Drug and Alcohol Dependence 155 (2015) 60–67

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Laboratory-induced stress and craving among individuals with prescription opioid dependence

Sudie E. Back[a,b,*], Daniel F. Gros[a,b], Matthew Price[c], Steve LaRowe[a,b], Julianne Flanagan[a], Kathleen T. Brady[a,b], Charles Davis[a], Maryanne Jaconis[a], Jenna L. McCauley[a]

[a] Department of Psychiatry & Behavioral Sciences, Medical University of South Carolina, Charleston, SC, United States
[b] Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC, United States
[c] Department of Psychology, University of Vermont, Burlington, VT, United States

ARTICLE INFO

Article history:
Received 23 February 2015
Received in revised form 10 July 2015
Accepted 17 August 2015
Available online 28 August 2015

Keywords:
Stress
Trier
Cues
Prescription opioids
Opiates

ABSTRACT

Background: Stress and conditioned drug cues have been implicated in the initiation, maintenance and relapse to substances of abuse. Although stress and drug cues are often encountered together, little research exists on whether stress potentiates the response to drug cues.
Method: Participants ($N = 75$) were 39 community recruited individuals with current prescription opioid (PO) dependence and 36 healthy controls. Participants stayed overnight in the hospital for one night and then completed laboratory testing the following morning. During laboratory testing, participants were randomly assigned to a stress task (Trier Social Stress Task; TSST) or a no-stress condition. Following the stress manipulation, all participants completed a PO cue paradigm. Immediately before and after the stress and cue tasks, the following were assessed: subjective (stress, craving, anger, sadness, happiness), physiological (heart rate, blood pressure, galvanic skin response), and neuroendocrine responses (cortisol and dehydroepiandrosterone).
Results: Internal validity of the stress task was demonstrated, as evidenced by significantly higher subjective stress, as well as cortisol, heart rate and blood pressure in the TSST compared to the no-stress group. Individuals with PO dependence evidenced significantly greater reactivity to the stress task than controls. Craving increased significantly in response to the drug cue task among PO participants. No stress × cue interaction was observed.
Conclusions: In this study, heightened stress reactivity was observed among individuals with PO dependence. Exposure to acute stress, however, did not potentiate craving in response to conditioned drug cues.

Published by Elsevier Ireland Ltd.

1. Introduction

Stress and conditioned drug cues are key factors associated with the etiology and maintenance of substance use disorders (SUD; Brady and Sinha, 2005; Enoch, 2011; Hyman and Sinha, 2009; Bruchas et al., 2010; Koob, 2009; Sinha, 2001, 2007; Stewart, 2003). Several models of addiction have attempted to explain the connection between stress and motivation to use alcohol or drugs (Breese et al., 2011; Sinha, 2001). These models relate that, for many individuals with SUD, substances are employed as a means of reducing negative affect; a pattern that is negatively reinforcing and may contribute to the subsequent development of SUD (Khantzian, 1985; Shiffman, 1982; Wills and Shiffman, 1985). However, not all substance use or relapses are precipitated by stress or negative affect. For example, Shiffman (1982) found that approximately one-third of relapses to nicotine were precipitated by smoking-specific stimuli (i.e., conditioned cues), in particular seeing someone else smoking.

The concept of craving also has a central role in theories concerning the development and maintenance of SUD (Breese et al., 2005; Childress et al., 1988; Drummond et al., 1990; Franken et al., 2000; Tiffany, 1990). One particularly salient feature that occurs during abstinence from drug use is the ability of drug-associated environmental cues to elicit craving, and consequently reinstate drug-seeking and drug-taking behaviors. The systematic investigation of craving has occurred largely through studies employing cue

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, Clinical Neuroscience Division, Medical University of South Carolina, 67 President St., P.O. Box 250861, Charleston, SC 29425, United States.
E-mail address: backs@musc.edu (S.E. Back).

http://dx.doi.org/10.1016/j.drugalcdep.2015.08.019
0376-8716/Published by Elsevier Ireland Ltd.

reactivity (Carter and Tiffany, 1999), which have given rise to a variety of theoretical models (Kosten et al., 2006; O'Brien et al., 1998; See, 2002; Siegel, 1999; Siegel and Ramos, 2002). Findings suggest that, through a process of associative learning, previously neutral stimuli (e.g., pill bottle, pharmacy) acquire incentive-motivational properties following repeated pairing with drug consumption. Conditioned stimuli thus play a critical role in ongoing drug-seeking behavior and relapse after periods of abstinence (Childress et al., 1988; O'Brien et al., 1998).

Stress and cues are frequently encountered together by patients, and the presence of stress may influence or change the rewarding value of a subsequently encountered conditioned stimuli (Bruchas et al., 2010). For example, if a person has an altercation with a coworker (stress) and then sees a billboard advertising their preferred alcoholic beverage (cue) on the commute home that day, does the stress experienced prior to seeing the cue modify the impact that the cue has on the person's craving or drug seeking behaviors? If the person had not experienced a stressful situation that day, would he/she have noticed the billboard, and if so would the effect of the billboard have been as strong? The primary question of interest in the current study is whether exposure to a stressor potentiates reactivity (e.g., craving, physiological arousal) to a conditioned drug cue.

Given the notable contribution of stress and conditioned cues on addictive behaviors, an increasingly robust literature has investigated their ability to prompt drug-seeking behavior in preclinical and human laboratory studies. A number of different types of clinical laboratory-based stress induction tasks have been employed to study the influence of stress and cues on addictive responses. Sinha and colleagues were the first to demonstrate in a controlled human laboratory setting that acute stress increased craving in cocaine-dependent individuals (Sinha et al., 1999). Our group and others have also demonstrated that physical stressors (e.g., cold pressor task), psychological stressors (e.g., Trier Social Stress Task [TSST]; Kirschbaum et al., 1993) and pharmacological stressors (e.g., corticotropin releasing hormone) increase stress and craving among individuals with nicotine, cocaine, alcohol, or marijuana dependence (Back et al., 2005, 2010; Buchmann et al., 2010; Brady et al., 2006; Childs and de Wit, 2010).

Several clinical and preclinical studies have investigated the interactive effects of stress and cues, and the data are equivocal. Thomas et al. (2011) demonstrated that, among individuals with alcohol dependence, the TSST resulted in significantly increased subjective stress, as well as cortisol, ACTH, and blood pressure as compared to controls, and the alcohol cue paradigm resulted in significant craving. However, no interaction between the TSST and alcohol cues was revealed. McRae-Clark et al. (2011) demonstrated similar findings in that prior exposure to a laboratory-based stress task did not enhance craving response to drug cues in individuals with marijuana dependence. In contrast to these clinical studies, Liu and Weiss (2002) found that footshock stress and ethanol conditioned drug cues interacted to augment the resumption of ethanol seeking behavior following extinction in rats. Rats exposed to both footshock stress and ethanol cues, as compared to stress or cues alone, demonstrated twice as many lever presses and the response rate was sustained for a longer period of time. In addition, Buffalari and See (2009) showed that while footshock stress and conditioned drug cues reinstate drug-seeking when presented in isolation, their interaction resulted in potentiated reinstatement.

The current study is focused on prescription opioid (PO) use disorders, which have been steadily increasing over the past decade and represent a significant public health concern (Back et al., 2010; Calcaterra et al., 2013; Garland et al., 2013; Hall et al., 2008; Kuehn, 2007; McHugh et al., 2015). To date, there have been no studies of the interaction of stress and cues in PO dependent individuals. In contrast to other types of SUD, individuals with PO use disorders may have different initiation histories (e.g., prescribed the drug by their physician, initially consumed by some for legitimate physical health reasons) and may present with different comorbidities, such as chronic pain, that could exert influences on stress reactivity. Using a human laboratory stress induction task (Back et al., 2014), the current study examined stress reactivity among individuals with and without PO dependence, as well as the interaction of stress and conditioned PO drug cues. Human laboratory paradigms offer a high degree of methodological precision and control, and are a reliable method of investigating the complexities of stress (Foley and Kirschbaum, 2010) and conditioned drug cues. We hypothesized that the PO group would demonstrate increased reactivity to the stress task, and that exposure to stress would potentiate craving in response to the drug cue task.

2. Methods

2.1. Participants

Participants ($N = 75$) were individuals with current (past 6 months) PO dependence ($n = 39$; 57.9% female) or healthy controls ($n = 36$; 50.0% female). PO dependence was defined as meeting the DSM-IV (American Psychiatric Association, 2000) criteria for substance dependence on opioid analgesics (e.g., oxycodone, hydrocodone). Newspaper and other media advertisements were the primary source of recruitment. Potential participants were initially screened by telephone using a brief form that was created for the purposes of this study and screened for current PO use and symptoms of SUD. Individuals meeting preliminary eligibility criteria came into the office for a clinical assessment and a history and physical examination. Exclusion criteria included: pregnancy or nursing; BMI ≥ 39; major medical problems (e.g., diabetes, HIV, Addison's or Cushing's disease) or comorbid psychiatric conditions that could affect the HPA axis (e.g., bipolar disorder, post-traumatic stress disorder); use of methadone in the past 3 months; use of antihypertensive medications, beta-blockers, synthetic glucocorticoid therapy, or treatment with other agents that may interfere with stress response in the past month. Individuals who met criteria for abuse of other substances had to identify POs as their primary drug of choice. Controls were excluded if they met DSM-IV criteria for current or history of substance dependence (except caffeine or nicotine); history of abuse was allowed. Participants were compensated $150 for completing the study.

2.2. Measures

2.2.1. Substance use. The Structured Clinical Interview for DSM-IV (SCID; First et al., 2002) and the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) were used to assess substance use disorders and other Axis I psychiatric disorders. Urine drug screens tests were performed using the On Track Test Cup®. Breathalyzer tests were administered to test for the presence of alcohol. Opioid withdrawal symptoms were assessed at the time of hospital admission using the Short Opioid Withdrawal Scale (Gossop, 1990). The Timeline Follow Back (TLFB; Sobell and Sobell, 1992) is a calendar-based assessment that was used to measure PO use during the one month prior to the laboratory test.

2.2.2. Subjective reactivity. A visual analog scale derived from the Within Session Rating Scale (Childress et al., 1986) and anchored with adjective modifiers (from 0 = "not at all" to 10 = "extremely") was used to assess subjective responses: craving, stress, anger, happiness, sadness, how hard it would be to resist using their opioid of choice, and the amount of money participants would be willing to spend on opioids (i.e., the "market value"). Participants responded to questions immediately before and after the TSST and at several time points after the drug cue paradigm (i.e., immediately, 15-, 30-, and 60-minutes post). The State-Trait Anxiety Inventory (STAI, Form Y1; Spielberger, 1983) was completed immediately before and after the TSST, and then immediately, 15-, 30- and 60-min after the drug cue paradigm.

2.2.3. Neuroendocrine assay. Unstimulated salivary samples were collected at baseline, immediately after the TSST, immediately after the drug cue paradigm, and at 15-, 30-, and 60-minutes post. Dehydroepiandrosterone (DHEA) was assayed in duplicate using a salivary DHEA enzyme immunoassay system that has an intra-assay precision of 5.6% with a sensitivity of 5 pg/mL. For cortisol, samples were assayed in duplicate using a high sensitivity salivary cortisol enzyme immunoassay system that has an intra-assay precision of 3.35–3.65% with a sensitivity of <0.003 μg/dL. Both DHEA and cortisol were analyzed using a PowerWave HT Microplate Spectrophotometer in conjunction with a Precision Series Automated Liquid Handling System.

2.2.4. Physiological reactivity. Heart rate (HR) was collected via electrodes along the bottom of the participant's ribcage and collarbone. Systolic (SBP) and diastolic blood pressure (DBP) were measured using a GE Pro 400 Dinamap automated monitor. Mean arterial pressure (MAP) was calculated using the formula $[(2 \times DBP) + SBP/3]$.