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Research article

Leptin levels and its correlation with crack-cocaine use severity: A preliminary study

Mariana Escobar[a,b,*], Juliana Nichterwitz Scherer[a], Felipe Ornell[a], Giovana Bristot[c,d], Cassia Medino Soares[b], Luciano Santos Pinto Guimarães[b], Lísia Von Diemen[a,b], Flavio Pechansky[a,b]

[a] Center for Drug and Alcohol Research, Hospital de Clínicas of Porto Alegre, Federal University of Rio Grande do Sul, Brazil
[b] Hospital de Clínicas de Porto Alegre, Federal University of Rio Grande do Sul, Brazil
[c] Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde (ICBS), Federal University of Rio Grande do Sul(UFRGS), Porto Alegre, RS, Brazil
[d] Bipolar Disorder Program, Laboratory of Molecular Psychiatry, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil

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ABSTRACT

Background: Crack-cocaine is an important public health problem in Brazil and worldwide. It is a potent form of cocaine which results in rapid and damaging stimulating effects on the central nervous system through inhibition of the dopamine transporter. Some studies have suggested that both food and drugs – including crack, can act on the same brain reward mechanisms, altering the dopamine pathways that modulate behavioral responses. Our hypothesis was that leptin, a well-known peptide that modulates energy metabolism and appetite, can be used as a biomarker for drug use.

Methods: Anthropometric data, drug use profiles, and leptin serum levels were evaluated in a cross-sectional study of 40 crack-cocaine users.

Results: Leptin showed an inverse correlation with the severity of crack use, and this correlation remained when corrected by body mass index (BMI) and body composition by bioimpedance (BIA). The majority of subjects were eutrophic or overweight/obese considering BMI and BIA, and these variables were not significantly associated with the severity of crack use, but positively correlated with leptin levels.

Conclusions: Our preliminary findings suggest that leptin could be involved in drug use severity, perhaps through pathways similar to those whereby it modulates food intake. Considering the anthropometric parameters, these findings provide additional evidence that low weight is not predominant in crack users.

1. Introduction

Crack-cocaine (crack) addiction is an important public health problem in Brazil and worldwide. Crack is a potent smoked form of cocaine, which results in rapid and damaging stimulating effects on the central nervous system by blocking the re-uptake of monoamine neurotransmitters (e.g. dopamine, serotonin, and norepinephrine), producing high levels of these neurotransmitters at postsynaptic receptors [15,20]. Identification of biomarkers may be useful in untangling neurobiological processes involved in drug abuse for both clinical and research purposes [22].

Jeynes and Gibson [9], in a recent narrative review assessing the relationship between substance use disorders and nutrition, noted the demand for detailed nutritional assessment to determine specific micronutrient needs, and found evidence of overlaps in brain chemical reward signaling between drug addictions and eating, suggesting a link between food restriction, satiety signaling, and substance abuse. Malnutrition in this population may be multifactorial, and the drug itself may act as an appetite suppressant, reducing body weight with its anorexic effects. On the other hand, weight gain and binge eating have been observed in recovering addicts [4,21]. Surprisingly, a pilot study conducted by our group showed high rates of crack users with normal weight and overweight at hospital admission [27].

Volkow et al. [23] suggested the possibility that food and drugs, such as crack, may act on the aforementioned brain reward mechanisms (i.e., disruption of dopamine pathways that modulate behavioral responses). Therefore, it is not surprising that neurotransmitters implicated in food intake would also be implicated in drug-seeking behaviors. In this line of though, peptides that regulate food intake—such as leptin—could also influence drug-reinforcing effects. Leptin is an

* Corresponding author at: Center for Drug and Alcohol Research, Hospital de Clínicas de Porto Alegre, Alvaro Alvim Unit, Rua Prof. Alvaro Alvim, 400, CEP 90420-020, Porto Alegre, Brazil.
E-mail address: mariescobar@hcpa.edu.br (M. Escobar).

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adipocyte-derived anorexic hormone that exerts its effects via the hypothalamus and other brain regions, including the reward system [16,17]. Within this context, our hypothesis is that neuroendocrine pathways involved in appetite may also be involved in the neurobiological processes that regulate crack consumption. Due to the fact that there is little description in the literature about the possible association between crack use and leptin levels, the main objective of this study was to investigate the correlation between serum concentrations of leptin and the severity of crack use. As a secondary objective, we evaluated possible correlations between the severity of crack use and anthropometric parameters.

2. Methods

2.1. Baseline subject characteristics, study design and variable definition

Forty individuals were recruited from the Addiction Psychiatry Unit of Hospital de Clínicas de Porto Alegre (HCPA), a large teaching hospital affiliated with the Federal University of Rio Grande do Sul, Brazil. Inclusion criteria were: being a male crack user with a positive urine screening test for cocaine (Bioeasy® cocaine test, Alere™, Recife, Brazil) at admission; being at least 18 years old, and agreeing to provide blood samples and a signed informed consent form. Subjects who were considered clinically unable to participate (e.g., in cases of tuberculosis, psychosis, dementia, or mental retardation) were excluded from the sample. These exclusion criteria were verified by a psychiatrist in a clinical interview, using the standard evaluation of the recruitment center.

Crack use was assessed by a standardized interview, using a questionnaire that included items related to the type, mode, and frequency of drug use. Severity of crack use was estimated using age at first crack use, years of crack use, and crack rocks smoked in the previous 30 days, as in previous studies of our group [14,19,25]. First crack use at age 11 years was assigned the maximum score of 10 points, from which 1 point was deducted per additional year of patient age at first use until age 20 (1 point); first use at age 21 or older was assigned zero points. Duration of crack use was scored using a simple system of 1 point per year. The number of crack rocks smoked in the last 30 days was scored as follows: 0–5.99 = 1, 6–21 = 2, 22–40 = 3, 41–72 = 4, 73–103 = 5, 104–142 = 6, 142–200 = 7, 201–343 = 8, 344–515 = 9, and ≥516 = 10. Finally, these three parameter scores were added to generate an overall score of crack use severity. Users were then categorized into two groups (more vs. less severe crack use) according to the median overall score.

2.2. Anthropometric evaluation and body composition

Anthropometric evaluation was performed within 48 h of admission. The body mass index (BMI) was calculated using the height and weight of each participant and classified according to the World Health Organization cutoff points [12]. Body composition (fat percentage) was analyzed by tetrapolar bioimpedance analysis (BIA) using a Maltron BF 906® device (Maltron, UK), following pre-test instructions described by the manufacturer. We used the American Council on Exercise parameters to classify individuals by body fat percentage [3].

2.3. Blood tests

Blood samples were collected by a trained nurse practitioner the morning after hospital admission, with a maximum of 24 h after admission. All blood samples were collected after a 10 h fasting, between 7:30 and 8:00 AM, following the HCPA institutional protocol that is based on guidelines of the Brazilian Society of Clinical Pathology and Laboratory Medicine [1]. Serum leptin levels were measured by sandwich-ELISA using a commercial kit, in accordance with the manufacturer's instructions (Invitrogen, USA). In short, samples were added to the appropriate microtiter wells and biotinylated anti-human leptin (biotin conjugate) solution was pipetted into each well (except for the chromogen blanks). The plate was covered and incubated for 2 h at room temperature. Plate wells were later washed four times and streptavidin-horseradish peroxidase working solution was added to each well (except for the chromogen blanks) and incubated for 30 min at room temperature. After washing, stabilized chromogen was added to each well and the plate was incubated for 30 min at room temperature in the dark. After addition of stop solution, leptin was quantitated (absorbance set at 450 nm). The standard curve (ranging from 0 to 1000 ng/mL) demonstrated a direct relation between optical density and leptin concentration.

2.4. Ethics

The study was approved by the Hospital de Clinicas de Porto Alegre Research Ethics Committee (project number 140146). Before data collection, all participants were informed of the procedures and objectives of the study and provided written informed consent for participation.

2.5. Statistical analysis

The Kolmogorov-Smirnov method (with Lilliefors significance correction) was used to test for normality of distribution. For descriptive analysis, we calculated means and standard deviations or medians and interquartile ranges as appropriate. Pearson and Spearman tests were used to calculate correlations, and the Mann-Whitney U and Student's *t*-tests were used to compare groups. Leptin levels were corrected by BMI and BIA. Statistical analyses were processed in PASW Statistics 18.0 (SPSS, Inc., Chicago, USA).

3. Results

3.1. Demographic and drug-use characteristics stratified by severity of crack use

Considering their BMI and BIA findings, few individuals were underweight (5%) or had low body fat (2.5%). Most had normal weight (65%) or overweight/obesity (30%). The group with less crack severity had higher levels of leptin and BMI. Table 1 lists the subjects' demographic, anthropometric and drug-use characteristics stratified by severity of crack use.

3.2. Severity of crack use and correlations

The severity of crack use showed an inverse correlation with leptin. After correcting leptin by BMI and BIA, the association with severity of use remained. BMI and BIA demonstrated no significance with severity of crack use, however; they showed a tendency to an inverse correlation ($p = 0.07$), and were positively correlated with leptin (Table 2).

4. Discussion and conclusions

The main finding of this study was that serum leptin levels showed an inverse correlation with the severity of crack use, and this correlation remained when corrected for BMI and BIA. When comparing the groups by severity of crack use, we also found that the group with higher severity had lower serum levels of leptin. It is possible that, in addition to appetite, leptin may be modulating crack consumption. This finding has its relevance in the identification of possible biological markers involved in the neurochemical modulation of crack use. However, there is little literature available regarding the association of leptin and crack cocaine addiction.

In an animal protocol, Hommel et al. [8] and Fulton et. al. [7], investigated the role of leptin in dopaminergic neurons and the multiple actions of leptin in the central nervous system, showing that leptin