ORIGINAL ARTICLE

Stress-Induced Cocaine Craving and Hypothalamic-Pituitary-Adrenal Responses Are Predictive of Cocaine Relapse Outcomes

Rajita Sinha, PhD; Miguel Garcia, MS; Prashni Paliwal, PhD; Mary Jeanne Kreek, MD; Bruce J. Rounsaville, MD

Background: Cocaine dependence is associated with high rates of relapse. Stress and drug cue exposure are known to increase cocaine craving and stress arousal, but the association between these responses and cocaine relapse has not been previously studied.

Objective: To examine whether stress-induced and drug cue–induced cocaine craving and hypothalamic-pituitary-adrenal axis responses evoked in the laboratory are associated with subsequent cocaine relapse.

Design: Prospective study design assessing cocaine relapse and drug use during a 90-day follow-up period after discharge from inpatient treatment and research. Data were analyzed by Cox proportional hazards regression and multiple regression.

Setting: Inpatient treatment and research unit in a community mental health center.

Patients: Forty-nine treatment-seeking cocaine-dependent individuals.

Main Outcome Measures: Time to cocaine relapse, number of days of cocaine use, and amount of cocaine used per occasion in the follow-up phase.

Results: Greater stress-induced, but not drug cue–induced, cocaine craving was associated with a shorter time to cocaine relapse. Stress-induced corticotropin and cortisol responses predicted higher amounts of cocaine use per occasion in the 90-day follow-up.

Conclusions: These results demonstrate that stress-related increases in cocaine craving and hypothalamic-pituitary-adrenal axis responses are each associated with specific cocaine relapse outcomes. The findings support the use of stress-induced drug craving and associated hypothalamic-pituitary-adrenal axis responses to evaluate cocaine relapse propensity. Furthermore, treatments that address stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses could be of benefit in improving relapse outcomes in cocaine dependence.

Arch Gen Psychiatry. 2006;63:324-331

COCAINE ADDICTION IS A chronic relapsing disorder of which the underlying mechanisms are not well understood.[1,2] Although significant strides have been made in the development of efficacious behavioral and pharmacologic treatments for cocaine addiction,[3-5] relapse rates in cocaine dependence remain high.[2,6,7] A better understanding of the mechanisms that increase relapse susceptibility could contribute to the development of more effective relapse prevention treatments in cocaine dependence.

Theoretical perspectives and clinical survey reports indicate that stress is a key factor that increases risk of relapse in cocaine dependence.[6,7] Drug use to escape from emotional distress or withdrawal-related distress (negative reinforcement models) and distress-related increases in incentive value or reinforcement threshold for the drug (incentive sensitization models) are commonly invoked to explain stress-related drug use.[8-11] Cocaine activates central and peripheral stress pathways, and both the extrahypothalamic and the hypothalamic corticotropin-releasing factor (CRF) systems are thought to be involved in cocaine reinforcement and relapse.[9,10] Increased levels of circulating glucocorticoids are associated with higher rates of psychostimulant self-administration.[11] Brain CRF and noradrenergic pathways are involved in stress-induced reinstatement of drug-seeking behavior in cocaine-experienced laboratory animals.[12] Furthermore, CRF antagonists, glucocorticoid antagonists, and α_2-adrenergic agonists are known to attenuate stress-induced drug self-administration and stress-induced reinstatement of cocaine-seeking behavior in dependent laboratory animals.[13,14] On the other hand, while several clinical studies document that stress and negative affect increase the risk of relapse,[15] no previous research, to our knowledge, has examined whether stress-related drug seeking or "craving" and its associated psychobiological responses increase relapse susceptibility.

Author Affiliations:
Department of Psychiatry, Yale University School of Medicine, New Haven, Conn (Drs Sinha, Paliwal, and Rounsaville and Mr Garcia); and Laboratory on the Biology of Addictive Diseases, Rockefeller University, New York, NY (Dr Kreek).

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/05/2016

On the basis of the aforementioned literature, we hypothesize that drug craving induced by stress imagery or by drug cue imagery and accompanying hypothalamic-pituitary-adrenal (HPA) axis activation (corticotropin and cortisol) in the laboratory will predict relapse outcomes in cocaine-dependent individuals. In previous laboratory research, our group has shown that imagery exposure to emotional stress and to drug cues increases drug craving and associated stress arousal in outpatient, treatment-engaged, cocaine-dependent individuals.[16] These findings were extended in the current inpatient treatment study design to examine whether stress-induced and drug cue–induced drug craving and HPA responses are predictive of cocaine relapse outcomes. Treatment-engaged, cocaine-dependent individuals, who participated in an inpatient laboratory study of imagery exposure to stress and to drug cues,[17] were followed up for 90 days after discharge from inpatient treatment of cocaine dependence to assess relapse outcomes. Findings from the laboratory study indicated that imagery exposures to stress and to drug cues each similarly increased drug craving and were accompanied by greater autonomic and HPA axis responses when compared with neutral imagery exposure in cocaine-addicted individuals.[17] On the basis of the proposed hypothesis, stress-induced and drug cue–induced cocaine craving and corticotropin and cortisol responses were the primary predictor variables examined for association with relapse outcomes. Because subjective anxiety and heart rate responses also showed differences between stress, drug cue, and neutral imagery exposure in the laboratory, these were included as secondary predictor variables in the relapse analyses.

METHODS

SUBJECTS

Men and women between the ages of 21 and 50 years (mean [SD] age, 37 [6.5] years) seeking inpatient treatment for cocaine dependence were examined for study participation. Fifty-four individuals (36 men and 18 women) who met *DSM-IV* criteria for current cocaine dependence were admitted to the Clinical Neuroscience Research Unit of the Connecticut Mental Health Center, New Haven, for 2 to 4 weeks of inpatient treatment and participation in 3 laboratory sessions. All subjects were invited for a face-to-face follow-up interview and urine toxicology screen to prospectively assess relapse and subsequent drug use 90 days after inpatient treatment and discharge. Forty-nine (91%) of the 54 subjects who completed the laboratory study[17] were successfully followed up for 90 days. Thus, the data analysis for the current study is based on the follow-up sample of 49 cocaine-dependent individuals.

All subjects reported regular weekly cocaine abuse that was documented by positive urine toxicology screens on study enrollment. Individuals who met current *DSM-IV* criteria for dependence on another psychoactive substance other than alcohol and nicotine were excluded. In addition, individuals taking medications for medical or psychiatric problems and those in need of alcohol detoxification were excluded from the study. All subjects underwent a complete medical evaluation, including electrocardiography and laboratory tests of renal, hepatic, pancreatic, hematopoietic, and thyroid functions, to ensure good physical health. The study procedures were approved by the Human Investigation Committee of the Yale University School of Medicine, New Haven, Conn, and all subjects signed a written informed consent.

PROCEDURES

The Clinical Neuroscience Research Unit is a locked inpatient treatment research facility with no access to alcohol or drugs and limited access to visitors. Drug testing is conducted regularly to ensure continued abstinence. All subjects admitted into the study also participated in specialized substance abuse treatment that included weekly individual therapy provided by the psychiatry residents on the Clinical Neuroscience Research Unit and twice-weekly group drug counseling[18] provided by an addictions specialist. The group drug treatment was part of the inpatient treatment program that was initiated on admission and included additional group programming from 9 AM to 3:30 PM that covered daily life skills and other structured activities.

During the first week of the inpatient stay, subjects underwent an initial medical evaluation and were interviewed by means of the Structured Clinical Interview for *DSM-IV*[19] to assess psychiatric and substance abuse diagnoses. Baseline demographic characteristics and drug use history were also assessed. In the second week of the inpatient stay, subjects participated in an imagery script development session during which they were asked to identify a highly stressful event from their own lives (rated by the subject as ≥8 on a 10-point Likert scale for stressfulness); a personal drug cue–related event that involved people, place, and objects related to cocaine use; and a personal neutral relaxing event. Examples of commonly reported stressful situations included breakup with a significant other, a verbal argument with a significant other or family member, or unemployment-related stress, such as being fired or laid off from work. Commonly reported drug cue situations were being paid and using crack; buying cocaine; meeting up with a drug-using buddy and buying crack; and being at a bar and watching others drink and use drugs. Examples of neutral relaxing situations included a summer afternoon at the beach, a fall day at the park, and taking a bubble bath. (Sample scripts and script development procedures may be obtained by contacting one of us [R.S.].) Stimulus and response details for each event were elicited by means of scene construction questionnaires[20,21] (see full description in Sinha et al[17]). A "script" or description of each of the 3 situations was developed for use in the laboratory sessions. The scripts were then audiotaped in random order for guided imagery presentation in the laboratory sessions.

LABORATORY SESSIONS

In the third week, subjects participated in a habituation and imagery training session (see Sinha et al[17] for details) followed by 3 laboratory sessions on consecutive days. Subjects were exposed to a stress, drug cue, or neutral script for guided imagery during the laboratory session; only 1 imagery condition was presented per day of laboratory testing, and the order of imagery conditions was randomized across subjects. On each day of the laboratory session, subjects abstained from breakfast and were brought into the testing room at 8:15 AM by the research nurse. After the subject settled into a sitting position in a hospital bed, a heparin-treated catheter was inserted by the research nurse in the antecubital region of the subject's nonpreferred arm, to periodically obtain blood samples. A blood pressure cuff was placed on the subject's preferred arm to monitor blood pressure, and a pulse sensor was placed on the subject's forefinger to obtain a measure of pulse. This was followed by a 1-hour adaptation period during which the subjects were instructed to practice relaxation. At 9:30 AM, subjects were provided headphones and the audiotape was played. The tape provided instructions for the imagery procedure and was followed by a description of the script for the session. The subject's task was to imagine the situation being described, as if it

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/05/2016

Table 1. Baseline, Peak Change, and Average Response During Laboratory Exposure to Stress and to Drug Cues

Predictor Variables	Mean (SD) (n = 49) Baseline	Peak Change	Average Response
Stress Exposure			
Cocaine craving*	0.6 (1.4)	2.4 (2.4)	1.4 (1.7)
Anxiety*	1.3 (2.1)	3.7 (2.9)	2.2 (1.9)
Heart rate, beats/min	66.1 (9.8)	6.0 (5.6)†	1.0 (4.1)†
Corticotropin, pg/mL	21.9 (12.2)	6.4 (8.9)†	−0.3 (6.4)†
Cortisol, μg/dL	10.9 (3.4)	1.1 (2.7)†	−1.1 (2.3)†
Drug Cue Exposure			
Cocaine craving*	0.6 (1.2)	3.7 (2.9)	1.6 (1.8)
Anxiety*	1.3 (1.7)	2.4 (2.3)	1.8 (1.8)
Heart rate, beats/min	65.4 (9.0)	6.7 (7.5)†	1.5 (4.2)†
Corticotropin, pg/mL	22.9 (14.4)	6.7 (9.2)†	−0.1 (5.7)†
Cortisol, μg/dL	11.3 (2.8)	0.5 (3.1)†	−1.6 (2.5)†

SI conversion factors: To convert corticotropin to picomoles per liter, multiply by 0.22; cortisol to nanomoles per liter, multiply by 27.59.

*Subjective ratings based on 10-point visual analog scales. Average responses for these measures include mean of baseline, image, and recovery time points.

†Represents average change from baseline across 6 repeated assessments during 75 minutes after imagery exposure. Also, because laboratory sessions occurred in the morning, the natural diurnal drop in morning hypothalamic-pituitary-adrenal axis responses influenced the average responses in corticotropin and cortisol across the repeated sampling during the 75-minute recovery period.

were happening at that time. The length of each taped script was approximately 4.5 minutes, with a total imagery period of 5 minutes. A complete description of laboratory procedures is provided by Sinha et al.[17]

LABORATORY MEASURES

Cocaine craving was assessed by means of a 10-point visual analog scale that measured responses to the item "desire for using cocaine at this moment." Subjective anxiety was measured on a 10-point visual analog scale in response to the item "how jittery, tense, and anxious do you feel at this moment?" Heart rate was measured with an electronic blood pressure monitor (model SD-700; IBS Corp, Waltham, Mass), and plasma samples for corticotropin and cortisol assessments were processed at the Kreek Laboratories at Rockefeller University, New York, NY, by standard radioimmunoassay procedures. All laboratory responses were assessed at baseline (5 minutes before imagery; −5 time point), during (for heart rate) or immediately after imagery (0 time point), and at repeated recovery time points every 15 minutes (+15, +30, +45, +60, and +75 time points) after imagery. To assess the association between these evoked responses and relapse outcomes, a single averaged measure across all time points for each response variable was computed. An averaged score rather than peak scores was selected for use in the relapse analysis to include the individual variation during the recovery time points after exposure to stress and drug cue imagery in the current analyses. In particular, we previously reported slow return to baseline during the laboratory sessions for craving and anxiety measures and little recovery in the corticotropin response during the 75 minutes after imagery exposure in this sample of subjects.[17] Such slow return to baseline could contribute to relapse susceptibility, and hence averaged response measures were used in the current analyses. Because cocaine craving and anxiety were measured by means of the 0 to 10 ordinal scale, the average response for these measures included baseline levels and the 6 postimagery time points. However, as physiologic (heart rate) and HPA axis (corticotropin and cortisol) measures vary considerably across subjects and within subjects across days of testing, an average of the change from baseline response for each of the 6 postimagery time points was computed to obtain a single measure of stress response for each of the stress and the drug cue imagery conditions. A summary of the baseline and average responses (craving and anxiety) and change from baseline responses (heart rate, corticotropin, and cortisol measures) for the stress and the drug cue conditions is presented in **Table 1**. Peak change from baseline is also provided in Table 1 as a validation check of the laboratory-based manipulation of stress and drug cue imagery exposure.

ASSESSMENT OF COCAINE RELAPSE AT 90 DAYS AFTER INPATIENT TREATMENT

All participants were given an appointment for a follow-up interview at 90 days after discharge from the inpatient unit. Reminders were sent in the month of the appointment. Cocaine use during baseline (90 days before inpatient treatment) and during follow-up (90 days after discharge from inpatient treatment) was assessed by means of the Substance Use Calendar,[22] an instrument that has been validated in drug-abusing samples[23] and widely used in assessing cocaine use outcomes in previous treatment studies.[4,5,24] Urine and breath alcohol samples were also obtained at the 90-day follow-up appointment.

To capture both initial lapse (any use) and relapse or return to regular patterns of drug use,[25] relapse was examined both as a dichotomous variable (no use [success] vs any use [failure]) and as continuous measures of drug use (eg, number of days of use and amounts of use per occasion) in the 90-day follow-up period. The following cocaine use measures were computed from the follow-up substance use calendar and the urine screen and used for the relapse analysis: (1) *time to relapse*, the interval to the first day of any cocaine use after discharge from inpatient treatment (success vs failure); (2) *frequency*, the total number of days of cocaine use; and (3) *quantity*, the average amount of cocaine use in grams per occasion of cocaine use.

DATA ANALYSIS

Baseline demographic data, drug use measures, and baseline laboratory responses of cocaine craving, corticotropin level, and cortisol level were first examined for association with measures of cocaine relapse. If any demographic, baseline cocaine use, or baseline response measure was significantly associated with any of the relapse outcome measures, they were included as covariates in examining the association between stress-induced and drug cue–induced craving and HPA axis response and the specific cocaine relapse measure.

Time to cocaine relapse was examined by means of Cox proportional hazards regression,[26] a statistical method to examine the effects of continuous variables on event-based outcomes such as when an event occurred during a specified time period (eg, first day of cocaine use after discharge during follow-up). Multiple regression or logistic regression (for demographic categorical variables) analyses were conducted to examine associations with frequency and amount of cocaine used in the follow-up period.

RESULTS

RELAPSE RATES

Two thirds of the sample (32/49 [65%]) reported using cocaine during the follow-up phase. Urine and self-

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/05/2016

Table 2. Baseline Demographics, Cocaine Use, and Rates of Other Lifetime Psychiatric Disorders

Subject Variable	Intent-to-Treat Sample (N = 54)	Follow-up Sample (n = 49)
Age, mean (SD), y	37.38 (6.47)	37.45 (6.64)
Education, mean (SD), y	12.39 (1.70)	12.47 (1.76)
Sex, No. (%) M	36 (67)	32 (65)
Race, No. (%)		
African American	28 (52)	26 (53)
White	17 (31)	15 (31)
Hispanic	1 (2)	1 (2)
Other	8 (15)	7 (14)
Employment, No. (%) full time	11 (20)	9 (18)
Married, No. (%)	10 (19)	10 (20)
Average y of cocaine abuse, mean (SD)	8.96 (3.13)	9.00 (6.16)
Average d of cocaine use per mo, mean (SD)	16.31 (9.54)	16.10 (9.78)
Average amount of cocaine use per week, mean (SD), g	224.20 (338.67)	223.61 (352.88)
Lifetime prevalence of PTSD, No. (%)	14 (26)	12 (24)
Lifetime other anxiety disorders, No. (%)	7 (13)	6 (12)
Lifetime major depression, No. (%)	27 (50)	24 (49)
Lifetime alcohol dependence, No. (%)	33 (61)	30 (61)

Abbreviation: PTSD, posttraumatic stress disorder.

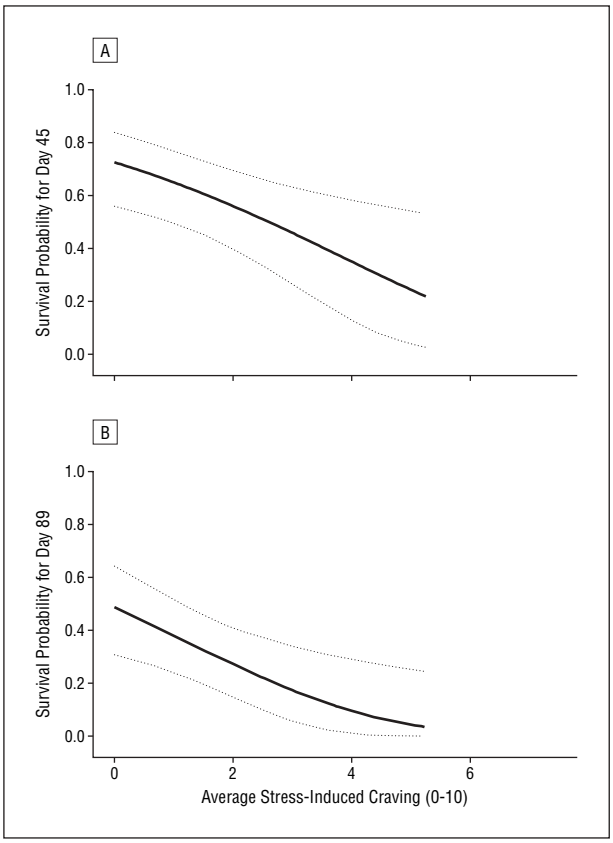

Figure 1. Day 45 (A) and day 89 (B) survival probability function for increasing values of average stress-induced cocaine craving using the parameter estimates from the Cox proportional hazards regression model. The probability of not relapsing with an average stress-induced cocaine craving of 0 was 0.67 on day 45 and 0.44 on day 89.

report data were concordant for 48 of 49 subjects. The subject with discordant data was considered to have relapsed at day 1, and his frequency and amount of cocaine use was considered invalid and not included in the regression analyses. (Exclusion of this subject from the analyses did not affect the result.)

SAMPLE DEMOGRAPHIC, SUBSTANCE USE, AND PSYCHIATRIC HISTORY

The demographic data, cocaine use history, and lifetime rates of other psychiatric diagnoses of the original sample who participated in the laboratory study (N=54) and the follow-up sample (n=49) were highly similar (**Table 2**).

BASELINE DEMOGRAPHIC AND COCAINE USE ASSOCIATIONS WITH RELAPSE OUTCOMES

Demographic measures of age, education level, employment status, race, marital status, history of alcohol dependence, and lifetime history of major depression, posttraumatic stress disorder, or other anxiety disorders were not associated with cocaine relapse outcomes. Baseline levels of cocaine craving, corticotropin, and cortisol levels were not associated with time to cocaine relapse or amount and frequency of follow-up cocaine use. However, baseline amount of cocaine use during the 90 days before inpatient admission was significantly associated with the time to cocaine relapse (baseline quantity: $\chi^2=5.81$, $P=.01$; hazard ratio, 0.49; 95% confidence interval, 0.28-0.87). Also, baseline frequency of cocaine use was significantly associated with follow-up frequency of cocaine use ($R^2=0.08$, $t=2.13$, $P=.04$).

STRESS-INDUCED COCAINE CRAVING, HPA AXIS RESPONSE, AND COCAINE RELAPSE OUTCOMES

Cox proportional hazards regression analyses showed that greater stress-induced cocaine craving response was associated with a shorter time to relapse after accounting for baseline cocaine use during the 90-day period before inpatient admission ($\chi^2=5.58$, $P=.02$; hazard ratio, 1.31; 95% confidence interval, 1.03-1.60). For each additional unit increase in stress-induced cocaine craving, there was a 31% increase in the likelihood of cocaine relapse in the 90-day follow-up period (**Figure 1**).

Stress-induced corticotropin and cortisol responses were not associated with time to cocaine relapse and frequency of cocaine relapse. However, stress-induced corticotropin response ($R^2=0.19$, $t=3.25$, $P=.002$) was significantly associated with average amount of cocaine used per occasion in the follow-up period and accounted for 19% of the variance in amount of cocaine used per occasion (**Figure 2**A). As a follow-up, a median split in the stress-induced corticotropin response was conducted to divide the sample into high and low responder groups. The cumulative amounts of

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/05/2016

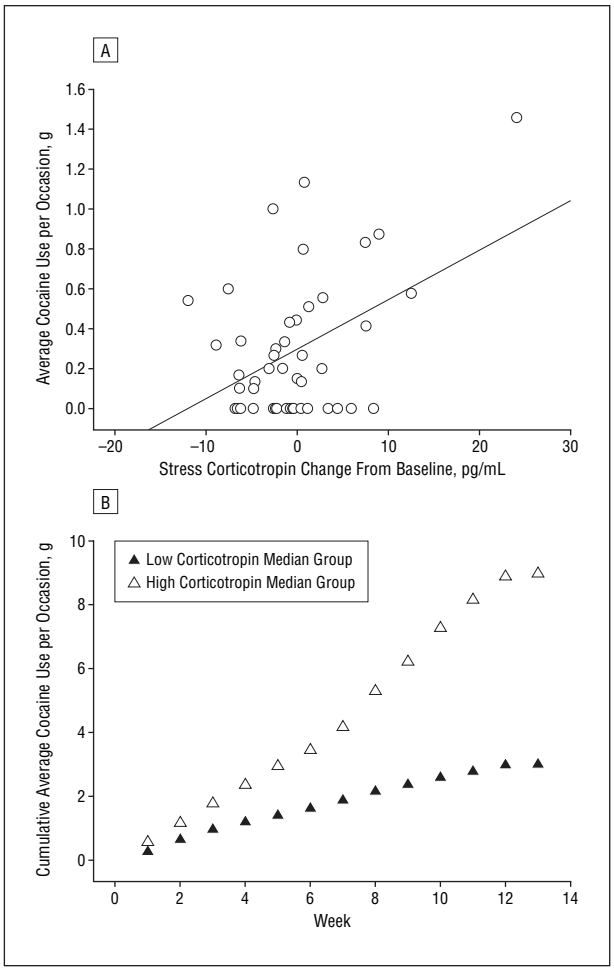

Figure 2. Relationship of corticotropin response to amount of cocaine use. A, Scatterplot for stress-induced corticotropin levels (r=0.44, P=.002, R^2=0.19) and average amount of cocaine use per occasion during the 90-day follow-up. B, Differences between high and low corticotropin responder groups in the cumulative amounts of cocaine used by week during follow-up ($F_{1,47}$=25.60, P<.001). To convert corticotropin to picomoles per liter, multiply by 0.22.

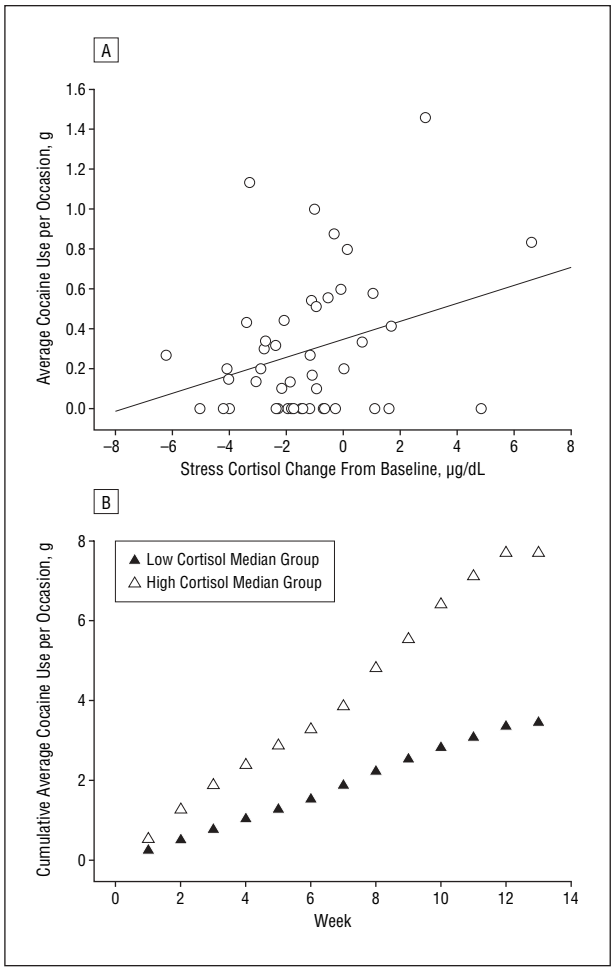

Figure 3. Relationship of cortisol response to amount of cocaine use. A, Scatterplot for stress-induced cortisol levels (r=0.31, P=.04, R^2=0.09) and average amount of cocaine use per occasion during the 90-day follow-up. B, Differences between high and low cortisol responder groups in the cumulative amounts of cocaine used by week during follow-up ($F_{1,47}$=17.34, P<.001). To convert cortisol to nanomoles per liter, multiply by 27.59.

cocaine used each week of the 90-day follow-up were then computed and a linear mixed-effects model analysis with group and time (each of the 12 weeks) as independent variables was conducted (using PROC MIXED SAS version 8.0; SAS Institute Inc, Cary, NC). Findings indicated that high corticotropin responders used significantly more cocaine over time than the low responder groups (group main effect: $F_{1,47}$=25.60, P<.001) (Figure 2B). Similarly, stress-induced cortisol response was significantly associated with average amount of cocaine used per occasion (R^2=0.09, t=2.12, P=.04) and accounted for 9% of the variance in amounts of cocaine used per occasion (**Figure 3**A). High and low stress-induced cortisol responder groups were also computed by means of a median split, and the cumulative amounts of cocaine used during the follow-up period were examined in the manner described for corticotropin. Findings indicated that the high cortisol responder group used significantly more cocaine over time than the low cortisol responder group (group main effect: $F_{1,47}$=17.34, P<.001) (Figure 3B).

DRUG CUE–INDUCED COCAINE CRAVING AND AROUSAL AND COCAINE RELAPSE OUTCOMES

There were no significant associations between drug cue–induced cocaine craving and time to cocaine relapse or frequency and amount of cocaine used at follow-up. Drug cue–induced corticotropin and cortisol responses were also not found to be significantly associated with cocaine relapse measures.

However, there were significant associations between stress-induced and drug cue–induced cocaine craving response (r=0.69, P<.001), and between stress-induced and drug cue–induced corticotropin (r=0.43, P=.003) and cortisol (r=0.32, P=.03) averaged change responses in the laboratory sessions, suggesting similar increases in cocaine craving and HPA axis responses during stress and drug cue imagery exposure conditions.

Secondary predictor variables of heart rate and subjective anxiety responses did not show any significant associations with cocaine relapse outcomes.

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/05/2016

COMMENT

The findings from this study are the first, to our knowledge, to document that stress-related drug craving and associated psychobiological responses in the laboratory are predictive of subsequent cocaine relapse in abstinent cocaine-dependent individuals. Greater stress-induced, but not drug cue–induced, cocaine craving predicted a shorter time to initial cocaine lapse. On the other hand, stress-related HPA axis responses were not associated with time to cocaine lapse, but rather with amounts of cocaine used per occasion during follow-up. Consistent with the clinical literature that recognizes relapse and recovery as a multidetermined process,[15,27] the current findings suggest that specific components of the stress response are associated with different aspects of the relapse process. While cocaine craving, a subjective measure of intent to use cocaine, was associated with the subsequent behavioral component of relapse (ie, initial lapse and reinitiation), the stress-related HPA responses were not associated with this behavioral aspect but rather with a measure of consumption, which may represent the ability to control intake after initiation, ie, occurrence of a full-blown relapse or binge.

Exposure to footshock stress reinstates cocaine-seeking behavior in abstinent, cocaine-experienced animals that have undergone extinction,[13] a behavior associated with the extrahypothalamic CRF and noradrenergic activity and not dependent on glucocorticoids.[14] Pharmacologic attenuation of HPA function in cocaine-addicted individuals does not block the subjective effects of cocaine, including cocaine craving,[28,29] suggesting a dissociation between the hypothalamic stress response and subjective or behavioral effects of cocaine. Our finding that the HPA measures are not associated with the behavioral lapse to drug use is consistent with these previous data and, together with the preclinical literature, suggests that the subjective and behavioral aspects of drug seeking and initial lapse are not dependent on HPA function but possibly associated with extrahypothalamic CRF and noradrenergic system activity.

Nonetheless, there is evidence that cocaine, like stress, stimulates the HPA axis via a hypothalamic CRF mechanism and that increased levels of corticosterone are important in the acquisition of cocaine self-administration.[30] In humans, cocaine stimulates the HPA axis and increases the peak amplitude of the secretory pulses of corticotropin and cortisol without altering the peak frequency.[31,32] These preclinical and clinical data support the notion that HPA axis stimulation plays a role in cocaine reinforcement.[15,30,31] This notion is supported by the current data in that increased stress-related corticotropin and cortisol responses were associated with greater amounts of cocaine consumption per occasion. It may be that increasing levels of corticotropin and cortisol during a stress-related lapse serve to "prime" higher bouts of cocaine consumption by virtue of reaching critical reward thresholds more quickly. Alternatively, it is also possible that stress-related increases in corticotropin and cortisol diminish the rewarding effects of the initial cocaine bout such that more cocaine is needed to reach satiety. Both explanations are speculative and need to be further assessed in the future.

Drug use as a way to escape from distress or as a means of coping with stress and negative affect is a commonly used explanation for addictive drug use.[33,34] Consistent with these models, stress-related increases in drug craving could represent a proximal marker of relapse susceptibility, perhaps as a signal for drug use to ameliorate distress. Previous research suggests that individuals are able to control impulses and show effective self-regulation skills under low or manageable levels of distress, but with increasing distress, the motivation to feel better overrides the need for self-control.[35] In the context of the current study, stress-induced increases in cocaine craving could signal the need for regulation of distress over self-control, thereby increasing the susceptibility of relapse. Recent evidence from brain imaging studies provides further insight into the potential neural substrates that could underlie emotional distress overriding cognitive control-related processing to influence behavioral outcomes. Sanfey et al[36] manipulated emotional engagement during an economic decision-making task and reported that emotion-activated limbic brain regions (anterior insula) supersede activity in cognitive-control–related brain regions (dorsolateral prefrontal cortex) to influence behavioral outcomes. Cocaine-dependent patients show lower activity in the anterior cingulate during stress compared with controls but increased activity in the dorsal striatum, and activity in both the dorsal striatum and insula correlate with stress-induced cocaine craving.[37] Thus, hypofunction in a region (anterior cingulate) involved in conflict monitoring and emotion regulation,[38,39] but greater stress-induced craving-related activity in limbic regions associated with obsessive-compulsive behaviors and negative emotion processing,[40,41] could provide the neural substrates for overriding self-control and commitment to abstinence during stress, increasing relapse susceptibility.

No significant associations between cue imagery–induced cocaine craving or HPA responses and cocaine relapse outcomes were found. These data are consistent with other studies showing that drug cue–related craving is not predictive of relapse outcomes.[2,42,43] On the other hand, the current results indicated that cocaine craving and HPA responses in the stress and the drug cue imagery conditions were significantly correlated, suggesting that cue imagery exposure produced responses similar to the stress condition, and with a larger sample size we might have seen a positive association between drug cue imagery responses and relapse. It is also important to note that this study used imagery of drug cues rather than actual exposure to drug cues themselves to produce cue reactivity. Imagery exposure to drug cues may produce a different pattern of response than those seen in actual drug cue reactivity paradigms and could have resulted in a lack of association between drug cue exposure and relapse susceptibility.

The current findings have significant clinical implications. First, stress-induced drug craving and associated HPA responses may be used as diagnostic markers to assess relapse propensity. Such assessments could inform clinicians of the need to tailor their interventions toward stress regulation and reduction of stress-induced craving. Sec-

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/05/2016

ond, while assessing stress-induced craving and hormonal responses can be informative in identifying individuals who are highly susceptible to relapse, the findings also underscore the importance of developing treatments that target attenuation of stress-induced cocaine craving and regulation of stress-related HPA axis responses in cocaine relapse prevention. There are currently no empirically validated treatments that address stress-induced drug craving and related arousal. Both CRF antagonists and α_2-adrenergic agonists attenuate stress-induced cocaine reinstatement in dependent laboratory animals.[13,14,44] Nonpeptide CRF antagonists are currently being investigated in the treatment of affective and anxiety disorders.[45,46] Our findings are consistent with previously cited preclinical data and support examining the efficacy of CRF antagonists in attenuating stress-induced cocaine craving and HPA responses to improve cocaine relapse outcomes. Furthermore, α_2-adrenergic agonists that inhibit norepinephrine centrally have shown promise in the treatment of attention-deficit/hyperactivity disorder,[47] in reducing opiate withdrawal symptoms,[48] and in reducing nicotine craving.[49] Their efficacy in reducing stress-induced cocaine craving and relapse susceptibility needs further testing in human studies. Behavioral treatments that target stress regulation and attenuation of stress-related cocaine craving could also have potential relevance in addressing cocaine relapse susceptibility. Finally, laboratory models of stress-induced drug craving could be effective in screening pharmacologic agents or testing behavioral strategies to attenuate stress-induced drug craving and HPA responses to reduce relapse susceptibility.

Specific limitations of the present study need to be acknowledged. While there are reports of sex differences in cocaine relapse precipitants,[50] we were not able to assess sex-specific associations because of the small number of women in the sample. It is also important to note recent evidence from the alcohol literature indicating that attenuated HPA responses are associated with alcohol relapse.[51] As such, the current findings may appear to be in contrast to these data. However, the effects of withdrawal from cocaine on HPA function are different from alcohol-related withdrawal effects on HPA function. For example, cortisol responses are altered during early cocaine abstinence but, unlike protracted withdrawal from alcohol,[52] cortisol responses are known to normalize within 2 weeks of cocaine abstinence.[53] Clearly, a more comprehensive study of the withdrawal-related changes in HPA function and their effects on relapse and the effects of stress-related activation of HPA responses on relapse in cocaine- and alcohol-abusing samples need further study.

Despite these caveats, the current study provides previously undocumented evidence that stress-related increases in cocaine craving and HPA responses are associated with cocaine relapse outcomes in cocaine-dependent individuals during early recovery. The findings suggest that stress-induced drug craving and hormonal responses could be used diagnostically to evaluate relapse propensity. They also support the need to address the effects of stress-induced craving and HPA responses on cocaine relapse susceptibility via pharmacologic and behavioral treatment development efforts.

Submitted for Publication: June 2, 2005; final revision received August 31, 2005; accepted September 8, 2005.
Correspondence: Rajita Sinha, PhD, Department of Psychiatry, Yale University School of Medicine, 34 Park St, Room S110, New Haven, CT 06519 (Rajita.sinha@yale.edu).
Funding/Support: This research was supported by grants R01-DA11077 (Dr Sinha), P50-DA16556 (Dr Sinha), M01-RR00125 (Yale University), P60-DA0510 (Dr Kreek), and K02-DA17232 (Dr Sinha) from the National Institutes of Health, Bethesda, Md.
Previous Presentation: This study was presented as a poster at the Annual Meeting of the American College of Neuropsychopharmacology; December 14, 2004; San Juan, PR.
Acknowledgments: We thank the staff at the Clinical Neuroscience Research Unit and the Substance Abuse Treatment Unit of the Connecticut Mental Health Center, New Haven; the General Clinical Research Center at Yale University School of Medicine, New Haven; and Kreek Laboratories at Rockefeller University, New York, NY, for their support of this research.

REFERENCES

1. Kang SY, Kleinman PH, Woody GE, Millman RB, Todd TC, Kemp J, Lipton DS. Outcomes for cocaine abusers after once-a-week psychosocial therapy. *Am J Psychiatry*. 1991;148:630-635.
2. O'Brien CP, Childress AR, Ehrman RN, Robbins SJ. Conditioning factors in drug abuse: can they explain compulsion? *J Psychopharmacol*. 1998;12:15-22.
3. Higgins ST, Budney AJ, Bickel WK, Badger GJ, Foerg FE, Ogden D. Outpatient behavioral treatment for cocaine dependence: one-year outcome. *Exp Clin Psychopharmacol*. 1995;3:205-212.
4. Carroll KM, Ball SA, Nich C, O'Connor PG, Eagan DA, Frankforter TL, Triffleman EG, Shi J, Rounsaville BJ. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence. *Arch Gen Psychiatry*. 2001;58:755-761.
5. Carroll KM, Fenton LR, Ball SA, Nich C, Frankforter TL, Shi J, Rounsaville BJ. Efficacy of disulfiram and cognitive behavioral therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. *Arch Gen Psychiatry*. 2004; 61:264-272.
6. McKay JR, Alterman AI, Mulvaney FD, Koppenhaver JM. Predicting proximal factors in cocaine relapse and near miss episodes: clinical and theoretical implications. *Drug Alcohol Depend*. 1999;56:67-78.
7. Sinha R. How does stress increase risk of drug abuse and relapse? *Psychopharmacology (Berl)*. 2001;158:343-359.
8. Khantzian EJ. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am J Psychiatry*. 1985;142:1259-1264.
9. Mendelson JH, Mello NK, Sholar MB, Siegel AJ, Mutschler N, Halpern J. Temporal concordance of cocaine effects on mood states and neuroendocrine hormones. *Psychoneuroendocrinology*. 2002;27:71-82.
10. Sarnyai Z, Shaham Y, Heinrichs SC. The role of corticotropin-releasing factor in drug addiction. *Pharmacol Rev*. 2001;53:209-243.
11. Piazza PV, Deminiere JM, Le Moal M, Simon H. Factors that predict individual vulnerability to amphetamine self-administration. *Science*. 1989;245:1511-1513.
12. Shaham Y, Erb S, Stewart J. Stress-induced relapse to heroin and cocaine seeking in rats: a review. *Brain Res Brain Res Rev*. 2000;33:13-33.
13. Erb S, Shaham Y, Stewart J. The role of corticotropin-releasing factor and corticosterone in stress- and cocaine-induced relapse to cocaine seeking in rats. *J Neurosci*. 1998;18:5529-5536.
14. Erb S, Hitchcott PK, Rajabi H, Mueller D, Shaham Y, Stewart J. Alpha-2 adrenergic receptor agonists block stress-induced reinstatement of cocaine seeking. *Neuropsychopharmacology*. 2000;23:138-150.
15. Miller WR, Westerberg VS, Harris RJ, Tonigan JS. What predicts relapse? prospective testing of antecedent models. *Addiction*. 1996;91(suppl):S155-S172.
16. Sinha R, Catapano D, O'Malley S. Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology (Berl)*. 1999;142:343-351.
17. Sinha R, Talih M, Malison R, Anderson GA, Cooney N, Kreek M. Hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary responses during stress-induced and drug cue-induced cocaine craving states. *Psychopharmacology (Berl)*. 2003;170:62-72.
18. Mercer D, Carpenter G, Daley D, Patterson C, Volpicelli J. *Group Drug Counseling Manual*. Philadelphia: University of Pennsylvania; 1994.

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/05/2016

19. First M, Spitzer R, Gibbon M, Williams J. *Structured Clinical Interview for DSM-IV: Patient Edition*. Washington, DC: American Psychiatric Press Inc; 1995.
20. Miller GA, Levin DN, Kozak MJ, Cook EW III, McLean A Jr, Lang PJ. Individual differences in imagery and the psychophysiology of emotion. *Cogn Emotion*. 1987; 1:367-390.
21. Sinha R, Lovallo WR, Parsons OA. Cardiovascular differentiation of emotions. *Psychosom Med*. 1992;54:422-435.
22. Hersh D, Mulgrew CL, Van Kirk J, Kranzler HR. The validity of self-reported cocaine use in two groups of cocaine abusers. *J Consult Clin Psychol*. 1999;67:37-42.
23. Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The Timeline Followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. *J Consult Clin Psychol*. 2000;68:134-144.
24. Higgins ST, Budney AJ, Bickel WK, Foerg FE, Donham R, Badger GJ. Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. *Arch Gen Psychiatry*. 1994;51:568-576.
25. Rohsenow DJ, Monti PM, Martin RA, Michalec RA, Abrams DB. Brief coping skills treatment for cocaine abuse: 12-month substance use outcomes. *J Consult Clin Psychol*. 2000;68:515-520.
26. Cox D. Regression models and life tables (with discussion). *J R Stat Soc B*. 1972; 34:187-220.
27. Rohsenow DJ, Monti PM. Relapse among cocaine abusers: theoretical, methodological, and treatment considerations. In: Platt JJ, Henkegend CG, eds. *Relapse and Recovery in Addictions*. New Haven, Conn: Yale University Press; 2001: 355-378.
28. Ward AS, Collins ED, Haney M, Foltin RW, Fischman MW. Ketoconazole attenuates the cortisol response but not the subjective effects of smoked cocaine in humans. *Behav Pharmacol*. 1998;9:577-586.
29. Ward AS, Collins E, Haney M, Foltin RW, Fischman MW. Blockade of cocaine-induced increases in adrenocorticotrophic hormone and cortisol does not attenuate the subjective effects of smoked cocaine in humans. *Behav Pharmacol*. 1999;10:523-529.
30. Goeders NE. The HPA axis and cocaine reinforcement. *Psychoneuroendocrinology*. 2002;27:13-34.
31. Mendelson JH, Mello NK, Teoh SK, Ellingboe J, Cochin J. Cocaine effects on pulsatile secretion of anterior pituitary, gonadal, and adrenal hormones. *J Clin Endocrinol Metab*. 1989;69:1256-1260.
32. Teoh SK, Sarnyai Z, Mendelson JH, Mello NK, Springer SA, Sholar JW, Wapler M, Kuehnle JC, Gelles H. Cocaine effects on pulsatile secretion of ACTH in men. *J Pharmacol Exp Ther*. 1994;270:1134-1138.
33. Koob GF, Ahmed SH, Boutrel B, Chen SA, Kenny PJ, Markou A, O'Dell LE, Parsons LH, Sanna PP. Neurobiological mechanisms in the transition from drug use to drug dependence. *Neurosci Biobehav Rev*. 2004;27:739-749.
34. Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychol Rev*. 2004;111:33-51.
35. Tice DM, Bratslavsky D, Baumeister RF. Emotion distress regulation takes precedence over impulse control: if you feel bad, do it! *J Pers Soc Psychol*. 2001; 80:53-67.
36. Sanfey AG, Rilling JK, Aronson JA, Nystrom LE, Cohen JD. The neural basis of economic decision-making in the ultimatum game. *Science*. 2003;300:1755-1758.
37. Sinha R, Lacadie C, Skudlarski P, Fulbright RK, Rounsaville BJ, Kosten TR, Wexler BE. Neural activity associated with stress-induced cocaine craving: a functional magnetic resonance imaging study. *Psychopharmacology (Berl)*. 2005; 183:171-180.
38. Carter CS, Botvinivk MM, Cohen JD. The contribution of the anterior cingulate cortex to executive process in cognition. *Rev Neurosci*. 1999;10:49-57.
39. Beauregard M, Levesque J, Bourgouin P. Neural correlates of conscious self-regulation of emotion. *J Neurosci*. 2001;21:RC165.
40. Graybiel AM, Rauch SL. Toward a neurobiology of obsessive-compulsive disorder. *Neuron*. 2000;28:343-347.
41. Hyman SE, Malenka RC. Addiction and the brain: the neurobiology of compulsion and its persistence. *Neuroscience*. 2001;2:695-703.
42. Harris DS, Batki SL. Fluoxetine attenuates adrenocortical but not subjective responses to cocaine cues. *Am J Drug Alcohol Abuse*. 2004;30:765-782.
43. Pickens RW, Johanson CE. Craving: consensus of status and agenda for future research. *Drug Alcohol Depend*. 1992;30:127-131.
44. Stewart J. Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug-taking. *J Psychiatry Neurosci*. 2000;25:125-136.
45. Nemeroff CB. The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. *Mol Psychiatry*. 1996;1:336-342.
46. Holsboer F. Corticotropin-releasing hormone modulators and depression. *Curr Opin Investig Drugs*. 2003;4:46-50.
47. Scahill L, Chappell PB, Kim YS, Schultz RT, Katsovich L, Shepherd E, Arnsten AF, Cohen DJ, Leckman JF. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *Am J Psychiatry*. 2001;158:1067-1074.
48. Kahn A, Mumford JP, Rogers GA, Beckford H. Double-blind study of lofexidine and clonidine in the detoxification of opiate addicts in hospital. *Drug Alcohol Depend*. 1997;44:57-61.
49. Glassman AH, Jackson WK, Walsh BT, Roose SP, Rosenfeld B. Cigarette craving, smoking withdrawal, and clonidine. *Science*. 1984;226:864-866.
50. McKay JR, Rutherford MJ, Cacciola JS, Kabasakalian-McKay R, Alterman AI. Gender differences in the relapse experiences of cocaine patients. *J Nerv Ment Dis*. 1996;184:616-622.
51. Junghanns K, Backhaus J, Tietz U, Lange W, Bernzen J, Wetterling T, Rink L, Driessen M. Impaired serum cortisol stress response is a predictor of early relapse. *Alcohol Alcohol*. 2003;38:189-193.
52. Adinoff B, Krebaum SR, Chandler PA, Ye W, Brown MB, Williams MJ. Dissection of hypothalamic-pituitary-adrenal axis pathology in 1-month-abstinent alcohol-dependent men, part 1: adrenal and pituitary glucocorticoid responsiveness. *Alcohol Clin Exp Res*. 2005;29:517-527.
53. Contoreggi C, Herning RI, Koeppl B, Simpson PM, Negro PJ Jr, Fortner-Burton C, Hess J. Treatment-seeking inpatient cocaine abusers show hypothalamic dysregulation of both basal prolactin and cortisol secretion. *Neuroendocrinology*. 2003;78:154-162.

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/05/2016