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Early life stress and tumor necrosis factor superfamily in crack cocaine withdrawal

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ABSTRACT

Background: Both early life stress (ELS) and substance abuse, especially cocaine, have robust effects on the inflammatory system. Considering the role of the tumor necrosis factor system in inflammatory signaling and its association with ELS, the aim of the study was to compare plasma levels of TNF-alpha, its soluble receptors and ligands during early abstinence of crack cocaine.
Methods: This study included 24 crack cocaine-dependent women with (CRACK-ELS) and 20 without (CRACK) a history of ELS. A healthy control group (HC), containing 25 participants, was included to provide reference values. The Childhood Trauma Questionnaire (CTQ) retrospectively assessed childhood maltreatment history of patients. Plasma levels of TNF-alpha, TNF-related weak inducer of apoptosis (TWEAK), TNF-related apoptosis-inducing ligand (TRAIL), soluble receptors TNFRI (sTNFRI) and TNFRII (sTNFRII) were assessed on the 18th day of treatment.
Results: The CRACK-ELS group had higher TNF-alpha and lower TWEAK levels compared to the CRACK and HC groups. sTNFRII was increased, but only in comparison with the crack cocaine group and the controls. TRAIL levels were slightly higher in the CRACK-ELS group, while no differences were found for sTNFRI levels. Also, TNF-alpha plasma level was positively predicted by abstinence severity and childhood maltreatment severity, and TWEAK was negatively predicted by childhood maltreatment severity.
Conclusions: This is the first study to evaluate the newly secreted tumor necrosis factor superfamily ligands, TWEAK and TRAIL, during crack cocaine abstinence, supporting the association between early life stress and peripheral pro-inflammatory levels.

1. Introduction

Substance abuse disorders include genetic and environmental factors in their etiological models (Kendler et al., 2007). Among those, childhood maltreatment has been shown to be associated with an increased risk of substance abuse disorders, including cocaine dependence in adult life, and particularly for heavy consumption of substances (Shin et al., 2013). In spite of this well recognized association, the pathophysiological mediators of this relation remain unknown.

Inflammation has been defined as a physiological response of the organism to external or internal deleterious stimuli, and, in normal conditions, this is a mechanism for the protection and reparation of tissues (Goetz et al., 2004). Nevertheless, when inflammation is severe or is maintained for a long time, it is toxic for neural substrates (Brietzke and Kapczinski, 2008). One critical

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group of substances involved in inflammatory response is cytokines. They are proteins or glucoproteins that act as communicators between immune cells such as macrophages and lymphocytes (Tansey and Szymkowski, 2009).

Recently, deregulation of immune system has been considered a possible link between the adverse experiences during childhood and psychiatric syndromes, including addictions (Coelho et al., 2014; Haroon et al., 2012). In fact, cytokines are now conceived as biomarkers of the degree of inflammation in many psychiatric disorders, including cocaine addiction (Shin et al., 2013). It is well established that these immune mediators interact with monoamine metabolism, neuroendocrine function, synaptic plasticity, and neurocircuits (Haroon et al., 2012).

TNF-alpha has been one of the most studied inflammatory mediators because of its crucial role in the modulation of innate immunity, which includes the regulation of macrophage-mediated cytotoxicity due to pro-apoptotic signaling (Goetz et al., 2004). The members of TNF superfamily are a diverse group of molecules that function as key mediators of TNF-alpha regulation (Tansey and Szymkowski, 2009). For example, TNF-alpha exerts its main effects by binding two specific receptors, TNFRI and TNFRII, both with markedly different functional endpoints. TNFRI leads to the recruitment of associated death domain protein-mediated apoptosis and Nuclear Factor-kappa B (NF-kB) activation. TNFRII is only associated with NF-kB activation and appears to have a dominant role in suppressing TNF-mediated inflammatory responses (Chen and Goeddel, 2002; Granell et al., 2004).

However, ligands of the TNF family control the immune and inflammatory responses at several levels, and other molecules can influence TNF-alpha synthesis and release, such as the two new TNF superfamily ligands: TNF-related weak inducer of apoptosis (TWEAK) and TNF-related apoptosis-inducing Ligand (TRAIL) (Tansey and Szymkowski, 2009). TWEAK, also known as Apo3L or TNFSF12, mediates different immune responses and one of its functions is to attenuate the transition from innate to adaptive immunity (Burkly et al., 2007), balancing TNF activity by repressing the production of pro-inflammatory cytokines such as IFN-γ and IL-12 (Maecker et al., 2005). TRAIL (Apo2L or TNFSF10), acts by triggering the extrinsic apoptotic pathway by interacting with death receptors DR4 (TRAILR1) and DR5 (TRAILR2) and is also capable of inducing apoptosis in cancer cells and seems to be involved in tumor suppression and immune cell homeostasis (Falschlehner et al., 2009; Wajant, 2004; Wang and El-Deiry, 2003).

Mounting evidence suggests a chronic pro-inflammatory state in individuals with compulsive drug consumption (Fox et al., 2012) and with histories of abuse or neglect during early childhood (Kiecolt-Glaser et al., 2011), including higher levels of acute-phase proteins and pro-inflammatory cytokines, such as interferon-gamma (IFN-gamma), Interleukin (IL)-6 and tumor necrosis factor alpha (TNF-alpha). In this vein, it is also suggested that a pro-inflammatory state might contribute to the reinforcement of the negative effects of cocaine use (Niwa et al., 2007). This can occur because TNF-alpha activates synaptosomal and vesicular dopamine uptake (Nakajima et al., 2004). In this line, Nakajima et al. (2004) also reported that TNF-alpha reduces methamphetamine and morphine-induced behavioral sensitization and rewarding effects by promoting plasmalemmal and vesicular dopamine uptake as well as attenuating the metamethamine and morphine-induced increase in overflow of DA in the Nucleus Accumbens (Nakajima et al., 2004; Niwa et al., 2007). Nevertheless, the mechanisms by which TNF-alpha regulates the uptake of dopamine as well as their relevance in addiction remain poorly understood.

Therefore the aim of the present study was to evaluate TNF-alpha, sTNFRI, sTNFRII, TRAIL and TWEAK plasma levels in crack cocaine-dependent women with and without a history of CM, during the period of early abstinence. Considering that ELS is associated with a chronic pro-inflammatory state independent of clinical comorbidities (Coelho et al., 2014) we expected to find higher levels of TNF-alpha in the crack cocaine users reporting childhood abuse and/or neglect.

2. Methods

2.1. Participants

Forty-eight women, crack cocaine users, inpatients of a 3-week detoxification program of a public psychiatric hospital in Southern Brazil were enrolled in this cross-sectional study by convenience sampling. All patients came from mental health community services. During an ongoing follow up study (Levandowski et al., 2013) we identified the first 24 patients with a positive history of childhood abuse and/or neglect (CRACK-ELS) and paired them considering age with other 24 patients without any form of child victimization (CRACK). In addition women without medication use, without medical conditions and who did not fulfill DSM-IV criteria for any psychiatric disorder were enrolled by convenience as healthy controls (HC, $n = 25$). The minimum sample size ($n = 23$) was estimated according TNF-alpha plasma levels found in schizophrenia patients with a history of childhood trauma and schizophrenia patients and controls with no history of childhood trauma (Dennison et al., 2012), since it was the only study found in this regard at the time.

Participants were not included if they: (1) had been taking corticosteroids, antibiotics or anti-inflammatory drugs; (2) had current infectious diseases or history of autoimmune, endocrine or coronary heart disease, rheumatoid arthritis, or neurological disorders; and (3) reported past or current psychotic disorders. We had to exclude four participants of CRACK group due undetected protein levels in ELISA assays.

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. Cross sectional assessments were conducted between the 15th and 18th day of abstinence. 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 of the participants provided written informed consent before enrollment.

2.2. Clinical assessment

Height and weight were measured by standardized protocols (Willett et al., 1997), to calculate the body mass index (BMI = kg/m^2). The Portuguese version of the Structured Clinical Interview for DSM Disorders (SCID I) has good inter-rater reliability (Del-Ben et al., 2001) and it was used to determine psychiatric disorders. Early life stress were assessed through the validated Portuguese version of Childhood Trauma Questionnaire (CTQ) (Grassi-Oliveira et al., 2014), including history of sexual, physical and emotional abuse, as well as physical and emotional neglect during childhood (Bernstein et al., 2003; Grassi-Oliveira et al., 2006). In this study, the CRACK-ELS 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 CTQ manual. The Fagerstrom Test for Nicotine Dependence was used to assess the degree of physical nicotine dependence (Heatherton et al., 1991), since nicotine has marked inflammatory effects (Steptoe and Ussher, 2006). The Brazilian version showed good validity and reliability (de Meneses-Gaya et al., 2009).

Severity of depressive symptoms was evaluated by the validated Brazilian version of Beck Depression Inventory (BDI-II) (Gomes-