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Effects of Bromocriptine Pretreatment on Subjective and Physiological Responses to IV Cocaine

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KUMOR, K., M. SHERER AND J. JAFFE. *Effects of bromocriptine pretreatment on subjective and physiological responses to IV cocaine*. PHARMACOL BIOCHEM BEHAV 33(4) 829–837, 1989.—We studied the effect of pretreatment with single doses of bromocriptine on the pattern of subjective and physiologic responses to single doses of intravenous (IV) cocaine. Placebo, bromocriptine 2.5 mg and, in five subjects only, 5 mg were administered orally 120 minutes before a dose of placebo or cocaine 40 mg IV to 9 male cocaine-using volunteers. Bromocriptine pretreatment diminished blood pressure generally, including cocaine-induced blood pressure increases, and augmented the heart rate after cocaine. It caused virtually no change in either augmentation or diminution of subjective responses including "rush" and "good feeling" scores, and scores for the MBG of the Addiction Research Center Inventory (ARCI), all measures of euphoria. However, a trend for the scores for the item "Would a dose of drug (cocaine) make you feel better?," suggested that bromocriptine may decrease the urge to use cocaine that was evoked by cocaine itself. However, this decreased desire was associated with a trend toward an increase in dysphoria as measured on the LSD scale of ARCI. These data support the view that euphoria and some forms of craving may be pharmacologically separable. We found no potentially toxic interactions of bromocriptine with cocaine in these single dose experiments.

Bromocriptine Subjective responses Physiological responses Cocaine

BROMOCRIPTINE has a complex pharmacology: it binds with high affinity to D_2 receptors (45) and like other D_2 agonists, it produces locomotor stimulation and stereotyped behavior, decreases in serum prolactin and induces rotation toward the contralateral side of animals with unilateral nigro-striatal dopamine pathway lesions (11–13, 25, 29). Bromocriptine also has agonist-like binding properties at the D_2 receptor (3,18). In addition, it has important presynaptic actions (13). Although dopamine depletion may block the activity of bromocriptine (13,29), the presence of D_1 agonist maximizes the effect of bromocriptine on locomotion in dopamine-depleted animals (24,25). Bromocriptine can inhibit the release and increase the uptake of dopamine presynaptically at low concentrations and can inhibit presynaptic uptake at high concentrations facilitating the effects of dopamine (48). Thus, bromocriptine may both potentiate or inhibit dopamine actions postsynaptically and may also potentiate or inhibit such actions presynaptically.

The interaction of bromocriptine with dopamine may influence brain "reward" systems involved in cocaine self-administration. Dopamine is thought to be an important transmitter in reinforcing behavior (5, 16, 17, 33, 53). Bromocriptine has been reported to potentiate the stimulant effects dopamine applied to the nucleus accumbens, an important site of brain "reward" systems (28). Also, bromocriptine can potentiate excitation induced by amphetamine, an indirectly acting dopamine releaser (27). In contrast, Tennant and Sagherian (50) have reported that 3 of 7 patients treated with bromocriptine for cocaine dependence said that the treatment blocked the cocaine euphoria when the patients had used cocaine. Woolverton has shown that D_2 antagonists decrease cocaine self-administration in animals (54). In man, laboratory studies have reported that euphoria induced by amphetamine, another stimulant, can be blocked by pretreatment with dopamine receptor blockers or metabolic inhibitors of dopamine (1, 19, 30, 38, 39). This is consistent with a large body of data on the reinforcing properties of cocaine in animals. However, four cocaine addicts given prescriptions for neuroleptics, drugs which postsynaptically inhibit dopaminergic transmission, stated that the neuroleptic use did not alter the acute euphoria they experienced when they continued to abuse cocaine (14). In our laboratory studies we found only small decreases in the euphoric responses to cocaine when 8 mg of haloperidol, a neuroleptic, was given intramuscularly 20 minutes before a cocaine challenge (47).

Several small double-blind studies of bromocriptine as treatment for cocaine dependence have been conducted. Bromocriptine has been reported to reduce cocaine craving associated with environmental stimuli (9) and to cocaine injection itself (26). Tennant and Sagherian (50) reported that bromocriptine 2.5 mg decreased symptoms of cocaine withdrawal in a small group (7) of patients desiring treatment for cocaine dependence. Giannini *et al.* (15) reported an improvement of Brief Psychiatric Rating Scale scores in cocaine addicts treated with bromocriptine during withdrawal as compared to placebo-treated controls in a double-blind study.

Whether drugs that interact with dopaminergic transmission can alter the subjective effects of cocaine such as euphoria and the sense of increased energy and sexuality which may play some role in the reinforcing effects of cocaine is still unclear. It is possible

that bromocriptine could alter the euphoria or "reward" induced by cocaine. It could decrease dopaminergic transmission by presynaptically inhibiting dopamine release and increasing dopamine uptake. Alternatively, it may potentiate dopaminergic transmission by its agonistic action postsynaptically.

Since low-dose bromocriptine has been reported to be effective in reducing postwithdrawal cocaine craving (9), we studied the effect of bromocriptine on the subjective effects produced by intravenous doses of cocaine 40 mg. Since, in the treatment of neurological disorders (e.g., in Parkinsonism) larger doses of bromocriptine are frequently used, we also conducted preliminary investigation of the effects of 5 mg bromocriptine on the acute effects of 40 mg of IV cocaine.

METHOD

Subjects

Nine male intravenous cocaine-using paid volunteer subjects completed the study. Two subjects participated but did not complete the study; one withdrew because of side effects (nausea, headache, vomiting) associated with bromocriptine and another stated there was illness in the family but had complained of headache and nausea prior to withdrawal. All subjects had recent histories of cocaine use, reporting use between 1 and 8 days out of the 14 days prior to admission. In the 14 days prior to admission to the research ward, three subjects also reported using intravenous heroin (range 1–6 days), eight subjects reported the use of alcohol (range 1–4 days), seven used marijuana (range 1–14 days), one used a tranquilizer on one occasion and one used amphetamine on one occasion.

All subjects were screened for mental health problems using a version of the NIMH Diagnostic Interview Schedule (DIS) modified for self administration. Four subjects met DSM-III criteria for antisocial personality and another had features of antisocial personality. One subject met criteria for borderline personality disorder. One subject had a history of a bipolar disorder in remission and one subject had history of depressive symptoms.

During the first three days of residing on the closed, secured research ward, prior to receiving any experimental drugs, subjects were observed by an experienced nursing staff for signs and symptoms of drug withdrawal. No signs of withdrawal were noted and no subject was rejected because of drug withdrawal. The protocol was approved by the IRB and all subjects consented to the study.

Design

After the initial period of observation, all subjects underwent an ascending series of administrations of the study medications and combinations to rule out undue sensitivity to any of the drugs. The drug schedule in chronologic order was cocaine 20 mg intravenously, cocaine 40 mg IV, bromocriptine 2.5 mg orally plus 20 mg cocaine IV, and bromocriptine 1.25 mg orally plus cocaine 40 mg IV. The schedule of vital signs measurements and questionnaire administrations during this preliminary stage was the same as for the study itself, described below. All subjects tolerated the drug effects well; none of the participants experienced toxic drug effects requiring exclusion from the study. All intravenous drug administrations were injected manually over 1–2 seconds in order to mimic the injection time used when the drug users self administer cocaine.

There was an interval of at least 48 hr between completion of the test dose series and the start of the formal study. An indwelling venous catheter was inserted into a forearm vein for drug administration. Approximately 30 minutes later subjects received a capsule of drug orally. Two hours after receiving the capsule, the test drug was given intravenously. The drug conditions were as follows:

Condition Notation	Oral Drug	IV Drug
PL/PL	Placebo	Placebo
PL/COC	Placebo	Cocaine 40 mg
2.5 BROM/PL	Bromocriptine 2.5 mg	Placebo
2.5 BROM/COC	Bromocriptine 2.5 mg	Cocaine 40 mg

The drugs were presented in a double-blind randomized design. There were two people who functioned as observers and one physician in the room during the experiments. They were aware of the general study design, that is, the possibility of combinations of bromocriptine or placebo pretreatments with cocaine or placebo challenges, but were blind to the study conditions throughout the experiment. During the study, staff members did not engage the subjects in conversation but would be supportive, though nondirective of conversation initiated by the subjects. Staff members recorded physiologic data and could observe the computerized questionnaire results during the study.

Following completion of the randomized study, we gathered preliminary information on a 5 mg dose of bromocriptine given 2 hr before a cocaine challenge (5 BROM/COC). This was done so as not to jeopardize completion of the study because the 5 mg dose of bromocriptine frequently causes nausea, vomiting and headache. Five of the 9 subjects received this drug combination which was conducted under double-blind conditions otherwise identical to the remainder of the study.

Measures

We measured pulse, blood pressure, and respiratory rate at 90, 60, and 30 minutes prior to the IV challenge (cocaine or placebo). After injection of the IV bolus of cocaine or placebo, pulse, blood pressure, and respiratory rate were recorded at 1, 5, 15, 30, 45, 60, 90 and 160 minutes.

We measured subjective experiences with four self-report questionnaires administered via a computer and one preliminary version of a paper and pencil rating scale administered by a staff researcher. The computer administered a series of items termed the Cocaine Sensitive Interval Scales (CSI), the Rushgraph Scale and the four point, Feel the Drug Scale which have been useful in our previous studies of cocaine-related subjective effects (34, 46, 47). We also administered the Single Dose Questionnaire which includes the Morphine Benzedrine Group Scale (MBG), the Pentobarbital, Chlorpromazine and Alcohol Group Scale (PCAG) and the Lysergic Diethylamide Group Scale (LSD) (20).

The CSI Scale consists of ten-point interval items which ask the subject to rate a series of sensations or feelings including good, bad, "rush," tired, happy, energetic, sad, restless, anxious, irritable, and relaxed. Additionally, subjects were to rate in the same fashion two statements and a question: I think someone wants to see me fail, the staff doesn't like me very much, and would a dose of the drug make you feel better? The Rushgraph Scale allows the subject to "draw" a computerized vertical bar graph of the intensity of rush versus time. Unlike all the other Scales we administered, this scale allows the subject to view but not alter his previous work. The schedule of administration for the CSI scales and the Single Dose Questionnaire was 90 minutes before the IV drug injections and then at 5, 15, 30, 60, 120, and 160 minutes after the IV injection. The Rushgraph was given on the same schedule with the exception that there was an additional

TABLE 1

THREE-WAY ANOVA RESULTS OF 4 CONDITION ANALYSIS (SIGNIFICANT AND NEAR SIGNIFICANT RESULTS)

Factors[a] Degrees of Freedom	1 (IV Challenge) 1,8	2 (Pretreatment) 1,8	3 (Time) §	1×2 1,8	1×3 §	2×3 §	1×2×3 §
Measures	F ratio/*p* value	F/*p*	F/*p*	F/*p*	F/*p*	F/*p*	F/*p*
Respirations							
−30 to 15 min	6.5*	—	13.5‡	3.9/=0.08	4.8†	—	2.5/=0.08
30 to 160 min	—	3.7/=0.09	6.0†	5.2*	3.0*	—	—
Systolic							
−30 to 15 min	16.6†	—	10.1‡	—	3.2*	—	—
30 to 160 min	7.4*	19.9†	3.2*	—	9.2‡	—	—
Diastolic							
−30 to 15 min	26.1‡	3.5/=0.09	10.8‡	—	3.9*	—	—
30 to 160 min	5.8*	7.4*	—	—	3.6*	—	—
Pulse							
−30 to 15 min	46.2‡	—	16.4‡	—	17.1‡	—	—
30 to 160 min	20.5‡	8.2*	14.1‡	—	5.5‡	—	—
Good	22.4‡	—	19.5‡	—	22.5‡	—	—
Rushgraph	17.7†	3.9/=0.08	18.2‡	—	12.4‡	2.4/=0.07	2.5/=0.06
Rush	7.9*	—	11.5†	—	4.6*	—	—
Anxious	—	—	—	5.4*	2.5/=0.06	—	—
Energetic	—	—	2.7*	—	—	—	—
Bad	—	—	2.7*	—	—	—	—
Tired	—	—	—	—	—	—	—
Happiest	—	—	—	—	—	—	3.5*
Saddest	—	—	—	—	—	—	2.8*
Irritable	—	—	—	—	—	—	—
Restless	4.4/=0.07	—	2.8*	—	2.8*	—	—
Relaxed	—	—	—	—	—	—	—
"Miss Rush"	—	—	5.8‡	—	—	—	—
"Dose Drug"	4.1/=0.07	—	—	7.9*	—	—	—
MBG	6.6*	—	9.7‡	—	5.4†	—	—
PCAG	5.1*	—	2.6*	—	—	3.7*	—
LSD	27.7‡	6.7*	13.5‡	—	12.7‡	—	—
"Feel Drug"	14.6†	—	25.9‡	—	29.8‡	—	—
Observer Measures							
Liking	58.1‡	—	10.1‡	—	7.8‡	—	—
Normal	64.5‡	—	7.8‡	—	6.3‡	—	—
Drug Effect	119‡	—	24.6‡	—	27.7‡	2.7*	2.3/=0.08

*$p \leq 0.05$; †$p \leq 0.01$; ‡$p \leq 0.001$.

§The degrees of freedom are 4/32 for all measures except the early points for respirations, blood pressures and pulse, for which the degrees of freedom are 3/24. The rush CSI had 2/16 degrees of freedom.

[a]Factor 1 is the IV challenge drug (cocaine vs. placebo); Factor 2 is the pretreatment drug (bromocriptine vs. placebo); Factor 3 is time.

measurement at one minute after the IV injections. This was done so as to maximize detection and quantitation of rush which peaks rapidly after IV use. The paper and pencil rating scale involved questions about craving and wanting drug and is the subject of a separate report (26).

Observers rated the subject volunteers on three items, "Drug Effect" "Normal," and "Liking" from the Observers Single Dose Questionnaire (Opiate Symptoms Scale) each scored on a 4-point interval scale. The observers used all behavior of the subject including verbal and facial expressions for estimating the intensity of the pharmacologic effect (Drug Effect) and the enjoyment of the subject (Liking). The item "Normal" was scored by estimating if the subject was completely "normal" (his usual state is rated 0) or how much different from "normal." The observers ratings were taken at 90, 60 and 30 minutes before IV drug administration and at 1, 5, 15, 30, 45, 60, 90 and 160 minutes after IV drug administration.

We employed a three-way analysis of variance comparing experimental measures for the PL/PL, PL/COC, 2.5 BROM/PL, and 2.5 BROM/COC conditions. The independent factors in the analysis were cocaine versus a placebo challenge, bromocriptine versus a placebo pretreatment and time. The analysis was done as a repeated measures design as all nine subjects completed all 4 drug conditions. If the F ratios for the three-way analysis of variance were >0.05, we interpreted the data as lacking significant differences among the conditions though we interpreted $p<0.1$ and >0.05 as trends.

We used a two-way analysis of variance with independent factors for dose and time comparing the data of the five subjects who completed the five conditions, comparing PL/COC, 2.5

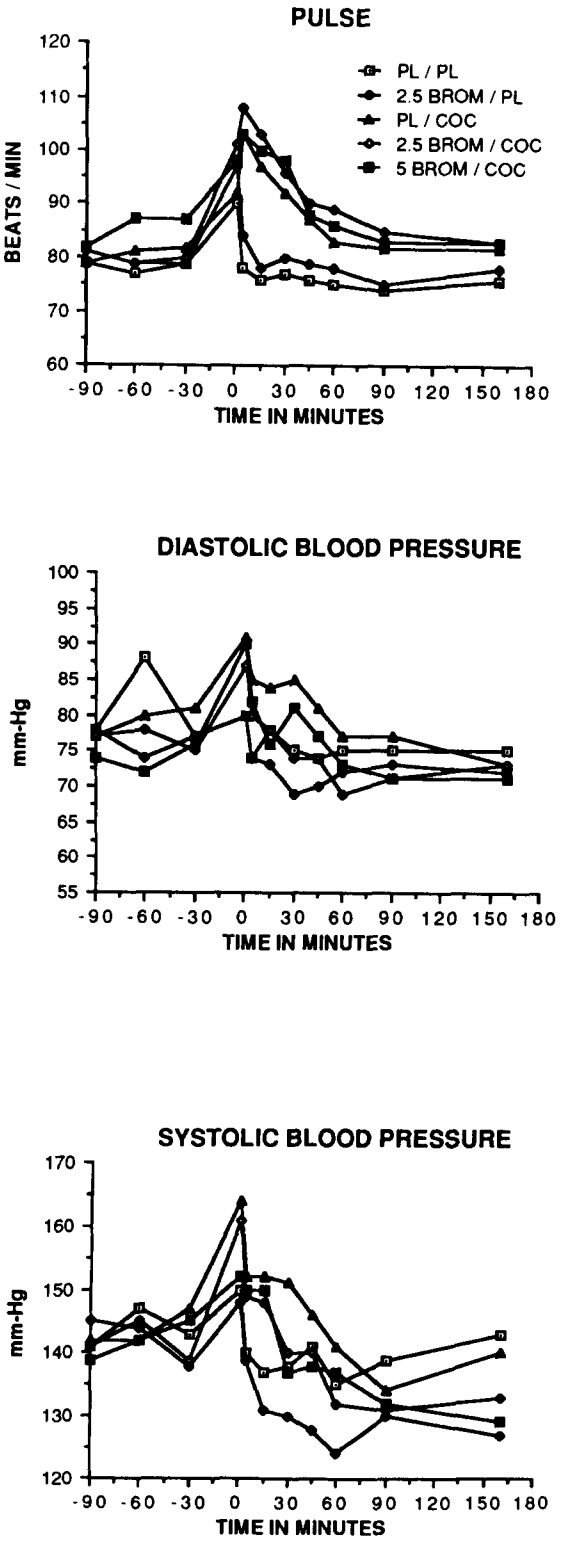

FIG. 1. Mean systolic and diastolic blood pressure and pulse are plotted versus time for all subjects who completed the conditions. Nine subjects completed four conditions presented in random order. These four conditions are placebo pretreatment/placebo challenge, 2.5 mg bromocriptine pretreatment/placebo challenge, placebo pretreatment/cocaine 40 mg challenge, and 2.5 bromocriptine pretreatment/cocaine 40 mg challenge. The bromocriptine 5 mg pretreatment/cocaine 40 mg challenge was given to five subjects and this condition was always presented as the last study day, i.e., the order was not randomized.

BROM/COC, and bromocriptine 5 mg plus a cocaine challenge of 40 mg (5 BROM/COC) in order to detect bromocriptine dose effects.

For the physiologic measures we split the data into two portions, after excluding the −90- and −60-minute baseline points: the first 4 time points and the last 5 time points. This was done to protect the experiment-wise error rate and the calculated p-values, since errors in the actual p-values occur as a consequence of having a large number of data points from a small population of subjects (31). For the subjective and observer measures, only the first four data points after injection were included along with the −30-minute baseline point for a total of 5 time points. This was done to protect the error rate and also, nearly all the variance in the experiment was contained within these data.

RESULTS

The analysis of variance for cocaine compared to the placebo IV challenge (factor 1 of the analysis) demonstrated significant differences on the physiologic measures of respiratory rate, pulse, systolic blood pressure, and diastolic blood pressure, as well as on two items from the CSI, good and rush, all three subscales of the Single Dose Questionnaire, the MBG, PCAG, and LSD, the Feel the Drug Scale, the Rushgraph Scale and the Drug Effect, Normal and Liking questions from the Observer Single Dose Questionnaire. It was nearly significant for the item restless from the CSI (see Table 1). These results were expected since all of these items and questionnaires have been shown previously to be sensitive to the effects of cocaine (34) (with the exception of the item "restless" and the PCAG scale). Although we did not observe statistically elevated scores for the items "energetic" and "anxious" following the cocaine injections compared to placebo (as we did in a previous study), the overall responses indicate that a number of measures were sensitive to the physiologic and psychopharmacologic effects of cocaine.

Bromocriptine pretreatment (the second factor in the ANOVA) caused statistically significant but clinically unimportant effects on the physiologic measures of blood pressure and pulse compared to the placebo pretreatment. These effects were found for the late time points only, between 30 and 160 minutes after the IV challenge, although in each case a corresponding trend was found early in the experiment. Bromocriptine reduced systolic blood pressure during the late portion of the experiment from a mean of 141 mmHg for placebo (the average of all subjects' values at 30, 45, 60, 90, and 160 minutes) to 131 mmHg. A trend was also present for the early portion of the experiment: the mean for the placebo pretreatment was 148 mmHg compared to 144 mmHg for the bromocriptine pretreatment. Similarly, bromocriptine produced a slight decrease in the mean diastolic blood pressure during the late portion of the experiment (30 to 160 minutes) from 77 mmHg after placebo to 72 mmHg. There was also a trend ($p=0.09$) toward a decreased diastolic blood pressure with bromocriptine pretreatment in the early portion of the experiment. During the late portion of the experiment bromocriptine increased the pulse from a mean of 81 beats per minute after placebo to 84 beats, again statistically significant, but clinically unimportant. The bromocriptine pretreatment per se decreased scores on the LSD subscale of the ARCI, but had no effect on any other subjective or observer measure.

The analysis of the third factor, time, demonstrated significant effects for 18 measures including all physiologic measures, all three subscales of the Subject Single Dose Questionnaire, the Rushgraph and Feel Drug Scales, the "rush," "good," "energetic," "bad," and "restless" items from the CSI and the scales from the Observer Single Dose Questionnaire. These findings were expected since drug and placebo responses are time-dependent (see Table 1).

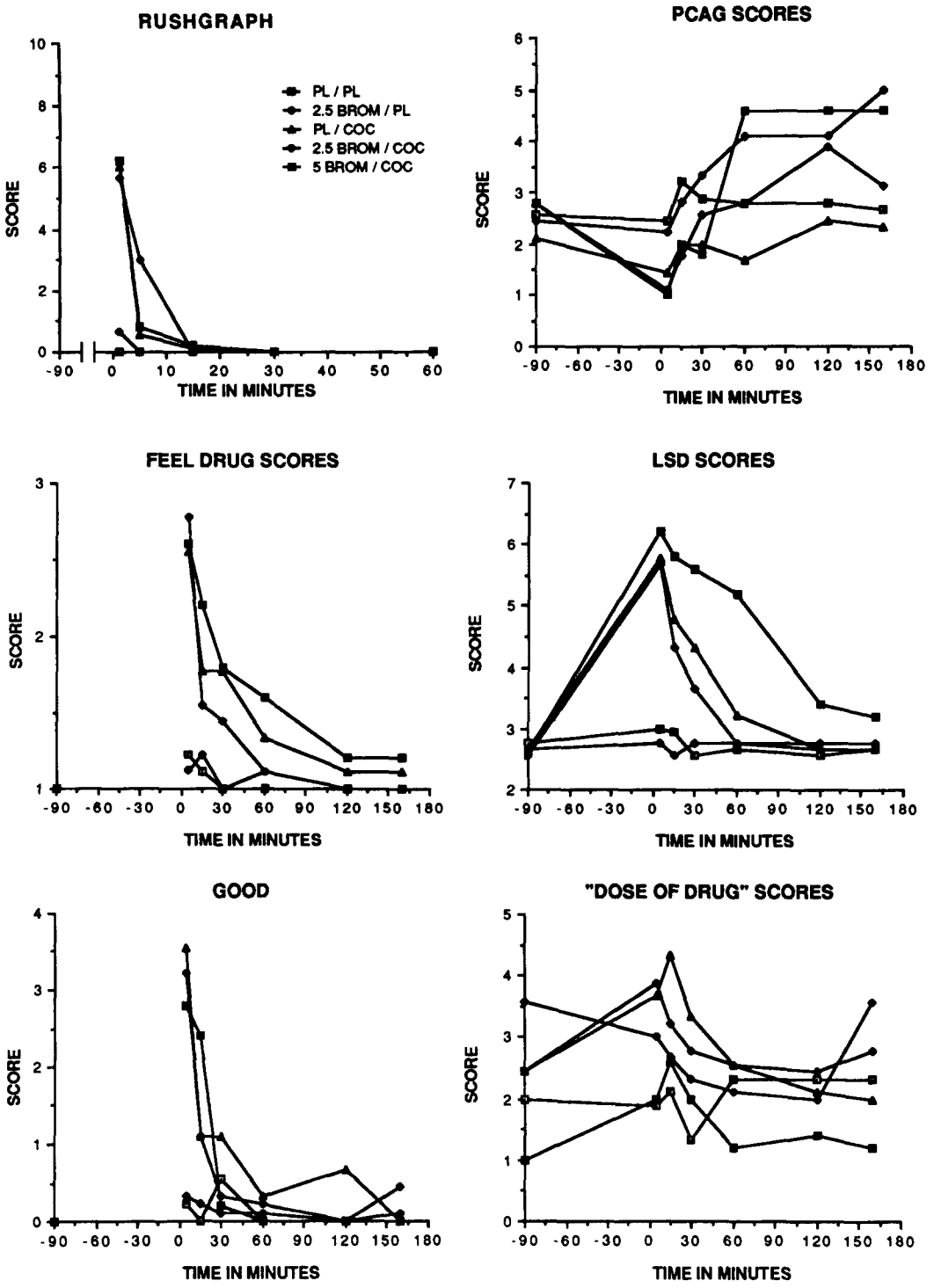

FIG. 2. Mean scores are plotted versus time for six selected scales—Rushgraph, Feel the Drug, Good, PCAG, LSD and the item "Would a dose of drug (cocaine) make you feel better?" Nine subjects completed four conditions presented in random order. These four conditions are placebo pretreatment/placebo challenge, 2.5 mg bromocriptine pretreatment/placebo challenge, placebo pretreatment/cocaine 40 mg challenge, and 2.5 bromocriptine pretreatment/cocaine 40 mg challenge. The bromocriptine 5 mg pretreatment/cocaine 40 mg challenge was given to five subjects and this condition was always presented as the last study day, i.e., the order was not randomized.

TABLE 2

ANOVA RESULTS FOR BROMOCRIPTINE DOSE RELATIONSHIP

Factor[a]	1 (Bromocriptine		
Degrees of	Dose)	2 (Time)	1 × 2
Freedom	2,8	§	§
Measures	F/p	F/p	F/p
Respirations	—	20‡	—
Systolic BP	5.2*	8.8‡	—
Diastolic BP	4.6*	7.0‡	—
Pulse	—	14.6‡	—
Good	—	15.2‡	2.0*
Rushgraph	—	13‡	—
Rush	—	5.0†	—
Anxious	—	—	—
Energetic	—	4.2†	—
Bad	—	—	—
Tired	—	—	—
Happiest	—	3.8†	—
Saddest	—	—	—
Restless	—	2.6*	—
Irritable	—	—	—
Relaxed	—	—	—
"Miss Rush"	—	—	—
"Dose Drug"	3.4/=0.08	—	—
MBG	—	6.2‡	—
PCAG	—	—	—
LSD	3.5/=0.08	16.0‡	—
"Feel Drug"	—	18.0‡	—
Observers' Measures			
Liking	—	15.2‡	—
Normal	—	6.2‡	—
Drug Effect	—	23.5‡	1.6/=0.08

*$p \leq 0.05$; †$p \leq 0.01$; ‡$p \leq 0.001$.

§The degrees of freedom for the physiologic measures of respirations, blood pressure and pulse and the observers measures had 10/40 degrees of freedom for factor 2 and 20/80 for the factor 1 × 2 interaction. All subjective measures except the Rushgraph had 6/24 degrees of freedom for factor 1 and 12/48 for the 1 × 2 interaction. The Rushgraph had respectively 7/28 and 14/56.

[a]Factor 1 is the three doses of bromocriptine 0, 2.5 and 5 mg given as a pretreatment before 40 mg of cocaine; Factor 2 is time.

An important test of the influence of bromocriptine on the effects of cocaine is the analysis of variance of the interaction between the intravenous challenge drug (placebo versus cocaine) and the pretreatment (placebo versus bromocriptine). Such an interaction can uncover a specific effect of bromocriptine exerting an influence in the presence of cocaine. However, we found only three significant interactions: an increase of respirations during bromocriptine/cocaine, and increased self-ratings on the items, "Would a dose of drug make you feel better?" and "anxious." The data for "anxious" self-ratings demonstrate that bromocriptine pretreatment decreases cocaine-associated anxiety but has only a small effect upon the ratings of "anxious" after a placebo challenge. Similarly for the "Dose of Drug" question, bromocriptine decreased the scores after a cocaine injection, but bromocriptine treatment itself without a cocaine injection did not show an effect. Thus, the effect existed only in the presence of cocaine.

A significant interaction of the bromocriptine pretreatment and time was observed for the PCAG Scale and the observer's Drug Effect Scale. These results reflect the subject's increased scores on the PCAG toward the end of the experiment when they received bromocriptine pretreatment, but this increase was absent for the placebo pretreatment (Fig. 2). The PCAG is a measure of sleepy or tired feelings. The item of tired on the CSI was not sensitive to this effect, but the pattern of responses was similar. Significant interactions were also observed between IV drug challenge, the pretreatment condition and time for the Rushgraph Scale. The Rushgraph result showed a change in the time course of cocaine rush: with bromocriptine pretreatment, the sensation of rush returned to baseline more slowly, compared to the placebo pretreatment. However, this finding with the Rushgraph was not at all reflected in the scores for the item "rush" from the CSI.

Numerous measures demonstrated an interaction of the IV challenge drug and time as would be expected (see Table 1).

In addition, we conducted a two-way ANOVA comparing the data from the five subjects who completed the bromocriptine 5 mg pretreatment with a cocaine 40 mg challenge. The first factor in the analysis was the three drug conditions, PL/COC, 2.5 BROM/COC and 5.0 BROM/COC, with time as the second factor. This analysis was undertaken to search for a dose response for the effect of bromocriptine on the cocaine response. None of the responses we measured demonstrated a dose response although the measures of systolic and diastolic blood pressure did result in significant differences among the three drug conditions (Table 2). The means of the 2.5 mg dose of bromocriptine were higher than those of the 5 mg dose in both cases. Strong trends toward significant differences were also noted for the LSD Scale scores ($p = 0.08$) and the scores of the item, "Would a dose of drug make you feel better?" ($p = 0.08$). However, these were not related to the dose of bromocriptine either. The 5 mg bromocriptine pretreatment had a strong effect on these two scores but the means of the remaining two conditions were nearly identical. In the case of the "Would a dose of drug make you feel better?" item, the 5 mg of bromocriptine was associated with low scores (mean = 1.6) compared to the placebo (mean = 2.7) and 2.5 mg bromocriptine (mean = 2.7) pretreatments. The mean scores for the LSD Scale pretreatments were similarly patterned: the means for the placebo, 2.5 and 5.0 mg bromocriptine pretreatments were 3.8, 3.7 and 4.6 respectively. Again, there was no evidence of an orderly dose response relationship (Table 2).

DISCUSSION

Generally, pretreatment with bromocriptine caused slight decreases in blood pressure and respirations and increases in the pulse. These effects on blood pressure and pulse occurred whether the IV challenge was cocaine or placebo (Fig. 1). However, for respiration, there was a significant interaction of bromocriptine with the challenge drug. Bromocriptine decreased respiratory rate after a placebo injection more effectively than after a cocaine injection. Clinically, these effects were trivial.

The hypotensive effect of bromocriptine is common and is probably due to partial alpha adrenergic blockade (52). Other classes of ergot alkaloids have been reported to enhance the effects of full alpha adrenergic agonists such as norepinephrine (40). Cocaine itself potentiates the effects of norepinephrine (32). Our results imply that the alpha adrenergic antagonistic activity of bromocriptine dominates the acute activity of bromocriptine administered prior to injection. However, these results should not be extrapolated to chronic administrations of the drugs involved nor to other doses as the possibility of adrenergic potentiation exists.

We have previously reported that, when these subjects reported their desire for cocaine to a researcher (blind to the experimental conditions), bromocriptine attenuated cocaine-induced craving

(26). In the present report, we analyze another set of data obtained from these subjects, and show that bromocriptine does not attenuate any of the euphoric effects associated with administered intravenous cocaine. It is possible that the minimal subjective and physiological effects of bromocriptine in these subjects is related to some degree of dopamine depletion or altered sensitivity of postsynaptic dopamine receptors. Johnson *et al.* (29) and Fuxe *et al.* (12) observed that dopamine depletion may block the activity of bromocriptine in animals. Dackis *et al.* (7,8) hypothesized that prolonged abuse of cocaine can lead to a state of dopaminergic depletion. This idea is supported by some observations that brain dopamine and dopamine synthesis rates decrease in rats following repeated administration of cocaine (49,51). Furthermore, cocaine users have been observed to have increased plasma prolactin concentrations which is compatible with a state of dopamine depletion, or altered receptor sensitivity (7,37). In previous studies of subjects from the same general population as that from which the present subjects were recruited, we have observed a very high frequency of dystonic reactions on exposure to haloperidol suggesting that our cocaine users may have alterations in the sensitivity of dopamine systems (35).

On the other hand, it is possible that lower doses of bromocriptine than used in this study might prove effective in altering the subjective responses of cocaine. In rats, low doses, but not high doses, of bromocriptine inhibit the release and increase the uptake of dopamine presynaptically (48). However, the bromocriptine dose in man comparable to the low doses of drug used in the rats is not known. We examined the data obtained as part of our safety screening (bromocriptine 1.25 mg pretreatment with cocaine 40 mg challenge) and we did not find any indication of important changes in the cocaine response. We recognize however, that this aspect of the study did not employ the necessary controls.

We do not interpret the lack of effect of bromocriptine pretreatment on cocaine-induced subjective responses as conflicting with the prevailing theory that dopamine is important in the "reward" systems involved in cocaine self-administration. A relationship between dopaminergic agonism and the reinforcing effects of cocaine is well established. Cocaine itself acts as an indirect agonist of dopamine (and other catecholamines), primarily via inhibition of synaptic reuptake of dopamine (2, 4, 21–23, 43). Multiple experiments have shown that acute manipulation of dopaminergic systems can alter patterns of behavior and self administration of cocaine in animals (16, 17, 41, 45). Specifically, stimulant reinforcement can be blocked by the dopaminergic antagonist pimozide (10, 54, 55). Although experiments with pimozide have not been conducted in man, it is probable that the euphorigenic qualities of cocaine reported in man are related to the reinforcing properties in animals.

In our study of the effects of haloperidol, a dopamine antagonist, given as a pretreatment shortly before a cocaine challenge, we found no effects of haloperidol on drug rush but did find a partial but substantive blockade of good feelings which predominate after rush is over (47). Thus, the pattern of cocaine-generated euphorigenic responses after haloperidol pretreatment is different from the effects of bromocriptine pretreatment patterns observed here.

Previously we reported that, in these subjects, cocaine itself induces an increase in feelings of craving, needing and wanting of cocaine (26). Pretreatment with bromocriptine decreased these cocaine-induced feelings. Chronic craving may involve biological sequelae of chronic cocaine use as well as conditioned responses (6). In this report, subject scores on the computer-administered question, "Would a dose of the drug (cocaine) make you feel better?," were decreased with bromocriptine pretreatment. We believe that this question is related to, or reflects, the feelings of craving, needing and wanting that were reported to the observer and were the subject of our earlier report (26). Similarly, in the presence of bromocriptine pretreatment, we observed increased scores on the LSD scale, a scale which measures dysphoria (Fig. 2). Thus, while bromocriptine may reduce a need state for cocaine, it may do so only with a concomitant dysphoria. It is also possible that the dysphoria is a nonspecific antagonist of the cocaine need state. These findings contrast with the fact that for the computer-administered scales of the present study, generally bromocriptine had no effect on other subjective sensations. The results are puzzling and suggest a disjunction of the pharmacologic mechanisms involved in cocaine-induced craving and certain of the perceived pleasurable feelings associated with cocaine while suggesting that some kinds of dysphoria can reduce the urge to use cocaine.

The study reported here was designed principally to examine the effects of a single 2.5 mg oral dose of bromocriptine. Any conclusions about the 5 mg dose are limited by the small number of subjects participating (5) and by the fact that the 5 mg dose was always administered after completion of the other study conditions. It is possible that the results of the 5 mg dose of bromocriptine (5 BROM/COC) condition reflect the effect of cumulative doses of cocaine or bromocriptine. We have previously reported a weak relationship between paranoid behaviors and cumulative doses of cocaine given as part of a research study (46). Also, bromocriptine has been reported to have long-lived (in terms of experiment duration) effects in vitro (3,36). We found no evidence for the potentiation of adverse effects to cocaine by single doses of bromocriptine. We observed only small changes in the physiologic responses to cocaine with bromocriptine pretreatment. Furthermore, we did not observe any disturbances of behavior or neurologic function which might suggest a toxic interaction between cocaine and bromocriptine. Such observations are of interest since bromocriptine may have value in the treatment of cocaine addiction (9, 15, 26, 50) where continued use of cocaine could occur. Although chronic administration of bromocriptine or repeated doses of cocaine after bromocriptine may produce effects that differ from our single dose studies, our results are encouraging and support the initiation of bromocriptine treatment trials.

What emerges from these studies of the interaction of cocaine with drugs known to have effects on dopamine receptors is that the subjective effects associated with cocaine seem to be multiply determined. The acute effect of bromocriptine appears to alter some of these determinants but not others. Our findings suggest that craving and euphorigenic responses associated with single doses of cocaine may be pharmacologically independent. It may be possible to define some of the diverse language for subjective effects induced by cocaine (e.g., rush, euphoria, craving) in terms of the pattern of cocaine subjective responses induced by pharmacological agents. Thus, one form of craving could be defined as a feeling state induced by cocaine injection or environmental cues, measured by subjective report and diminished by pretreatment with bromocriptine. The question of whether chronic treatment with bromocriptine would decrease this form of drug craving and alter drug seeking behavior without a concurrent effect on the ability to achieve euphoric sensations is an interesting one. In the past, the pharmacologic treatment of drug abuse has been founded on the principle of producing reductions in the experience of drug-induced euphoria or the relief of the sense of need for the drug (craving) that is typically associated with withdrawal. Our studies suggest that the neurochemical determinants of cocaine-related craving and euphoria can be affected directly and differentially by pharmacologic agents.

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