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Distinct behavioral and immunoendocrine parameters during crack cocaine abstinence in women reporting childhood abuse and neglect

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ABSTRACT

Aim: To assess plasma levels of cortisol and cytokines between cocaine-dependent women with and without childhood maltreatment (CM) history during cocaine detoxification treatment.
Method: We assessed immunoendocrine and clinical parameters of 108 crack cocaine female users during 3 weeks of inpatient detoxification treatment, and 24 healthy women to obtain reference values. Women with (CM+, n = 53) or without (CM-, n = 55) CM history were identified answering the Childhood Trauma Questionnaire (CTQ). Blood samples and clinical assessment were collected before lunch during the first, second and third week post-treatment admission. Flow cytometry was used to assess TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-10, IL-17A plasma levels and ELISA assay was used to measure plasma cortisol levels.
Results: At baseline, lower Th1 and Th17-related cytokines levels and higher Th2 cytokines levels were observed in crack cocaine users compared with reference values. Cytokines levels of cocaine dependents gradually became closer to reference values along detoxification treatment. However, when CM+ and CM- groups were compared, increased levels of IL-6, IL-4 and TNF-α across time were observed in CM+ group only. Additionally, a Th1/Th2 immune imbalance was observed within CM+ group, which was negatively correlated with the severity of the crack withdrawal. Finally, loading trauma exposure severity, immunoendocrine and clinical parameters in factor analysis, we identified three clusters of observed variables during detoxification: (1) systemic immunity and trauma exposure, (2) pro-inflammatory immunity and (3) behavior
Conclusion: Our results suggest the existence of an immunological phenotype variant associated with CM exposure during crack cocaine detoxification of women.

1. 'Introduction

Substantial evidence indicates that childhood maltreatment is associated with increased risk of substance use disorders (Enoch, 2011; Giordano et al., 2014; Teicher and Samson, 2013). For example, childhood sexual abuse exposure in women increases the risk of alcohol or illicit drug dependence 6.6-fold (Kendler et al., 2000). These effects of early-life stress (ELS) exposure are particularly evident in individuals with patterns of heavy substance consumption, as in the case of cocaine use disorder (Shin et al., 2013). Moreover, cocaine dependents with a history of childhood neglect might exhibit more severe depressive and abstinence symptoms during drug withdrawal (Francke et al., 2013; Rovaris et al., 2015), partially contributing to a complex neurobiological derangement including hypothalamo-pituitary-adrenal (HPA) axis and dopamine system dysfunctions (Gerra et al., 2009; Shin et al., 2013).

Considering that ELS effects on development include the reprogramming activity of the HPA axis and subsequently the stress response (Grassi-Oliveira et al., 2008) and the effects of stress on the immune system (Priyadarshini and Aich, 2012), a promising pathway for biomarker searches regarding the link between ELS and cocaine addiction includes the identification of peripheral immune mediators. Thus, it has been reported that childhood

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abuse and neglect exposure can drive a developmental programming of immune responses that increases vulnerability to health problems in adulthood (Roque et al., 2014) and there is evidence of a low-grade pro-inflammatory state across the lifespan, including increasing levels of circulating cytokines such as interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α; Baumeister et al., 2015; Coelho et al., 2014; Haroon et al., 2012; Levandowski et al., 2013).

Similarly, cocaine abuse has robust effects on immunity. *In vitro* experiments documented that cocaine exposure can inhibit cytokine release by spleen cells and macrophages (Wang et al., 1994), and a recent study also found decreased plasma levels of pro-inflammatory cytokines and chemokines in prolonged abstinent powdered cocaine users (Araos et al., 2015). However, clinical studies have shown that early abstinent cocaine dependents present elevated TNF-α and reduced IL-10 (anti-inflammatory cytokine) levels both pre and post-cocaine cue exposure (Fox et al., 2012). In addition, we reported previously that peripheral TNF-α levels predicted crack cocaine acute withdrawal symptom severity (Levandowski et al., 2014). Hence, it seems that acute abstinence is associated with higher levels of peripheral pro-inflammatory cytokines and this condition plays a role in the behavioral negative reinforcing effects of cocaine use disorder, particularly in craving incubation and negative mood (Fox et al., 2012).

Therefore, we hypothesized that crack cocaine users with and without prior ELS history are clinically and biologically distinct. Moreover, we hypothesized that a preexisting or concomitant pro-inflammatory immune profile might be associated with the symptoms of crack cocaine acute abstinence, particularly taking into account that ELS can "prime" the immune system with long-lasting effects on its functioning (Coller and Hutchinson, 2012). Thus, we investigated a comprehensive immune panel, including cytokines related to cellular immune responses (Th1), humoral immunity and anti-inflammatory signaling (Th2), as well as cytokines involved in the recruitment of neutrophils and macrophages to participate in and amplify the inflammatory reaction (Th17) (Souto et al., 2014) in a sample of crack cocaine addict women with and without a history of ELS. Since previous cytokine findings are derived mostly from males or mixed gender samples reporting cocaine abstinence of at least 3 weeks, we decided to use a longitudinal approach that allowed us to explore the role of ELS and peripheral cytokines on withdrawal and depressive symptom severity during the first 3 weeks of detoxification (Souto et al., 2014). We also examined plasma cortisol levels since cortisol could impact the expression of cytokines (Kunz-Ebrecht et al., 2003) and has been found associated with CM in cocaine patients (Gerra et al., 2009).

2. Materials and methods

2.1. Study design

The research was designed as a longitudinal study (Fig. 1) of treatment-seeking women with crack cocaine use disorder admitted to a three-week inpatient detoxification treatment in Southern Brazil in a protocol previously described (Viola et al., 2014). Patients were recruited in the first week of treatment. A total of 108 crack cocaine addict patients were included and assessed for immunoendocrine and clinical parameters at baseline (4th day post-admission), 7 days (11th day post-admission) and 14 days later (18th day post-admission). Twenty-four healthy control (HC) non-drug users also were included in this study in order to allow researchers to get reference values regarding protein levels. The ethical committee of institutions approved this study, and all of the participants provided written informed consent before enrollment.

2.2. Crack cocaine sample

The 108 patients were recruited from an inpatient detoxification unit according to the following procedure: (1) At the first week, patients were assessed regarding psychiatric diagnosis, childhood trauma exposure, crack cocaine abstinence symptoms and depression symptoms and blood samples were drawn; (2) At the second and third week, they completed crack cocaine abstinence symptoms and depression symptoms inventories and underwent another blood draw.

Inclusion criteria for the crack cocaine addict women were as follows: age between 18 and 55 years; diagnosis of a crack cocaine use disorder with physiological dependence according to DSM-IV; absence of comorbidity with psychotic syndromes; absence of medical conditions, including infectious, neurological, rheumatologic, endocrine, allergic and cardiovascular diseases; absence of history of use of corticosteroids, antibiotics or anti-inflammatory drug use. After the history of childhood abuse and/or neglect had been assessed, women with childhood maltreatment (CM+, n = 53) and without (CM-, n = 58) were identified and separated into two distinct groups.

2.3. Control participants

Healthy and unmedicated control participants (HC, n = 24) were selected by convenience sampling (advertising) from the same age and socio-economic background in order to provide peripheral cytokine and cortisol reference values. We excluded from the HC group any individuals with past or current Axis I disorders, history of childhood maltreatment, severe or unstable clinical illness, neurologic disorder, or any substance use in the 30 days preceding the study.

2.4. Crack cocaine detoxification treatment

The crack cocaine detoxification program consisted of 21 days of inpatient treatment for women with drug use disorders. The treatment was voluntary and free. During detoxification, patients had no access to alcohol, cigarettes or drugs, and they were asked to take part in daily psychoeducation, relapse prevention and support groups. In addition, all patients had access to prescriptions for first-generation antipsychotic medications if psychomotor agitation occurred, or mood stabilizers and antidepressants if necessary. Moreover, participants received constant nursery care, occupational therapy, nutritional care, including a normocaloric diet of 2200 Kcal/day, and light physical activity three times per week.

2.5. Childhood maltreatment

The presence of ELS history was investigated in the first week of detoxification through the validated Portuguese version of the Childhood Trauma Questionnaire (CTQ; Grassi-Oliveira et al., 2006; Viola et al., 2014), including any history of sexual, physical and emotional abuse, as well as physical and emotional neglect during childhood (Bernstein and Fink, 1998). The participants were asked whether they had enough to eat, whether their parents' drinking interfered with their care, whether they ever wore dirty clothes and whether there was someone to take them to the doctor during childhood (Bernstein et al., 2003). In this study, the CM+ group consisted of participants who reported having been exposed to at least one moderate-to-severe modality type of child abuse or neglect according to the CTQ manual (Bernstein and Fink, 1998).

2.6. Clinical evaluation

Severity of crack cocaine withdrawal and depression symptoms were evaluated on the fourth, eleventh and eighteenth day of the 3-