was assessed with the circular lights task (Roache and Griffiths 1985). A randomly sequenced illumination of lights was presented to the volunteers for 60 s. Volunteers were instructed to press the button adjacent to each illuminated light with their dominant hand as quickly and accurately as possible. A correct answer would turn that light off and illuminate another.

Smoking questionnaire

A four-item smoking questionnaire was administered immediately after the first cigarette of the day and included "how soon after you woke up did you smoke your first cigarette?," "how strong was your desire to smoke when you woke up this morning?," "how much did you like smoking your first cigarette?," and "how satisfying was your first cigarette?." Immediately after the last cigarette of the day, these seven questions were answered: "how many cigarettes did you smoke in the last 24 h?," "rate your desire to smoke during the last 24 h?," "rate how much you enjoyed smoking during the last 24 h?," "rate how satisfying smoking has been during the last 24 h?," "how strong was your desire to smoke your last cigarette?," "how much did you like smoking your last cigarette?," and "how satisfying was your last cigarette?." Both the morning and evening smoking questionnaires were rated from zero (indicating "not at all") to four (indicating "extremely").

Cocaine challenge sessions

Intravenous cocaine challenge sessions were conducted from 1:00–5:00 p.m. in a testing room designed to provide a consistent environment. The subjects were seated in comfortable chairs throughout the session in front of a personal computer (Apple IIGS) which recorded subjective and physiological responses. Cocaine (0, 25, and 50 mg) was administered to the subjects at 1 h intervals (1:45 p.m., 2:45 p.m., 3:45 p.m.) via indwelling i.v. catheters. A slow drip i.v. line remained in place throughout each session. A physician monitored the electrocardiogram (ECG) continuously for 15 min following each injection. The criteria for aborting an intravenous cocaine challenge session after intravenous cocaine included abnormal ECG, systolic blood pressure >180 mmHg, diastolic blood pressure >120 mmHg, or heart rate >170 beats per min, or [(220-subjects age)×0.85] for >4 consecutive min. Cocaine challenge sessions, conducted at 20 h post-ecopipam dosing, were timed to coincide with ecopipam trough plasma concentrations based on a reported plasma half-life for ecopipam of 13–22 h. The research assistant remained seated behind the computer, initiated the data collection, monitored the sub-

jects, and provided observer ratings. Data collection proceeded from 30 min prior to the first injection through 60 min after the last injection.

Physiological measurements

Physiological measures, including skin temperature, systolic and diastolic blood pressure, heart rate, and pupil diameter, were monitored throughout the session. Respiratory rate was recorded by an observer who counted the number of breaths taken by the subject for a 15-s period. Skin temperature, systolic and diastolic blood pressure, and heart rate were collected every minute by use of an automatic physiologic monitoring device (Noninvasive Patient Monitor model 506; Criticare Systems, Waukesha, Wis., USA) that was interfaced with the Macintosh computer. Photographs of the eye were taken using a camera (Polaroid, Cambridge, Mass., USA) modified with a mounted bracket to ensure a standard distance from the eye. The photographs, for later pupil diameter measurement, were taken 15 min prior to the first injection and at 5, 15, 30, and 45 min following each injection.

Subjective measurements

Subject-rated measurements during session included visual analog scales, the ARCI short form (Martin et al. 1971), a street value question, an adjective checklist, and observer ratings. The subjects responded to the visual analogs, the ARCI, and the adjectives using a joystick to select the most appropriate response on the computer screen. The visual analog questions included "do you feel any drug effect?," "how high are you?," "does the drug have any good effects?," "does the drug have any bad effects?," "do you like the drug?," "how much do you desire cocaine?," "do you feel anxious?," and "do you feel drowsy/tired?." These were presented at baseline, once each minute for 15 min following the start of each injection, and at 15, 30, and 45 min after each injection. The subjects responded by positioning an arrow along a 100-point line labeled with "none" at one end and "extremely" at the other. The ARCI short form presented forty-nine true/false questions at 15 min before the first injection and 15 and 45 min after each injection. The ARCI questions are subdivided in scales that are sensitive to euphoria (morphine-benzedrine group; MBG), sedation (phenobarbital-chlorpromazine-alcohol group; PCAG), dysphoria (lysergic acid diethylamide; LSD), and amphetamine-like effects (benzedrine group; BG, and amphetamine; A). Street value was estimated by asking "how much would you pay for this drug?" 15 min before the first injection, and at 15, 30, and 45 min after each injection. The adjective checklist consisted of 21 items that the subjects rated from 0 (indicating "not at all") to 4 (indicating "extremely"). The adjectives included fearful, feeling of power, stomach upset/nausea, suspicious, sweating, dizzy/light-headed, craving for cocaine, hallucinations, irritable, sleepy, tremor, thirsty, excited, jittery, tingling, dry mouth, fidgety, feel a thrill, nervous, stimulated, and drug effect. The observer-rated adjective scales included the following: liking, excited, restlessness, positive vocalizations, nervous, agitated, fearful, fidgety, irritable, tremor, drug effect, tired, sweating, smiling/laughing, depressed/sad, drowsy, jittery, stuffy nose, and suspicious. These were rated on the same scale as the subject-rated adjectives. Both subject and observer adjectives were presented 15 min before the first injection, and at 15, 30, and 45 min after each injection.

Drugs

Ecopipam (5 and 25 mg tablets) and matching placebo tablets that were all identical in appearance were provided by the Schering-Plough Research Institute. All doses (0, 10, 25, and 100 mg) were dispensed as four tablets using a combination of the placebo, 5, or 25 mg tablets. Cocaine HCl for intravenous administration was dissolved in 0.9% sterile saline and filtered through a 0.22-mm filter (Millipore Products Division, Bedford, Mass., USA) into a sterile pyrogen-free vial. Intravenous cocaine and placebo (saline vehicle) were administered in a volume of 1 ml over 1 min.

Data analysis

For measures of the direct effects of ecopipam that were taken once daily (for example, POMS, ARCI, smoking questions), two-factor repeated measures ANOVA was used to determine the effect of dose of ecopipam and day of treatment (i.e., day 1–7). For measures of ecopipam's direct effects that were taken both prior to and following the daily dosing (for example, DSST, balance task, circular lights task, subjective questionnaire), two data analytic strategies were employed. First, time course analyses using a three-factor repeated measures ANOVA with ecopipam dose, day of treatment, and time since dosing was performed. Second, peak change from baseline (PCFB) scores were analyzed using a two-factor ANOVA (ecopipam dose and day) in order to test the maximal effect of each daily dose while precluding the influence of carry-over effects from preceding doses. Additionally, baseline measurements from the cocaine challenge sessions on the 7th day of dosing were analyzed using a one-factor ANOVA to determine if ecopipam was producing direct physiological or subjective effects just prior to the cocaine challenge session.

Cocaine challenge session data were analyzed using three-factor repeated measures ANOVA (ecopipam dose, cocaine dose, and time). The data were also analyzed with a two-factor ANOVA (ecopipam and cocaine dose) using the maximum (Max) or minimum (Min) scores following each cocaine injection. All repeated measures data were adjusted for sphericity using Huynh-Feldt corrections. *Post hoc* comparisons of each active dose of ecopipam to placebo for all analyses were made using Tukey's honestly significant differences (HSD). Differences with a probability of $P<0.05$ were considered statistically significant.

Results

Direct effects of ecopipam alone

Physiological

Ecopipam dose-dependently increased pupil diameter as measured just before the cocaine challenge sessions ($P<0.01$), with both the 25 and 100 mg doses differing from placebo ($P<0.05$). Ecopipam did not alter daily measures of heart rate, blood pressure, or body temperature. Although there was a significant interaction between ecopipam and day of treatment ($P<0.05$) for respiration, there were no orderly dose effects and respiratory rate declined with repeated dosing during the placebo treatment, suggesting the statistical finding may have been spurious (data not presented).

Subjective

The analyses of subjective data revealed modest sedative-like effects of ecopipam. Ecopipam decreased scores on the POMS composite scales for Vigor ($P<0.01$) and Friendly ($P<0.05$), as well as the individual item "lively" ($P<0.05$; data not presented). Analysis of the adjective checklist produced convergent results. Ecopipam decreased ratings of "do you feel talkative?" ($P<0.05$) and

produced a marginal increase from baseline in ratings of "do you feel tired or lazy?" ($P<0.10$). Ecopipam did not significantly alter any of the ARCI scales, remaining items on the POMS, or the 34-item adjective checklist. The data collected at the start of each cocaine challenge session failed to reveal any significant subjective effects of ecopipam. However, the observers rated a significant effect of ecopipam on the item fidgety ($P<0.05$), whereby 25 mg produced increased ratings of fidgety over placebo ($P<0.05$).

Performance

Analysis of the data from the DSST task revealed a decrease in the total number of trials attempted (i.e., speed; $P<0.05$). As displayed in Fig. 1 (upper panel), ecopipam produced a significant and dose-dependent decrease in the speed of responding on the 1st day of dosing (i.e., the total number of trials attempted in a 90-s test period; see figure legend for statistical outcome). The time course reveals that this effect peaked at 120 min after ecopipam dosing and was returning toward baseline at 240 min post-dosing. Data are shown in the lower panel for the speed of responding over the 7-day course of dosing. Ecopipam produced a significant and graded dose-dependent decrease in the speed of responding. This impairment gradually waned over the 7-day dosing period with performance returning toward placebo levels. Ecopipam did not significantly alter the accuracy of responding (i.e., percentage of correct trials) either acutely or over the 7-day treatment. Ecopipam impaired performance on the circular lights task (PCFB analyses; $P<0.001$; data not shown). This impairment was dose-dependent and did not significantly change with repeated dosing ($P>0.05$). There was no effect of ecopipam on the balance task.

Smoking questionnaires

Ecopipam did not affect smoking behavior or the subjective effects of smoking in the subset of seven smokers. The time course analyses for both the morning and evening smoking questionnaires failed to reveal any effects of ecopipam on any items.

Cocaine challenge

Physiological

Cocaine alone produced significant and dose-dependent increases in both systolic and diastolic blood pressure when examined for the first 15 min after each injection as evidenced by a significant main effect of cocaine dose ($P<0.001$; see Fig. 2). For systolic blood pressure, there was also a significant main effect of ecopipam dose, although the interaction between ecopipam and cocaine

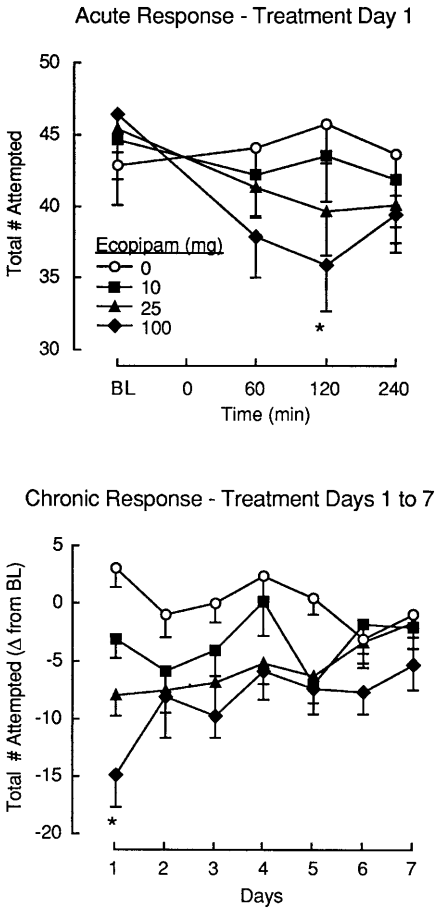

Fig. 1 Data shown are the mean (n=10; - SEM) total number of items attempted (i.e., speed) on the digit symbol substitution task. The *upper panel* illustrates the time course of ecopipam's acute effects on the 1st day of dosing with assessments taken at baseline and up to 4 h post-dosing. The *lower panel* illustrates the mean peak change from baseline (*BL*) on each of the 7 dosing days. Analyses of the time course data (*upper panel*) revealed statistically significant effects for ecopipam dose [$F(3,27)=5.22$, $P<0.01$], time since ecopipam [$F(3,27)=11.82$, $P<0.001$], day of dosing [for clarity only day 1 is shown here; $F(6,54)=6.67$, $P<0.001$], and the ecopipam dose and time interaction [$F(9,81)=4.85$, $P<0.01$]. The peak change from baseline analyses (*lower panel*) revealed a significant effect of ecopipam dose [$F(3,27)=11.15$, $P<0.001$] and a trend for day of dosing ($P=0.054$). *Asterisk* denotes a significant difference from placebo ecopipam according to Tukey's honestly significant differences (HSD; $P<0.05$)

failed to reach significance ($P=0.063$). Inspection of these data suggest that ecopipam produced little direct effect on blood pressure (i.e., at 0 mg cocaine; data not shown), but that the magnitude of the pressor response to cocaine (50 mg) was potentiated during treatment with active ecopipam in comparison to placebo. For example, systolic blood pressure was increased on average by 10–15 mmHg when cocaine (50 mg) was given concomitantly with 100 mg ecopipam (see Fig. 2). With diastolic pressure, the data also suggest that ecopipam potentiated the effects of high-dose cocaine (Fig. 2 lower right panel). However, in this case, the significant interaction between ecopipam dose and cocaine dose ($P<0.01$) ap-

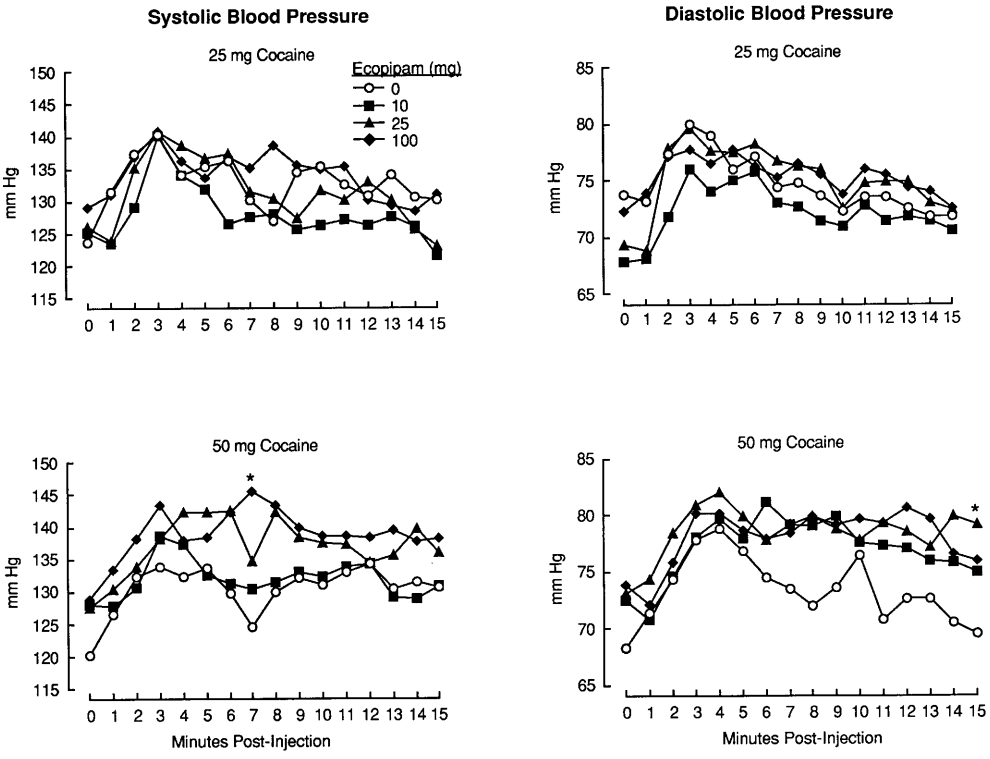

Fig. 2 Data shown are mean (n=10) systolic and diastolic blood pressure after 25 (*upper panels*) and 50 mg (*lower panels*) i.v. cocaine in combination with each dose of ecopipam. There were no effects of ecopipam following 0 mg cocaine (data not shown). Time course analyses revealed the following statistical values: systolic pressure [ecopipam dose: $F(3,27)=3.33$, $P<0.05$; cocaine dose: $F(2,18)=39.67$, $P<0.001$; time: $F(15,135)=4.45$, $P<0.01$; ecopipam and cocaine interaction: $P=0.063$; cocaine and time interaction: $F(30,270)=4.74$, $P<0.001$] and diastolic pressure [ecopipam dose: $P=0.077$; cocaine dose: $F(2,18)=45.05$, $P<0.001$; time: $F(15,135)=10.95$, $P<0.001$; ecopipam and cocaine interaction: $F(6,54)=3.94$, $P<0.01$; cocaine and time interaction: $F(30,270)=5.02$, $P<0.001$]. *Asterisk* denotes a significant difference from placebo ecopipam according to Tukey's HSD ($P<0.05$)

peared largely attributable to all active doses of ecopipam producing a protracted elevation of diastolic pressure, rather than a change in the absolute magnitude of the response. These pressor interactions were not apparent when ecopipam was administered with cocaine at 25 mg (upper panels).

Cocaine alone produced significant and dose-related increases in maximal heart rate as expected ($P<0.001$). Ecopipam did not produce any direct effects on heart rate nor did it alter the direct effects of cocaine. Although cocaine produced dose-related decreases in skin temperature, this effect failed to reach significance ($P=0.051$) and there was no interaction between ecopipam and cocaine. Finally, both cocaine ($P<0.001$) and ecopipam ($P<0.05$) dose-dependently increased pupil diameter, however there was no statistically significant interaction between the two.

Subjective

Cocaine produced dose- and time-dependent effects on a number of visual analog measures. Figure 3 depicts the time course data for the global measure of drug effect. A similar profile of action was observed for measures of high, good effects, and liking for the drug. For all of these measures, there were no significant effects of ecopipam on the response to cocaine. The onset, peak, and rate of decline of cocaine's effects were unchanged by ecopipam. Other subjective measures, illustrated as the peak response, are shown in Fig. 4. As can be seen, the dose-effect function for ratings of liking for cocaine were unchanged by treatment with ecopipam at any dose. In the middle panel, data are shown for ratings of craving for cocaine. Although scores were modestly increased during treatment with 10 and 25 mg ecopipam ($P<0.10$), there were no main effects of ecopipam or interaction effects for this measure. In the lower panel, the participants' estimates of the street value for cocaine reveal dose-related increases for cocaine, but again, no evidence of ecopipam influencing these estimates. In addition to these measures, cocaine also increased ratings of desire for cocaine, anxious, bad effects, sweating, dizzy, thirsty, excited, jittery, tingling, dry mouth, feel a thrill, and stimulated, and the BG, A, MBG, and LSD scales of the ARCI ($P<0.05$). Consistent with other subjective measures, these responses were unchanged by the administration of ecopipam when analyzed both by time course and peak effect. Observer ratings were consistent with subject ratings. Cocaine produced reliable effects on 5 of 19 items (liking, restlessness, tremor, drug effect, sweating); ecopipam failed to significantly change any of cocaine's effects.

Discussion

The present study demonstrates that ecopipam, over a range of doses, failed to alter the subjective effects of cocaine and modestly potentiated the cocaine pressor response. Although these ecopipam doses were pharmacologically active based upon their observed direct effects on psychomotor performance and pupil diameter, the prototypic dynamic profile of cocaine observed here re-

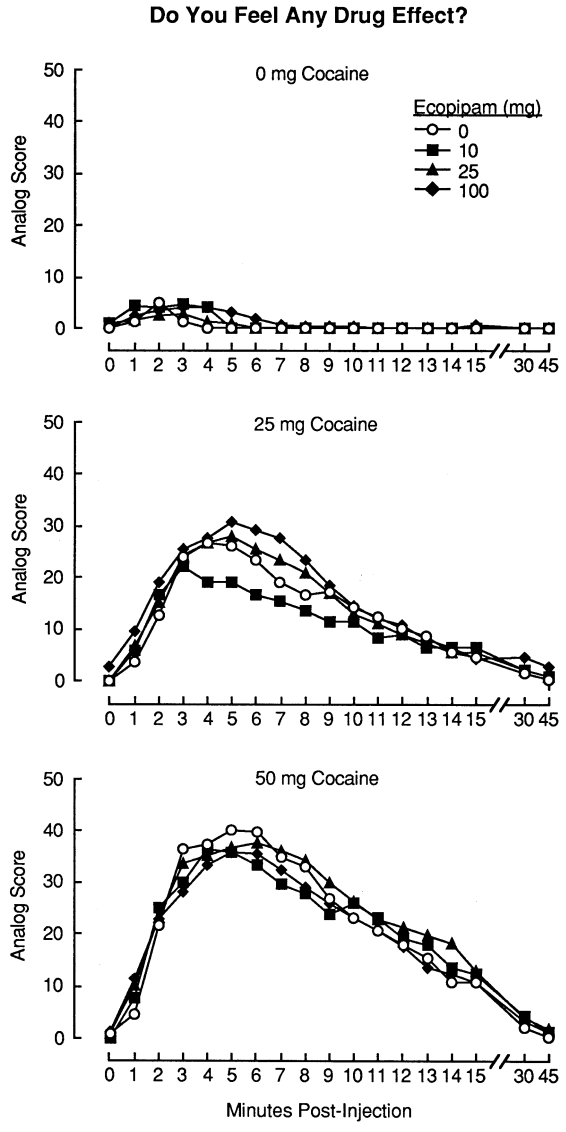

Fig. 3 Data shown are mean (n=10) rating of "do you feel any drug effect?" following i.v. challenge with 0 (*upper*), 25 (*middle*), and 50 mg (*lower*) at each dose of ecopipam. The maximum possible score is 100. Significant main effects of cocaine [$F(2,18)=34.96$, $P<0.001$], time [$F(17,153)=17.3$, $P<0.001$], and a cocaine and time interaction [$F(34,306)=13.45$, $P<0.001$] were found

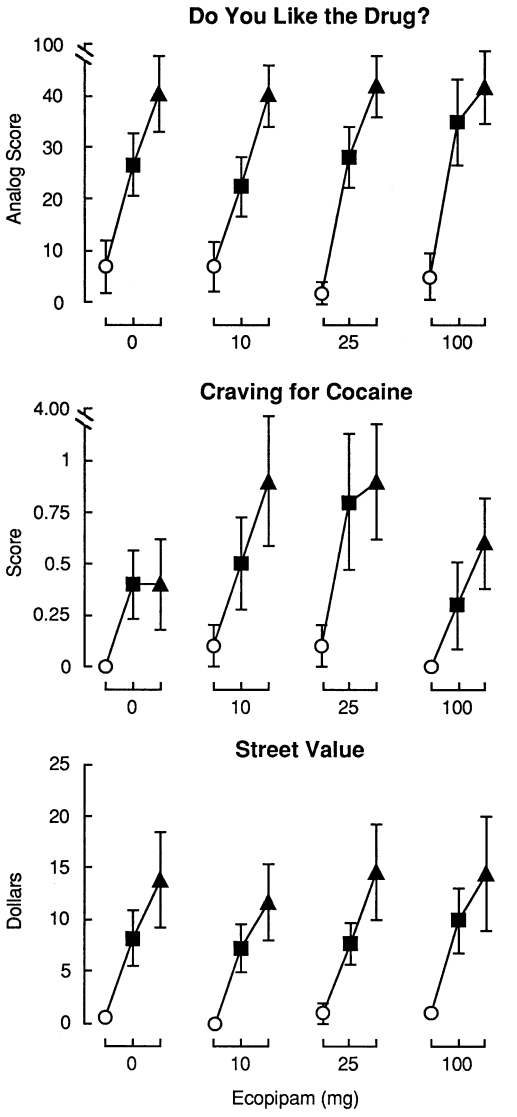

Fig. 4 Data shown are mean (n=10; ± SEM) maximal scores on the visual analog question "do you like the drug?" (*upper*; maximum score 100), ratings of "craving for cocaine" (*middle*; maximum score 4), and estimates of the street value (*lower*) after cocaine challenge at each dose of ecopipam (*abscissa*). *Open circles*, *closed squares*, and *closed triangles* denote 0, 25, and 50 mg i.v. cocaine, respectively (1 h apart in ascending order). Analyses of the peak data revealed the following statistical results: "do you like the drug?," [cocaine: $F(2,18)=53.19$, $P<0.001$], "craving for cocaine" [ecopipam: $P=0.054$; cocaine: $F(2,18)=6.4$, $P<0.01$], and street value [cocaine: $F(2,18)=9.79$, $P<0.01$]

mained largely unchanged in both its magnitude and duration when given after 7 days of daily ecopipam. These data are inconsistent with an earlier study on the acute interaction between ecopipam and cocaine in which an attenuation of the subjective response was reported (Romach et al. 1999). The lack of a therapeutic interaction and enhanced cardiovascular effects observed in the present study are consistent with the only other study of repeated ecopipam dosing reported to date (Haney et al. 2001).

The differences between these three studies may arise from either the duration of treatment with ecopipam and/or the timing of cocaine administration relative to ecopipam dosing. With respect to the duration of treatment, Romach and colleagues reported that single-dose administration of ecopipam attenuated the response to cocaine when the cocaine challenge was administered 2 h after ecopipam dosing. In the present study, prominent sedative-like performance impairing effects were observed on the 1st day of ecopipam dosing and these effects peaked at approximately 2 h after oral administration of ecopipam (see Fig. 1). Moreover, these effects tended to dissipate with repeated administration. Thus, it is possible that tolerance may develop to some or all of

the direct effects of ecopipam and account for the failure to detect a significant interaction with cocaine during chronic ecopipam treatment. Interestingly, an earlier preclinical study also reported that chronic administration of SCH 23390, a related $D_{1/5}$ antagonist, produced only a transient attenuation of the reinforcing effects of cocaine in non-human primates (Kleven and Woolverton 1990).

The second major methodological difference among these studies is the timing of the ecopipam dosing relative to cocaine challenge. Challenges occurred at 20 h post-dosing in the present study, and at 15 (Haney et al. 2001) and 2 h (Romach et al. 1999) in the other studies. Our 20-h post-ecopipam interval was based upon the estimated 16–20 h half-life for this range of doses of ecopipam (data on file; Schering-Plough, N.J., USA). Our intent was to provide a practical assessment of the effectiveness of once daily dosing with ecopipam against cocaine when ecopipam concentrations would be close to trough levels. The same dosing procedure was employed in a concurrent multisite outpatient clinical trial that was terminated prematurely by the sponsor because of lack of effectiveness at interim analysis. The present data indicate that once daily dosing does not produce lasting antagonism of cocaine's effects over this range of ecopipam doses. Similarly, the data of Haney and colleagues (2001) indicate that repeated administration of 100 mg ecopipam failed to antagonize cocaine 15 h after dosing. Thus, evidence suggests that chronic once daily administration of 10–100 mg ecopipam may have either no impact on cocaine's actions or may actually lead to potentiated subjective and cardiovascular responses under some dosing conditions.

One notable effect of ecopipam in combination with cocaine was the tendency for ecopipam pretreatment to enhance the pressor effects of cocaine. In this study, ecopipam alone produced no change in blood pressure, but increased the magnitude of the systolic response to cocaine while prolonging the elevation in diastolic pressure (see Fig. 2). Haney and colleagues (2001) also observed an increased pressor response with the combination of ecopipam and cocaine and noted that ecopipam alone elevated blood pressure independent of cocaine administration. Additionally, they reported a potentiation of cocaine-induced tachycardia following active ecopipam; although a similar trend was observed in the present study, it failed to reach significance. Again, these data suggest a dichotomy between the acute and chronic dosing studies as the acute dosing study found that ecopipam attenuated the blood pressure and heart rate response to cocaine (Romach et al. 1999). The clinical significance of the ecopipam-induced potentiation of cocaine's pressor action is uncertain. Although the blood pressure increases observed here were modest (for example, 10–15 mmHg), the amount of cocaine administered under these controlled acute dosing conditions is not representative of the pattern and doses typically used illicitly. Thus, the effects observed here may not accurately reflect the effects of ecopipam in combination with larger individual doses or repeated administration of cocaine.

It is possible that changes in the dopaminergic system resulting from repeated exposure to ecopipam may have led to the observed enhancement of the cardiovascular response to cocaine. The pressor actions of cocaine are generally attributed to sympathetic activation, resulting from both blockade of norepinephrine reuptake in the periphery and a centrally mediated increase in sympathetic outflow (see Vongpatanasin et al. 1999 for discussion). Acute antagonism of the $D_{1/5}$ dopamine receptor may decrease sympathetic activity, while chronic antagonism may cause a compensatory increase in $D_{1/5}$ receptors, providing a mechanism by which cocaine produces an enhanced sympathoexcitatory effect (Mukai et al. 1996).

Based upon preclinical data, one might predict that acute and chronic treatment regimens with dopamine antagonists could yield differential outcomes (see Haney et al. 2001 for additional discussion). For example, acute administration of haloperidol attenuates the development of a cocaine conditioned place preference, while chronic pretreatment with haloperidol enhances the development of place preference to low doses of cocaine in rats (Kosten et al. 1996). Chronic treatment with dopamine antagonists also results in hypersensitivity to other behavioral effects of cocaine including rate-dependent responding, locomotor activity, and the development of sensitization (Howell and Byrd 1992; LeDuc and Mittleman 1993). The increased sensitivity to dopaminergic agents following chronic dopamine antagonist treatment has been attributed to an increase in both the number and sensitivity of dopamine receptors (Creese and Chen 1985; Hess et al. 1986). Thus, the findings of Haney and colleagues (2001), whereby some of the acute effects of cocaine were actually enhanced after 5 days of ecopipam treatment, may be accounted for by changes in response to chronic $D_{1/5}$ blockade. Given that our study and that of Haney and colleagues employed a generally comparable ecopipam dosing regimen for the 100-mg dose, it is unclear why some subjective responses to cocaine were significantly potentiated in their study and those in the present study were largely unchanged. One notable difference between the studies is that cocaine doses were self-administered in the Haney et al. (2001) study and were experimenter-administered here; preclinical studies have shown substantive differences in responding under these two experimental arrangements (see, for example, Dworkin et al. 1995; Donny et al. 2000).

Given the potential role of dopamine receptors in nicotine reinforcement (Corrigall and Coen 1991b), we also collected data of smoking behavior and subjective smoking experience in order to determine if the doses of ecopipam used here might attenuate some of the reinforcing effects of cigarettes. We found no evidence for an effect of ecopipam on desire to smoke, smoking satisfaction, or the number of cigarettes smoked. These data are based on a small sample and were incorporated as measures of interest secondary to the evaluation of ecopipam's direct effects and its interaction with cocaine. Therefore, although the present data do not support a role for ecopipam in the treatment of nicotine de-

pendence, its potential efficacy for this indication cannot be precluded without further controlled studies of ecopipam on smoking behavior.

In summary, although preclinical data (see, for example, Bergman et al. 1990; Caine and Koob 1994) and a recent human study (Romach et al. 1999) have suggested that ecopipam may have utility as a treatment for cocaine dependence, we found no evidence that chronic ecopipam modifies the subjective effects of cocaine which are predictive of its abuse liability. These data, along with those of Haney et al. (2001), provide no evidence that ecopipam will be useful in treating cocaine dependence. The contrast between ecopipam's acute and chronic effects highlights the importance of testing potential pharmacotherapies under chronic dosing conditions. These findings do not necessarily rule out the potential efficacy of all $D_{1/5}$ agents for this indication, however, there are now several studies indicating that neither $D_{1/5}$ antagonists or agonists (Haney et al. 1999a) are likely to have robust therapeutic effects. Similarly, the development of pharmacotherapies targeting the $D_{2/3/4}$ family of receptors has failed to produce promising results (see, for example, Preston et al. 1992; Handelsman et al. 1997; Haney et al. 1998; Malcolm et al. 2000). A growing body of research has highlighted the importance of individual subtypes within the $D_{2/3/4}$ family (Caine et al. 1997; Pilla et al. 1999) as well as non-dopaminergic systems (Mello and Negus 1996; Bigelow and Walsh 1998). These directions may ultimately provide the best chance for finding an effective pharmacotherapy for cocaine dependence.

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