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Adipokines during early abstinence of crack cocaine in dependent women reporting childhood maltreatment

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ABSTRACT

Childhood maltreatment has been associated with addiction and immune dysregulation, although neurobiological substrates underlying this association remain largely unknown. The aim of the study was to compare plasma levels of adipokines during early abstinence in crack cocaine dependent women with (CM+) and without history of childhood maltreatment (CM−). One hundred four crack cocaine female users were followed for 20 days in a detoxification inpatient treatment unit. Plasma levels of adiponectin, resistin and leptin were assessed every 7 days during 3 weeks of follow-up. The Childhood Trauma Questionnaire (CTQ) retrospectively assessed childhood maltreatment history. A healthy control group was included to provide adipokines reference values (HC). All crack users increased leptin plasma levels during early abstinence despite concentrations remained lower in comparison with non-users group. Crack users reporting childhood maltreatment exhibited a significant reduction in plasma levels of adiponectin and resistin when compared to CM− group. In addition, only CM− participants increased plasma levels of adiponectin during detoxification. This is the first study evaluating adipokines during crack cocaine abstinence. Our results suggest a modulator effect of childhood maltreatment on inflammatory status in treatment-seeking crack cocaine dependents during early abstinence.

1. Introduction

Childhood maltreatment has been associated with the development of substance-related disorder across life span (Kendler et al., 2000; Enoch, 2011), especially with a progression toward heavy substance abuse (Hyucksun Shin, 2012; Shin et al., 2013), despite the underlying mechanism of this association still is unknown. However, recent studies have demonstrated that both early life stress (ELS) (Rooks et al., 2012) and substance abuse, especially cocaine (Fox et al., 2012), have robust effects on the inflammatory system. Childhood adversities have been associated with increased pro-inflammatory markers during adulthood and mental and physical health related problems (O'Donovan et al., 2012). Particularly, childhood abuse and neglect seem to increase pro-inflammatory markers such as basal C-reactive protein (CRP), interleukin (IL)-6 (Rooks et al., 2012) and circulating tumor necrosis factor-alpha (TNF-alpha) (Kiecolt-Glaser et al., 2011). In line with it, data from a birth cohort show that more than 10% of cases of low-grade inflammation, assessed by increased levels of high-sensitivity CRP, might be attributable to childhood maltreatment (Danese et al., 2007). Therefore, some authors have been suggesting that ELS may program immune cells through epigenetic changes, modifying them to easily engage in inflammatory response or increasing resistance to anti-inflammatory signaling (i.e. glucocorticoid effects) (Rooks et al., 2012). In addition, adults exposed to ELS seems to overreact in their emotional and physiological stress response and this could impact immune system.

Regarding cocaine, chronic and acute use can induce protracted decreases in innate immune mechanisms interfering with autonomic activity in humans (Irwin et al., 2007) and have general suppressive effects on the mouse immune system (Ou et al., 1989). Moreover, in vivo experiments with the protozoan Tetrahymena, suggests that its phagocytic activity was decreased after the administration of cocaine, an effect that was more extensive after

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the administration of crack cocaine – very potent cocaine in pellet form that is smoked (Stefanidou et al., 2011). These effects might be observed even after 10 days withdrawal from cocaine when cue previously associated with cocaine self-administration suppress some parameters of cell-mediated immunity (Th1) (Kubera et al., 2008). On the other hand, other authors have showed that in response to the acute administration of cocaine or methamphetamine, at the protein and mRNA level, primary pro-inflammatory cytokines are upregulated (Clark et al., 2013). Therefore, a growing body of evidence has indicated that cocaine-dependent individuals have a dysregulation in the inflammatory system that is involved in the reinforcement of the negative effects of substance use (Niwa et al., 2007). Fox et al. (2012) showed that treatment-seeking cocaine-dependents exhibited elevated levels of TNF-alpha in baseline and during stress response. Additionally, acute cocaine abstinence periods are related to lower production of TNF-alpha and IL-6 in cocaine-dependents compared with healthy controls (Shen et al., 1994; Irwin et al., 2007). In line with such observations, some authors have suggested that a disruption of energetic homeostasis, including the immune system, could interfere with clinical responses to cocaine treatment, since cocaine dependent individuals demonstrate increased immune system inflammation both at the baseline and in response to stress and cue imagery conditions in comparison with social drinkers controls (Fox et al., 2012).

The modulation of energetic homeostasis has been associated with inflammatory mediators called adipokines, including adiponectin, resistin and leptin (Soczynska et al., 2011). Specifically, leptin is considered as a mediator of satiety and is involved in signaling within midbrain reward circuits and regulating reward-related behavior (Davis et al., 2010). Interesting recent findings showed that adipokine expression is associated with childhood trauma exposure (Lehto et al., 2012) and substance use (Housova et al., 2005). However, there is little available literature on adipokines in the cocaine addiction. Therefore, this exploratory follow-up study aimed to investigate plasma levels of adiponectin, resistin and leptin during the early abstinence period of crack cocaine dependent women with and without a history of childhood maltreatment.

2. Methods

2.1. Participants

This follow-up study included 104 treatment-seeking crack cocaine female dependents. The sample was divided into two groups: crack cocaine patients with (CM+, $n=67$) and without a history of childhood maltreatment (CM−, $n=37$). The CM+ group consisted of participants who reported having been exposed to at least one moderate-to-severe type of child abuse or neglect according to the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003; Grassi-Oliveira et al., 2006). For reference purposes, the study included a healthy female control group using convenience sampling (HC, $n=18$). The control participants were assessed by clinical interview and were not using any medication and did not fulfill criteria for any psychiatric disorder.

Participants were included if they (1) had the primary diagnosis of cocaine dependence according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders IV (SCID IV); (2) had not been using corticosteroids, antibiotics or anti-inflammatory drugs; (3) did not have current infectious diseases or history of autoimmune, endocrine or coronary heart disease, rheumatoid arthritis, or neurological disorders; and (4) did not report past or current psychotic disorders. This investigation was carried out in accordance with the latest version of the Declaration of Helsinki, the ethical committee of institutions approved this study and all the participants provided written informed consent before enrollment.

2.2. Procedures

All patients were recruited and followed up for a 3 week period after admission to a locked detoxification treatment facility for female drug and alcohol abusers. All participants received a normal diet of 2200 cal/day with light physical activity three times per week. Additionally, they had no access to cigarettes, alcohol or other drugs.

The Fagerstrom Test for Nicotine Dependence was used to assess the degree of physical nicotine dependence (Heatherton et al., 1991). The Cocaine Selective Severity Assessment (CCSA) (Kampman et al., 1998) assessed crack cocaine abstinence symptoms and The Addiction Severity Index (ASI-6) (Cacciola et al., 2011; Kessler et al., 2012) assessed the severity of drug and alcohol use in the last 30 days prior admission.

2.3. Assessment of adipokines

Ten milliliters of blood were drawn from each participant by venipuncture in an EDTA tube. The blood samples of crack cocaine patients were collected at the 4th, 11th and 18th days of the 3 week hospitalization; the control group had only a single blood draw. The protocol started in Day 4 due ethical aspects, since some patients could have difficulties to understand the Informed Consent or still be under influence of acute crack cocaine effects during the first hours after admission. All blood samples were collected between 11:00 and 11:30 A.M. and after 3 h of fasting to minimize differences due to biological variation. The blood was centrifuged immediately at 3000g during 5 min and 4 °C. Plasma was collected and stored in a −80 °C freezer until assayed. Plasma levels of adiponectin, resistin and leptin were measured by an enzyme-linked immunosorbent assay (ELISA) according to the procedures supplied by the manufacturer. All samples were assayed in duplicate. Detection limits were defined at 5 pg/mL for adiponectin, resistin and leptin. All concentrations were expressed in ng/mL.

2.4. Statistical analysis

Differences among groups in demographic and clinical variables were assessed using Chi-Squared tests for categorical variables. Because all variables showed a non-normal distribution, the Mann–Whitney *U*-test or the Kruskal–Wallis test was used for comparisons between groups regarding continuous variables and rank analysis of covariance (Quade ANOVA) was used to compare adipokine levels between crack groups and the control group using age and BMI as co-variants. Spearman bivariate correlations were used to verify the relationship between adipokines and abstinence symptoms.

To examine adipokine plasma level differences between CM+ and CM− in crack users during follow-up, multiple regression analyses that applied Generalized Estimating Equations (GEE) (Hanley et al., 2003) were used to assess the effect of TIME (Days 4, 11 and 18) and GROUP (CM+ vs. CM−). BMI was included as a covariant together with age and days of abstinence prior to enrollment. The model-based estimator was assumed and specified as exchangeable (Ghisletta and Spini, 2004). The few non-detectable adipokine values were not included in the analyses (see degree of freedom in each analysis). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Demographic and clinical features of all participants are shown in Table 1. There were no statistically significant differences between the two crack cocaine dependent groups regarding age, BMI, caloric intake, severity of drug use behavior, degree of physical nicotine dependence, addiction severity and severity of abstinence. Both crack cocaine dependent groups were younger than the control group.

All comparisons and adipokines values can be followed in Fig. 1. In general, crack cocaine users presented lower levels of leptin during early abstinence in comparison with healthy controls (HC) (Day 4: $U=336.0$, $p<0.001$; Day 8: $U=421.0$, $p=0.001$; Day 11: $U=482.0$, $p=0.01$).

Pairwise comparison in rank analysis of covariance between crack cocaine users reporting childhood maltreatment (CM+), crack users without it (CM−) and HC, taking age and BMI as covariants, revealed: (1) only the CM− group increases the levels of adiponectin during detoxification days in comparison with the HC group; (2) no between group differences regarding resistin plasma levels were observed; (3) CM+ and CM− groups exhibited similar levels of leptin but lower levels in comparison with HC participants. The proportion of non-detectable values were equally distributed between both crack cocaine groups – maximum of 14%