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Effects of adverse childhood experiences on the association between intranasal oxytocin and social stress reactivity among individuals with cocaine dependence

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ABSTRACT

Background: Drug dependence and adverse childhood experiences (ACE) are commonly reflected by dysregulation of the hypothalamic-pituitary-adrenal axis (HPA). Accumulating research indicates that the neuropeptide oxytocin may regulate HPA function, resulting in reductions in neuroendocrine reactivity to social stress among individuals with drug dependence. However, emerging literature suggests that individual differences may differentially impact intranasal oxytocin's effects on human social behaviors.
Methods: This study employed a double-blind, placebo-controlled design to examine the extent to which ACE influenced the effects of intranasal oxytocin (40 IU) on neuroendocrine reactivity to a laboratory social stress paradigm in a sample of 31 cocaine-dependent individuals.
Results: ACE scores modified the relationship between intranasal oxytocin and cortisol reactivity. While ACE modified the relationship between intranasal oxytocin and DHEA response in a similar direction to what was seen in cortisol, it did not reach statistical significance.
Conclusions: Findings are congruent with the emerging hypothesis that intranasal oxytocin may differentially attenuate social stress reactivity among individuals with specific vulnerabilities. Future research examining the nuances of intranasal oxytocin's therapeutic potential is necessary.

1. Introduction

Abundant research has demonstrated an association between substance dependence and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Clarke et al., 2008; Koob, 2008; Sinha, 2008). The effects of adverse childhood experiences (ACE; e.g. physical, psychological, or environmental threats to stable and functional development) on drug dependence (Benjet et al., 2013; Enoch, 2011; Mersky et al., 2013) and HPA axis function are also salient (Carpenter et al., 2011; Heim et al., 2002; MacMillan et al., 2009). Indeed, recent research illustrates the combined negative effects of ACE and substance dependence on stress reactivity in the HPA axis (Doan et al., 2014; Gerra et al., 2014; Schäfer et al., 2010).

Epidemiological studies have found that ACE increases the risk for the development of substance use disorders (SUD) (Anda et al., 2002; Dube et al., 2003). Previous studies indicate that childhood maltreatment is associated with earlier initiation of illicit drug use (Nomura et al., 2012) and that child abuse and maltreatment is more prevalent among cocaine-dependent individuals compared to the general population (Medrano et al., 2002). Studies of cocaine-dependent individuals have found a significant association between exposure to childhood maltreatment and psychological distress in response to aversive psychosocial stimuli. For example, one study found that the severity of childhood maltreatment was positively associated with greater perceived threat and harm-avoidance coping strategies in cocaine-dependent individuals (Hyman et al., 2007). These data are particularly alarming as stress is a significant acute and long-term risk factor for drug craving and relapse (Back et al., 2010; McKay et al., 1995).

Perturbations in the HPA axis as a result of ACE play an important role in the development and maintenance of SUDs. Glucocorticoid receptors are ubiquitous in corticolimbic brain regions that regulate emotion (Aronsson et al., 1988). A growing literature suggests that chronic stress produces a persistent elevation in glucocorticoid levels and subsequently accelerates neuronal loss, delays myelination, and attenuates neuronal growth in

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corticolimbic brain regions which may be manifested as maladaptive coping strategies such as drug use (De Bellis, 2002; De Bellis et al., 2002; Dunlop et al., 1997; Gould et al., 1997; Sapolsky et al., 1990). Of note, one study of treatment seeking cocaine-dependent individuals found that changes in HPA hormones to a laboratory stress task were associated with higher amounts of cocaine use during relapse episodes (Sinha et al., 2006). Preclinical studies have found that postnatal stressors increase the reinforcing properties of drugs of abuse, an effect that appears to be related to HPA hormones (Daskalakis and Yehuda, 2015). Thus, the HPA axis may be an important mechanistic link between childhood maltreatment and substance use disorders.

The neuropeptide oxytocin appears to mitigate the effects of stress in individuals with SUDs. For example, compared with placebo, intranasal oxytocin produced significantly lower symptoms of alcohol withdrawal and anxiety in alcohol-dependent subjects (Pedersen et al., 2013). Others have found that intranasal oxytocin produces significantly less craving and anxiety to a social stress task than placebo in marijuana-dependent subjects (Carson et al., 2013; McRae-Clark et al., 2013; Pedersen et al., 2013). Intranasal oxytocin is also known to enhance prosocial and affiliative behaviors in rodents (Ferguson et al., 2001; Witt et al., 1992) and non-human primates (Chang and Platt, 2013). Indeed, some researchers attribute intranasal oxytocin's therapeutic potential to its capacity to enhance reward pathways in response to non drug-related stimuli (e.g. interpersonal relationships, mitigating stress responses) which are commonly eroded by drug abuse over time (see McGregor and Bowen (2012), for review).

However, recent literature suggests that individual and contextual differences may impact the effects of intranasal oxytocin on social stress reactivity (Bartels, 2012; Bertsch et al., 2012; Campbell and Hausmann, 2013; DeWall et al., 2014). For example, in a study of non-human primates, oxytocin increased social contact in subordinate males but not in dominant males (Winslow and Insel, 1991). Collectively, these findings have illuminated critical nuances regarding intranasal oxytocin's therapeutic potential (Bartz et al., 2011; Olff et al., 2013). As a result, one new hypothesis regarding intranasal oxytocin's effects on human behavior suggests that intranasal oxytocin attenuates stress responses more effectively for those with vulnerabilities such as poor coping and emotion regulation skills compared to those equipped with more adaptive stress responses (Bartz et al., 2010; Cardoso et al., 2012; Quirin et al., 2011). Interestingly, alterations in the oxytocin system have been found in adults with a history of childhood maltreatment. For example, women with a history of child abuse exhibit lower levels of oxytocin as compared to women without abuse histories (Heim et al., 2009). Men with a history of maternal neglect exhibit lower oxytocin regulation of HPA axis hormones than men without a history of maternal neglect (Meinlschmidt and Heim, 2007). Thus, in light of the association between ACE and substance use disorders (Douglas et al., 2010; Kessler et al., 1997), it is essential to investigate intranasal oxytocin's potential therapeutic benefits while also taking into consideration the influence of ACE on intranasal oxytocin's effects.

Translational research focusing on oxytocin is currently limited by the scarcity of studies aimed at identifying populations for whom intranasal oxytocin may be beneficial. One critical gap in this literature is that studies examining the effects of intranasal oxytocin on social stress reactivity in the context of commonly co-occurring vulnerabilities, such as substance dependence and ACE, are scant. Addressing this question is essential to better understand potential therapeutic applications of intranasal oxytocin and pathways to treatment for this high risk population. This exploratory study addressed this gap in the literature by examining whether ACE severity influenced the effects of intranasal oxytocin on measures of HPA axis function (e.g. salivary cortisol and Dehydroepiandrosterone [DHEA]) to a social stress laboratory paradigm among cocaine-dependent individuals.

2. Material and methods

2.1. Participants

Our sample was comprised of 31 cocaine-dependent individuals who responded to local media advertisements. Inclusion criteria included current cocaine dependence consistent with DSM-IV diagnostic criteria (Sheehan et al., 1998a). Exclusion criteria included (1) pregnancy, nursing, or ineffective means of birth control; (2) premenstrual dysphoric disorder; (3) history of or current significant hematological, endocrine, cardiovascular, pulmonary, renal, gastrointestinal, or neurological diseases; (4) history of or current psychotic, panic, eating, or bipolar affective disorders; (5) current major depressive disorder or PTSD; (6) history of or current medical conditions that might affect HPA axis activity; (7) synthetic glucocorticoid or exogenous steroid therapy within one month of testing; (8) psychotropic medications, opiates or opiate antagonists, benzodiazepines, antipsychotics, beta-blockers and other medications that might interfere with HPA axis activity; (9) acute illness or fever; (10) body mass index ≥ 35; (11) DSM-IV criteria for other substance dependence except caffeine, nicotine or marijuana within the past 60 days or (12) unwillingness or inability to maintain abstinence from alcohol and other drugs of abuse (except nicotine) for three days prior to the laboratory sessions.

2.2. Measures

Inclusion and exclusion criteria were determined by The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998b) and the substance use module of the Structured Clinical Interview for DSM-IV (SCID-IV; First et al., 1994).

The Adverse Childhood Experiences (ACE) Survey (Felitti et al., 1998) is a 10-item self-report survey used to assess 10 domains including childhood abuse (emotional, sexual and physical), neglect (emotional and physical) and household dysfunction (domestic violence, substance abuse, mental illness, criminal household member and parental divorce/separation). Responses to each item have 1 (*yes*) and 0 (*no*) options. Total scores were obtained by summing all items (Cronbach's $\alpha = 0.65$). While no specific cutoff scores exist for the ACE, higher are associated with increased risk for physical and mental health problems and functional impairment in adulthood (Anda et al., 2002; Chapman et al., 2004; Dube et al., 2002).

2.3. Procedures

All procedures received Institutional Review Board (IRB) approval. To minimize the impact of recent drug/alcohol use on stress reactivity and minimize potential for interaction between study medication and cocaine or alcohol, participants were asked to remain abstinent from cocaine and other drugs for a minimum of three days prior to the study procedures. Abstinence was assessed using self-reports, urine drug screens (Roche Diagnostics, Indianapolis, Indiana), and breathalyzer tests (AlcoSensor III, Intoximeters, Inc., St. Louis, Missouri). Participants were assessed at the same time of day (beginning at 11:00 a.m.) to control for diurnal variations in HPA function. Female participants performed a urine pregnancy test prior to study procedures. THC positive urine drug screens were allowed if the participant denied use in the past three days due to the extended period of detection of THC in urine. Smokers were provided with a nicotine patch.