

Attenuation of the Euphoric Effects of Cocaine by the Dopamine D1/D5 Antagonist Ecopipam (SCH 39166)

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Background: The subjective and reinforcing effects of cocaine in humans are associated with the enhancement of endogenous dopamine function in the mesolimbic system. This study examined the role of dopamine D1-like receptors in the behavioral and mood effects of cocaine by evaluating the effects of the selective D1/D5 antagonist ecopipam (SCH 39166) on subjective responses to intravenous cocaine in 11 subjects with cocaine dependence as defined by DSM-IV.

Methods: Subjects were pretreated in a randomized double-blind fashion with either placebo or 10 mg, 25 mg, or 100 mg of ecopipam orally on 4 separate occasions. Two hours later a single intravenous injection of 30 mg of cocaine was administered. Subjective and car-

diovascular responses were measured and blood samples for pharmacokinetic evaluation were obtained prior to cocaine dosing and at various times after dosing.

Results: The euphoric ($P = .004$) and stimulating ($P = .03$) effects of cocaine were attenuated in a dose-dependent manner by ecopipam, while ratings of desire to take cocaine were diminished ($P = .02$). Ecopipam in combination with cocaine was safe and well tolerated.

Conclusion: These data indicate a potentially important role for D1-like receptors in the acute mood-altering and rewarding effects of cocaine in humans.

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IN HUMANS, addictive drugs promote drug-taking behavior because of their direct reinforcing properties and because long-term exposure to the drug often generates a strong subjective desire, or craving, to use the drug again. Cocaine is highly reinforcing in both humans and animals.^{1,2} In laboratory animals, cocaine produces dose-related increases in schedule-controlled behavior and locomotor activity, serves as a discriminative stimulus, and maintains self-administration.³⁻⁶ These behaviors correspond to the psychomotor stimulant effects, subjective effects, and reinforcing properties, respectively, of the drug in humans. These effects of cocaine are associated with the enhancement of endogenous dopamine function in the mesolimbic system, particularly in the nucleus accumbens, as determined by electrochemical, microdialysis, lesion, and behavioral studies.³⁻⁶ This increase in mesolimbic dopamine transmission is critical for the initiation and maintenance of cocaine dependence and is hypothesized to play a key role in drug craving and eventual relapse.⁷ Cocaine is a potent inhibitor of the dopamine transporter,⁸ prolong-

ing the effects of dopamine by blocking its reuptake. The dual effects of cocaine on the dopamine system (enhancing its release and blocking its reuptake) are hypothesized to account for the highly addictive nature of this drug.^{8,9} Dopamine acts at 5 different receptor subtypes. The exact contribution of D1-like (D1, D5) and D2-like (D2, D3, D4) receptor families to the behavioral and mood effects of cocaine is not well established.^{1,10-13}

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Many dopaminergic effects of cocaine seem to be specifically mediated through stimulation of dopamine D1 receptors. Transgenic mice in which the D1 receptor is knocked out are insensitive to the stimulant and cellular effects of cocaine.¹⁴ In rodents and nonhuman primates, the D1/D5 receptor antagonists ecopipam and its analogue, SCH 23390, can block the behavioral effects of cocaine, including self-administration of cocaine, in a dose-dependent and specific manner.^{3-6,15,16} A preliminary report suggests ecopipam is able to prevent relapse behavior after cocaine withdrawal in pri-

SUBJECTS AND METHODS

SUBJECTS

Subjects were recruited by advertisements in a community newspaper and in a treatment clinic. Participation in the study in no way compromised access to or involvement in treatment for any subject. Individuals could not participate in the trial if they had a significant medical history for heart disease (arrhythmia requiring medication, angina, documented myocardial infarction), a history of hypertension, or a diastolic blood pressure of 90 mm Hg or higher or a systolic blood pressure of 140 mm Hg or higher at screening. Subjects positive for human immunodeficiency virus antibodies or those with previous medical or psychiatric adverse reactions to cocaine were also excluded. Other exclusion criteria consisted of a history of infectious disease within 6 weeks of study participation; a positive pregnancy test; treatment for mood disorders, schizophrenia, or other *DSM-IV* Axis I disorders; a current diagnosis of substance dependence other than for cocaine or nicotine; and administration of an investigational drug within 60 days prior to the start of the trial.

Fifteen subjects (3 women, 12 men; mean age, 34 years; age range, 26-44 years; mean weight, 72 kg; weight range, 43-110 kg) with cocaine dependence who were otherwise in good health were enrolled in the trial. Cocaine dependence was diagnosed by experienced clinicians according to a *DSM-IV* checklist. All subjects had to have a urine drug screen positive for benzoylecgonine on their screening visit (2 weeks prior to admission) and on the day of their admission. Participants were paid for their involvement and the inconvenience of a 2-week hospitalization. The study protocol was conducted with the written informed consent of all patients and was approved by the Ethics Committee of the Women's College Hospital, Toronto, Ontario, and the subcommittee on human subjects at the Department of Veterans Affairs Medical Center, Philadelphia, Pa.

Subjects were given a copy of the consent form outlining the most common adverse effects associated with ecopipam, the dose of cocaine they were to receive, and the possible medical consequences of cocaine ingestion, including an increase in heart rate and abnormal heart rhythms. They were advised that their heart rate and blood pressure would be continuously monitored during and immediately after the cocaine injection. A total of 11 male patients completed the study.

PROCEDURES AND MEASUREMENTS

This was a randomized, double-blind, placebo-controlled, rising single-dose drug interaction study. Cocaine challenge testing was performed on 4 occasions (days 1, 4, 7, and 11) during a 2-week hospitalization, each test beginning with double-blind oral ecopipam (10 mg, 25 mg, or 100 mg, in that order) or placebo at -2 hours after an overnight fast. These ecopipam doses were based on a previous positron emission

tomography study showing central D1 receptor occupancy of approximately 50% (25 mg) and 70% (100 mg), and it was calculated that a 10-mg dose would occupy approximately 10% of D1 receptors.²³ The time at which ecopipam reaches maximal concentrations (T_{max}) occurs at 2 hours after dosing (unpublished data, Schering-Plough Research Institute, 1992). At the 0 hour, 30 mg of open-label cocaine in isotonic saline solution was administered intravenously over 60 seconds.

A battery of safety evaluations (blood pressure, heart rate, electrocardiogram), 24 visual analog scale ratings to assess subjective effects of cocaine, and safety laboratory tests were conducted and blood samples for pharmacokinetic evaluation of cocaine were collected. The visual analog scales were lines scored to the nearest unit, rating individual items from 0 mm (not at all) to 100 mm (the most ever). Data collected included ratings of feeling "high," "anxious," "confused," "sedated," "good drug effect," "bad drug effect," and "desire to take cocaine." Ratings were obtained at -30, -15, 5, 15, 60, and 90 minutes relative to the intravenous cocaine administration on each test day. Cocaine plasma samples and cardiovascular measures were collected at -15, 5, 15, 30, 45, 60, 90, and 180 minutes relative to cocaine administration. Blood was collected into heparinized tubes prepared with 25 μ L of saturated sodium fluoride and 2.5 μ L of 10% acetic acid per 1 mL of whole blood. Samples were kept chilled until centrifugation, and plasma was stored at -20°C until analyzed by a validated high-performance liquid chromatography/mass spectroscopic method with a limit of quantitation of 50 ng/mL. Areas under the curve were computed by the trapezoidal rule from 0 to 3 hours.

STATISTICAL ANALYSIS

The visual analog scale data were analyzed as time-weighted means of the unevenly spaced responses in the 90 minutes after the cocaine infusion. These means were analyzed using the PROC-GLM application of SAS 6.12 (SAS Institute, Cary, NC), with subject and ecopipam dose as categorical predictors and with the mean of the 2 preinfusion baseline measurements as the covariate. That is, an appropriate fraction (the regression coefficient) of any baseline differences was subtracted from the time-weighted means prior to graphing and to statistical comparisons. In separate analyses, the means of the 2 baseline scores were taken as dependent variables, with subject and dose as predictors. Vital sign data were analyzed similarly, except that only the -10-minute observation was used as the baseline, and each of the 5-minute and 15-minute observations were used separately as dependent variables. The cocaine plasma kinetics were analyzed similarly, except that there was no covariate to include. To control for the type I error rate for each set of comparisons, *t* tests for differences between the doses' least square means were considered significant only if the overall type III sum-of-squares *F* test for dose with 3 *df* was also significant. The criterion of $P \leq .05$ was used for all statistical significance tests, and all were 2 tailed.

mates.¹⁷ Thus, the blockade of the stimulant, discriminative, and reinforcing properties of cocaine may help prevent craving and play a potential role in treatment of cocaine dependence. In contrast to its effects on D1 receptors in the stimulant and rewarding properties of

cocaine, ecopipam does not block the cardiovascular effects of cocaine in animals (unpublished data, Schering-Plough Research Institute, Kenilworth, NJ, 1990), nor does its analogue, SCH 23390, block these effects in nonhuman primates.¹⁸

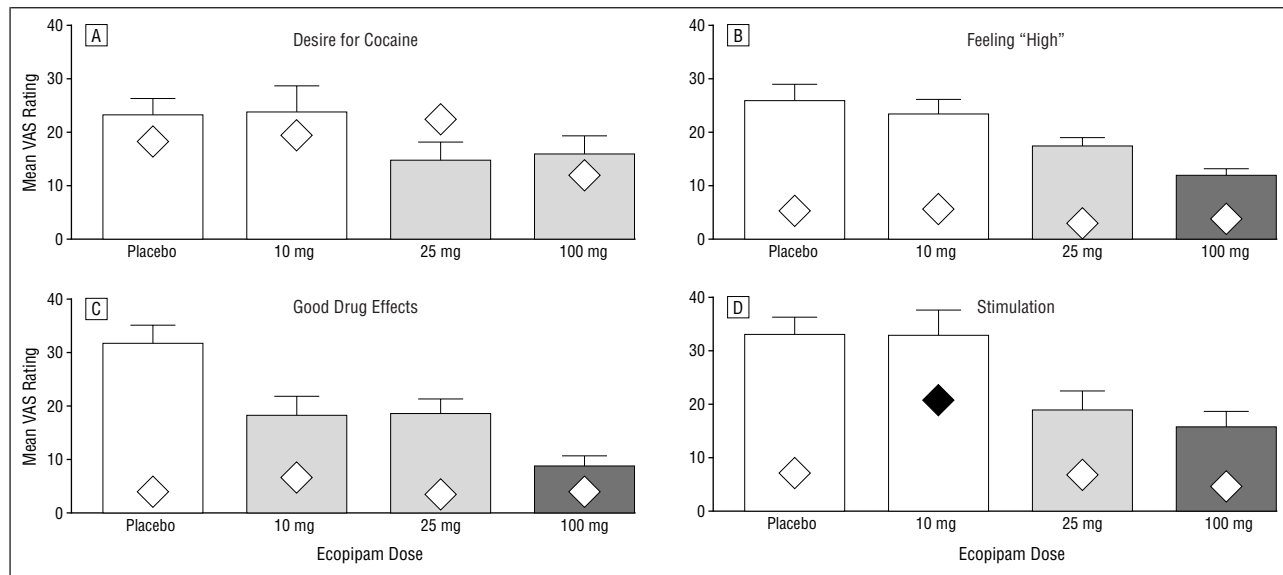


Figure 1. Effects of ecopipam ($n = 11$) at baseline (diamonds) and after cocaine (bars) on mean (SD) responses to 4 visual analog scales (VAS): desire for cocaine (A), feeling "high" (B), good drug effects (C), and stimulation (D). The baseline responses are unadjusted, and the postcocaine responses are adjusted as if there had been no baseline differences (using the regression coefficient from an analysis of covariance). Significant differences from placebo are indicated as gray ($P < .05$) or black ($P < .01$) shading. Black diamond indicates baseline response significantly different from placebo ($P < .01$).

Cocaine has well-characterized physiological and subjective pharmacodynamic effects in humans.^{9,19-21} Subjectively, cocaine produces euphoria, anxiety, and other mood changes. Physiological effects include increases in blood pressure and heart rate. The preclinical studies suggest that D1/D5 antagonists such as ecopipam may represent a novel approach to treating cocaine addiction and relapse. The mechanism of action involves blocking the rewarding properties of the drug and the craving associated with drug abstinence, without altering the negative feedback from cocaine's peripheral effects on heart rate.

Ecopipam is a potent selective antagonist of dopamine D1 and D5 receptors ($K_i = 5.0$ and 4.4 nmol, respectively), with at least 200-fold selectivity over other dopamine family receptors, 80- and more than 500-fold selectivity over 5-HT₂ and muscarinic receptors, respectively, and no affinity for other receptor types.²² The objectives of the present study were to examine the effects of this selective dopamine D1/D5 antagonist on the physiological and subjective responses to cocaine in humans, to ensure its safety and tolerability in combination with cocaine, and to determine the effects of ecopipam on cocaine's pharmacokinetics.

RESULTS

ECOPIPAM EFFECTS AT BASELINE

Following pretreatment with placebo, intravenous cocaine increased visual analog scale self-ratings of euphoria (eg, feeling high) and anxiety. These changes were maximal within a few minutes after single-dose cocaine administration and returned to predose values during the next 15 to 90 minutes. Pretreatment with ecopipam reduced these cocaine-induced changes in a dose-related manner; 10 mg of ecopipam had little or no effect, 25 mg

had an intermediate effect, and 100 mg had the greatest effect. There was a main effect of ecopipam dose on 11 of the 24 dependent variables' baseline values. These included stimulation ($F_{3,30} = 7.27$; $P < .001$), which was substantially increased at the 10-mg dose, and sedation, which was moderately increased at the 10-mg dose and substantially increased by the 100-mg dose ($F_{3,30} = 3.11$; $P = .04$). However, ecopipam did not alter the baseline ratings of either good or bad drug effects, suggesting that any modulation of cocaine-induced euphoria was not due to a nonspecific anhedonic or dysphoric effect of ecopipam.

ECOPIPAM MODULATION OF COCAINE EFFECTS

Figure 1 shows the baseline ratings and baseline-adjusted mean ratings of desire for cocaine ($F_{3,29} = 4.06$; $P = .02$), good drug effects ($F_{3,29} = 7.51$; $P < .001$), feeling "high" ($F_{3,29} = 5.60$; $P = .004$), and stimulation ($F_{3,29} = 3.87$; $P = .03$). The 100-mg dose had the most substantial effects on the responses to cocaine, and any reversals of the generally monotone dose-response trend were small and not statistically significant. In no case where ecopipam significantly modulated the cocaine effect did it also modify the baseline response at the same dose. The time course of the high ratings is shown in **Figure 2**, A. Not shown in Figure 1 is sedation ($F_{3,29} = 7.97$; $P < .001$), where cocaine increased self-rated sedation after placebo and where 100 mg of ecopipam significantly increased both baseline and postcocaine sedation.

COCAINE PLASMA KINETICS

Mean plasma cocaine concentrations were maximal at 5 minutes after dosing (the first postdose sample) and sub-

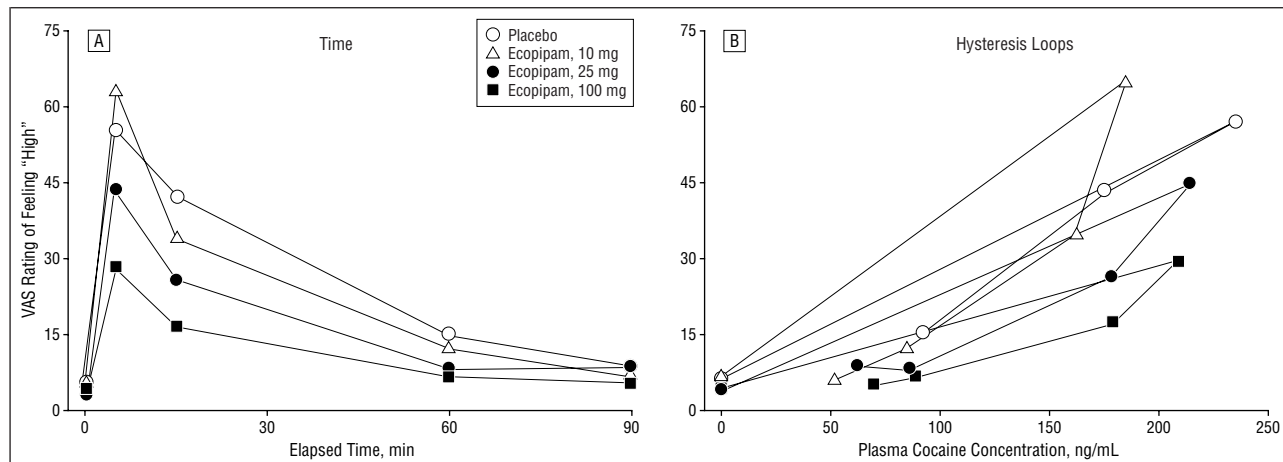


Figure 2. Response on the visual analog scale (VAS) feeling "high" rating at each time point ($n = 11$), expressed as a function of (A) elapsed time and (B) mean plasma cocaine concentrations. In panel B, the flow of time is from 0 concentration clockwise around all loops, with the 4 markers at 5, 15, 60, and 90 minutes after cocaine dose.

Mean (SD) Cocaine Pharmacokinetic Parameters ($n = 11$)*

Measure	Treatment			
	Placebo	Ecopipam, 10 mg	Ecopipam, 25 mg	Ecopipam, 100 mg
AUC_{0-t} , $ng \times h/mL$	239 (90)†	206 (94)	231 (89)	247 (100)†
C_{max} , ng/mL	238 (134)	200 (95)	220 (138)	224 (116)

* AUC_{0-t} indicates area under the concentration time curve to the final measurable time point; C_{max} , maximal plasma concentration.
† $P < .01$ compared with ecopipam, 10 mg.

sequently decreased monoexponentially over the next 2 to 3 hours (data not shown). Mean maximal plasma cocaine concentration (C_{max}) values were similar in all treatment groups, although mean area under the concentration time curve to the final measurable time point (AUC_{0-t}) differed significantly among the 4 treatments ($F_{3,30} = 3.09$; $P = .04$), with the 10-mg ecopipam dose AUC_{0-t} differing from both the placebo AUC_{0-t} and 100-mg ecopipam dose AUC_{0-t} by the protected t test (**Table**). A hysteresis plot of plasma cocaine concentrations vs self-ratings of feeling "high" (Figure 2, B) shows their relationship following placebo pretreatment. Attenuation of the euphoric effects of cocaine following pretreatment with the 25-mg and 100-mg doses of ecopipam was evident in Figure 2, B, as a flattening of the ascending slope.

SAFETY EVALUATIONS

Figure 3 shows the effect of ecopipam on vital signs, which was generally to attenuate the postcocaine increase at 15 minutes but not at 5 minutes. Ecopipam did not affect systolic pressure before cocaine, but there was an apparent monotone trend for systolic pressure at 15 minutes to drop with the ecopipam dose ($F_{3,26} = 2.18$; $P = .11$). Ecopipam affected baseline diastolic pressure, for which there was an 8 mm Hg range of no obvious trend direction ($F_{3,27} = 3.75$; $P = .02$). There were significant differences among the ecopipam doses' effects on diastolic pressure ($F_{3,26} = 3.55$; $P = .03$) at 15 minutes after cocaine administration, with the 25-mg dose significantly lowering the pressure compared with placebo ($t_{26} = 3.21$;

$P = .004$) and the 100-mg dose nearly doing so. Ecopipam did not affect heart rate before cocaine administration, but there were baseline-adjusted differences at 15 minutes ($F_{3,26} = 7.79$; $P < .001$), with both the 25-mg dose ($t_{29} = 3.49$; $P = .002$) and the 100-mg dose ($t_{29} = 3.67$; $P = .001$) associated with decreases to levels about 12 beats per minute slower than associated with placebo.

There were no drug-related changes in safety laboratory tests and no electrocardiogram changes of note during the study. The overall incidence of adverse events following administration of ecopipam and cocaine was 47% to 82%, which was similar to the incidence following placebo and cocaine (73%). The most frequently reported adverse events were headache, dyspepsia, and somnolence; only somnolence was reported more frequently after the 100-mg dose (55%) compared with placebo or the 10- or 25-mg ecopipam doses (0%-17%). Subjects receiving 100 mg of ecopipam were more tired during the 2 hours prior to the administration of cocaine.

COMMENT

The main findings of this study are that the selective D1/D5 antagonist, ecopipam, attenuated the euphoric and anxiogenic effects of cocaine, the desire to use cocaine, and the immediate cardiovascular effects of cocaine. There was no alteration in the pharmacokinetics of cocaine. Ecopipam in combination with cocaine was safe and well tolerated.

In general, the attenuation of the subjective effects of cocaine was maximal after the 100-mg dose, with an

intermediate effect at the 25-mg dose and no effect at the 10-mg dose. The apparent dose-effect relationship coincides with the reported receptor occupancy data from positron emission tomography studies with ecopipam.²³ This attenuation was associated with a diminished desire to take cocaine. Priming effects of previous cocaine doses may modulate repeated cocaine self-administration. If the euphoric effects of cocaine can be diminished, repeated cocaine dosing may be reduced or prevented. It is of interest that the dose-related reduction in the subjective effects of cocaine was not due to dysphoric effects of ecopipam, as have been reported for D2 antagonists,^{24,25} as precocaine visual analog scale ratings of "bad drug effect" were similar in all 4 treatments.

An acute (albeit smaller) increase in euphoria was noted after cocaine dosing even at the highest dose level of ecopipam. This could be due to nondopaminergic effects of cocaine (eg, increases in synaptic serotonin and/or norepinephrine) that could potentially be involved in the acute subjective effects of cocaine, or it may indicate a degree of incomplete antagonism due to extremely high synaptic dopamine concentrations immediately following cocaine administration.

Previous clinical experience with ecopipam has shown increased self-reports of sedation at and above doses of 100 mg (unpublished data, Schering-Plough Research Institute, 1992), consistent with the study's results. This raises the possibility that some or all of the observed pharmacodynamic observations could be secondary to a nonspecific sedative effect. This explanation is unlikely because a lower and nonsedating dose of ecopipam (25 mg) also reduced the effects of cocaine. In addition, a previous study²⁶ showed that single doses of the antidepressant drug trazodone increased baseline sedation ratings prior to cocaine administration in a similar paradigm, without altering subjective pharmacodynamic responses to cocaine relative to placebo pretreatment. The reason for the increase in sedation after administration of cocaine following placebo pretreatment is unclear.

The pharmacokinetic parameters calculated for intravenous cocaine administered in this study are consistent with previous reports (for review see Johanson and Fischman¹⁹). The finding that the mean AUC_{0-t} differed significantly among the treatments may be a chance finding; the differences were somewhat attenuated but still statistically significant when the treatment order of the unbalanced study design was included in the analysis.

Overall, the safety and tolerability of cocaine were not changed by preadministration of ecopipam, as assessed by safety laboratory tests, electrocardiograms, and reported adverse events. The finding that acute cardiovascular responses (5 minutes after cocaine dose) following ecopipam pretreatment were of similar magnitude to those of placebo (Figure 3) suggests a limited effect of D1/D5 antagonism on the noradrenergically mediated sympathomimetic effects of cocaine. The clinical importance of the statistically significant reductions in heart rate and diastolic blood pressure by ecopipam relative to placebo 15 minutes after cocaine dose must be determined in a therapeutic setting. Although this can be viewed as a positive safety feature of ecopipam, conceiv-

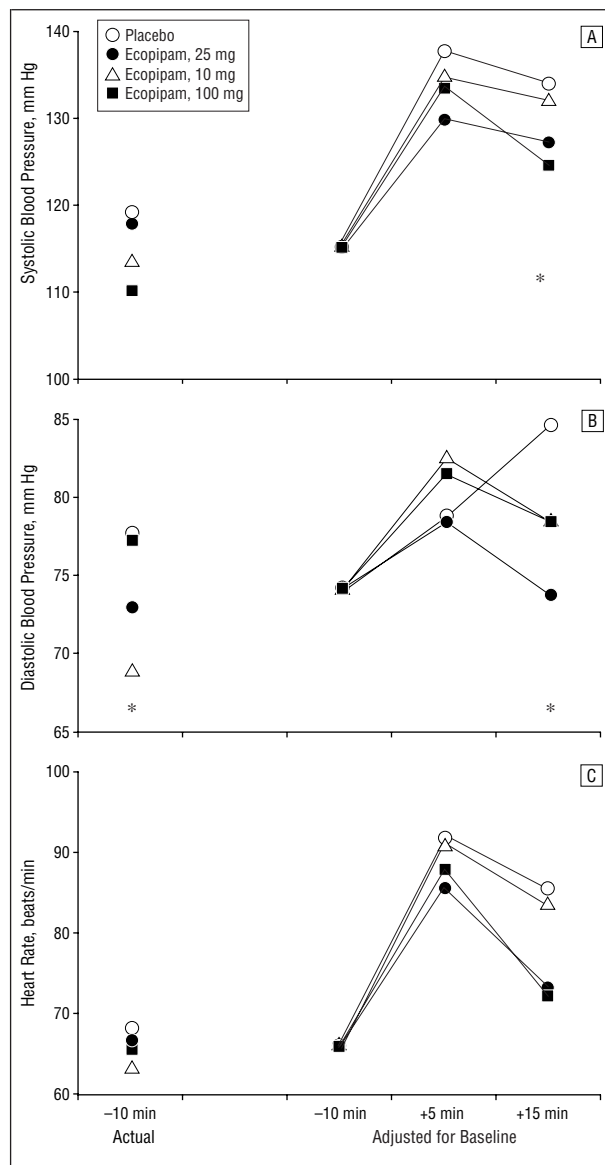


Figure 3. Effects of ecopipam on cardiovascular measures at -10 minutes (baseline), 5 minutes, and 15 minutes after cocaine administration. The actual responses at baseline are shown at the left, and the subsequent responses, adjusted as if there had been no baseline differences (using the regression coefficient from an analysis of covariance) are shown at the right. An asterisk indicates a significant ($P < .05$) F test for the difference among doses.

ably these effects could reduce the negative feedback of increased heart rate and lead individuals to take more cocaine in an attempt to augment its subjective effects. This in turn could increase cardiovascular toxic effects.

Several limitations of our study deserve comment. First, our study demonstrated that single doses of ecopipam are effective in blocking the acute stimulant effects of cocaine. Multiple or long-term dosing with ecopipam may not be as effective and needs to be evaluated in humans. This is of particular relevance with respect to the possible therapeutic utility of ecopipam in the treatment of cocaine dependence. Preclinical studies have reported that repeated high doses of an analogue of ecopipam (SCH 23390) enhanced the responsiveness of D1

receptors in the nucleus accumbens²⁷ and produced supersensitivity to the behavioral effects of cocaine. Conversely, the antagonism by a single dose of ecopipam of the effects of repeated cocaine "doses" within 1 session of use is not known and would need to be determined for clinical extrapolation. Second, the study lacked a placebo control injection for cocaine, which might have helped to distinguish between "injection" effects and the pharmacologic effects of cocaine. Third, as mentioned earlier, although the effects of ecopipam were significant, even the highest dose of the drug did not completely antagonize the feelings of euphoria and desire for cocaine, suggesting that other components (possibly D2 or other monoaminergic receptors) interact with the D1 receptors to mediate the residual reinforcing properties of cocaine. This may be of clinical importance, as continued use of cocaine could "override" the blockade produced by ecopipam to produce euphoria through other mechanisms. Last, while investigating the neuropharmacologic mechanisms that underlie the effects of acute and long-term cocaine administration using experimental paradigms, it is important to remember the crucial influence of environmental and behavioral factors on responses to cocaine, which would likely be different in a nonlaboratory setting.

In conclusion, our study indicates a substantial role for D1-like receptors in the acute mood-altering and rewarding effects of cocaine in humans. The application and implication of these findings in a controlled treatment setting have yet to be determined.

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