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Research article

Evaluation of oxidative stress and brain-derived neurotrophic factor levels related to crack-use detoxification

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ABSTRACT

Crack is a central nervous system stimulant extracted from the *Erythroxylum coca* plant. It is considered the most potent and addictive form of cocaine, and its euphoric effects are attained within a few seconds after consumption. Alteration of biological markers of oxidative stress and brain-derived neurotrophic factor (BDNF) could be related to the severity of crack withdrawal symptoms in patients undergoing rehabilitation. Thus, the objective of this study was to evaluate if the crack consumption and the drug detoxification process during 14 days in hospitalization regime was able to modify the oxidative status and BDNF levels, in male crack-abstinent patients. The crack detoxification process increased the glutathione (GSH), total thiol content (GST), nitric oxide (NO), and superoxide dismutase (SOD) levels, and reduced the mean BDNF levels. Moreover, a positive correlation was found between the number of hospital admission days and SOD values and between the GST levels and crack-use time after 14 days of detoxification. Furthermore, a negative correlation between the frequency of crack use and NO levels on the first day of hospitalization was also found. In conclusion, the results of this study indicated that crack consumption causes increased oxidative stress in drug users and that the detoxification process during 14 days was sufficient to improve oxidative parameters and antioxidant defenses of the patients, which could positively contribute to rehabilitation process. In addition, we also observed a great variability in the BDNF levels of the patients during the detoxification process, resulting in a reduction in the mean values of this neurotrophin.

1. Introduction

Coca has been consumed for thousands of years by pre-Incan and pre-Columbian populations. However, cocaine became popular in Europe and the United States only in the early 19th century. In particular, it was in the late 1970s and early 1980s that cocaine became popular in Western societies as a “glamor” drug [7,30].

Studies have shown that the consumption of cocaine leads to an increase in the production of reactive oxidative species [19], which involves the direct activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and secondary activation of xanthine oxidase in cardiomyocytes [28,33]. Moreover, cocaine consumption results in a reduction of antioxidant defenses, such as reduced glutathione (GSH) [2,17,18,51], glutathione reductase (GPx) [44],

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superoxide dismutase (SOD), and catalase activities [18,20]. GSH acts by protecting the mammalian cells against oxidative damage. A decrease or total exhaustion of GSH levels have been reported in different tissues following cocaine administration in mice [33,55].

Crack is a central nervous system stimulant extracted from the *Erythroxylum coca* plant. Although crack has the same chemical form as cocaine, it is derived by a different method (i.e., dissolution of cocaine hydrochloride in water with sodium bicarbonate to extract the hydrochloride). This process renders it volatile at low temperatures and stable under heat, which allows crack to be smoked. Crack is considered the most potent and addictive form of cocaine, and its euphoric effects are reached within only few seconds [23,35]. Furthermore, there is evidence that the reduction of biological markers of oxidative stress could be related to the severity of crack withdrawal symptoms in patients undergoing rehabilitation [64].

Psychostimulant dependence is a chronic disease that is related to frequent relapses, even after long periods of drug abstinence [8,11,49]. Recently, studies have shown that the chronic compulsive drug use and relapse of users are related to the development of neurochemical and cellular adaptations that result in long-lasting neuroplastic changes in brain circuits [47,63]. In particular, one of the most abundant neurotrophins in the brain, known as the brain-derived neurotrophic factor (BDNF), acts as an adaptive regulator of synaptic plasticity in the central nervous system in response to environmental requirements in adult mammals [56]. BDNF-mediated signaling positively regulates various proteins, including antioxidant enzymes. Evidence indicated that insufficient exposure to BDNF could lead to brain vulnerability to neurodegenerative disorders and injuries, such as Alzheimer's, Parkinson's, and Huntington's diseases [56]. Furthermore, BDNF have been concomitant with psychiatric disorders associated with the use of substances such as crack [37,38]. Recent evidence suggested that BDNF is involved in the neuroadaptive changes of the dopaminergic or glutamatergic system related to abuse and dependence on psychostimulants such as cocaine, and that BDNF increases the initial stimulant effect caused by cocaine [4,22,26,41,52]. Moreover, previous clinical studies have reported an increase in plasma BDNF levels during initial crack withdrawal, related to increasing craving for the drug and reduced time to relapse [13,16,62].

However, despite the similarities between crack and cocaine, there are only a few studies reporting on the effects of crack consumption and abstinence on oxidative stress and BDNF levels. Moreover, crack withdrawal during the detoxification process is a critical time frame for the patients' response and may be associated with redox imbalance and BDNF levels. Considering that crack is a social problem, it is important to understand better the factors that could be related to crack dependence, and to seek to improve the efficiency of crack detoxification treatments. Thus, the objective of this study was to evaluate the effects of crack consumption and detoxification on oxidative stress and BDNF levels during inpatient treatment, before and after detoxification, in male crack abstinent patients.

2. Material and methods

2.1. Participants

The population of this study was composed of 46 male crack users who agreed to participate and started the detoxification program in the psychiatric unit of two general public hospitals in the northwest region of the state of Rio Grande do Sul, Brazil. After 15 patients left the detoxification program during the treatment, 31 patients in total were included in the final analysis.

The selection of the users was performed after registration and admission at the public hospital. The users were registered and linked to the services, which had their own medical records, including information about the time of use and the forms of treatment until the moment of hospitalization.

The interview was conducted with patients who had physical and mental conditions for data collection during the detoxification period (mean of 7 days of drug abstinence), as recommended by Oliveira and Santos [50].

The inclusion criteria of the participants were as follows: (1) over 18 and under 59 years of age and (2) male sex. The exclusion criteria were as follows: (1) clinical and mental inability to provide blood sample, respond to interview, or participate in the survey; (2) significant problems at birth or during the psychomotor development; (3) neurological problems or problems that compromise the central nervous system; and (4) learning disorder.

The sample population consisted of individuals chosen consecutively who met the inclusion criteria and agreed to participate in the study. Participants were classified by variables that could modify the results of the neuropsychological tests such as age, schooling, socioeconomic level, occupation, marital status, number of crack stones in use (weekly average), value spent on drugs expressed in dollars (the amounts were converted from reais, currency of the country, to dollars, the dollar value is R$ 3.23), total time of use, relapses, and hospital readmissions.

2.2. User profile ratings

Participants were referred for an initial interview during the period of hospitalization, which occurred preferably in the second week of hospitalization, where they have already passed the "withdrawal" period. The interviews were conducted individually at the place of hospitalization.

The information detailing the intensity of drug addiction was performed using a questionnaire composed of objective questions regarding the intensity of use, frequency, time of use, financial value spent, physical consequences of use, social and economic problems related to use, according to the sixth version of the Addiction Severity Index (ASI-6) and Mini International Neuropsychiatric Interview test (MINI).

2.3. Ethical considerations

This protocol was analyzed and approved by the Research Ethics Committee of the University of Cruz Alta and CONEP, through opinion number 920,959. At the time of inclusion of the study participants, they were given the necessary information about the nature and purpose of the study. Our research followed the guidelines of the Declaration of Helsinki and Tokyo for human experimentation. All participants declared their voluntary participation in a signed informed consent.

2.4. Blood collection and processing

Blood samples were collected from participants immediately after hospital admission, as well as 14 days after the start of the detoxification treatment. Blood was obtained by venipuncture of the median brachial vein, with a 20-ml syringe. A total of 10 ml of blood samples was placed in tubes without anticoagulant and was subsequently centrifuged at 3000 rpm for 10 min to obtain the serum. To obtain the plasma, the remaining 10 ml of blood were placed into tubes containing the anticoagulant heparin (Vacuplast®) and processed in the same way as the previous one.

2.5. Evaluation of detoxification based on the antioxidant function and oxidative profile in blood samples

2.5.1. Effects of detoxification on antioxidant enzymes

SOD was measured by the inhibition of adrenaline oxidation, which was adapted from a previous study [5]. Plasma samples were homogenized in glycine buffer. Volumes of 5, 10 and 15 µl of sample were separated after homogenization and 5 ml of catalase (0.0024 mg/ml of