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Cocaine Tolerance: Behavioral, Cardiovascular, and Neuroendocrine Function in Men

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Cocaine tolerance was assessed by comparing the acute effects of cocaine in drug-abstinent men who reported occasional cocaine use ($n = 6$) and in men who met DSM-III-R diagnostic criteria for dependence on both cocaine and opiates ($n = 6$). Peak plasma cocaine levels were equivalent in the two groups, and pharmacokinetic analyses revealed no significant differences in cocaine levels at any time. Cocaine induced a significantly greater increase in ACTH in the occasional cocaine users than in the cocaine dependent men ($p < .01$). Heart rate and systolic and diastolic blood pressure increases after cocaine were also significantly greater in the occasional cocaine users than in the cocaine-dependent men ($p < .05$). These neuroendocrine and physiologic differences were paralleled by significantly greater subjective reports of "high" and "euphoria" by the occasional cocaine users ($p < .03$ to $.0001$). These data are consistent with the conclusion that tolerance to cocaine's physiologic, neuroendocrine, and subjective effects may occur as a function of chronic use.

[Neuropsychopharmacology 18:263–271, 1998]

KEY WORDS: *Cocaine; Pharmacokinetics; ACTH; Blood pressure; Tachycardia; Euphoria*

There is considerable evidence that administration of cocaine induces acute tolerance for behavioral and cardiovascular effects in humans (Ambre et al. 1988; Chow et al. 1985; Fischman et al. 1983, 1985; Foltin and Fischman 1991, 1992). However, acute tolerance for cocaine's behavioral and cardiovascular responses was not observed when an initial acute bolus dose of cocaine was followed by continuous cocaine infusions for 12 to 240 min (Kumor et al. 1989). It has been postulated that chronic administration may result in a decrement in cocaine-induced elevations of blood pressure, reflecting tolerance to cocaine's effects (Jaffe 1985). Behavioral tolerance has been observed in experimental animals during a 14-day period of continuous cocaine administration (King et al. 1994). Chronic tolerance for cocaine's local anesthetic effects has also been reported in preclinical studies (Castellani et al. 1978). Tolerance for cocaine at doses that induce lethal intoxication in naive animals may also occur as a consequence of chronic cocaine administration (Ellenhorn and Barceloux 1988). One clinical case report of cocaine tolerance was believed to have occurred as a concomitant of long-term cocaine self-administration (Howell and Ezell 1990).

A major criterion for the diagnosis of substance dependence (including cocaine dependence) specified in the Diagnostic and Statistical Manual of Mental Disorders (1994) is as follows: "1. Tolerance, as defined by either of the following: a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect; b. Markedly diminished effect with continued use of the same amount of the substance." We have been unable to locate any controlled studies to determine if *chronic cocaine use* is associated with tolerance for cocaine's behavioral, cardiovascular, and neuroendocrine effects in men. The purpose of this study was to

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Received April 9, 1997; accepted August 8, 1997.

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/98/$19.00
PII S0893-133X(97)00146-2

compare the acute effects of cocaine in two groups of subjects with different histories of cocaine use; occasional cocaine users and men who fulfilled the diagnostic criteria (DSM-III-R) for cocaine dependence and dual dependence on opiates. We postulated that persons with a long-term history of cocaine abuse might be less responsive to the effects of an acute cocaine challenge than occasional users. If significant differences in responsivity occurred after a controlled period of cocaine abstinence, this would be consistent with the notion that chronic cocaine exposure induces tolerance to some of its effects.

METHODS

Subjects

Twelve adult men between the ages of 21 and 35 provided informed consent for participation in studies to determine the acute effects of cocaine on behavioral, cardiovascular, and neuroendocrine function. Six men between the ages of 26 to 35 with a mean weight of 77.4 kg met DSM-III-R axis I diagnostic criteria for concurrent opioid and cocaine dependence. Six men between the ages of 21 and 32 years reported occasional cocaine use. There were no statistically significant differences between the two groups with respect to weight, height, and body mass index (BMI). Subject characteristics are summarized in Table 1.

Men diagnosed with concurrent opioid and cocaine dependence reported an average of 13 years of chronic intravenous opiate use and 9 years of chronic cocaine use. These men stated that they occasionally used speedballs, i.e., simultaneous intravenous injections of cocaine and heroin, but usually they self-administered heroin before or after intravenous injection of cocaine. In contrast, occasional cocaine users reported using cocaine by inhalation and insufflation on five to 10 occasions per year during the year before the study. All men (occasional cocaine users and those with concurrent heroin and cocaine dependence) were in good physical health, had normal medical and laboratory screening examinations, and provided informed consent for participation in the studies. All subjects were drug-free at the time of the study as assessed by urine-drug screens. Men with concurrent heroin and cocaine dependence participated in a study to determine the safety and effectiveness of buprenorphine for the treatment of their drug-dependence disorder. A report of these studies in 20 subjects has been described previously (Teoh et al. 1993). The subset of six subjects described in the present report were selected on the basis of their comparability to the occasional cocaine users with respect to age, weight, height, body mass index (BMI), and the intravenous dose of cocaine administered in the study.

Experimental Procedures

The cocaine- and opioid-dependent men resided on a clinical research ward during methadone detoxification. After the conclusion of methadone detoxification, men were drug-free for 9 days. On study days 7, 8, or 9, men were given an intravenous challenge dose of 0.39 ± 0.02 mg/kg cocaine intravenously over a 1-min interval. Cocaine injections were administered by a physician. All men were studied in a semisupine position, and continuous cardiovascular monitoring was carried out for 10 min before intravenous cocaine administration and for 2 h after drug injection. A trained physician certified for cardiopulmonary resuscitation was present during each study, and a cardiac defibrillator and appropriate emergency treatment medications were located in the study room.

The occasional cocaine users also were studied on a clinical research ward. Identical procedures for intravenous cocaine administration were used in occasional cocaine users and in men who were heroin and cocaine dependent. A challenge dose of cocaine (0.4 mg/kg) was administered intravenously over a 1-min period.

Subjects were asked to report their perception of drug intensity and drug quality (euphoria) 5 min after completion of intravenous cocaine injection. Measurements of heart rate and systolic and diastolic blood pressure were recorded before intravenous cocaine injection and at +5, +10, +15, +20, +30, +45, +60, +90 and +120 min in all

Table 1. Cocaine- and Opiate-Dependent Men ($n = 6$)

				Years of Chronic Use	
Age (years)	**Weight (kgs)**	**Height (cms)**	**BMI (kg/m2)**	**Opioids**	**Cocaine**
$\bar{x}$ 31.00	77.44	183.34	23.67	13.00	8.83
SE 3.95	3.79	7.39	1.86	3.90	3.31

	Occasional Cocaine Users ($n = 6$)			
Age (years)	**Weight (kgs)**	**Height (cms)**	**BMI (kg/m2)**	**Occasional Cocaine Use**
$\bar{x}$ 29.83	81.06	182.88	24.50	5-10x (during past year)
SE 4.62	8.04	5.56	1.97	

subjects. Blood samples for determination of plasma cocaine levels and adrenocorticotropic hormone (ACTH) were obtained at baseline and at +5, +15, +30, +45, +60, +90 and +120 min after intravenous cocaine injection. All plasma samples for cocaine and ACTH analyses were obtained from an intravenous catheter in the arm opposite the arm into which cocaine was intravenously injected.

Cocaine Hydrochloride and Placebo Preparation. Cocaine hydrochloride was acquired from the National Institute of Drug Abuse in powder form and was dissolved in sterile water for intravenous injection. Sterility was ensured by passing the solution through a 0.22-micron millipore filter and subjecting it to a Limulus Amebocyte Lysate (LAL) test for detection of gram negative bacterial endotoxins. The test kit was manufactured by Whittaker Bioproducts (Walkersville, MD). Commercial preparation of 0.9% saline (1 ml) in sterile vials was used as the placebo challenge.

ACTH Radioimmunoassay Procedures. Plasma ACTH concentrations were measured in duplicate using an immunoradiometric assay (IRMA) kit purchased from Nichols Institute Diagnostics (Allegro, CA). The assay sensitivity was 0.15 pmol/L and the intra- and interassay coefficients of variance were 2.9% and 8.2%, respectively.

Plasma Cocaine Analysis. Plasma cocaine levels were measured in duplicate using a liquid/liquid extraction method described by Jacob (Jacob et al. 1987) with a Hewlet-Packard Model 5890A gas chromatograph equipped with a capillary column and a Nitrogen-Phosphorous detector. The assay sensitivity was 6.5 ng/ml and the intra-assay coefficient of variance was 2.2%.

Data Analysis. Subjective responses were analyzed with a one-way analysis of variance (ANOVA). Plasma ACTH and cocaine values for subjects were analyzed using a 2 (group) × 8 (time) repeated measures ANOVA. If significant main effects were detected, one-way ANOVAs were performed to identify the times at which groups significantly differed. Heart rate, systolic blood pressure, and diastolic blood pressure were evaluated by similar procedures. Cocaine pharmacokinetics were analyzed with a pharmacologic calculation system based upon the *Manual of Pharmacologic Calculations with Computer Programs*, 2nd ed. (Tallarida and Murray 1991), using PHARM/PCS Version 4.2, MicroComputer Specialists (MCS), Philadelphia, PA 19106.

RESULTS

Plasma cocaine levels in the cocaine-and opiate-dependent men and the occasional cocaine users are shown in Figure 1. Peak plasma cocaine levels exceeded 200 ng/ml in both groups. Cocaine pharmacokinetics are presented in Table 2. There were no significant differences in plasma cocaine levels in the cocaine-opiate–dependent men and occasional users at any time.

ACTH levels before and after placebo and cocaine administration are shown in Figure 2. There were no significant differences in baseline plasma ACTH levels before intravenous placebo or cocaine administration. There were no significant placebo-induced changes in ACTH levels. ACTH levels in the cocaine- and opiate-dependent men were significantly lower than in occasional cocaine users ($p < .0113$) at time points 5, 15, 30, 45, and 120 min after intravenous cocaine administration.

Cardiovascular effects of cocaine and placebo administration (heart rate, systolic blood pressure, and diastolic blood pressure) in the cocaine- and opiate-dependent

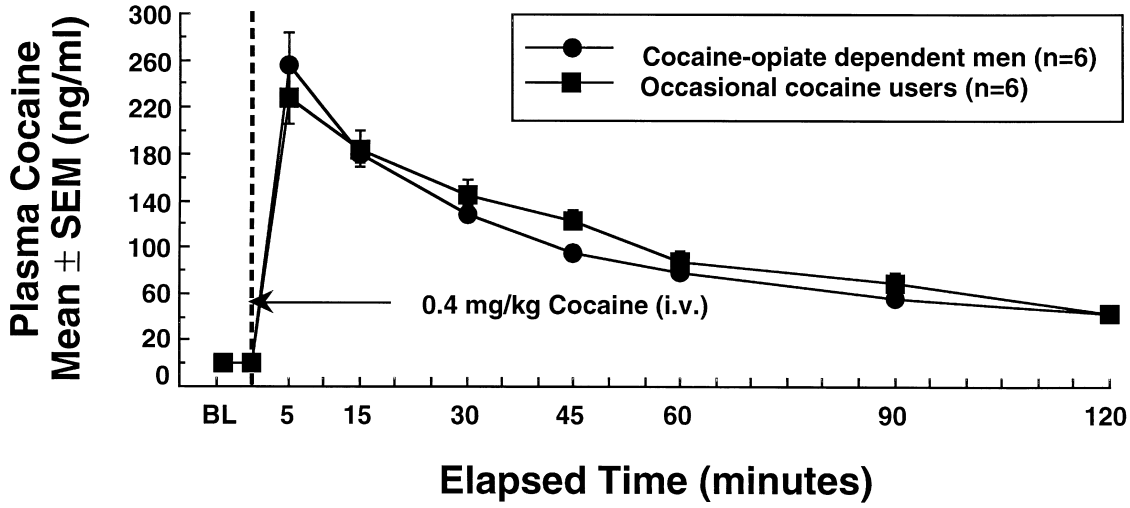

Figure 1. Plasma cocaine concentration for cocaine-opiate dependent men and occasional cocaine users after intravenous administration of 0.4 mg/kg cocaine (BL- = precocaine baseline).

Table 2. Cocaine Pharmacokinetics

	Occasional Users	Dependent Users
tmax=	5.00 min	5.00 min
cmax=	229.50 ± 21.69 ng/ml	254.67 ± 27.68 ng/ml
t 1/2=	49.93 ± 3.60 min	46.99 ± 2.58 min
AUC=	12692 ± 929 ng·min/ml	11559 ± 430.33 ng·min/ml

men and the occasional cocaine users are shown in Figure 3. There were no significant changes in heart rate and blood pressure after intravenous placebo in either group. Cocaine-induced increases in heart rate, systolic blood pressure, and diastolic blood pressure were significantly greater in the occasional cocaine users than in the cocaine- and opiate-dependent men ($p < 0.05$).

Subjective responses of the cocaine- and opiate-dependent men and the occasional cocaine users at 5 min after completion of intravenous placebo and cocaine administration are shown in Figure 4. No statistically significant changes were reported after intravenous placebo in either group. Occasional cocaine users reported a significantly greater perception of "high" ($p = .03$) as well as significantly greater euphoria ($p < .0001$) 5 min after cocaine administration.

DISCUSSION

There is considerable clinical evidence that people who abuse or who are dependent upon cocaine "report requiring more cocaine over time to obtain euphoria, i.e., tolerance" (O'Brien 1996). However, the current study is the first controlled assessment of persistent behavioral, cardiovascular, and neuroendocrine tolerance for cocaine during a period of cocaine abstinence. Cocaine-induced increases in ACTH, cardiovascular, and subjective effect measures were significantly greater in the occasional cocaine users than in the cocaine-dependent men. These differences occurred even though peak plasma cocaine levels, and the rate of decrement in plasma cocaine levels after intravenous drug administration did not differ significantly between the two groups. The computed half-life of cocaine levels in plasma in both the occasional cocaine users (49 ± 3 min) and the cocaine-dependent men (46 ± 2.5 min) was virtually identical to data (48 ± 13 min) reported by Chow and coworkers (Chow et al. 1985). Subjects who participated in the research carried out by Chow and co-workers (Chow et al. 1985) were four men and one woman who reported cocaine use at least one time per week for 2 months before the study. The cocaine-dependent men described in this report had been drug-free for 9 days after admission to the clinical research ward and before administration of the cocaine challenge dose. These data further suggest that prolonged cocaine exposure may be associated with persistent alterations in physiologic and subjective responses to cocaine without significant changes in cocaine pharmacokinetics. These data suggest that cocaine may induce prolonged neurobiologic changes in chronic users.

The occasional cocaine users were also drug-free prior to the study, and this was verified by urine drug screens. Consequently it was unlikely that recent cocaine use could account for an enhanced responsivity to cocaine's physiologic and behavioral effects in these men. Sensitization to cocaine's effects has been reported in experimental animal studies after administration of cocaine and other stimulants (Cunningham et al. 1992;

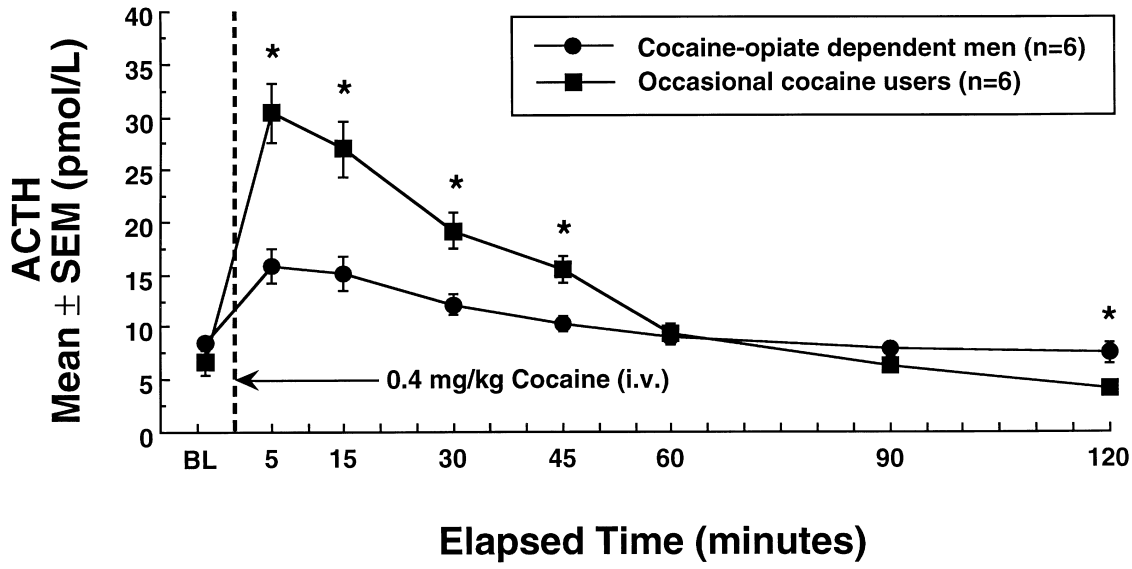

Figure 2. Plasma ACTH levels before (BL = precocaine baseline) and after intravenous cocaine administration to cocaine-opiate–dependent men and occasional cocaine users.

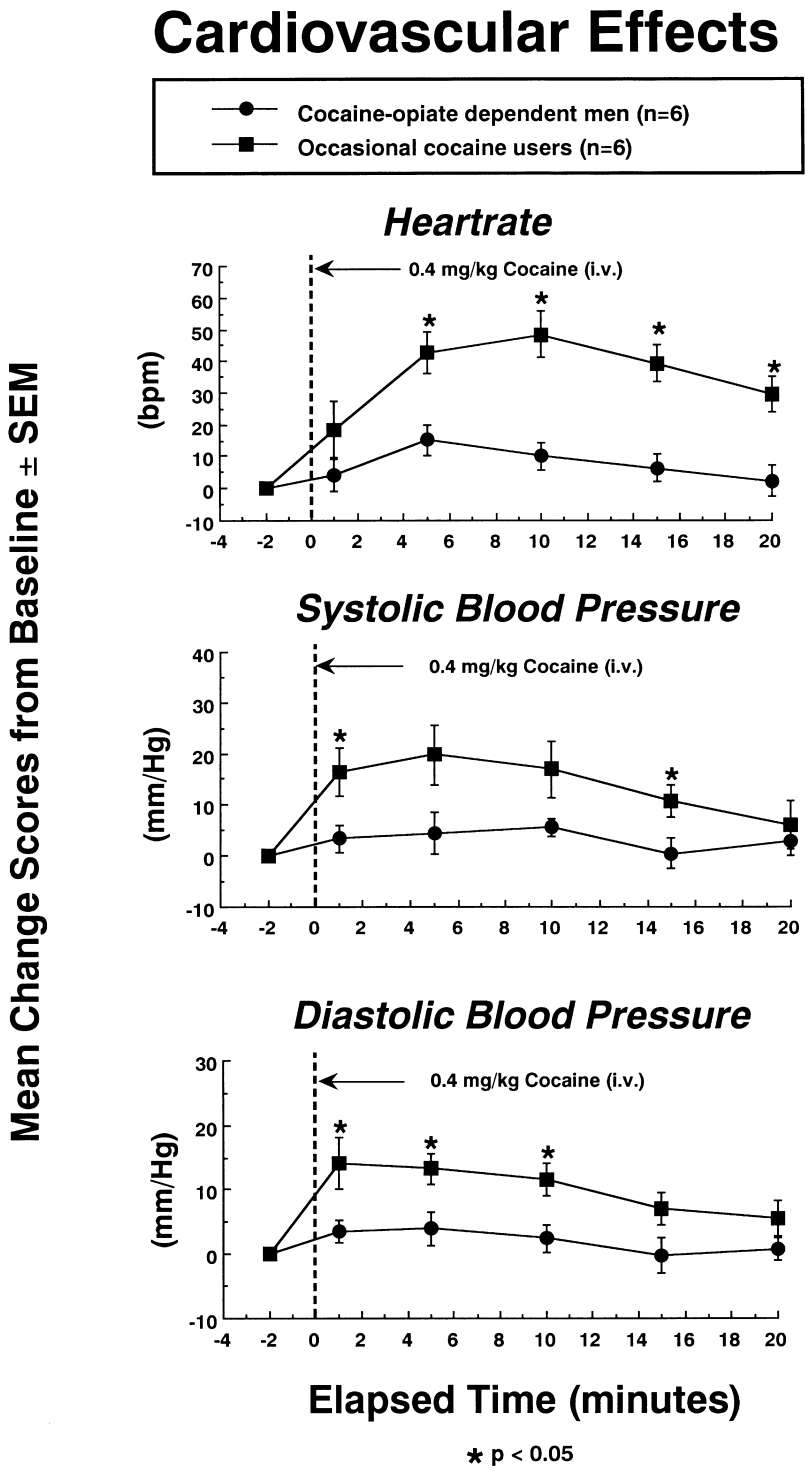

Figure 3. Heart rate, systolic blood pressure, and diastolic blood pressure before and after intravenous administration of cocaine to cocaine-opiate–dependent men and occasional cocaine users.

Kalivas et al. 1992; Post and Weiss 1988; Post et al. 1988; Stripling and Ellinwood 1977; Unterwald et al. 1994; Zahniser et al. 1988), but sensitization to drug-induced euphoria or cardiovascular responsivity has not been observed in humans (O'Brien 1996). Because our occasional cocaine users reported using cocaine quite infrequently, it is unlikely that an antecedent cocaine-induced sensitization could explain the results obtained. Ethical and medical considerations precluded administration of intravenous cocaine to drug-naive individuals.

Cocaine and Opiate Interactions

It is also possible that the preexisting condition of dual dependence on both opioids and cocaine contributed to the results observed. There is considerable clinical evi-

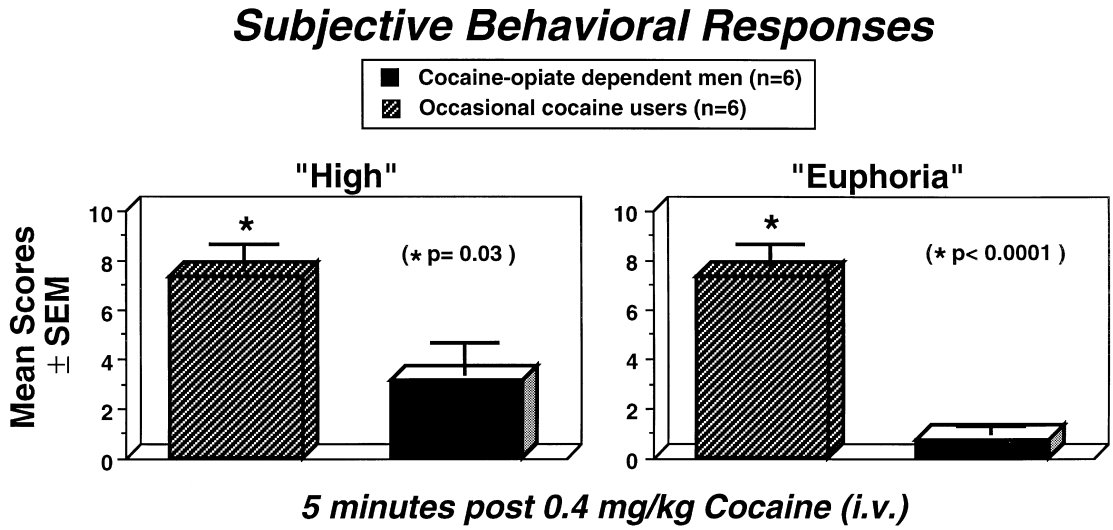

Figure 4. Subjective responses, "high" and "euphoria," 5 min after intravenous cocaine administration to cocaine-opiate–dependent men and occasional cocaine users.

dence that cocaine dependence is often associated with concurrent opiate abuse and dependence (Condelli et al 1991; Gastfriend et al. 1993; Kosten et al. 1989, 1987; Schottenfeld et al. 1993). Moreover, controlled clinical studies report that methadone maintenance may enhance the subjective effects of cocaine in experienced users under some conditions (Foltin et al. 1995; Preston et al. 1996). Although opiate dependence in a drug-free individual (as in the present study) and concurrent maintenance on an opiate (as in the studies by Foltin et al. 1995; Preston et al. 1996) are not equivalent conditions, these clinical data are more consistent with the possibility that opioid exposure may increase, rather than decrease, the acute effects of cocaine. Preclinical studies often indicate that opiates increase, rather than decrease, the effects of cocaine on some behavioral endpoints. For example, pretreatment with mu receptor selective opioids potentiated cocaine's discriminative stimulus effects in squirrel monkeys (Spealman and Bergman 1992, 1994). Similarly, in rhesus monkeys, pretreatment with the mu opioid agonist fentanyl and morphine increased cocaine's discriminative stimulus effects in some monkeys (Negus et al., in press).

Experimental studies in rodents have demonstrated that opiate administration may induce locomotor sensitization after administration of cocaine or amphetamines (DuMars et al. 1988; Kalivas 1985; Vezina et al. 1989; Vezina and Stewart 1990). In addition, opiate administration before cocaine administration may facilitate rather than inhibit cocaine-conditioned place preferences (Bilsky et al. 1992) and conditioned reinforcement (Cunningham and Kelley 1992). One important mechanisms underlying opiate-cocaine cross sensitization may be related to the effects of both drugs on the cyclic adenosine monophosphate AMP system (Cunningham et al. 1997). Because men who were concurrently dependent upon heroin and cocaine had significantly *lower* cardiovascular and neuroendocrine responses to intravenous cocaine administration than the occasional cocaine users, opiate-induced sensitization to cocaine effects is unlikely to account for the different responses observed in the current study. The significant differences in cocaine-induced increments in plasma ACTH levels in occasional cocaine users and cocaine-dependent men were paralleled by statistically significantly greater increments in heart rate and diastolic blood pressure and the perception of "high" and "euphoria" in the occasional cocaine users than in cocaine and opiate-dependent men.

Cocaine and ACTH Interactions

It has been postulated that cocaine-related stimulation of corticotrophin releasing factor (CRF) may be one mechanism underlying the reinforcing properties of cocaine in experimental animals and humans (Borowsky and Kuhn 1991b; Calogero et al. 1989; Levy et al. 1991; Mendelson et al. 1992a,b; Moldow and Fischman 1987; Rivier and Vale 1987; Sarnyai et al. 1992; Teoh et al. 1994; Vescovi et al. 1992). Several studies that have assessed sensitization and tolerance associated with chronic cocaine administration to rodents did not reveal any significant degree of tolerance for cocaine-induced stimulation of ACTH. Borowsky and Kuhn found no changes in cocaine-stimulation of ACTH after 3 and 7 days of chronic cocaine administration to rats (Borowsky and Kuhn 1991a). Levy et al. (1992) also did not observe any changes in ACTH stimulation after cocaine administration for 14 days. The differences observed in this study between occasional cocaine users and men with

concurrent cocaine and opiate dependence and data obtained with rodents may reflect species differences. However, the cocaine-dependent men who participated in this study reported a very long duration (mean 8.83 years) of heavy cocaine use. It is possible that chronic cocaine administration for up to 14 days may not be long enough to result in tolerance for cocaine-induced ACTH stimulation in rodents.

There is evidence that synthetic CRF administration has a number of cocaine-like effects, including induction of stereotyped behaviors and increased locomotor activity (Dunn and Berridge 1990). Recent studies have demonstrated that some cocaine-induced changes in the behavior of rodents can be modulated by blockade of corticosterone secretion (Marinelli et al. 1997). Moreover, adrenalectomy completely eliminated cocaine self-administration in rats (Goeders and Guerin 1996), a finding consistent with the notion that ACTH (and by inference CRF) may be important for cocaine's reinforcing effects. We have previously observed that maintenance on buprenorphine, an opioid mixed agonist-antagonist, suppressed both cocaine-induced euphoria and ACTH secretion in humans (Mendelson et al. 1992a). Buprenorphine also reduced cocaine self-administration by rhesus monkeys (Mello and Mendelson 1993, 1995; Mello et al. 1989, 1990). The current observations that cocaine induces greater increments in ACTH secretion and greater behavioral and cardiovascular responses in occasional cocaine users than in men with a past history of cocaine and heroin dependence suggests that there is a relationship between neuroendocrine, cardiovascular, and behavioral tolerance for cocaine in humans.

ACKNOWLEDGMENTS

This research was supported in part by grants DA 04059, DA 06116, DA 00064, and DA 00101 from the National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD. We are grateful to Gloria Yong Hong Cheng and Howard Gelles for analysis of plasma cocaine and ACTH samples. The six cocaine- and opiate-dependent men described in the present report were selected from a larger sample of 20 men to match characteristics of the occasional cocaine users. Group data for the 20 cocaine- and opiate-dependent men were previously reported in Teoh et al. (1993).

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