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ORIGINAL INVESTIGATION

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Effects of ecopipam, a selective dopamine D1 antagonist, on smoked cocaine self-administration by humans

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Abstract *Rationale:* Data obtained in laboratory animals and humans suggest that dopamine D1 receptor antagonists decrease cocaine self-administration and block cocaine's discriminative stimulus and subjective effects. *Objectives:* This study investigates the effects of the selective dopamine D1 antagonist, ecopipam (SCH 39166), on the reinforcing, cardiovascular, and subjective effects of cocaine in humans. *Methods:* Ten non-treatment-seeking cocaine smokers (two females, eight males), residing on an inpatient research unit, were maintained on placebo and ecopipam (100 mg p.o.) in random order using a within-subjects, cross-over design. Cocaine self-administration (0, 12, 25, and 50 mg) was tested beginning on the 5th day of each 8-day maintenance condition. A six-trial choice procedure (cocaine vs $5 merchandise vouchers) was utilized, with sessions consisting of one sample trial, when participants smoked the cocaine dose available that day, and five choice trials, when participants chose between smoking the available cocaine dose or receiving one merchandise voucher. *Results:* In the presence of placebo cocaine, ecopipam significantly decreased cocaine craving while increasing alcohol and tobacco craving. In the presence of active cocaine, ecopipam increased cocaine self-administration (12 mg) and increased ratings of "good drug effect," "high," "stimulated," and dose quality (25 and 50 mg). Ecopipam produced small but significant increases in blood pressure, regardless of cocaine dose. *Conclusions:* Maintenance on the long-acting dopamine D1 antagonist, ecopipam, enhanced both cocaine self-administration as well as its subjective effects compared to maintenance on placebo. These data suggest that chronic antagonism of the dopamine D1 receptor may not be a useful approach for the treatment of cocaine abuse.

Keywords Cocaine · Human · Self-administration · D1 antagonist · Subjective effect · Craving · Cardiovascular effect · SCH 39166

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Introduction

There is no effective pharmacotherapy currently available to treat cocaine dependence. Since cocaine's reinforcing effects are largely mediated by the inhibition of dopamine re-uptake (Fibiger 1978; Ritz et al. 1987; Wise and Bozarth 1987), many preclinical investigations of potential pharmacotherapies have focused on the medications acting either directly or indirectly on the dopamine neuron. Given that blocking dopamine re-uptake results in dose-dependent increases in extracellular dopamine levels in a variety of brain regions (Hurd et al. 1997; Wise et al. 1995), one potential approach for the treatment of cocaine abuse is to pharmacologically attenuate dopamine's effects at the level of the dopamine receptor.

Five dopamine receptor subtypes have been identified (Jackson and Weslind-Danielsson 1994; Kebabian and Calne 1979), although the terms "D1" and "D2" receptor will be used throughout this report to refer to the two classes of receptors that are pharmacologically and biochemically distinct (D1/D5 and D2/D3/D4). Both D1 and D2 receptors contribute to cocaine's reinforcing and discriminative stimulus effects. Acute pretreatment with D1 or D2 antagonists appear to block cocaine's reinforcing effects in rats (Caine and Koob 1994; Depoortere et al. 1993; Hubner and Moreton 1991) and monkeys (Bergman et al. 1990; Campbell et al. 1999). Some studies report that acute pretreatment with the D1 antagonists, SCH 23390 (Howell and Byrd 1991; Woolverton 1986; Woolverton and Virus 1989) or SCH 39166 (ecopipam; Winger 1994) only suppressed cocaine self-

administration at doses that produced catalepsy or decreased responding for food, yet others indicate that D1 antagonists act selectively, by altering cocaine self-administration at doses that do not result in motor incapacitation or impaired responding for food in rats (Caine and Koob 1994; McGregor and Roberts 1993) or monkeys (Kleven and Woolverton 1990).

In humans, D2 antagonists have not shown promise for the treatment of cocaine dependence (see Rothman and Glowa 1995). By contrast, a recent study has shown that pretreatment with a single dose of the D1 antagonist, ecopipam, dose-dependently decreased the effects of intravenous cocaine on ratings of "high" and "good drug effect" while decreasing the reported desire for cocaine (Romach et al. 1999). Comparable results have been reported in laboratory animals. Drug discrimination studies, which are hypothesized to model the subjective effects of drugs in humans (Woolverton and Schuster 1983), have shown that the acute administration of D1 antagonists block cocaine's discriminative stimulus effects in both rats (Barrett and Appel 1989; Callahan et al. 1995) and monkeys (Mansbach et al. 1995; Spealman 1990; Spealman et al. 1991, 1997; Vanover et al. 1991), although in certain cases, D1 antagonists only blocked cocaine's discriminative stimulus effects at doses that appeared to produce sedation (Kleven et al. 1988, 1990; Lane et al. 1992). D1 antagonists also protect against cocaine's cardiovascular toxicity and lethality in most (Kanani et al. 1998; Schechter and Meehan 1995; Witkin et al. 1993) but not all (Schindler et al. 1991) studies using laboratory animals, without producing the extrapyramidal side effects associated with D2 antagonist administration (Coffin et al. 1989). These data suggest that D1 antagonists may be useful as treatment medications for cocaine abuse.

The present study investigated how maintenance on ecopipam, a selective antagonist at the D1 receptor (Chipkin et al. 1988; Sedvall et al. 1991), affected smoked cocaine self-administration by humans in a controlled laboratory setting. Cocaine users who were not seeking treatment for their cocaine use were maintained on ecopipam and placebo in a cross-over design and were given the opportunity to repeatedly self-administer cocaine over several hours, under careful medical observation. Alternatives to drug-taking were available, just as they are outside of the laboratory. The effects of ecopipam on cocaine self-administration, cocaine "craving," subjective-effects ratings, and cardiovascular effects were determined.

Materials and methods

Participants

Two female and eight male research volunteers (eight African-American, two Hispanic), 38±4 years of age (mean ± SD), and currently smoking cocaine 3.9±1.5 days/week were solicited through word-of-mouth referral and newspaper advertisement in New York, N.Y. Recruitment focused on current crack cocaine users who were not interested in treatment, and who had no major psychiatric or medical disorders. Participants had an average of 13 years of education. They reported smoking cocaine for 10.6±6.7 years, and currently spending $251±119 per week on cocaine. All participants tested positive for benzoylecgonine during screening and met DSM-IV criteria for cocaine dependence. None were interested in treatment for their cocaine use. Six participants reported drinking alcohol weekly (16±15 drinks/week). The seven participants who smoked cigarettes were permitted to smoke ad libitum, except during laboratory sessions. Five participants reported occasional heroin use but none were opiate-dependent. No participant had a major affective illness or schizophrenia. Further, no participant had a significant medical history for heart disease or hypertension, none were seropositive for HIV or hepatitis B or C, and no female was pregnant or using oral contraceptives. Each participant signed a consent form, approved by the Institutional Review Boards of the College of Physicians and Surgeons of Columbia University and the New York State Psychiatric Institute. The consent form described the study, outlined the possible risks, indicated that participants would be maintained on an experimental medication, and that cocaine would be available, possibly on a daily basis. Data from ten participants who completed the study were analyzed. Four additional participants (one female, three males) were enrolled in the protocol but did not complete it: one because of electrocardiogram changes occurring prior to the first cocaine self-administration session, one for personal reasons, and two because of elevated blood pressure during the cocaine self-administration sessions. Data from another female participant who completed the protocol were not used because there was no cocaine present in her plasma at any timepoint during the study, indicating that she did not inhale during the cocaine smoking procedure. All study volunteers were compensated for their participation.

Procedure

Participants resided on the Irving Center for Clinical Research in the New York Presbyterian Hospital for the duration of the 18-day inpatient study. They had access to television, radio, and videotaped movies and were free to smoke cigarettes in their rooms. Participants were not permitted to leave the unit unescorted, and visitors were prohibited.

Ecopipam (100 mg; 13–22 h half-life) and matching placebos, provided by Schering-Plough Research Institute and distributed by the Presbyterian Hospital Manufacturing Pharmacy, were orally administered double blind at 10 p.m. for 8 consecutive days each. Ecopipam was administered in the evening because it caused drowsiness in preliminary studies. The dose (100 mg) was selected because it has been shown to more effectively block D1 receptor sites than lower doses, without producing the gastrointestinal upset seen at higher doses (data on file; Schering-Plough, N.J., USA).

Five consecutive days of active or placebo ecopipam preceded the onset of cocaine self-administration sessions. A total of eight cocaine self-administration sessions occurred over the course of the study: four doses of smoked cocaine (0, 12, 25, and 50 mg) were tested on 4 consecutive days during maintenance on placebo and active ecopipam (0 and 100 mg). The doses of cocaine base, derived from cocaine hydrochloride (provided by the National Institute on Drug Abuse) were prepared by the Presbyterian Hospital Manufacturing Pharmacy (Foltin et al. 1990). The order of ecopipam and cocaine dosing was randomized, except that for safety reasons, a lower cocaine dose was tested before the highest cocaine dose.

During self-administration sessions, participants were seated in a comfortable lounge chair in front of a computer used for the completion of subjective-effects questionnaires and for indicating choice between cocaine and vouchers. Session started at 1:00 p.m. Blood was withdrawn through an 18-gauge catheter (Quik-Cath; Travenol Laboratories, Deerfield, Ill., USA) inserted into an arm or hand vein. The intravenous lines were kept patent by an infu-

sion of a physiological saline solution at 2 cc/min. Electrocardiograms were continuously monitored via chest electrodes (MAC PC; Marquette Electronics, Milwaukee, Wis., USA) while heart rate and systolic and diastolic blood pressure were recorded every 2 min (Sentry II – Model 6100 automated vital signs monitor; NBS Medical, Costa Mesa, Calif., USA) beginning 20 min prior to cocaine administration. An Apple Macintosh computer was used for automated data collection.

Each self-administration session consisted of six trials. Participants were instructed that they would be repeatedly given the choice to smoke a dose of cocaine or receive a $5.00 merchandise voucher redeemable at specific stores, payable upon discharge. Sessions began with one "sample" trial, where participants responded on a keyboard under a fixed ratio schedule (FR200) to receive the cocaine dose available that day. Subsequently, there were five "choice" trials, spaced 14-min apart, in which participants had the opportunity to self-administer the same dose of cocaine as the sample dose, or receive a voucher (Fischman and Johanson 1998). Each trial was indicated by a visual cue on the computer screen. Participants selected the left or right option with their computer mouse (illuminating the square associated with that position), and pressed the spacebar or enter key on their computer keyboard until they completed the response requirement and the message "left (or right) option chosen" appeared at the bottom of the screen. Participants were instructed that the left option would be associated with cocaine and the right option would be associated with vouchers. During each of the five choice trials, participants could choose to smoke the cocaine dose again, or receive a voucher. Blood for determination of cocaine plasma level was drawn at baseline, 4, and 12 min after the "sample" cocaine administration, and 4 min after the last option delivery. The session ended 30 min after the last option delivery.

During cocaine administration, participants were presented with cocaine base in a glass pipe stem fitted with smoke screens. A research nurse held a flame from a pipe lighter on the cocaine and participants were instructed to take one large inhalation and to hold it as long as they would outside the laboratory. Participants were blinded to the contents of the pipe. For the placebo cocaine condition, participants were presented with an empty glass pipe stem. Cocaine was administered third party blind, i.e., the nurse administering the cocaine knew the cocaine dose, but the nurse responsible for data management, drawing blood, and monitoring the participant did not. Throughout the session, participants were monitored via a one-way mirror by research nurses located in the adjacent room, with whom they could communicate via an intercom system. Neither cocaine nor vouchers were given on any trial where cardiovascular activity was above the criteria for safe drug administration (heart rate >130 bpm, diastolic pressure >100 mmHg, systolic pressure >165 mmHg).

Subjective-effects battery

A computerized subjective-effects battery, comprised of a series of 100-mm visual analog scales (VAS) labeled "not at all" (0 mm) at one end and "extremely" at the other end, was completed prior to the first cocaine administration, 4 min after each option was delivered, and 30 min after the last option of the session. Eighteen of these VAS were labeled "I feel..."stimulated," "anxious," "depressed," "sedated," "high," "hungry," "focused," "calm," "able to concentrate," "alert," "tired," "talkative," "self-confident," "social," "irritable," "confused," "a good drug effect," and "a bad drug effect." Four VAS were used to operationalize drug craving and were labeled "I want..."cocaine," "heroin," "alcohol," and "tobacco." Three VAS were used for ratings of dose and were labeled "the choice was..."high quality," "potent," and "I liked the choice." The last VAS asked participants to indicate how much they would pay for the dose of cocaine they had just received, anchored with $0 and $25.

Data analysis

The effects of ecopipam maintenance on the number of choices to smoke cocaine within a session, and on subjective-effects and cardiovascular measures were analyzed using planned comparisons. Four planned comparisons were completed for each measure: placebo and active ecopipam (100 mg) were compared at each dose of cocaine (0, 12, 25, and 50 mg). Comparisons were made following the first dose of cocaine, i.e., the "sample dose," and also following repeated cocaine. For the effects of repeated cocaine, subjective-effects data obtained 4 min after each option delivery were averaged, and cardiovascular data obtained 2–12 min after each option delivery were averaged. Cardiovascular data were also analyzed as a change from baseline. Plasma cocaine data obtained at baseline, 4, and 12 min after the first cocaine dose, and 4 min after the last option delivery during placebo and active ecopipam maintenance were compared for each dose of cocaine. *P* values less than 0.05 were considered statistically significant for cardiovascular and self-administration data. A more conservative criterion was used for the subjective-effects data ($P<0.01$) due to the number of comparisons made ($n=26$). Huynh-Feldt corrections were used, when appropriate.

Results

Self-administration

Maintenance on ecopipam significantly increased the number of times the 12 mg dose of cocaine was self-administered (Fig. 1). Ecopipam did not affect self-administration of the other cocaine doses.

Subjective-effects measures

Ecopipam maintenance significantly increased the effects of cocaine (50 mg) on ratings of "high," and "good drug effect" and how much participants would pay for both the 25 and 50 mg doses of cocaine (Fig. 2). Ecopipam also increased cocaine's effects on ratings of "stim-

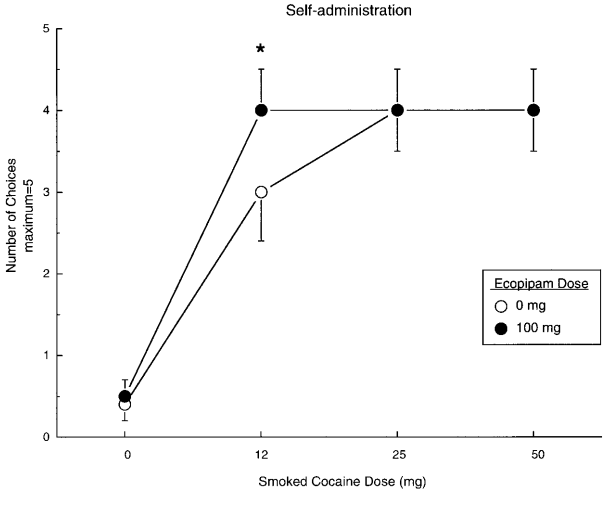

Fig. 1 Mean number of cocaine choices as a function of cocaine dose and ecopipam maintenance condition ($n=10$). *Error bars* represent ± SEM. *Asterisks* denote a significant difference between active and placebo ecopipam at that dose of cocaine (* $P<0.05$)

ulated," (50 mg), dose quality (25 mg), and "sedated" (25 mg), while decreasing ratings of "hungry" (25 mg), and "talkative" (12 and 25 mg) (Table 1). Under placebo cocaine conditions, ecopipam significantly decreased ratings of "I want cocaine," and increased ratings of "I want tobacco" and "I want alcohol." Following active cocaine (50 mg), ecopipam continued to decrease ratings of "I want cocaine" (Table 1). Ecopipam maintenance did not significantly alter cocaine's effects on any of the other subjective-effects measures.

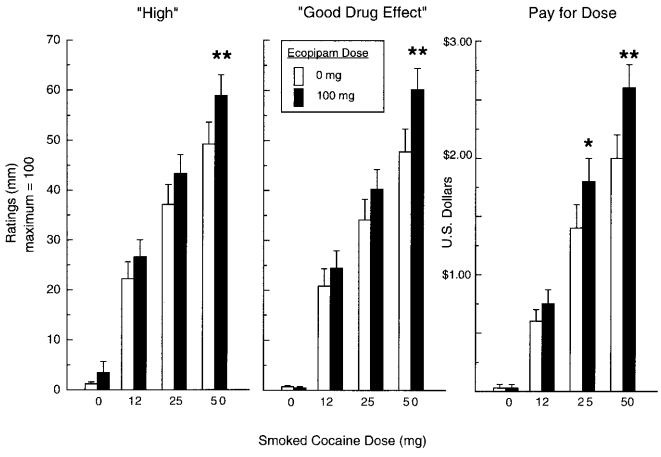

Fig. 2 Mean ratings of "high," "good drug effect" and amount participants would pay for each dose as a function of cocaine dose and ecopipam maintenance condition (n=10). Ratings scales range between 0–100. *Error bars* represent ± SEM. *Asterisks* denote a significant difference between active and placebo ecopipam at that dose of cocaine (* P<0.01, ** P<0.005)

Cardiovascular measures

For the participants who completed the study, the reinforcer was withheld on 10 of the 480 trials (2.1%) due to either temporary elevations in blood pressure or heart rate, or for one participant, due to neurological symptoms (slurred speech). Four of these symptoms occurred during placebo maintenance and six occurred during active ecopipam maintenance.

Ecopipam maintenance had no direct effects on heart rate, based on a comparison of the effects of placebo cocaine administration during placebo maintenance (79±3 bpm) and during ecopipam maintenance (80±4 bpm). However, heart rate following a single administration of cocaine (50 mg) was significantly higher during ecopipam maintenance (102±5 bpm) than it was during placebo maintenance (96±6 bpm: F=7.01, P<0.01; data not shown). Further, following repeated co-

Table 1 Subjective-effects ratings (mean ± SEM) following repeated smoked cocaine administration. Ratings (0–100 mm, visual analog scale) measured 4 min after cocaine administration (n=10). Only cigarette smokers were included in ratings of "I want tobacco" (n=7); only alcohol drinkers were included in ratings of "I want alcohol" (n=6). *Asterisks* represent significant differences between ecopipam maintenance condition at each dose of cocaine

	Cocaine dose (mg)			
Ecopipam (mg)	0	12	25	50
	"Stimulated"			
0	3.8 (1.2)	19.9 (3.3)	33.6 (3.4)	43.3 (4.0)
100	1.4 (0.9)	25.4 (3.5)	38.7 (3.5)	54.8 (4.5)**
	Dose quality			
0	0.7 (0.2)	17.4 (2.9)	30.9 (3.7)	51.5 (4.3)
100	0.2 (0.1)	20.3 (3.0)	38.3 (3.6)**	56.0 (4.6)
	"I want cocaine"			
0	26.6 (5.0)	40.4 (4.9)	44.2 (4.5)	50.0 (4.5)
100	16.4 (3.5)**	36.9 (3.8)	39.4 (3.6)	42.0 (4.0)*
	"I want tobacco"			
0	25.2 (2.6)	43.2 (2.7)	45.2 (3.5)	47.9 (5.1)
100	52.6 (4.1)**	47.6 (4.6)	55.4 (2.9)	57.3 (4.3)
	"I want alcohol"			
0	1.0 (0.3)	17.2 (1.7)	15.9 (0.3)	17.4 (1.9)
100	10.4 (0.7)*	19.6 (2.5)	19.2 (2.6)	24.4 (1.2)
	"Sedated"			
0	1.3 (0.4)	13.3 (2.8)	18.7 (3.5)	29.7 (4.6)
100	1.2 (1.5)	14.9 (2.9)	26.0 (3.7)**	31.1 (4.7)
	"Hungry"			
0	39.5 (5.3)	27.3 (4.6)	34.5 (5.3)	27.5 (4.3)
100	33.1 (4.9)	28.6 (4.4)	24.9 (4.2)**	21.8 (4.0)
	"Talkative"			
0	38.7 (4.8)	43.3 (4.6)	40.4 (4.7)	40.3 (4.7)
100	38.2 (4.3)	33.3 (4.2)**	31.1 (3.5)**	33.5 (4.8)

*P<0.01, **P<0.005

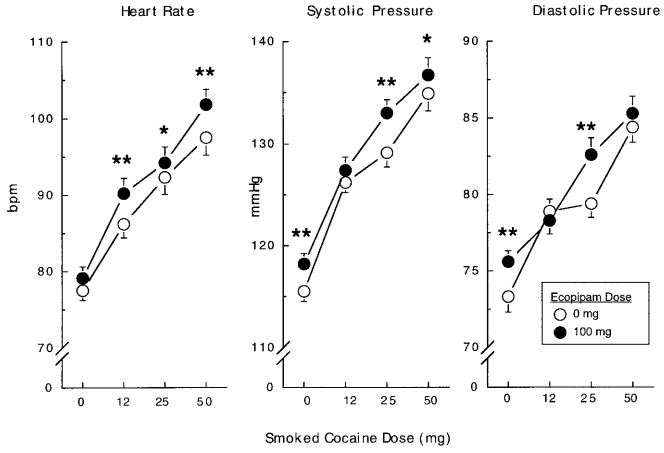

Fig. 3 Mean heart rate, systolic blood pressure and diastolic blood pressure as a function of cocaine dose and ecopipam maintenance condition (n=10). Cardiovascular measures obtained 2, 4, 6, 8, 10, and 12 min after each cocaine administration were averaged. See Fig. 2 for further details

caine administration, ecopipam significantly enhanced the effects of each active cocaine dose on heart rate, as compared to placebo maintenance (Fig. 3).

Ecopipam had direct pressure-enhancing effects, demonstrated by a significant increase in systolic and diastolic pressure under placebo cocaine conditions (Fig. 3). Systolic and diastolic pressure were also significantly increased when ecopipam was combined with at least one active dose of cocaine. When data were analyzed as a change from baseline (i.e., prior to the first cocaine administration), the effects of ecopipam on blood pressure or heart rate were not significant.

Adverse events

Seven of the ten participants experienced at least one adverse event, but their occurrence did not vary as a function of maintenance condition. Headaches were reported six times during placebo maintenance and five times during ecopipam maintenance, while gastrointestinal upset (constipation, stomach ache) occurred twice during placebo maintenance and twice during ecopipam maintenance.

Plasma cocaine

Plasma cocaine levels, which were available for seven of the ten participants, did not vary as a function of maintenance condition. Cocaine plasma levels (ng/ml) were 59.3±28.7 after the first 12 mg cocaine dose, and 227.5±80.9 after the final option delivery of the session. Cocaine plasma levels were 144.1±22.3 after the first administration of the 50 mg cocaine dose and 453.8±67.2 after the final option delivery of the session.

Discussion

Maintenance on the long-acting D1 antagonist, ecopipam, enhanced both cocaine self-administration as well as its subjective effects compared to maintenance on placebo. Specifically, ecopipam increased self-administration of a low cocaine dose (12 mg), without altering self-administration of the higher cocaine doses tested (25 and 50 mg). Ecopipam also increased ratings of "high," "good drug effect," "stimulated," and how much participants would be willing to pay for the cocaine dose, as well as the perceived quality of the higher cocaine doses tested.

Increased cocaine self-administration following the administration of a dopamine antagonist may suggest an attenuation of cocaine's reinforcing effects, i.e., more cocaine is taken to overcome the blockade (Koob et al. 1987), yet the present data suggest cocaine's reinforcing effects were enhanced rather than diminished by ecopipam maintenance. First, a rightward shift in the dose-response curve due to an antagonism of cocaine's reinforcing effects would decrease the self-administration of doses on the ascending limb of the cocaine dose-response curve and increase self-administration of doses on the descending limb of the cocaine dose-response curve (Glowa and Wojnicki 1996; Woolverton 1986), i.e., self-administration of lower cocaine doses would be blocked, while higher doses would be taken in greater number. In the present study, ecopipam increased self-administration of the cocaine dose on the ascending limb of the dose-response curve, suggesting that ecopipam maintenance enhanced rather than attenuated cocaine's reinforcing effects. Second, cocaine's subjective effects were enhanced during ecopipam maintenance, even when the amount of cocaine self-administered was identical to the placebo maintenance condition. Although reinforcing and subjective-effects measures are not always concordant (Fischman et al. 1990), it is not likely that cocaine's subjective effects would be increased by a medication, simultaneous to a suppression of cocaine's reinforcing effects [unless the medication had reinforcing or subjective effects of its own (Foltin and Fischman 1994)].

Despite this enhancement of cocaine's reinforcing and subjective effects, ratings of "I want cocaine" were significantly decreased by ecopipam maintenance when placebo or 50 mg cocaine were available. Dissociations between cocaine "craving" and cocaine self-administration are not uncommon. Studies from our laboratory have shown that cocaine self-administration is extremely robust, and is often unaltered by even substantial medication effects on cocaine "craving" or its subjective effects (Fischman et al. 1990; Haney et al. 1998, 1999). For example, maintenance on the antidepressant, desipramine, resulted in a 40% decrease in ratings of "I want cocaine," yet had no effect on the amount of cocaine self-administered (Fischman et al. 1990). Maintenance on the antiparkinsonian medication, pergolide mesylate, significantly increased cocaine "craving," while leaving co-

caine self-administration unaltered (Haney et al. 1998). This dissociation emphasizes the importance of measuring cocaine self-administration when investigating potential pharmacotherapies.

Clearly there are important ethical considerations to administering cocaine to humans, although it is essential to consider the ethics of *not* determining the safety and efficacy of a medication that may contribute to the prevention or treatment of cocaine abuse (Fischman and Johanson 1998). Studying the effects of a medication on cocaine's reinforcing effects under carefully controlled laboratory conditions, in a relatively small number of individuals who are unambiguous in their stated desire to continue to use cocaine, is both scientifically necessary and ethical. The laboratory study currently described is a model that can be used as an important precursor to exposing hundreds of treatment seekers to a medication with unknown effects on cocaine use. In fact, a controlled, multisite clinical trial, in which ecopipam was directly used in cocaine-dependent treatment seekers, was recently terminated due to ecopipam's lack of efficacy (see Grabowski et al. 2000). This finding supports the validity of the laboratory model.

In the present design, the fact that cocaine's effects were enhanced by ecopipam is most likely a reflection of its chronic administration. Acute pretreatment with ecopipam in humans decreases a range of cocaine's effects, including ratings of "high" and "good drug effects" (Romach et al. 1999); similarly, the acute administration of D1 antagonists blocks cocaine's stimulatory and discriminative stimulus effects in laboratory animals (see Introduction). Yet, chronic administration of dopamine antagonists often results in a diminution or reversal of the effects seen following acute administration. For example, in rats, acute dopamine D1 or D2 antagonist administration blocked cocaine's reinforcing and discriminative stimulus effects, while chronic antagonist administration enhanced sensitivity to cocaine in these measures (Emmett-Oglesby and Mathis 1988; Kosten 1997; Kosten et al. 1996). For these studies, cocaine's effects were tested during maintenance on the antagonist, as in the present study. Other studies assessed the behavioral effects of cocaine after discontinuation of antagonist treatment. In rhesus monkeys, acute pretreatment with a D1 antagonist initially decreased cocaine self-administration in two out of four monkeys, but following termination of antagonist maintenance, responding for cocaine was *increased* in three out of four monkeys compared to the period prior to antagonist exposure (Kleven and Woolverton 1990). Thus, similar to the present study, doses of cocaine that maintained relatively low levels of self-administration maintained higher levels following chronic exposure to a D1 antagonist. Finally, studies in rodents have reported that termination of chronic D1 antagonist administration was associated with a leftward shift in the discriminative stimulus and locomotor effects of cocaine. Similar findings have been obtained using non-selective dopamine receptor antagonists (Barone et al. 1988; Braun et al. 1997; Dall'Olio et al. 1988; Vaccheri et al. 1987). These behavioral shifts were associated with an increased density of D1 receptors (Creese and Chen 1985; Gui-Hua et al. 1992; Hess et al. 1986) and enhanced D1 receptor sensitivity within the nucleus accumbens (White et al. 1998). Overall, the data suggest that maintenance on a D1 antagonist results in dopamine receptor supersensitivity, which increases the reinforcing and subjective effects of cocaine. Furthermore, the majority of studies indicate that cocaine's effects continue to be enhanced after the antagonist administration is terminated. Both the laboratory animal data and the present findings support the suggestion by Kosten (1997) that therapeutic maintenance on dopamine antagonists may partly contribute to the high incidence of cocaine abuse seen in schizophrenics treated with neuroleptics.

It is worth noting that the acute administration of a full dopamine D1 receptor agonist, ABT-431, tested in a design closely similar to the present study, produced effects opposite to those observed with ecopipam. ABT-431 dose-dependently decreased ratings of "high," "stimulated," and how much participants liked and would be willing to pay for the cocaine dose. ABT-431 also substantially decreased craving for tobacco cigarettes (Haney et al. 1999), while ecopipam had opposite effects in the present study. It is not clear whether the dopamine D1 agonist and antagonist produced divergent effects because of their opposing action at the dopamine D1 receptor, or if the differences in part reflect chronic versus acute medication administration.

Ecopipam had few intrinsic effects in the absence of cocaine. There were small but significant increases in blood pressure under both placebo and active cocaine conditions during ecopipam maintenance, in direct contrast to the effects of acute ecopipam administration (Romach et al. 1999). Ecopipam did not enhance the hypertensive effects of cocaine per se, but blood pressure was significantly higher when cocaine was given during ecopipam maintenance compared to placebo maintenance, due to the higher baselines. Although these effects were often not clinically significant, as blood pressure and heart rate infrequently exceeded our cardiovascular criteria for cocaine administration, and did so equally often during placebo or ecopipam maintenance, the two participants discharged for blood pressure elevations were receiving ecopipam at the time, suggesting that there could be a potentially toxic interaction between cocaine and ecopipam for certain individuals. Finally, ecopipam produced few side effects. Although headaches and gastrointestinal upset were reported during the study, these symptoms occurred equally often during ecopipam and placebo maintenance.

To conclude, maintenance on the dopamine D1 antagonist, ecopipam, increased self-administration of a low cocaine dose, while enhancing the subjective effects of higher doses of cocaine. These data do not support the clinical efficacy of ecopipam for the treatment of cocaine dependence. Although antagonists such as naltrexone can be useful in the treatment of drug abuse (Mello and

Negus 1996), chronic administration of dopamine antagonists may produce adaptations that decrease their viability for the long-term treatment of cocaine abuse.

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