

Cocaine-primed craving and its relationship to depressive symptomatology in individuals with cocaine dependence

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Several lines of evidence suggest a link between cocaine-primed craving and depressive symptomatology. The purpose of this study was to directly relate these two clinical phenomena. Thirty-three cocaine-dependent subjects were rated on the Hamilton Rating Scale for Depression (HRSD) at baseline and then administered an i.v. bolus of cocaine (0.2 mg/kg). Multiple regression analysis revealed that only the HRSD score was an independent predictor of cocaine-primed craving ($F = 4.09$; d.f. = 10,22; $r = 0.81$, $p < 0.003$) when baseline spontaneous craving during early withdrawal, age, gender, frequency of use, time since last use, monetary expenditure on cocaine and the Addiction Severity Index Drug Composite Scores were considered. These data support the hypothesis that depressive symptomatology affects cocaine-primed craving and that this relationship is relatively specific to symptoms defined by the HRSD and is not seen with a number of other clinical and demographic variables.

Key words: Addiction Severity Index, cocaine infusion, euphoria, Hamilton Rating Scale for Depression, high, multidimensional craving questionnaire, non-treatment seekers

Introduction

Relapse to cocaine use after some period of abstinence poses one of the most difficult challenges in the treatment of cocaine dependence (Simpson *et al.*, 1999). Clinical and laboratory experience suggest that even a low priming dose of the drug may trigger craving, which can contribute to the risk of relapse (Jaffe *et al.*, 1989; Fischman *et al.*, 1990; Gawin, 2001). Hence, finding clinical predictors of drug-primed craving may provide new leads for the development of therapeutic interventions aimed at curbing cocaine use (Ziedonis and Kosten, 1991a).

Depressive symptoms are considered a key component in cocaine withdrawal (Markou and Koob, 1991; American Psychiatric Association, 1994), and it is commonly hypothesized that dependence develops via negative reinforcement mechanisms (i.e. the drug is used to ameliorate the unpleasantness of the post-cocaine state) (Khantzian, 1985; Gawin and Kleber, 1986; Weiss *et al.*, 1992; Koob and Le Moal, 2001; Schmitz *et al.*, 2001). Recent work by Uslaner *et al.* (1999) reported a significant relationship between Beck Depression Inventory (BDI) scores and cocaine-induced high, leading to the adaptation of this idea in the form of a positive reinforcement hypothesis (i.e. that depressive symptomatology enhances cocaine use through amplification of its reinforcing properties).

Presently, no clinical studies directly link cocaine-primed craving and depressive symptomatology. Research on this topic is complicated by the heterogeneity of the clinical construct of

craving. The possibility that there may be distinct categories of drug craving is supported by human neuroimaging research implicating different neuroanatomical substrates for craving due to cocaine priming versus cue-induced or withdrawal-related craving (Hommel, 1999). However, the term craving can be operationally defined and measured as a monofocused motivational state increasing the probability of seeking and consuming the drug (Markou *et al.*, 1993; Breiter and Rosen, 1999).

An approach developed by our group to study drug-primed craving in humans involves the laboratory-based administration of a low dose of cocaine (Breiter *et al.*, 1997). This paradigm is advantageous for clinical studies because it is likely to produce a robust effect, whereas cues fail to elicit craving in 30–40% of subjects (Rohsenow *et al.*, 1990; Avants *et al.*, 1995; Wang *et al.*, 1999).

From a clinical perspective, several lines of evidence support the hypothesis that cocaine-primed craving and depressive symptomatology are two linked phenomena. First, pre-treatment of cocaine-dependent volunteers with desipramine diminishes cocaine craving after drug self-administration (Fischman *et al.*, 1990). Moreover, a depressive state predicts heavy cocaine consumption (Ziedonis and Kosten, 1991a; Schmitz *et al.*, 2000; Schmitz *et al.*, 2001) and poor prognosis with addiction psychosocial therapy alone, whereas the combination of psychosocial therapy with antidepressant pharmacotherapy is associated with reduction in both depressive symptoms and cocaine use (Ziedonis and Kosten, 1991a,b; Kosten *et al.*, 1998; Markou *et al.*, 1998).

The purpose of this study was to evaluate the relationship between depressive symptomatology and cocaine-primed craving. In addition, the relationship between baseline assessment of spontaneous craving during early withdrawal and later cocaine-primed craving was explored. We hypothesized that pre-infusion scores on the Hamilton Rating Scale for Depression (HRSD) would predict ratings of cocaine-primed craving.

Materials and methods

Thirty-three individuals (mean age \pm SD, 34.2 ± 6.0 years; weight 78.45 ± 14.75 kg; five females and 28 males; 23 Caucasian and 10 African-American; education 13.3 ± 1.5 years) meeting DSM-IV criteria for cocaine dependence were recruited by advertisement. The subjects were in good physical health (as evidenced by physical examination, electrocardiogram and screening blood work including β -human chorionic gonadotropin to rule out pregnancy) and had no past or current major depression or other Axis I psychiatric diagnosis besides alcohol and/or marijuana abuse.

The subjects were diagnosed by a research psychiatrist using a best estimate format utilizing all available sources of information, including clinical history, interview and structured clinical assessment instruments (e.g. Addiction Severity Index, ASI) (McLellan *et al.*, 1992), 27-item HRSD and the Structured Clinical Interview for DSM-IV. Women were studied at the midfollicular phase of their menstrual cycle. All subjects were active cocaine users (confirmed by urinalysis) and were not seeking or participating in addiction treatment. ASI Drug Composite Score was 0.22 ± 0.09 (range 0–1.00). They primarily smoked cocaine 13.2 ± 7.0 times in the month prior to study, with the last use being 1.7 ± 1.2 days prior to the study, spending $\text{US}\$288.8 \pm 272.0$ per week on the drug. Importantly, introduction of the intravenous route of cocaine administration used in this study did not appear to worsen clinical outcomes, as evidenced by our follow-up study (Elman *et al.*, 2001b). All subjects gave their written informed consent to the Massachusetts General Hospital Institutional Review Board-approved protocol.

The structured assessments were carried out on the day of the cocaine infusion. Depressive symptoms were assessed by total scores on the HRSD (mean score 8.3 ± 6.4), including its two superfactors (Faustman *et al.*, 1990): vegetative (sleep disturbance, diurnal variation, genital symptoms, hypochondriasis, weight loss, somatic anxiety, general and gastrointestinal somatic symptoms) and cognitive (suicidal ideations, guilt, psychic anxiety, insight, paranoia, depersonalization, work/activities, depressed mood, retardation and agitation).

Spontaneous craving during early withdrawal (pre-infusion) was assessed with a multidimensional questionnaire which has been shown to be a useful predictor of short-term cocaine use (Weiss *et al.*, 1995, 1997), measuring the following aspects of craving on a Likert-type scale (each item rated 0–9): (i) current intensity; (ii) desire to avoid using; (iii) capacity to resist using; (iv) responsiveness to drug-related conditioned stimuli; and (v) imagined likelihood of use if in a setting with access to drugs. The total craving score (mean score 17.6 ± 10.3) was achieved by adding together the ratings on items 1, 4 and 5 and subtracting those on items 2 and 3 (Elman *et al.*, 2001a).

At 09.00 h on the day of the study, subjects were admitted to the

clinical research unit, having refrained from cocaine for at least 10 h and completed medical workup and structured clinical assessments (i.e. ASI, HRSD and the multidimensional craving questionnaire). To avoid the confounding effects of nicotine withdrawal, nicotine intake prior to the study was not limited. At 17.00 h, the intravenous catheter was placed and, after a 60-min rest period, unblinded cocaine (0.2 mg/kg) was administered as an intravenous bolus. Cocaine craving was proactively defined with the subject, clinically as an urge to use the drug and operationally in terms of the action the individual wanted to engage in to get more cocaine; high was defined by feelings of well being and self-confidence (Breiter *et al.*, 1997). Continuous cardiac monitoring was performed throughout the course of the study. Computerized behavioural ratings for craving and high (Likert-type scale, range 0–3) were initiated 2 min pre-infusion and collected every 1 min until 20 min post-infusion (Breiter *et al.*, 1997).

Data were analysed using Statistica (StatSoft, Inc., Tulsa, OK, USA). The baseline score for cocaine-primed craving and high were determined from the mean of the self-reported ratings at 1 min and 2 min prior to cocaine administration. Cocaine-primed craving and high measures were quantified as the area under the curve (AUC, Uslander *et al.*, 1999) using the trapezoid rule.

To determine the effects of cocaine administration on the ordinal ratings of craving and high, Friedman's analysis of variance (ANOVA) was conducted. A one-way ANOVA was used for the continuous physiological variables (i.e. heart rate and mean arterial blood pressure). When the overall effect of time was significant, post-hoc Wilcoxon matched pairs signed ranks tests were used for nonparametric analyses and Newman-Keuls *t*-tests were used for parametric analyses to determine if, and at what times, the change from the pre-cocaine administration baseline was significant.

Multiple linear regression analysis was performed using a model in which the dependent variable was the AUC value for craving, with the following independent variables: HRSD scores, total scores on the baseline assessments of spontaneous craving during early withdrawal and the first measure in these assessments (current intensity), along with other demographic and clinical variables, including age, gender, frequency of cocaine use, time since last use, monetary expenditure on cocaine and the ASI Drug Composite Score. Both post-hoc and exploratory correlative analyses were conducted using Spearman coefficients. All analyses were two-tailed with $\alpha < 0.05$ set as the threshold for statistical significance.

Results

Cocaine produced significant increases in self-reported ratings for craving (chi squared = 76.1, d.f. = 20,32, $p < 0.00001$) and high (chi squared = 161.6, d.f. = 20,32, $p < 0.00001$, Fig. 1). Post-hoc Wilcoxon matched pairs signed ranks tests revealed that craving ratings were significant at the 3-min time point ($p = 0.03$), peaked at 6 min ($p = 0.00006$) after cocaine administration and were still elevated at the 20th and final time point ($p < 0.01$). High elevations were significant at the 2-min time point ($p = 0.00002$), reached their peak at the 3-min time point ($p = 0.000003$) and also persisted for the duration of the study ($p < 0.05$).

Heart rate and blood pressure were examined to characterize the response to cocaine.

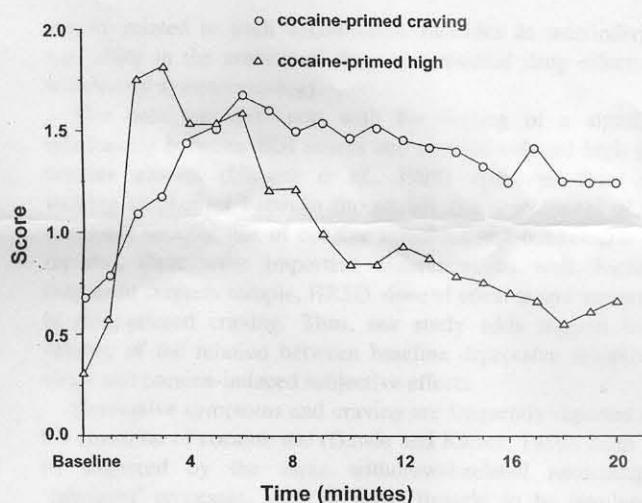


Figure 1 Effects of cocaine administration on behavioural ratings of craving and high in individuals with cocaine dependence ($n = 33$). Values represent means. Statistical differences were determined using the Friedman ANOVA with time as the within subjects factor and post-hoc Wilcoxon matched pairs tests. Significant effects of time were observed for both craving (chi squared = 76.1, d.f. = 20,32, $p < 0.00001$) and high (chi squared = 161.6, d.f. = 20,32, $p < 0.00001$)

Cocaine produced significant increases in heart rate ($F = 26.8$, d.f. = 20,32, $p < 0.00001$) and mean arterial blood pressure ($F = 7.2$, d.f. = 20,32, $p < 0.00001$). Both physiological responses were significant at the 2-min time point, peaked at the 6-min time point ($p = 0.00005$) and continued to be elevated ($p < 0.05$) through 20 min.

Multiple linear regression was used to determine whether the HRSD scores predict cocaine-primed craving. When baseline spontaneous craving during early withdrawal, baseline score for cocaine-primed craving, age, gender, frequency of use, time since last use, monetary expenditure on cocaine and the ASI Drug Composite Scores were considered, only the HRSD score was an independent predictor of cocaine-primed craving, accounting for approximately 64% of the variance ($F = 4.09$, d.f. = 10,22, $r = 0.81$, $p < 0.003$; Table 1). When regression was performed using only HRSD as a predictor, the effect was also significant ($F = 21.72$, d.f. = 1,31, $r = 0.64$, $p = 0.00006$) (Fig. 2).

Post-hoc analyses (using Spearman coefficients) detected significant correlation between HRSD vegetative ($r_s = 0.63$,

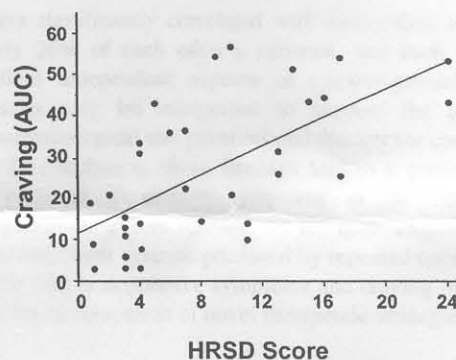


Figure 2 Regression relationship between Hamilton Rating Scale for Depression scores and area under the curve values for cocaine-primed craving ($n = 33$). When clinical/demographic variables were considered, only the HRSD score was an independent predictor of cocaine-primed craving ($F = 4.09$, d.f. = 10,22, $r = 0.81$, $p < 0.003$)

d.f. = 31, $p = 0.00009$) and cognitive ($r_s = 0.52$, d.f. = 31, $p = 0.002$) factors and cocaine-primed craving. The vegetative and cognitive factors were also correlated with one another ($r_s = 0.51$, d.f. = 31, $p = 0.002$). No significant relationship was observed in exploratory analysis between cocaine-primed craving and baseline spontaneous craving ($r_s = 0.22$, d.f. = 31, $p = 0.23$). Finally, similar to a previous report (Uslaner *et al.*, 1999), a correlation was observed between HRSD scores and AUC values for cocaine-primed high ($r_s = 0.40$, d.f. = 31, $p = 0.03$).

Discussion

Our results indicate that baseline HRSD scores predict self-rated craving after cocaine administration. The correlational nature of our results does not yet prove a direct depression–craving interaction. Further studies exploring the relationship of drug-primed craving to clinical indices of depression before and after antidepressant therapy may help to clarify this issue. Also, in this study, we produced a 100% expectancy condition for reward (Schultz *et al.*, 1997). Changing the motivational or expectancy contexts, such as matching a potential cocaine infusion to a potential saline infusion (50% expectancy) may have yielded different findings (Hommer, 1999). Additional methodological limitations that may affect the interpretation of our results are

Table 1 Results of multiple regression analysis of relationship between cocaine-primed craving and demographic/clinical variables ($n = 33$, r^2 for the model = 0.65)

Variable	Coefficient	t (22)	p
HRSD score	0.53	3.34	0.003
Craving questionnaire			
Total score	-0.44	-1.53	0.14
Current intensity	0.46	1.61	0.12
Baseline score for cocaine-primed craving	0.26	1.69	0.10
Age	-0.21	-1.53	0.14
Gender	-0.15	-1.07	0.29
Frequency of use (days/month)	-0.14	-0.77	0.45
Last use (days)	0.05	0.31	0.76
Monetary expenditure (US\$/month)	0.04	0.3	0.76
ASI drug composite score	-0.09	-0.58	0.57

mainly related to such uncontrolled variables as interindividual variability in the amount of drug use, residual drug effects and withdrawal symptomatology.

Our data are consistent with the finding of a significant relationship between BDI scores and cocaine-induced high in 17 cocaine abusers (Uslaner *et al.*, 1999). Although there were striking similarities between the studies (i.e. enrollment of non-treatment seekers, use of cocaine infusions and behavioural self-reports), there were important differences as well, including outpatient subjects sample, HRSD, dose of cocaine and assessment of drug-primed craving. Thus, our study adds support to the validity of the relation between baseline depressive symptomatology and cocaine-induced subjective effects.

Depressive symptoms and craving are frequently reported after the cessation of cocaine use (Gawin and Kleber, 1986). Both may be triggered by the same withdrawal-related neuroadaptive 'opponent' processes, such as those thought to be involved in hypofunctionality of the brain reward systems (Gardner, 1999). In this study, we captured an independent state of cocaine craving triggered by the drug itself and theoretically mediated via 'proponent' neural processes. Our finding of no association between cocaine-primed craving and baseline assessments of spontaneous craving during early withdrawal suggests that different neurobehavioural mechanisms may be involved in various types of craving (Hommer, 1999; Kilts *et al.*, 2001) and demonstrates the heuristic value of subtyping craving according to the technique used to provoke it.

The association between depressive symptoms and drug-primed craving raises interest in antidepressant medications as a therapeutic option for cocaine dependence. Indeed, an early double-blind, placebo-controlled study found a substantial decrease in cocaine use in desipramine-treated cocaine abusers (Gawin *et al.*, 1989). Later trials produced conflicting results, but some did report improved depressive symptomatology and reduction in cocaine use with antidepressant pharmacotherapy (Ziedonis and Kosten, 1991a,b; Arndt *et al.*, 1992; Carroll *et al.*, 1994; Carroll *et al.*, 1995; Nunes *et al.*, 1995).

The reasons for these mixed findings are unclear and may be related to the delayed onset of action and narrow therapeutic window of tricyclic antidepressants and/or heterogeneity of subject populations (i.e. varied degrees of addiction severity, treatment motivation and compliance, as well as comorbid psychopathology and other drug use). It is also possible that primary and secondary (to cocaine) depressive symptomatology are neurochemically distinct and may not respond similarly to pharmacotherapy (Markou *et al.*, 1998; Schmitz *et al.*, 2001). In recent studies, venlafaxine (McDowell *et al.*, 2000) and bupropion (Margolin *et al.*, 1995), which are both third generation antidepressants affecting a wider range of neurotransmitters than their predecessors, improved not only depressive symptoms, but also reduced cocaine use in depressed individuals. These observations suggest that treatment of cocaine dependence may require complex neurochemical effects.

The significant relationship between vegetative and cognitive HRSD superfactors and cocaine-primed craving is further consistent with preclinical (Koob and Le Moal, 2001) and clinical (Weinstein *et al.*, 1998) studies showing that craving is a mixed motivational state, with both physiological and psychological manifestations. Even though the vegetative and cognitive scores

were significantly correlated with each other, scores account for only 26% of each other's variance, and each factor appears to reflect independent aspects of cocaine-primed craving. These results may be interpreted to support the use of integrated pharmacological and psychosocial therapy for cocaine dependence.

In conclusion, these findings add to a growing body of data implicating depressive symptoms in the course of cocaine dependence. Future research on the neuroadaptations in the brain reinforcement systems produced by repeated cocaine exposure and their role in depressive symptoms and craving may point the way for the development of novel therapeutic strategies for this disease.

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