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Frequency of recent cocaine and alcohol use affects drug craving and associated responses to stress and drug-related cues

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Summary *Rationale*: Stress is known to increase drug craving, associated physiological arousal and risk of relapse in drug dependent individuals. However, it is unclear whether these responses are altered by recent frequency of drug use. The current study examined whether frequency of cocaine and alcohol abuse alters drug craving and associated arousal with laboratory exposure to stress and to drug related cues.
Methods: Fifty-four recently abstinent treatment-seeking cocaine abusers who were part of a study on stress and drug craving were categorized into high- and low-frequency users on the basis of their recent cocaine use. The high use cocaine group also consumed significantly more alcohol than the low use cocaine group. Participants were exposed to a brief 5-min guided imagery procedure that involved imagining a recent personal stressful situation, a personal drug-related situation and a neutral-relaxing situation, one imagery session on separate days presented in random order. Subjective (craving and anxiety), cardiovascular (heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP)) and biochemical (adrenocorticotropic hormone (ACTH), cortisol, prolactin) measures were assessed.
Results: High-frequency abusers demonstrated a significantly greater drug craving, anxiety and associated cardiovascular and hypothalamic-pituitary-adrenal (HPA)

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response to both stress and drug-cue exposure as compared to low-frequency abusers.
Conclusions: Increased frequency of recent cocaine and alcohol use is associated with an enhanced stress and cue-induced drug craving and arousal response that appears to be similar to the effects of cocaine, and one that may increase the vulnerability to drug-seeking behavior and relapse in drug dependent individuals.

1. Introduction

Considerable preclinical and clinical research has highlighted the ability of both stressors and drug-related environmental cues in facilitating drug craving in humans and re-instatement and/or relapse in animals (Shaham et al., 2000; Sinha, 2001). Rats have been found to significantly enhance psychostimulant and alcohol administration following both physical and social stressors (Lê and Shaham, 2001; Kosten et al., 2004; McFarland et al., 2004). Clinical studies in humans have shown that drug users and alcoholics usually site stress and negative affect as reasons for relapse (Sinha, 2001; Goeders, 2002). Increased drug craving, anxiety and biological responses to stress and to drug cues have been documented in drug dependent individuals (Sinha et al., 1999, 2000) suggestive of interacting and overlapping neural circuitry involved in stress and putative reward circuits.

Preclinical research has shown that intensity of recent drug use is an important aspect of drug-seeking behavior in laboratory animals. Rats allowed to self-administer high compared with low cocaine doses were shown to demonstrate increased intake and a more regular pattern of dosing (Mantsch et al., 2001). Similarly, various escalating patterns of cocaine administration are known to result in a range of neuroadaptive responses associated with the transition to addiction (Koob et al., 2004). Repeated rather than single dose regimens have been shown to culminate in higher levels of ambulatory sensitization (Davidson et al., 2002; Segal and Kuczenski, 1997) as well as increased D1 receptor binding in the nucleus accumbens and olfactory tubercle (Unterwald et al., 2001). In humans, increased length of binge cocaine self-administration has been associated with higher subjective ratings of both anxiety and craving (Foltin and Fischman, 1997; Evans et al., 2002). In addition, regularity (and related increases in quantity of drug use) has also been associated with greater problematic behavioral and cognitive sequelae (Hammersley et al., 1999; Fox et al., 2001). Clinically, it is worth noting that individuals who have been using drugs at a higher frequency have greater difficulty maintaining abstinence and achieving treatment success (Carroll et al., 1993; Dodge et al., 2005).

Whilst studies such as these indicate an integral role of both stress and frequency of drug use on relapse, there is less data on the effects of dose frequency on drug craving, stress response and its potential effects on vulnerability to further drug use. One recent preclinical study has, however, revealed that extended drug escalation is associated with increased sensitivity to the reinstating effects of stress (Ahmed et al., 2000). However, no human research has examined whether stress and drug-cue induced craving is altered by recent frequency of drug use.

In a recent comprehensive inpatient study we demonstrated that exposure to stress and to non-stress related drug cues increased cocaine craving in cocaine dependent individuals. Our findings also indicated that these drug craving states were accompanied by an increase in arousal comprising heightened peripheral HPA and cardiovascular response in response to stress and drug cue exposure when compared to neutral imagery exposure (Sinha et al., 2003). Most recently, we've documented that such increases in stress-induced cocaine craving and associated arousal responses predict cocaine relapse after inpatient cocaine treatment (Sinha et al., 2004). These findings are consistent with previous preclinical research and clinical observations suggesting that stress related drug craving and physiological alterations play a significant role in the pathophysiology of relapse in cocaine addiction (Sinha, 2001). It remains of etiological and clinical significance, however, to assess whether these associations between stress and drug craving are modified by recent drug use. Thus, we conducted secondary analyses by grouping subjects who participated in the Sinha et al. (2003) study according to their recent frequency of drug use to examine whether their stress and drug cue related responses were affected by recent levels of drug use. As both stressors and drug-related stimuli are thought to produce effects similar to that of cocaine itself, we hypothesized that the neuroadaptive changes associated with frequency of cocaine use