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Intravenous cocaine increases plasma epinephrine and norepinephrine in humans

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Abstract

Cocaine has been shown to activate the sympathoadrenal system in both animal and human studies. Controlled human studies have found inconclusive results regarding whether acute cocaine treatment elevates plasma epinephrine and norepinephrine concentrations. The purpose of this study was to investigate whether commonly abused doses of cocaine increase plasma epinephrine and norepinephrine concentrations in humans, in a double-blind, placebo-controlled study. Five male cocaine users were given an intravenous injection of 0.46 mg/kg dose of cocaine or placebo, on two consecutive days. Plasma epinephrine and norepinephrine concentrations were significantly increased in response to cocaine injection compared to placebo. Peak plasma epinephrine and norepinephrine concentrations were reached 3 and 12 min after cocaine injection, respectively. While changes in epinephrine levels following cocaine were correlated with systolic blood pressure and heart rate changes, changes in plasma norepinephrine were correlated with diastolic blood pressure and heart rate changes following cocaine administration. These results suggest that plasma epinephrine and norepinephrine can be used as a measure for cocaine induced sympathoadrenal system activation.

Keywords: Cocaine; Epinephrine; Norepineprine; Catecholamines

1. Introduction

Cocaine activates the noradrenergic system, which consist of the central noradrenergic system and its peripheral counterpart, the sympathoadrenal system. Noradrenergic system activation may mediate some of the diverse cardiovascular, endocrine and psychoactive effects of cocaine (Mello and Mendelson, 1997). In animal studies, activation of the central noradrenergic and sympathoadrenal system by cocaine is well documented (Chiueh and Kopin, 1978; Kiritsy-Roy et al., 1990; Schwartz et al., 1998). In contrast, few human studies have been conducted on the noradrenergic system activation in response to cocaine. In a recent study, intranasal cocaine administration in cocaine-naïve humans increased skin sympathetic nerve activity suggesting noradrenergic system activation by cocaine, possibly by central mechanisms (Vongpatanasin et al., 1999). On the other hand, in controlled studies, using plasma norepinephrine as a measure of sympathetic system activity, cocaine administration did not increase the plasma norepinephrine concentrations (Jacobsen et al., 1997; Sherer, 1988). Considering the potential role of plasma catecholamines as a readily available measure of sympathoadrenal system activity, we decided to revisit the question of whether commonly used cocaine doses increase plasma epinephrine and norepinephrine levels in humans. Since both epinephrine and norepinephrine have significant effects on the cardiovascular system, the relationship between cocaine-induced blood pressure and heart rate changes and changes in plasma epinephrine and norepinephrine levels was also investigated.

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2. Method

2.1. Subjects

Six subjects were enrolled in the study, data from one subject was excluded from the analyses because of a technical error during the sample collection on the first experimental day. The remaining subjects were five male crack-cocaine users, four White and one African American. The average (S.D.) age was 36.3 (7.4) years and duration of cocaine use was 14.0 (5.1) years. Drug use was confirmed with urine analysis before study participation. Other drugs used within the past month were cigarettes ($n=4$), alcohol ($n=4$) and marijuana ($n=3$). Subjects had normal physical, laboratory and psychiatric examinations and were not dependent on drugs other than cocaine and nicotine according to DSM-IV criteria (APA, 1994). In addition, daily users of drugs other than cocaine and nicotine were also excluded from the study irrespective of whether the use of that substance fulfilled criteria for abuse or dependence. Prior

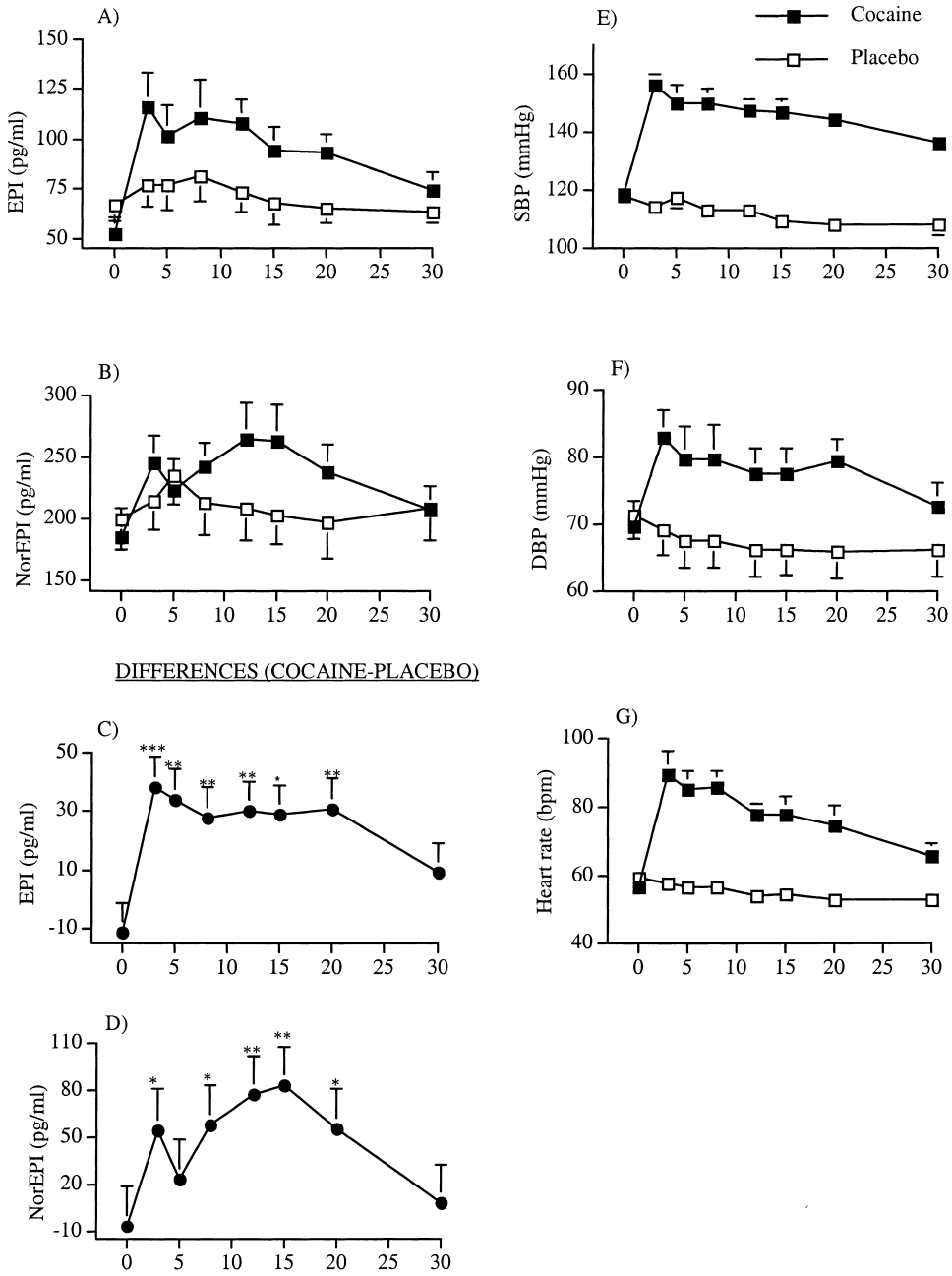

Fig. 1. The time course of the changes in the average (±S.E.) epinephrine (A), norepinephrine (B), systolic blood pressure (E), diastolic blood pressure (F) and heart rate (G), in response to intravenous cocaine, 0.46 mg/kg, or placebo, administered to five subjects on consecutive days. The time course (minutes) of the average (S.E.) of differences between cocaine and placebo treatment are shown for plasma epinephrine (C) and norepinephrine (D). $*P<.05$, $**P<.01$, $***P<.001$, cocaine compared to placebo treatment.

to their participation, subjects signed informed consent. These studies were approved by the Institutional Review Board of the University of Minnesota. Subjects were paid for their participation.

2.2. Study procedure

During the study, subjects were housed for 5 days at the General Clinical Research Center. Urine drug screening was obtained after admission to rule out any drug use that may interfere with the study protocol. Subjects were not permitted to smoke or eat after midnight on session days. Two experimental sessions were carried out on the third and fourth days, starting at 7 a.m. Two indwelling catheters were placed, one on the forearm and the other on the dorsum of the hand, for drug infusion and blood sampling, respectively. After the catheter placement, subjects had a 30-min rest period to recover from the stressful effects of this procedure. At 8 a.m., subjects received either a dose of 0.46 mg/kg (32 mg for a 70-kg individual) of cocaine or placebo. The order was balanced and randomized, so half of the subjects received cocaine on the third day and the other half received cocaine on the fourth day. This dose of cocaine has been safely administered and elicits physiological and subjective effects in humans (Foltin and Fischman, 1996). We used arterialized venous samples for catecholamine assays (Veith et al., 1984). To arterialize the venous blood, the hand of the subject that had the blood sampling catheter was kept in a warming box with a temperature of 50°C. This procedure diverts the blood from arterial to the venous circulation locally. The venous blood samples, obtained under this heating procedure, are called "arterialized" since they closely approximate the arterial samples for a variety of metabolites. Blood samples were drawn at -5, -3, 0, 3, 5, 8, 12, 15, 20 and 30 min in relation to cocaine or placebo infusion. Subjects were kept in a recumbent position during the session and remained in the laboratory until all vital signs returned to baseline levels.

Sterile solutions of cocaine hydrochloride and placebo were prepared by a research pharmacist at the University of Minnesota. Cocaine hydrochloride (0.46 mg/kg in a 5-cc volume of saline), was administered intravenously via an indwelling catheter over 60 s.

2.3. Biochemical analysis

Blood samples were drawn into chilled tubes on ice and were separated within 30 min. Plasma samples for catecholamine assays were stored at -80°C. Plasma catecholamines levels were measured by radioimmunoassay (Evans et al., 1978). The interassay and intraassay coefficient of variation for catecholamine assays were 4% and 8%, respectively.

2.4. Data analysis

Standard F tests for a main effect for the drug administered (cocaine vs. placebo) and for an interaction between drug and time of assessment from a repeated measures analysis were used to test for an effect of cocaine administration on the change in epinephrine and norepinephrine concentrations. If either test was significant ($P<.05$) then Bonferroni adjusted comparisons ($P<.0063$) of the average changes in concentration following cocaine and placebo administration were made at each assessment time.

Examination of the associations between change in epinephrine concentration and changes in cardiovascular measures used simple linear regressions of the changes in cardiovascular measures on the change in epinephrine after intravenous cocaine administration. Similar regressions examined the association between change in norepinephrine concentration and changes in cardiovascular measures. These analyses were expanded using random regressions that modeled the within-subject longitudinal nature of the data. The two sets of regressions yielded similar results. For simplicity, we present only the results of the simple regression models.

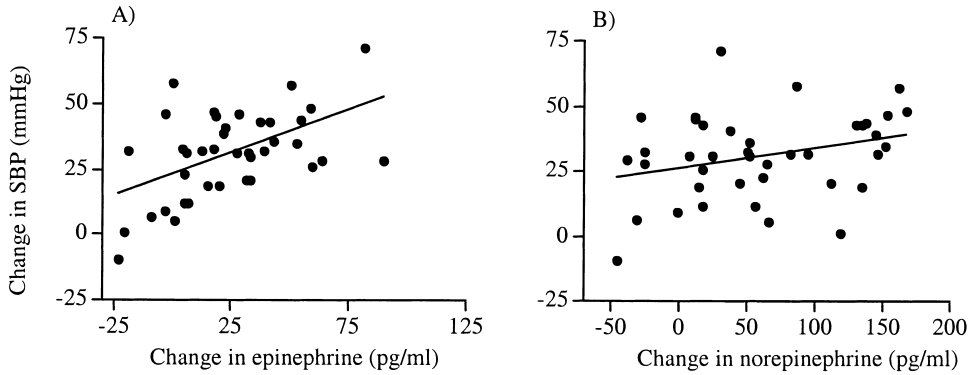

Fig 2. Relationship between the changes in systolic blood pressure and plasma epinephrine (A) and norepinephrine (B) levels. Each point represents the change from baseline in response to 0.46 mg/kg iv cocaine administration.

3. Results

The peak plasma concentrations after cocaine administration were reached at approximately 3 min for epinephrine and 12 min for norepinephrine (Fig. 1). The analysis of plasma epinephrine concentrations revealed a significant drug effect ($P<.001$) and a Drug × Time interaction ($P<.05$). Pairwise comparisons revealed significant differences between cocaine and placebo at 3, 5, 8, 12, 15 and 20 min ($P<.006$). Analysis of norepinephrine measurements revealed a significant drug effect ($P<.001$). There were significant differences between cocaine and placebo treatment groups at 12, 15 and 20 min ($P<.006$).

Regression analyses revealed significant correlations between the changes in plasma epinephrine and norepinephrine levels and blood pressure and heart rate changes (Fig. 2). Changes in plasma epinephrine levels were significantly correlated to systolic blood pressure (R^2=.37, $P<.0001$) and heart rate (R^2=.32, $P<.0001$) changes. Plasma norepinephrine levels were correlated to changes in diastolic blood pressure (R^2=.24, $P<.001$) and heart rate (R^2=.20, $P<.01$).

4. Discussion

In this study, intravenous administration of 0.46 mg/kg of cocaine increased plasma norepinephrine and epinephrine concentrations in male cocaine users, compared to placebo treatment. Epinephrine increased more than norepinephrine, consistent with previous reports. The mechanisms of plasma catecholamine response to cocaine may involve both peripheral catecholamine re-uptake inhibition and central sympathetic system stimulation. The dose of cocaine used in this study was 4 to 10 times smaller than doses of cocaine that increased plasma epinephrine and norepinephrine concentrations in animal studies (Kiritsy-Roy et al., 1990; Schwartz et al., 1988; Tella et al., 1993). These results suggest that the sympathoadrenal system is activated following single cocaine doses that are commonly abused by humans.

The previous human studies have shown either a decrease or no change in plasma norepinephrine in response to cocaine administration. This lack of an increase in plasma norepinephrine might be due to differences in the route of administration. Intravenous cocaine administration, by circumventing the absorption process, achieves faster and less variable plasma cocaine levels, compared to intranasal or oral administration. In addition, peak plasma cocaine levels reached following intravenous administration are higher than those achieved with similar doses given orally or intranasally (Favier et al., 1996; Jacobsen et al., 1997; Rowbotham et al., 1984). Another possibility is the differences in sampling for catecholamines: in this study, we used arterialized venous samples for catecholamine assays, compared to venous samples in the previous studies. Arterialized samples of catecholamines have been shown to closely approximate the arterial samples and provided a more accurate assessment of the sympathoadrenal activity than the venous samples (Halter et al., 1980; Liu et al., 1993). It would be interesting to compare the plasma catecholamine response to cocaine in humans by simultaneous venous and arterial sampling.

Similar to the results of previous animal studies, peak concentrations of epinephrine were reached earlier than norepinephrine (3 vs. 12 min). The reason for the earlier peak of epinephrine than for norepinephrine is unclear. The time course of the epinephrine and norepinephrine response may have important implications for the cocaine response in various organ systems including the cardiovascular effects. Epinephrine has been shown to increase heart rate and systolic blood pressure when its plasma concentrations reach 50–100 pg/ml range in humans (Clutter et al., 1980). Since similar epinephrine concentrations were reached in our study, it is likely that epinephrine contributed to the cocaine-associated increase in heart rate and systolic blood pressure. This conclusion was further supported by the significant correlations between changes in plasma epinephrine and changes in both systolic blood pressure and heart rate following cocaine administration. Changes in norepinephrine levels, on the other hand, were correlated with the diastolic blood pressure and to a lesser extent with heart rate increases following cocaine administration. This would be expected considering the vasoconstrictor effects of noradrenaline by the stimulation of the vascular alpha-adrenergic receptors. Following cocaine administration, heart rate and systolic pressure increased more than diastolic pressure suggesting that epinephrine may have a predominant effect in cardiovascular response to cocaine.

In a recent report (Mendelson et al., 1998), cocaine- and opiate-dependent men, compared to occasional users, showed lower blood pressure and heart rate response to intravenously administered cocaine suggesting tolerance development as a result of long-term cocaine use. In our study, the magnitude of the blood pressure and heart rate response to cocaine was similar to the occasional users' response in the Mendelson et al. study. A possible explanation for this discrepancy is that in contrast to the cocaine and opioid-dependent subjects of their study, none of our subjects were opioid users. Our small sample size in this study did not allow us to examine whether the increased duration of cocaine use was associated with attenuated blood pressure and heart rate response. However, we have recently observed that the frequency and amount of cocaine use within the past month predicted an attenuated cardiovascular response to smoked cocaine, suggesting tolerance development to the cardiovascular effects of cocaine (Sofuoglu et al., 2000) similar to the findings from the Mendelson et al. study.

There are several limitations of this study. First, we did not obtain subjective ratings of cocaine response. This would have made it possible to correlate the subjective effects with epinephrine and norepinephrine changes. How-

ever, we decided not to collect subjective data because (1) subjects had intravenous catheters on both arms, which limited their ability to use their hands, (2) responding to frequent questionnaires would potentially be distracting and stimulating, which could interfere with the study. Second, subjects were nicotine deprived for 8 h at the time of cocaine administration. Smoking deprivation may potentially affect the plasma catecholamine response to cocaine. The placebo group helps to address the smoking deprivation effect on catecholamine response. Third, the study sample size was small. In the planning phase, six subjects provided enough power to detect approximately 50% increase in plasma catecholamines from baseline, in response to cocaine. Our analysis of plasma catecholamines included only five subjects, less than initially planned. However, hormone and vital-sign changes were large and consistent enough to be highly significant. Future studies with a larger sample size and investigating the dose-related effects of cocaine on plasma catecholamines with different routes of administration may help to address these limitations.

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