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Differences in biomarkers of crack-cocaine adolescent users before/after abstinence

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ABSTRACT

Aims: To measure the variation in Brain-Derived Neurotrophic Factor (BDNF), Thiobarbituric Acid Reactive Substances (TBARS) and interleukin (IL) levels in crack-cocaine dependent adolescents after 21 days of abstinence, comparing to levels found in a group of healthy controls.
Design: Cross-sectional nested on a short follow-up study.
Setting: Two inpatient treatment units for adolescents, and a low-income neighborhood.
Participants: 90 adolescents, of both genders, with diagnosis of crack cocaine dependence, and 81 healthy adolescents.
Measurements: Serum levels of IL-6, IL-10, TBARS and BDNF were assessed on admission and discharge. Drug addiction severity was assessed by the Addiction Severity Index – Teen Version (T-ASI) and Cocaine Craving Questionnaire – Brief version (CCQ-b). Psychiatric comorbidities were assessed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL). Generalized Estimating Equations (GEE) were used to estimate the IL-6, IL-10, TBARS and BDNF levels, adjusted for confounders. Hedges' g was used to estimate effect size.
Findings: TBARS ($p = 0.005$, $d = 0.04$), IL-6 ($p = 0.027$, $d = 0.40$) and IL-10 ($p = 0.025$, $d = 0.41$) were elevated and BDNF ($p < 0.001$, $d = 0.62$) was reduced ($p < 0.001$), in patients, in comparison to controls, at admission time. Variation in those levels between admission and discharge were not significant.
Conclusions: Crack-cocaine use seems to be associated with inflammatory and oxidative imbalances in adolescents.

1. Introduction

Adolescence is a vulnerable period for the development of drug addiction (Chambers, 2003; Kandel and Yamaguchi, 1993). Possible determinants for this vulnerability include not only psychosocial reasons (Kliewer and Murrelle, 2007), but also differences in the physiological functioning of the brain (Chambers, 2003), and, quite possibly, different effects in the reaction of the brain to the drugs of dependence. The identification of biomarkers associated with drug dependence is of extreme importance in understanding how addiction affects the brain, and, hopefully, in developing prevention and treatment strategies.

One possible model for understanding the effects of drugs of abuse on the developing brain is the allostatic load model. This model proposes that the brain will change its hormonal and immunologic equilibrium in order to adapt to the presence of chronic stressors, reaching the so-called “allostatic state”. The consequences sustained in order to keep this abnormal equilibrium state are called allostatic load (McEwen, 2000). Proposed biomarkers involved in the allostatic load model include neurotrophins, oxidative stress parameters and inflammatory cytokines, among others (Koob, 2009).

The Brain Derived Neurotrophic Factor (BDNF) is one of such potential biomarkers. It is the most abundant neurotrophin in the brain (Thoenen, 1995) and is involved in neurogenesis, neuroplasticity and cognitive functioning (Huang and Reichardt, 2001). Animal studies suggest that it crosses the blood-brain barrier (Pan et al., 1998) and a high correlation between cortical and peripheral blood concentrations

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(Karege et al., 2002; Rasmussen et al., 2009; Sartorius et al., 2009). It has been associated with responses to anxiety and stress (Malter Cohen et al., 2013) and with many other psychiatric disorders (Balaratnasingam and Janca, 2012). It seems to play a crucial role in addictive behaviors, such as in addictions to alcohol (D'Sa et al., 2012) and psychostimulants (McGinty et al., 2010). Regarding the use of cocaine, there seems to be an increase in mesolimbic dopamine system BDNF levels that is withdrawal-time-dependent, with levels increasing up to 90 days after withdrawal has begun (Grimm et al., 2003). In humans, a recent study has shown that high BDNF levels after 3 weeks of cocaine abstinence are a possible predictor of earlier and more severe relapse (D'Sa et al., 2011). In another study with 23 cocaine dependents, BDNF was found to be increased after a period of 2 weeks of abstinence, and the baseline levels were reduced in relation to healthy controls. von Diemen et al. (2014) has already shown that BDNF levels increase during early crack abstinence with an inverse correlation with both the quantity of crack used in the previous 30 days and years of crack cocaine use in a study including 49 adult male patients. Another recent study suggests the absence of elevation in BDNF levels during cocaine abstinence is associated with cocaine-induced psychotic symptoms (Corominas-Roso et al., 2013a). Viola et al. (2014) has shown, in a sample of 104 female crack users that BDNF levels were higher than in controls in the 4th and 18th day of detoxification treatment.

Oxidative stress has been implicated in the mechanisms underlying dependence and toxicity of many psychoactive substances (Ng et al., 2008), including cocaine. One possible way to assess oxidative stress is through the measurement of Thiobarbituric Acid Reactive Substances (TBARS). The levels of TBARS have been assessed on a few studies with cocaine dependent patients, with conflicting results. The study by Narvaez et al. (2013) found no difference between cocaine dependent outpatients and healthy controls, whereas another study from the same group (Sordi et al., 2014) showed an increase of TBARS levels after a period of abstinence of cocaine on severe dependent crack-cocaine patients, but not on those with less severe dependence.

Interleukin-6 (IL-6) is mostly regarded as a pro-inflammatory cytokine (Tanaka et al., 2014), mainly due to the recruitment of lymphocytes through chemokine expression (Scheller et al., 2011). Interleukin-10 is primarily an anti-inflammatory cytokine, having a potent inhibitory effect on production of several pro-inflammatory mediators, including Tumoral Necrosis Factor (TNF), and many pro-inflammatory cytokines, like IL-1β and IL-1α. (Woodcock and Morganti-Kossmann, 2013). Few studies have assessed the relationship between Interleukins and cocaine dependence. Gan et al. (1998) studied IL-10 levels in cocaine-dependent patients after 4 days of abstinence, before and after an IV cocaine infusion, and compared such levels to controls without drug use. They found increased IL-10 levels in patients, and such levels decreased after the cocaine injection. With a similar methodology, Irwin et al. (2007) found reduced levels IL-6 in cocaine dependent patients after 2 days of abstinence and, after an IV cocaine infusion, reduced secretion of IL-6 in those patients. The previously mentioned study by Narvaez et al. (2013) found elevated levels of IL-10 in cocaine-dependent patients in relation to controls, but no difference in IL-1Beta, IL-6, IL-8 a and IL-12 levels.

Cocaine is a potent stimulant, and its use, especially in the smoked form (crack-cocaine), is a severe health problem in many countries (Fischer and Coghlan, 2007; Haasen et al., 2004; Werb et al., 2010), including Brazil (Galduróz et al., 2004; Nappo et al., 2012; Pianca et al., 2016). Its use by adolescents has increased considerably in the last few years (Duailibi et al., 2008), and the importance of adolescence as a developmental stage is extremely relevant for our understanding of the pathogenesis of addictions. Despite that, studies on biomarkers in this age group are very scarce. All of the human studies mentioned so far investigated adult patients, and we are not aware of studies on adolescent populations. We postulate that crack cocaine adolescent abusers will present with biomarker alterations similar to the ones described in the adult studies above, and that those alterations will be altered after a period of abstinence, resulting in biomarker levels closer to those of controls. Thus, the objective of this study is to assess the peripheral levels of BDNF, TBARS, IL-6 and IL-10 in crack cocaine adolescent users before and after a period of abstinence, and compare those levels to a control group.

2. Material and methods

2.1. Participants

Patients were enrolled as a consecutive sample, from May 2011 to August 2012. All adolescents referred to two inpatient units for treatment of crack-cocaine related problems in the city of Porto Alegre, Brazil were included. The inclusion criteria were 12–18 years of age, recent crack cocaine use − verified with a cocaine urine screen test upon admission (Bio easy® cocaine test, Alere™, Brazil). Exclusion criteria included institutionalized or acutely psychotic patients who would not be able to give informed consent. A total of 94 patients were invited for the study. Two refused to participate. One was institutionalized and did not have proper legal guardians who could give informed consent. One was excluded due to an acute psychotic episode. Eleven subjects had only one blood sample collected, due to transference to another unit (n = 1), early discharge (n = 6) or running away (n = 4) from the unit. During the hospital stay, patients were not allowed to use any kind of psychoactive substance, including nicotine.

Controls were selected from a community sample. This location is in the coverage area of the hospital wards cited above. After reviewing this community unit's records, the houses in which there were adolescents (12–18 years of age) were randomly selected to be interviewed, according to the proximity to the healthcare unit. In this system, everybody who lives inside this geographically limited area is covered by the healthcare records (Family Health model). The only exclusion criterion was self-reported use of any psychoactive substances. Only one individual was excluded for this reason. Controls were not matched to the cases.

2.2. Data collection

Cases were assessed through a three-stage procedure. First, they were clinically assessed by a Child and Adolescent Psychiatrist (RLR) upon admission for eligibility to the study and in order to deliver treatment as usual. Afterwards, a semi-structured interview, Schedule for Affective Disorders and Schizophrenia for School-Age Children − Present and Lifetime Version (K-SADS-PL) (Brasil and Bordin, 2010; Kaufman et al., 1997), was applied to all subjects by trained research assistants. All positive diagnoses were discussed in a clinical committee with another Child and Adolescent Psychiatrist (TGP), and if any uncertainty about the diagnosis remained, this psychiatrist would re-evaluate the patient clinically. Patients could be treated with medication for any comorbidity diagnosed. Also, the Teenage version of the Addiction Severity Index (T-ASI)(Sartes et al., 2009) was administered.

Controls were first assessed by the same trained research assistants using the K-SADS-PL. Positive diagnoses were discussed and re-evaluated by the same method above. The ASSIST scale was used to detect any possible drug abusers, who were excluded for the sample. The T-ASI interview was not applied on controls.

2.3. Blood collection and analysis

As per determination of the local public health system policy, the length of inpatient treatment for drug detoxification is usually 21 days, with few exceptions. Therefore, blood samples in our study were planned to be collected at two occassions: 1) On admission or on the day after, while cocaine use was yet recent and could still be detected by urine test, and 2) 21 days later, before discharge.