Psychopharmacology (1999) 143 : 102–110

ORIGINAL INVESTIGATION

Margaret Haney · Eric D. Collins · Amie S. Ward
Richard W. Foltin · Marian W. Fischman

Effect of a selective dopamine D_1 agonist (ABT-431) on smoked cocaine self-administration in humans

Received: 18 August 1998/Final version: 16 October 1998

Abstract *Rationale*: Data in laboratory animals suggest that D_1 receptor agonists may have potential utility for the treatment of cocaine abuse. *Objective*: The effects of ABT-431, a selective agonist at the dopamine D_1 receptor, on the reinforcing, cardiovascular and subjective effects of cocaine were investigated in humans. *Method*: Nine experienced cocaine smokers (8M, 1F), participated in nine self-administration sessions while residing on an inpatient research unit: three doses of ABT-431 (0, 2, 4 mg IV) were each given in combination with three doses of smoked cocaine (0, 12, 50 mg). ABT-431 was intravenously administered over a 1-h period immediately prior to cocaine self-administration sessions. A six-trial choice procedure (cocaine versus $5 merchandise vouchers) was utilized, with sessions consisting of: (a) one sample trial, where participants received the cocaine dose available that day, and (b) five choice trials, where participants chose between the available cocaine dose and one merchandise voucher. *Results*: ABT-431 did not affect the number of times participants chose to smoke each dose of cocaine, but produced significant dose-dependent decreases in the subjective effects of cocaine, including ratings of "High," "Stimulated," dose liking, estimates of dose value, "Quality," and "Potency." Furthermore, there was a trend for ABT-431 (4 mg) to decrease cocaine craving. ABT-431 also increased heart rate, while decreasing systolic and diastolic pressure at each dose of cocaine. *Conclusions*: These data suggest that D_1 agonists may have potential utility for the treatment of cocaine abuse.

M. Haney (✉) · E.D. Collins · A.S. Ward · R.W. Foltin · M.W. Fischman
Department of Psychiatry, College of Physicians and Surgeons of Columbia University and Division on Substance Abuse, New York State Psychiatric Institute, 1051 Riverside Drive, Unit 120 New York, NY 10032, USA
e-mail: mh235@columbia.edu, Fax: +1-212-543-5991

Key words Cocaine · Human · Self-administration · D_1 agonist · Subjective effect · Craving · Cardiovascular effect

Introduction

Unlike opioid or alcohol dependence, no medication has yet been shown to be an effective adjunct for the treatment of cocaine abuse (Kleber 1995; Mendelson and Mello 1996). Many preclinical and clinical investigations of potential pharmacotherapies have focused on agents acting at the dopamine receptor, since cocaine's reinforcing effects are largely mediated by inhibition of dopamine re-uptake (Fibiger 1978; Wise and Bozarth 1987). The five identified subtypes of the dopamine receptor are classified into the D_1 group (D_1, D_5) and the D_2 group (D_2, D_3, D_4), based on their pharmacological and biochemical properties (Kebabian and Calne 1979; Jackson and Westlind-Danielsson 1994); for convenience, the term "D_1" or "D_2" receptor will be used throughout the manuscript to refer to the group of receptors, rather than to the particular subtypes.

Both laboratory and clinical studies suggest that D_2 agonists may not be effective treatment medications for cocaine abuse. In laboratory animals, D_2 agonists are self-administered, suggesting that they have the potential for abuse in humans (Davis and Smith 1977; Woolverton et al. 1984; Caine and Koob 1993). Reinforcing effects per se do not preclude the use of a medication to treat drug abuse, since these properties may facilitate treatment compliance. However, D_2 agonists also enhance cocaine's reinforcing effects (Parsons et al. 1996; Caine et al. 1997a), and reinstate non-reinforced responding for cocaine in an animal model of cocaine-seeking behavior (Wise et al. 1990; Self et al. 1996a), which may indicate that these agents would increase the likelihood that cocaine users in treatment

would relapse to cocaine use. Most data in humans support this hypothesis. In a laboratory study of cocaine self-administration, the dopamine agonist pergolide mesylate, at a dose presumed to be selective for D_2 receptors, increased self-reported "craving" for cocaine in non-treatment-seeking cocaine users (Haney et al. 1998). In a treatment setting, pergolide appeared to impair rather than facilitate treatment compliance, compared to placebo maintenance (Levin et al. 1999; Malcolm et al. 1999). Another D_2 agonist, bromocriptine, was also ineffective in double-blind laboratory (Preston et al. 1992) and clinical investigations (Tennant and Sagherian 1987) in cocaine users.

By contrast, data in laboratory animals suggest that D_1 receptor agonists may have potential utility for the treatment of cocaine abuse. Unlike D_2 agonists, D_1 agonists increased the latency to initiate cocaine self-administration (Self et al. 1996a; Caine et al. 1997b). Further, D_1 agonists do not reinstate non-reinforced responding on a cocaine-paired lever, and in fact decrease the ability of cocaine to reinstate non-reinforced responding in an animal model of cocaine-seeking (Self et al. 1996a), suggesting that D_1 agonists might decrease the likelihood that cocaine abusers in treatment would relapse to cocaine use. There is the possibility that these agents have abuse potential, since they are self-administered by rats (Self and Stein 1992; Self et al. 1996b) and non-human primates (Weed et al. 1993, 1997; Weed and Woolverton 1995; Grech et al. 1996). However, as mentioned earlier, reinforcing effects are not necessarily incompatible with clinical utility.

The present study investigated the effects of the D_1 agonist, ABT-431 on smoked cocaine self-administration by humans in a controlled laboratory setting. ABT-431 is a potent and selective full agonist at the D_1 receptor, with a rapid onset of action (Shiosaki et al. 1996). Cocaine users who were not seeking treatment for their cocaine use were pretreated with intravenous (IV) ABT-431 and were given the opportunity repeatedly to self-administer cocaine over several hours each day, under careful medical observation. Alternatives to drug-taking were available, just as they are outside of the laboratory. The effects of ABT-431 on cocaine self-administration, cocaine "craving," subjective-effects ratings, and cardiovascular effects were determined.

Materials and methods

Participants

One female and eight male research volunteers (six African-American, two Hispanic, one Asian), 31–39 years of age (mean: 35.6 years), and currently smoking cocaine 3–7 days/week were solicited through word-of-mouth referral and newspaper advertisement in New York, NY. Participants had an average of 12 years of education. They reported spending $\$275 \pm 32$ (mean ± SD) per week on cocaine. Four participants reported drinking alcohol weekly (17 drinks/week). The eight participants who smoked cigarettes were permitted to smoke ad libitum, except during laboratory sessions. Four participants reported occasional heroin use but none were opiate-dependent (no opiate metabolites in urine upon admission or throughout study; no symptoms of opiate withdrawal). All participants passed medical and psychological evaluation prior to the study. The single female participant was given a serum pregnancy test at screening, and a urine pregnancy test upon commencing the inpatient stay in the laboratory; she was not taking 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 any possible risks, indicated that participants would be maintained on an experimental medication, and that cocaine would be administered, possibly on a daily basis. Two additional participants (1M, 1F) were enrolled in the protocol but ended their participation during the first week of the study: one for personal reasons and one because of side-effects attributed to ABT-431 (nausea, vomiting).

Apparatus

During experimental sessions, participants were seated in a comfortable lounge chair in front of a computer used for the completion of subjective-effects questionnaires. An 18-gauge catheter (Quik-Cath®, Travenol Laboratories, Deerfield, Ill., USA) was inserted into a subcutaneous vein on each arm; one catheter was used for blood withdrawal, and the other was used for ABT-431 infusion. The IV lines were kept patent by an infusion of a dextrose (5%) solution at 100 cc/h. Electrocardiograms (ECG) were continuously monitored via chest electrodes (MAC PC®, Marquette Electronics, Milwaukee, Wisc., 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 4 min prior to the onset of the ABT-431 infusion. An Apple Macintosh® computer located in an adjacent room was used for automated data collection.

Procedure

Participants resided on the Irving Center for Clinical Research in The Presbyterian Hospital for the duration of the 15-day study. They had access to television, radio, and video-taped movies and were free to smoke cigarettes in their rooms. Visitors were prohibited.

There were nine cocaine self-administration sessions: three doses of smoked cocaine (0, 12, 50 mg) were each tested in combination with three doses of ABT-431 (0, 2, 4 mg/100 ml). Doses of ABT-431 were chosen based on preliminary studies determining the tolerability and pharamacokinetics of a range of ABT-431 doses. The first self-administration session occurred on the third inpatient hospital day. The order of ABT-431 and cocaine dosing was randomized, except that for safety reasons, a low dose of cocaine was tested before the highest dose of cocaine, and the highest ABT-431 dose was only administered if participants had received another active dose of ABT-431 within 2 days, since a previous investigation suggested that this dose build-up decreased the risks of side-effects (Malison et al. 1999). Self-administration sessions began with a 60-min IV ABT-431 infusion; a slow infusion was used to minimize injection site reactions. Participants were repeatedly given a choice between a particular dose of cocaine and a $5.00 merchandise voucher redeemable at specific stores, payable upon discharge. Sessions began with one "sample" trial, where participants responded on a keyboard on a fixed ratio schedule (FR200) to receive the cocaine dose available that day. Subsequently, there were

five "choice" trials, in which participants had the opportunity to self-administer the same dose of cocaine as the sample dose, or receive a voucher (see Fischman et al. 1990). Each trial was indicated by a visual cue (two squares: 3 cm × 3 cm) 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. During each session, the left cue was associated with cocaine and the right cue was 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 and after the first and the last options were delivered. The session ended 30 min after the last option delivery.

During drug 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 blind to contents of the pipe. 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, diastolic pressure > 100, systolic pressure > 165).

Subjective-effects battery

A computerized subjective-effects battery, which was completed prior to the onset of the ABT-431 infusion, 40 min after the start of the ABT-431 infusion, 4 min after each option was delivered, and 30 min after the last option of the session, comprised a series of 100-mm visual analog scales (VAS) labeled "Not at all" (0 mm) at one end and "Extremely" (100 mm) at the other end. Eighteen of these VAS were labeled "I Feel..." High," "Stimulated," "Anxious," "Sedated," "Depressed," "Hungry," "Friendly," "Miserable," "On edge," "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," "Ethanol," and "Nicotine." 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.

Drugs

Cocaine base, derived from cocaine hydrochloride (provided by The National Institute on Drug Abuse) was prepared by the Presbyterian Hospital Manufacturing Pharmacy, as described in Foltin et al. (1990). ABT-431 IV solution (0, 2, 4 mg in 5% dextrose solution) provided by Abbott Laboratories, was also prepared by the Presbyterian Hospital Manufacturing Pharmacy. The serum half-life for ABT-431 is estimated at 2 h. ABT-431 and cocaine were administered under double-blind conditions, with the exception that nurses, but not investigators or research assistants, were aware of the daily cocaine dose.

Data analysis

Repeated-measures analyses of variance (ANOVA) with planned comparisons (Keppel 1991), having two within-group factors [cocaine dose (0, 12, 50 mg), ABT-431 dose (0, 2, 4 mg)], were used to compare the following: (1) the number of choices to smoke cocaine within a session, and (2) subjective effects and cardiovascular measures following the first dose of cocaine, i.e. the "sample dose." Six planned comparisons were completed for each measure: the 2 mg and 4 mg doses of ABT-431 were compared to the 0 mg dose of ABT-431 for each dose of cocaine (0, 12, 50 mg). The effects of repeated cocaine doses on subjective-effects, cardiovascular and plasma cocaine measures were analyzed using a repeated-measures ANOVA with three within-group factors [cocaine dose (0, 12, 50 mg), ABT-431 dose (0, 2, 4 mg), time within session (4 min after each of the six option deliveries, 30 min after the final option delivery)]. There were technical difficulties with the blood drawing on nine of the 81 attempts to obtain cocaine plasma levels after the first active cocaine dose. Because the pattern of missing values was random and not related to cocaine dose or ABT-431 dose, plausible estimates of the missing values were calculated, using multiple imputation, to complete the dataset for analysis (Little and Rubin 1987; Rubin and Schenker 1991; Solas For Missing Data Analysis Statistical Package, Statsol Solutions, Sargus, Mass., USA. There were six planned comparisons completed for each measure: subjective-effects and cardiovascular data were averaged across the session and comparisons were made between the 0 mg ABT-431 condition and the 2 and 4 mg ABT-431 condition for each dose of cocaine. Plasma cocaine data obtained at baseline, 4 min after the first cocaine dose and 4 min after the last option delivery following 0 mg ABT-431 administration were compared to the results obtained at each of these time-points following 2 or 4 mg ABT-431 administration. Given the large number of planned comparisons overall, only those with P values less than 0.01 were considered statistically significant, in an effort to control for type I error. Hunyh-Feldt corrections were used, when appropriate.

A Chi square analysis was completed to determine if the number of adverse events varied as a function of cocaine dose. A separate Chi square analysis was completed to determine if the number of adverse events varied as a function of ABT-431dose. P values less than 0.05 were considered statistically significant.

Results

Self-administration

Figure 1 presents cocaine self-administration as a function of cocaine dose and ABT-431 dose. The number of times cocaine was chosen each session increased as a function of cocaine dose [$F(2,16) = 32.79$, $P < 0.0001$]. Pretreatment with ABT-431 had no effect on cocaine self-administration.

Subjective effects measures

Single cocaine doses

Table 1 presents the effect of ABT-431 on selected subjective-effects ratings completed 4 min after the first administration of each "sample" cocaine dose. Ratings of "Good Drug Effect," "High," "Stimulated," dose liking, dose potency, and the amount of money participants would pay were increased as a function of cocaine dose ($P < 0.01$). Both active doses of ABT-431 (2,4 mg) significantly decreased the effects of 12 mg cocaine on ratings of "Good Drug Effect," "High,"

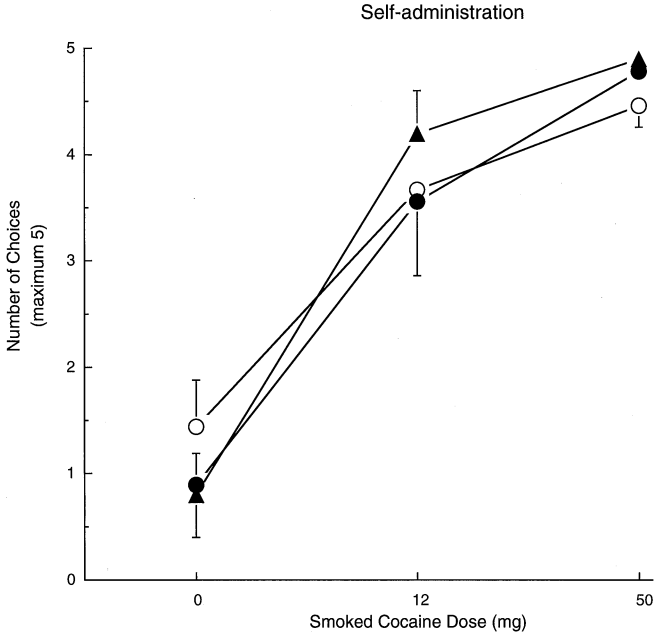

Fig. 1 Mean number of cocaine choices as a function of cocaine dose and ABT-431 dose. *Error bars* represent ± SEM. ○ 0 mg, ● 2 mg, ▲ 4 mg ABT-431

"Stimulated," dose liking, and dose potency. Only the 2 mg ABT-431 dose significantly decreased the amount of money participants would pay for the 12 mg cocaine dose. Neither dose of ABT-431 reduced the effects of the 50 mg dose of cocaine. Further, ABT-431 in the absence of active cocaine had no significant effect on any of the subjective-effects ratings.

Repeated cocaine doses

Figures 2–4 present selected subjective effects as a function of ABT-431 dose and repeated cocaine

Table 1 Selected mean (± SEM) subjective-effects ratings following the first smoked cocaine dose each session, i.e., the "sample" cocaine dose

	Cocaine dose		
	0 mg	12 mg	50 mg
"Good Drug Effect"			
ABT-431 (mg)			
0	1.3 (1.0)	34.0 (10.4)	42.4 (9.6)
2	0.2 (0.1)	21.6 (10.7)*	35.2 (11.2)
4	0.7 (0.5)	21.6 (10.6)*	43.4 (9.6)
"High"			
ABT-431 (mg)			
0	1.0 (0.9)	34.2 (10.2)	41.2 (10.5)
2	0.1 (0.1)	21.1 (10.0)**	39.6 (10.0)
4	0.9 (0.6)	21.7 (10.7)**	44.2 (9.2)
"Stimulated"			
ABT-431 (mg)			
0	1.2 (0.8)	33.3 (10.3)	34.0 (10.7)
2	0.1 (0.1)	18.8 (10.2)**	30.3 (10.1)
4	3.0 (2.9)	18.4 (10.8)**	30.6 (9.8)
Dose Liking			
ABT-431 (mg)			
0	3.6 (3.1)	41.7 (10.9)	47.3 (9.9)
2	0.0 (0.0)	22.7 (10.2)**	45.2 (10.1)
4	1.1 (1.1)	19.7 (10.5)**	41.3 (10.3)
Dose Potency			
ABT-431 (mg)			
0	2.1 (1.6)	37.4 (10.7)	44.3 (10.2)
2	5.0 (5.0)	21.7 (9.9)*	37.7 (10.6)
4	1.7 (1.1)	19.4 (10.8)**	39.8 (9.5)
Pay for Dose			
ABT-431 (mg)			
0	$0.02 (0.02)	$2.00 (0.73)	$2.33 (0.50)
2	$0.00 (0.00)	$0.50 (0.00)*	$2.50 (0.80)
4	$0.02 (0.02)	$0.80 (0.40)	$2.25 (0.70)

Ratings (0–100 mm, visual analog scale) measured 4 min after cocaine administration. *Asterisks* denote a significant difference from the placebo ABT-431 dose at each dose of cocaine; *$P < 0.01$, **$P < 0.005$

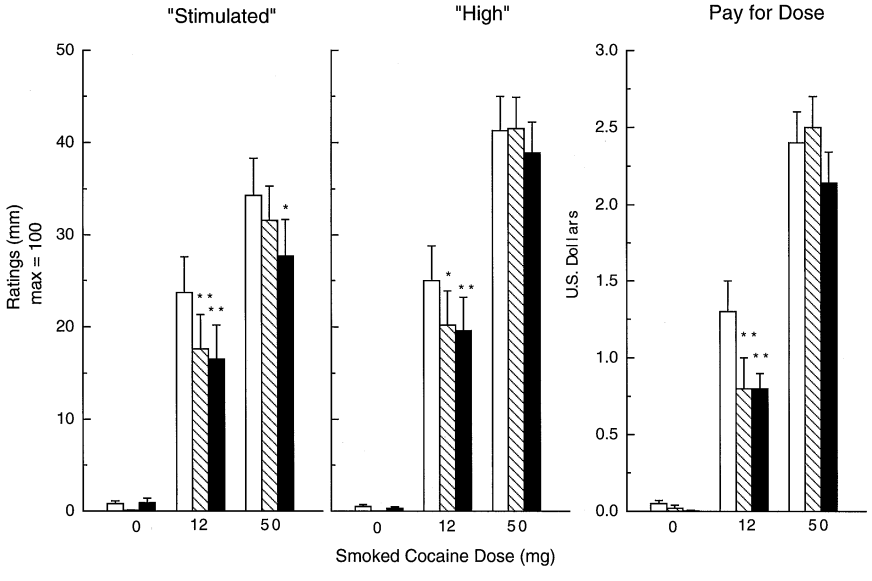

Fig. 2 Selected mean subjective-effects ratings as a function of cocaine dose and ABT-431 dose. Ratings completed 4 min after each of the six option deliveries, and 30 min after the final option delivery were averaged across the session. *Error bars* represent ± SEM. *Asterisks* denote a significant difference from the placebo ABT-431 dose at each dose of cocaine (*$P < 0.01$, **$P < 0.005$). □ 0 mg, ▨ 2 mg, ■ 4 mg ABT-431

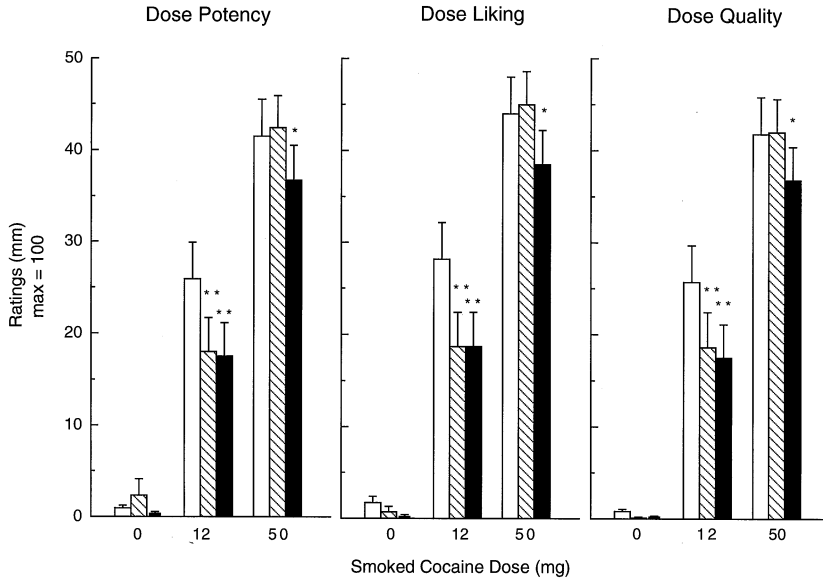

Fig. 3 Selected mean ratings of cocaine dose as a function of cocaine dose and ABT-431 dose. See Fig. 2 for details. □ 0 mg, ▨ 2 mg, ■ 4 mg ABT-431

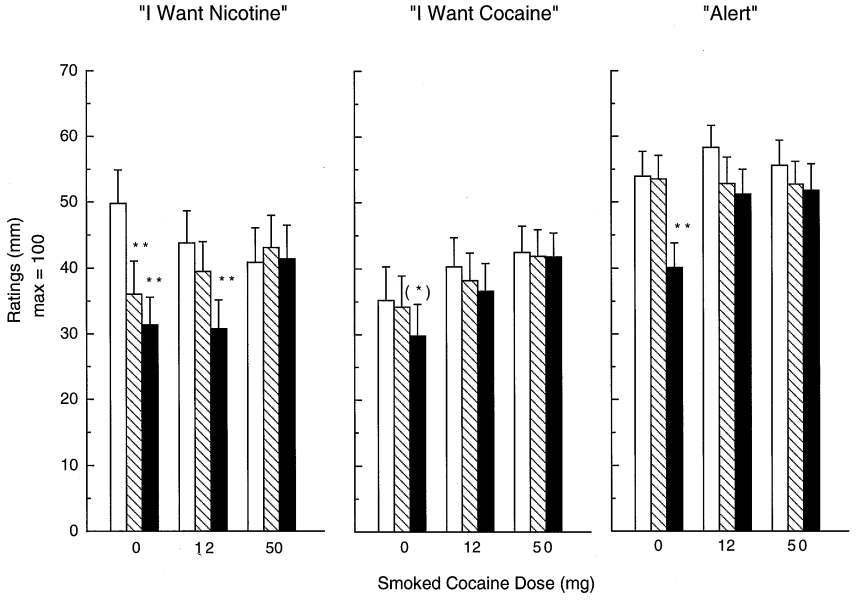

Fig. 4 Mean subjective-effects ratings as a function of cocaine dose and ABT-431 dose. See Fig. 2 for details. □ 0 mg, ▨ 2 mg, ■ 4 mg ABT-431

administration. Figure 2 shows that ratings of "Stimulated," "High" and how much participants would be willing to pay for the dose increased as a function of cocaine dose ($P < 0.01$). Both active doses of ABT-431 (2,4 mg) decreased each of these ratings following 12 mg cocaine; the 4 mg ABT-431 dose also significantly decreased ratings of "Stimulated" following 50 mg cocaine. In Fig. 3, cocaine is shown to increase ratings of dose potency, dose liking and dose quality ($P < 0.001$). These ratings were decreased by both doses of ABT-431 at the 12 mg dose of cocaine, while the effects of the 50 mg cocaine dose were only attenuated by the 4 mg dose of ABT-431. ABT-431 (4 mg) also decreased ratings of "Good Drug Effect" following the 12 mg cocaine dose [$F(1,192) = 10.48$, $P < 0.01$; data not shown]. ABT-431 did not significantly affect any of these ratings under placebo cocaine conditions.

As shown in Fig. 4, cocaine did not significantly influence ratings of "I Want Nicotine," "I Want Cocaine, or "Alert," while both doses of ABT-431 decreased ratings of "I Want Nicotine" in the 0 mg cocaine condition. The 4 mg ABT-431 dose decreased nicotine craving at the 12 mg cocaine dose as well. ABT-431 (4 mg) decreased ratings of "I Want Cocaine" under placebo cocaine conditions, although the effect just failed to attain significance ($P < 0.03$). Under placebo cocaine conditions, the 2 mg dose of ABT-431 increased ratings of "Hungry" [$F(1,192) = 11.66$, $P < 0.01$; data not shown], while the 4 mg dose of ABT-431 decreased ratings of "Alert" (Fig. 4), and increased ratings of "Tired" [$F(1,192) = 15.60$, $P < 0.007$; data not shown], and "Hungry" [$F(1,192) = 20.12$, $P < 003$; data not shown]. At the 12 mg cocaine dose, ABT-431 (4 mg) also decreased ratings of "Friendly" compared

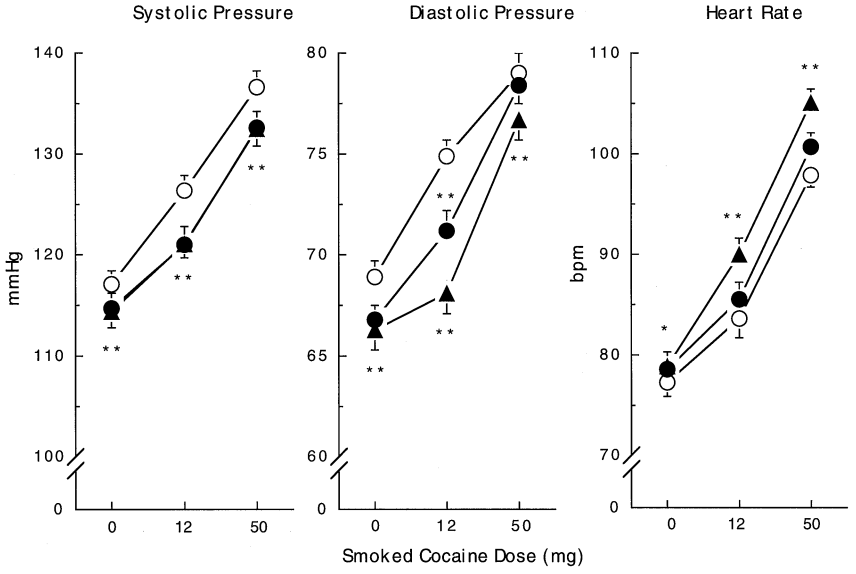

Fig. 5 Mean systolic blood pressure, diastolic blood pressure and heart rate as a function of cocaine dose and ABT-431 dose. Cardiovascular measures obtained 2, 4, 6, 8 and 10 min after each cocaine administration were averaged. See Fig. 2 for further details. ○ 0 mg, ● 2 mg, ▲ 4 mg ABT-431

to placebo ABT-431 [$F(1,192) = 14.00$, $P < 0.009$; data not shown].

Cardiovascular measures

Single cocaine doses

Cocaine doses-dependently increased heart rate, systolic pressure and diastolic pressure ($P < 0.0009$). ABT-431 (2 mg) significantly decreased the effects of 12 mg cocaine on systolic pressure [$F(1,32) = 8.25$, $P < 0.01$; data not shown]. The 4 mg dose of ABT-431 significantly decreased the effects of cocaine on diastolic [12 mg: $F(1,32) = 12.89$, $P < 0.001$; 50 mg: $F(1,32) = 6.93$, $P < 0.01$] and systolic pressure [12 mg: $F(1,32) = 18.71$, $P < 0.0005$; data not shown], while increasing heart rate regardless of cocaine does [0 mg: $F(1,32) = 11.27$, $P < 0.005$; 12 mg: $F(1,32) = 7.89$, $P < 0.01$; 50 mg: $F(1,32) = 9.25$, $P < 0.009$; data not shown].

Repeated cocaine doses

There were a total of 486 trials during the study; on three trials, cocaine or a voucher was withheld because of elevated heart rate. Fig. 5 portrays the effects of ABT-431 on diastolic pressure, systolic pressure and heart rate following repeated cocaine administration. Each of these measures was significantly increased by repeated cocaine administration ($P < 0.0001$). Both active doses of ABT-431 had direct pressure-lowering effects, demonstrated by the significant decreases in systolic and diastolic pressure under placebo cocaine conditions. Systolic pressure was also significantly lower when active ABT-431 (2,4 mg) preceded 12 and 50 mg cocaine, as compared to placebo ABT-431 administration. Both active ABT-431 doses also decreased diastolic pressure following 12 mg cocaine, while the effects of 50 mg cocaine were only attenuated by the higher ABT-431 dose (4 mg). Heart rate was increased by both active ABT-431 doses under placebo cocaine conditions and at each active dose of cocaine.

Table 2 Number of adverse events as a function of ABT-431 dose. Maximum potential number of occurences of each side-effect at each dose of ABT-431 = 27 (9 participants × 3 exposures to each ABT-431 dose). Maximum potential number of ocurrences of any side-effect at each dose of ABT-431 = 162 (9 participants × 3 exposures to each ABT-431 dose × 6 side-effects)

	ABT-431 dose		
	0 mg	2 mg	4 mg
Nausea	0	3	6
Vomiting	0	2	3
Headache	2	2	7
Fatigue	0	1	1
Lightheadness	0	1	2
Injection site reaction	0	2	1
Total	2/162	11/162	20/162

Adverse events

Table 2 shows the range of adverse events reported by participants as a function of ABT-431 dose. Data reflect the five participants who experienced at least one symptom; four participants reported no side-effects of ABT-431. The number of adverse events significantly varied as a function of ABT-431 dose [$\chi^2(2)=15.55$, $P < 0.001$)] but did not vary as a function of cocaine dose. The most frequent symptoms were headache and nausea.

Plasma cocaine

Plasma cocaine levels were dose-dependently increased by cocaine ($P < 0.0001$); ABT-431 had no effect on this measure. Cocaine plasma levels (ng/ml) were 65.6 ± 7.2 after the first 12 mg cocaine dose, and 161.8 ± 17.5 after the final option delivery of the session. Cocaine plasma levels were 227.2 ± 25.3 after the first administration of the 50 mg cocaine dose and 843.0 ± 76.0 after the final option delivery of the session.

Discussion

The D_1 receptor agonist, ABT-431, did not significantly decrease smoked cocaine self-administration in cocaine abusers. However, ABT-431 dose-dependently decreased mean ratings of "High," "Stimulated," how much participants liked and would be willing to pay for the cocaine dose, as well as the perceived potency and quality of the cocaine dose. There was also a trend for the 4 mg ABT-431 dose to decrease cocaine craving ($P < 0.03$), consistent with findings from another laboratory study in humans investigating the interaction between ABT-431 (0,2,4,8 mg IV) and IV cocaine (20 mg/70 kg) (Malison et al. 1998). Although most of the effects of ABT-431 were limited to the 12 mg dose of cocaine, and were largely overcome at the higher cocaine dose, the direction in which cocaine craving and cocaine's subjective effects were modulated clearly support further investigations of D_1 agonists as potential treatment medications for cocaine abuse.

It is of interest to note that even a 50% decrease in certain of cocaine's subjective effects by ABT-431 (e.g., Table 1) did not shift cocaine self-administration. A similar pattern was seen with the tricyclic antidepressant, desipramine in an IV cocaine self-administration procedure in humans (Fischman et al. 1990). Desipramine markedly decreased cocaine craving, and decreased a range of cocaine's subjective effects without affecting cocaine self-administration. It may be that a medication has to decrease cocaine's subjective effects markedly before cocaine self-administration is affected, at least in individuals who report no interest in stopping their drug use. Attenuating cocaine craving and its subjective effects may influence cocaine use in individuals seeking treatment for their cocaine dependence, as an adjunct to other therapeutic techniques. In fact, desipramine has shown promise in certain clinical investigations, although the effects appear to be limited to a subpopulation of cocaine users, e.g., those who are depressed, use cocaine intranasally, or do not have a personality disorder (see Arndt et al. 1994; Kleber 1995; Mendelson and Mello 1996). These data emphasize the robust nature of cocaine self-administration, and indicate that potential pharmacotherapy for cocaine use may require substantial alterations of subjective effects.

The fact that the 2 mg dose of ABT-431 only attenuated the effects of 12 mg cocaine, while the 4 mg dose also decreased certain effects following administration of 50 mg cocaine might indicate that larger doses of ABT-431 would attenuate the effects of cocaine to a greater extent. However, side-effects such as nausea and headache also increased as a function of ABT-431 dose, suggesting that larger acute doses of the medication would not be tolerated. Despite this dose-related increase in side-effects, it does not appear that the attenuation of cocaine's subjective effects and cocaine craving by ABT-431 was indirect, i.e., ABT-431 decreased ratings of dose potency and quality due to an overall malaise. First, the 2 mg dose of ABT-431 decreased the effects of 12 mg cocaine while only infrequently producing side-effects. Second, only one individual left the study due to medication side-effects, while the remaining participants seemed to tolerate ABT-431 well. Third, only five of the nine individuals who completed the study experienced even a single adverse event.

There are a number of important differences between the present findings with ABT-431 and data obtained with another dopamine agonist, pergolide mesylate, tested in a similar laboratory design (Haney et al. 1998). Pergolide, which is 50–500 times more selective for the D_2 receptor than the D_1 receptor (Dwoskin et al. 1998; Fuller and Clemens, 1991), was administered at a low dose (0.05 mg bid) in the laboratory investigation, and therefore was assumed to be acting selectively at the D_2 receptor. Both ABT-431 and pergolide significantly decreased ratings of the cocaine dose, e.g., potency, liking, amount participants would pay, etc. However, one difference between the two compounds occurred on ratings of cocaine "craving," which were significantly increased by pergolide while tending to be decreased by ABT-431 ($P < 0.03$). ABT-431 and pergolide also had opposite effects on reported craving for nicotine, which was significantly increased by pergolide (Haney et al. 1998) and significantly decreased by ABT-431.

These differences between ABT-431 and pergolide administration in humans parallel findings in a laboratory animal model of cocaine seeking, where D_2 agonist administration initiated responding on a nonreinforced lever that had been paired with cocaine, while D_1 agonist administration, including ABT-431 (Self, personal communication), did not (Self et al. 1996a). D_2 agonists also enhanced responding maintained by a conditioned reinforcer in laboratory animals, whereas D_1 agonists did not (Beninger and Ranaldi 1992; Beninger and Rolfe 1995). The findings in laboratory animals, which suggest that maintenance on D_2 agonists would be less effective than placebo in decreasing cocaine use in cocaine users, are supported by clinical data showing that cocaine abusers maintained on pergolide have poorer treatment outcome than those maintained on placebo (Levin et al. 1999; Malcolm et al. 1999). These data, combined with the

fact that D_2 agonists increased laboratory measures of cocaine craving while D_1 agonists did not, suggest that D_1 agonists may be more useful than D_2 agonists for the treatment of cocaine abuse.

In laboratory animals, full D_1 agonists have been shown to be self-administered (Weed et al. 1993; 1997; Weed and Woolverton 1995; Grech et al. 1996) and to substitute partially for or to enhance cocaine's discriminative-stimulus effects (Spealman et al. 1991, 1997; Witkin et al. 1991). By contrast, ABT-431 administration under placebo cocaine conditions did not increase ratings of "High" or "Good Drug Effect," which might have occurred if these doses function as reinforcers. Further, ABT-431 decreased ratings of "Alert" and increased ratings of "Tired" under placebo cocaine conditions, and it did not increase reports of cocaine "craving". Thus, under the present conditions, there was little evidence that ABT-431 had effects that mimicked cocaine or that were reinforcing.

In terms of the safety of ABT-431 administration, ABT-431 increased heart rate, while decreasing systolic and diastolic pressure under placebo cocaine conditions. ABT-431 continued to lower blood pressure and increase heart rate following active cocaine administration. The effect of ABT-431 on heart rate did not appear to be clinically significant, in that heart rate exceeded our criteria for cocaine administration on only 0.6% of the self-administration trials. Further, the attenuation of blood pressure by ABT-431 may indicate that it would decrease the toxic effects of cocaine.

In conclusion, the 2 mg and 4 mg doses of ABT-431 decreased many of the subjective effects of the 12 mg dose of cocaine by up to 50%, but did not affect the choice to self-administer this dose under controlled conditions. The 4 mg dose of ABT-431 also attenuated certain subjective effects of the 50 mg cocaine dose, but did not affect the choice to self-administer this dose of cocaine. Despite the absence of an effect on cocaine self-administration, the robust decrease in the subjective effects of the low cocaine dose argue that dopamine D_1 agonists might decrease cocaine use in individuals seeking treatment for cocaine abuse. While the required 1-hour infusion of ABT-431 and its short half-life precludes its clinical utility, the current data, combined with the previous negative data with the presumed D_2 agonist, pergolide (Haney et al. 1998; Levin et al. 1999), indicate that future research with D_1 agonists is warranted.

Acknowledgements The nursing assistance of Thomas Palumbo, the technical assistance of Deborah Lichtman, and the medical assistance of Drs. Eric Rubin, Maria Sullivan, and Robert MacArthur, are gratefully acknowledged. This research was supported by Abbott Laboratories and the Aaron Diamond Foundation (M.H.). Participants resided on the lrving Center for Clinical Research of The Columbia-Presbyterian Medical Center, supported by Grant No. MOI-RR-00645 from the National Institutes of Health.

References

Arndt IO, McLellan TA, Dorozynsky L, Woody GE, O'Brien CP (1994) Desipramine treatment for cocaine dependence. Role of antisocial personality disorder. J Nerv Ment Dis 182:151–156

Beninger RJ, Ranaldi R (1992) The effects of amphetamine, apomorphine, SKF 38393, quinpirole and bromocriptine on responding for conditioned reward in rats. Behav Pharmacol 3:155–163

Beninger RJ, Rolfe NG (1995) Dopamine D_1-like receptor agonists impair responding for conditioned reward in rats. Behav Pharmacol 6:785–793

Caine SB, Koob GF (1993) Modulation of cocaine self-administration in the rat through D-3 dopamine receptor. Science 260:1814–1816

Caine SB, Koob GF, Parsons LH, Everitt BJ, Schwartz J-C, Sokoloff P (1997a) D_3 receptor test in vitro predict decreased cocaine self-administration in rats. Neuropharmacol Neurotoxicol 8:2373–2377

Caine SB, Mello NK, Bergman J, Negus SS (1997b) Different effects of D_1 versus D_2 dopamine agonists on cocaine discrimination and self-administration in rats. Soc Neurosci Abstr 23:1103

Davis MW, Smith SG (1977) Catecholaminergic mechanisms of reinforcement: direct assessment by drug self-administration. Life Sci 20:483–492

Dwoskin LP, Peris J, Yasuda RP, Philpott K, Zahniser NR (1988) Repeated cocaine administration results in supersensitivity of striatal D-2 dopamine autoreceptors to pergolide. Life Sci 42:255–262

Fibiger HC (1978) Drugs and reinforcement mechanisms: a critical review of the catecholamine theory. Annu Rev Pharmacol Toxicol 18:37–56

Fischman MW, Foltin RW, Nestadt G, Pearlson GD (1990) Effects of desipramine maintenance on cocaine self administration by humans. J Pharmacol Exp Ther 253:760–770

Foltin RW, Fischman MW, Nestadt G, Stromberger H, Cornell EE, Pearlson GD (1990) Demonstration of naturalistic methods for cocaine smoking by human volunteers. Drug Alcohol Depend 26:145–154

Fuller RW, Clemens JA (1991) Pergolide: a dopamine agonist at both D_1 and D_2 receptors. Life Sci 49:925–930

Grech DM, Spealman RD, Bergman J (1996) Self-administration of D_1 receptor agonists by squirrel monkeys. Psychopharmacology 125:97–104

Haney M, Fischman MW, Foltin RW (1998) Effects of pergolide on cocaine self-administration in men and women. Psychopharmacology 137:15–24

Jackson DM, Westlind-Danielsson A (1994) Dopamine receptors: molecular biology, biochemistry and behavioural aspects. Pharmacol Ther 64:291–369

Kebabian JW, Calne DB (1979) Multiple receptors for dopamine. Nature 277:93–96

Keppel G (1991) Design and analysis: a researcher's handbook. Prentice Hall, Englewood Cliffs, N.J.

Kleber HD (1995) Pharmacotherapy, current and potential, for the treatment of cocaine dependence. Clin Neuropharmacol 18:S96–S109

Levin FR, McDowell D, Evans SM, Brooks D, Spano C, Nunes EV (1999) Pergolide mesylate for cocaine abuse: a controlled preliminary trial. Am J Addict (in press)

Little RJA, Rubin DB (1987) Statistical analysis with missing data. Wiley, New York

Malcolm R, Brady K, Moore J, Sutherland S (1999) Dose response effects of pergolide in the treatment of cocaine dependence. NIDA Res Monogr Series (in press)

Malison RT, Wright S, Sanacora G, Potenza M, Mechanic K, Haroon E, Carpenter L, Pelton G, Self D, Kostel T, Krystal J, Nestler E (1999) The dopamine D_1 receptor agonist ABT-431 reduces cocaine-induced craving in human cocaine abusers. NIDA Res Monogr Series (in press)

Mendelson JH, Mello NK (1996) Management of cocaine abuse and dependence. N Engl J Med 334:965–972

Parsons LH, Caine SB, Sokoloff P, Schwartz J-C, Koob GF, Weiss F (1996) Neurochemical evidence that postsynaptic nucleus accumbens D_3 receptor stimulation enhances cocaine reinforcement. J Neurochem 67:1078–1089

Preston KL, Sullivan JT, Strain EC, Bigelow GE (1992) Effects of cocaine alone and in combination with bromocriptine in human cocaine abusers. J Pharmacol Exp Ther 262:279–291

Rubin DB, Schenker N (1991) Multiple imputation in health-care data bases: an overview and some applications. Statist Med 10:585–598

Self DW, Stein L (1992) The D_1 agonists SKF 82958 and SKF 77434 are self-administered by rats. Brain Res 582:349–352

Self DW, Barnhart WJ, Lehman DA, Nestler EJ (1996a) Opposite modulation of cocaine-seeking behavior by D_1 and D_2-like dopamine receptor agonists. Science 271:1586–1589

Self DW, Belluzzi JD, Kossuth S, Stein L (1996b) self-administration of the D_1 agonist SKF 82958 is mediated by D_1, not D_2, receptors. Psychopharmacology 123:303–306

Shiosaki K, Jenner P, Asin KE, Britton DR, Lin CW, Michaelides M, Smith L, Bianchi B, Didomenico S, Hodges L, Hong Y, Mahan L, Mikusa J, Miller T, Nikkel A, Stashko M, Witte D, Williams M (1996) ABT 431: the diacetyl prodrug of A-86929, a potent and selective dopamine D_1 receptor agonist: in vitro characterization and effects in animal models of Parkinson's disease. J Pharmacol Exp Ther 276:150–160

Spealman RD, Bergman J, Madras BK, Melia KF (1991) Discriminative stimulus effects of cocaine in squirrel monkeys: involvement of dopamine receptor subtypes. J Pharmacol Exp Ther 258:945–953

Spealman RD, Bergman J, Rosenzweig-Lipson S (1997) Differential modulation of behavioral effects of cocaine by low- and high-efficacy D_1 agonists. Psychopharmacology 133:283–292

Tennant FS, Sagherian AA (1987) Double-blind comparison of amantadine and bromocriptine for ambulatory withdrawal from cocaine dependence. Arch Int Med 147:109–112

Weed MR, Woolverton WL (1995) The reinforcing effects of dopamine D_1 agonists in rhesus monkeys. J Pharmacol Exp Ther 275:1367–1374

Weed MR, Paul IA Dwoskin LP, Moore SE, Woolverton WL (1997) The relationship between reinforcing effects and in vitro effects of D_1 agonists in monkeys. J Pharmacol Exp Ther 283:29–38

Weed MR, Vanover KE, Woolverton WL (1993) Reinforcing effect of the D_1 dopamine agonist SKF 81297 in rhesus monkeys. Psychopharmacology 113:51–52

Wise RA, Bozarth MA (1987) A psychomotor stimulant theory of addiction. Psychol Rev 94:469–492

Wise RA, Murray A, Bozarth MA (1990) Bromocriptine self-administration and bromocriptine-reinstatement of cocaine-trained and heroin-trained lever pressing in rats. Psychopharmacology 100:355–360

Woolverton WL, Goldberg LI, Ginos JZ (1984) Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. J Pharmacol Exp Ther 230:678–683