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Short communication

Cocaine abuse and effects in the serum levels of cytokines IL-6 and IL-10

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ABSTRACT

Background: Cocaine abuse is capable of activating the innate immune system in the CNS resulting in deregulation of homeostasis between pro and antiinflammatory cytokines. The aim of this study was to investigate serum levels of pro and antiinflammatory cytokines, IL-6 and IL-10 respectively, in cocaine users from a young population-based sample.
Methods: This is a case–control study nested in a cross-sectional population-based survey, with individuals of 18 and 35 years old. Two groups were selected: 24 healthy controls and 12 subjects who reported cocaine use. Serum IL-6 and IL-10 were measured by ELISA using a commercial kit.
Results: There was a statistically significant increase in IL-6 ($p = 0.037$) and decrease in IL-10 ($p = 0.007$) serum levels, between cocaine users and the control group. There was also an increase in the ratio IL-6/IL-10 ($p = 0.013$) among cocaine users individuals, when compared to the control group.
Conclusions: Our results suggest that cocaine users showed an activation of the immune system when compared a control group, demonstrating a disruption in the balance of pro and antiinflammatory cytokines. Thus, peripheral cytokines may represent a putative biomarkers for cocaine users, contributing to the development of diagnosis and effective treatments.

1. Introduction

Cocaine abuse is an important public health problem, with a high prevalence in young adults. In 2010, cocaine use on a global level in the population between 15 and 64 years old was 0.3–0.5% (UNODC, 2014). Psychostimulant use in general, including cocaine, has been associated with behavioral and cognitive alterations, such as impaired decision making, negative social, financial, psychological and physical consequences (Goldstein et al., 2007; Kalivas and Volkow, 2005; Porter et al., 2011). Recent studies have suggested that the chronic and acute use of cocaine is able to activate specific innate immune response components (Yamamoto et al., 2010), which include alterations in the cellular homeostasis of the liver, heart and brain, leading to cellular toxicity processes (Hanisch and Kettenmann, 2007; Narvaez et al., 2013; Streit, 2010). Regarding this cellular damage, several studies there demonstrated that cocaine promotes oxidative stress in these organs, increasing the production of reactive oxygen species (ROS; Hermida-Ameijeiras et al., 2004; Smythies and Galzigna, 1998). In the brain, the cocaine oxidative stress-induced inflammation stimulates the hypothalamus–pituitary–adrenal (HPA) axis, changing the levels of cytokines (Narvaez et al., 2013; Rivest, 2001).

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Cytokines have the function of stimulating cellular immune response and play a fundamental role in the control and modulation of local and systemic inflammatory responses, causing a constant balance between proinflammatory and anti-inflammatory cytokines (Bromander et al., 2012). Interleukin-6 (IL-6) is the main proinflammatory cytokine activated in the innate immune process, resulting in microglial activation (Porrino and Lyons, 2000). In turn, Interleukin-10 (IL-10) is known as a factor that inhibits the cytokine's synthesis, thus being one of the most important endogenous anti-inflammatory agents produced by the organism (Bromander et al., 2012; Fox et al., 2012).

Assessing different peripheral biomarkers in cocaine users, like inflammatory cytokines, can be relevant for a better understanding of the pathophysiological burdens associated with this drug use. There are few studies concerning the effects of cocaine use and the possible changes in the immune system in a population-based sample. Clinical and pre-clinical studies have shown that the use of cocaine incurs in the increase of proinflammatory cytokines and decrease of anti-inflammatory ones (Piechota et al., 2010). The aim of the present study is to evaluate the serum levels of proinflammatory cytokines, IL-6, and anti-inflammatory, IL-10, in cocaine users from a young population-based sample.

2. Methods

This is a case-control study nested in a population-based one, of people aged 18–35, involving 2348 participants living in the city of Pelotas, (Brasil), between June, 2011 and October, 2012. Sample selection was performed by clusters, considering the census division of the city (Pelotas) in 2010 (IBGE—*InstitutoBrasileiro de Geografia e Estatística*; http://www.ibge.gov.br).

After identifying the subjects, they were invited to participate in the study and signed the informed consent form. This study was approved by the committee of ethics in research from the Catholic University of Pelotas (UCPEL), under Protocol number 15/2010.

Sociodemographic issues and psychoactive substance use data were collected through a self-administered questionnaire. To evaluate alcohol use disorder, the participants also answered the CAGE questionnaire (Buchsbaum et al., 1992). Socioeconomic evaluation was carried out using the IEN criteria (National Economic Index—*ÍndiceEconômico Nacional*), which is based on the accumulation of material assets and on the schooling of the head of the household. These criteria generate a continuous variable which was presented in tertiles (Barros and Victora, 2005).

From the interview, all individuals who reported cocaine use were selected ($n = 26$ individuals). However, those individuals diagnosed with mood disorder, or who used alcohol concomitantly, were excluded from the sample ($n = 14$ individuals), totaling 12 individuals. From these, 24 other individuals who reported no use of licit and illicit substances and no psychiatric disorder were matched by sex and age, constituting a control group.

For the biochemical analysis, 10 mL of blood were withdrawn from each subject after the interview by means of venipuncture into an anticoagulant-free *vacuum* tube, between 8:00 and 11:00 am. The blood was immediately centrifuged at $4000 \times g$ for 10 min, and serum was kept frozen at −80 °C until analysis. Serum IL-6 and IL-10 levels were measured using a commercial immunoassay kit (DuoSet ELISA Development, R&D Systems, Inc., USA). Serum IL-6 and IL-10 levels were expressed in pg/mL.

Statistical analysis was performed with the Statistical Program for Social Sciences (SPSS) 21.0 and *Graph Pad Prism* 6.0. Serum IL-6 and IL-10 levels had non-Gaussian distributions. For nonparametric data, we utilized the Mann–Whitney test, the Spearman correlation test, and the Kruskal–Wallis. Serum cytokines levels were presented as median and interquartile range. A linear regression analysis was applied to control for possible confounding factors with a p value ≤ 0.2 in the bivariate analysis. Results with p values ≤ 0.05 were considered statistically significant.

3. Results

Among the 36 analyzed subjects, 12 (33.3%) cocaine users and 8 (22.2%) cannabis sativa users were identified. Table 1 shows socio-demographic characteristics of the subjects according to cocaine use. Our results reveal no difference between control and the cocaine users groups for sociodemographic characteristics. However, among cocaine users, 8 (66.7%) subjects are cannabis users, and show a significant difference between the cocaine and control groups ($p \leq 0.001$; Table 1). Table 2 shows the serum cytokines levels (IL-6, IL-10) and socio-demographic characteristics and cannabis sativa users, between cocaine users and controls groups.

There was a statistically significant difference between cocaine users and the control group IL-6 ($p = 0.037$) and IL-10 ($p = 0.007$) serum levels. IL-6 levels were higher in the cocaine users group with a median of 19.35 (13.37–34.57) pg/mL in relation to the control group with a median of 13.13 (12.05–15.88) pg/mL, while the levels of IL-10 were lower in the cocaine users group, where the median was 40.37 (33.56–57.50) pg/mL in relation to the control group with a median of 56.68 (48.09–92.23) pg/mL (Fig. 1).

In order to evaluate the influence of possible confounding factors interfering in the results, we performed an adjusted analysis according to gender, socio-economic index and cannabis use for serum cytokines levels and the results remained significant (IL-6: $p = 0.039$; IL-10: $p = 0.045$).

For verifying, the relationship between the pro-inflammatory cytokines (IL-6) with the anti-inflammatory cytokines (IL-10) was made as a ratio of these cytokines levels for each subject. There was a statistically significant difference between the two groups in IL-6/IL-10 ($p = 0.013$). The median ratios were 0.22 (0.15–0.31) in the control group and 0.53 (0.32–0.98) in cocaine user to IL-6/IL-10. After adjustment for potential confounders, both ratios remained statistically significant (IL-6/IL-10: $p \leq 0.001$; Fig. 1).

Table 1
Socio-demographic and clinical characteristics of the sample according with cocaine use.

	Total sample	Controls	Cocaine users	p Value
Gender[a]				
Female	9 (25.0)	6 (25.0)	3 (25.0)	1.000
Male	27 (75.0)	18 (75.0)	9 (75.0)	
Ethnicity[a]				
Caucasian	27 (75.0)	19 (79.2)	8 (66.7)	0.414
No caucasian	9 (25.0)	5 (20.8)	4 (33.3)	
Age (years) [b]	25.83 ± 4.59	26.29 ± 4.52	24.92 ± 4.80	0.405
Years of study[b]	12.25 ± 3.04	12.92 ± 2.31	10.92 ± 3.92	0.302
Brazilian Economic Index[a]				0.325
1 (minor)	12 (33.3)	9 (37.5)	3 (25.0)	
2 (intermediate)	12 (33.3)	6 (25.0)	6 (50.0)	
3 (highest)	12 (33.3)	9 (37.5)	3 (25.0)	
Cannabis use[a,c]				
Yes	8 (22.2)	0 (0.0)	8 (66.7)	0.001
No	28 (77.8)	24 (100.0)	4 (33.3)	
Total	**36 (100.0)**	**24 (66.7%)**	**12 (33.3%)**	

[a] $\chi 2$ test, displayed as n (%).
[b] Student t *test*, displayed as mean ± standard deviation.
[c] Our controls are healthy and did not cannabis use.

Table 2
Socio-demographic and clinical characteristics of the sample according to serum levels of IL-6 and IL-10.

	Cocaine Users ($n = 12$)		Controls ($n = 24$)	
	IL-6 level (pg/mL)	IL-10 level (pg/mL)	IL-6 level (pg/mL)	IL-10 level (pg/mL)
Gender[a]	$p = 0.182$	$p = 0.182$	$p = 1.00$	$p = 0.640$
Female	36.07 (29.83–40.03)	59.80 (55.20–66.34)	13.73 (8.07–14.79)	62.81 (53.04–112.29)
Male	17.15 (13.11–20.10)	37.63 (33.23–41.51)	13.05 (12.12–20.84)	55.13 (43.39–85.06)
Ethnicity[a]	0.545	0.545	1.00	0.317
Caucasian	16.37 (11.58–27.56)	36.87 (22.23–55.23)	12.87 (9.17–15.56)	55. 89 (43.72–96.23)
No caucasian	13.78 (11.07–21.25)	46.66 (38.91–67.31)	14.54 (13.73–27.65)	65.78 (51.11–83.94)
Age (years)[b]	$p = 0.486$ $r = 0.234$	$p = 0.827$ $r = -0.067$	$p = 0.241$ $r = -0.249$	$p = 0.316$ $r = 0.214$
Years of study[b]	$p = 0.837$ $r = -0.064$	$p = 0.671$ $r = -0.137$	$p = 0.837$ $r = -0.067$	$p = 0.689$ $r = -0.089$
Brazilian Economic Index[c]	$p = 0.513$	$p = 0.534$	$p = 0.411$	$p = 0.062$
1 (minor)	36.07 (23.26–40.06)	42.71 (42.12–51.26)	14.54 (13.13–27.65)	68.30 (40.21–102.67)
2 (intermediate)	16.37 (13.11–23.58)	36.87 (33.23–50.61)	13.13 (12.69–14.69)	55.43 (48.54–73.39)
3 (highest)	20.10 (18.62–32.04)	37.64 (24.65–55.25)	9.17 (8.25–16.16)	54.37 (48.68–92.35)
Cannabis use[a,d]	$p = 0.654$	$p = 0.545$	–	–
Yes	19.35 (11.58–28.43)	36. 87 (22.24–48.34)	–	–
No	26.61 (14.89–42.04)	51.26 (38.90–67.74)	13.13 (12.04–15.88)	56.68 (48.09–92.23)
Total	**19.35 (13.36–34.56)**	**40.37 (33.55–57.50)**	**13.13 (12.05–15.88)**	**56.68 (48.09–92.23)**

[a] Mann–Whitney test.
[b] Spearman correlation test.
[c] Kruskal–Wallis.
[d] Our controls are healthy and did not cannabis use.

4. Discussion

The present study evaluated the serum interleukins levels in young subjects related to cocaine use. These subjects showed higher serum IL-6 levels and lower serum IL-10 levels, when compared to subjects without reported cocaine use. Moreover, to evaluate the balance between Th1 and Th2 response, the IL-6/IL-10 ratio was evaluated and this parameter presented increased in cocaine users. Thus, these results pointed to an inflammatory status associated to cocaine use.

Cocaine use, it has been described, can interfere in the production and release of cytokines, demonstrating its role on immunomodulatory capacity and infection (Mao et al., 1996). Psychostimulant abuse is associated with exaggerated innate immune response activation in CNS (Narvaez et al., 2013; Wisor et al., 2011). This substance exposure results in the increase of pro-inflammatory citokynes in various regions of the brain (Chen et al., 2008). In this sense, Wisor et al. (2011) showed that microglial activation, in response to psychostimulants increased pro-inflammatory cytokines, including IL-6. In this case, there is a cellular response that will lead to exaggerated production of proinflammatory cytokines (Benito et al., 2008). Therefore, circulating cytokines can cross the blood brain barrier, and central changes will reflect in peripheral circulation (Ghosh et al., 2014).

A study performed by Ersche et al. (2014), found increased salivary levels of IL-6 in cocaine-dependent men when compared to the control group, which had no personal or family history of substance use disorders. Moreover, he did not find a difference in salivary levels of IL-10 between the groups (Ersche et al., 2014). Our present study evaluated the pro-inflammatory cytokine IL-6 and found increased levels of this cytokine in individuals who used cocaine. In the study, we suggested that this increase in the cocaine

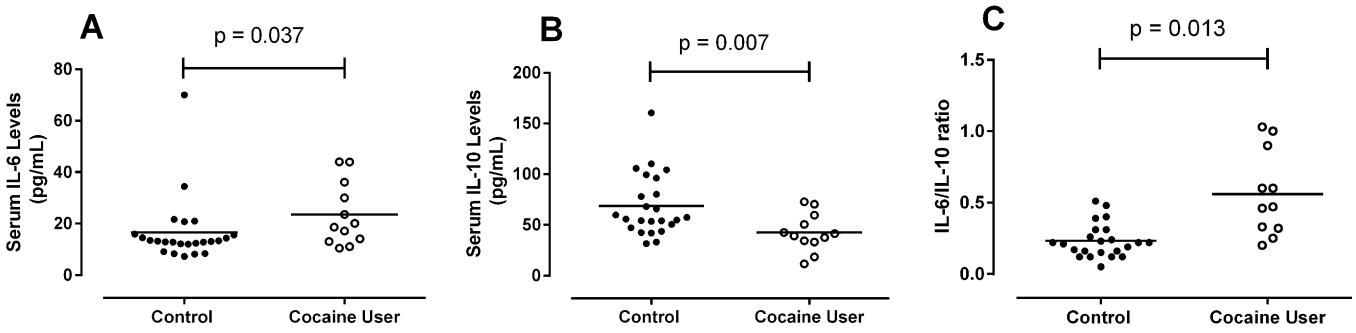

Fig. 1. (A) The serum levels of pro-inflammatory cytokines (IL-6) were increased in cocaine users when compared to controls. Median: 19.35 (13.37–34.57) pg/mL; median: 13.13 (12.05–15.88) pg/mL; respectively $p = 0.037$). (B) The serum levels of antiinflammatory cytokines (IL-10) were decreased in cocaine users when compared to controls. Median: 40.37 (33.56–57.50) pg/mL; median 56.68 (48.09–92.23) pg/mL; respectively $p = 0.007$). (C) IL-6/IL-10 ratio were increased in cocaine users when compared to control group median: 0.53 (0.32–0.98); median: 0.22 (0.15–0.31); respectively $p = 0.013$).

users may be indicative of neuronal damage, once we found similar results with the literature.

Chronic and acute psychostimulants exposure is related to an activation of specific components of the innate immune response (Yamamoto et al., 2010), thus altering the homeostasis in the CNS leading to toxicity damage (Hanisch and Kettenmann, 2007; Mao et al., 1996). Cocaine users will present an exaggerated neuroinflammatory state, and thus, this process will promote a decrease in circulating levels of IL-10. Previous studies have shown that IL-10 was induced by pro-inflammatory cytokines, and that IL-10 diminished the cytokine response (Taniguchi et al., 1999). This diminished cytokine response is relevant for the inhibition of the synthesis of proinflammatory cytokines; the decrease in serum levels of IL-10 will stimulate the local inflammatory process and increase the cell damage (Fox et al., 2012; Gan et al., 1998).

Chronic cocaine use is associated to the development of comorbidities, such as affective disorders, reinforcing negative maintenance and relapse effects of drug abuse (Araos et al., 2014; Chahua et al., 2015; Fox et al., 2012). Fox et al. (2012) evaluated the serum levels TNF-α, IL-10 and IL-1 in cocaine dependents (without any mental disorder or dependence on any other illegal drug or alcohol) and social drinker patients, used as a control group. Cocaine-dependent individuals demonstrated reduced plasmatic levels of IL-10 compared to social drinkers (Fox et al., 2012). Our results are in accordance to this study; we found the decrease in the serum levels of IL-10 in individuals who used cocaine compared to those in the healthy controls, emphasizing the importance of cytokines as a neuromodulatory role in the abuse of psychostimulants.

In a study by Narvaez et al. (2013), an increase in pro-inflammatory cytokines IL-1β and TNF-α was observed in crack abusers. It is important to note that crack is the cocaine in its free base form (Narvaez et al., 2013). Ersche et al. (2014) found increased salivary levels of IL-6 in cocaine-dependent men when compared to the control group, which has no personal or family history of substance use disorders. Moreover, he did not find difference in salivary levels of IL-10 between the groups (Ersche et al., 2014). Our present study evaluated the pro-inflammatory cytokine IL-6 and found increased levels of this cytokine in individuals who used cocaine. The use of psychostimulant substances, such as cocaine and crack, can be associated with cellular damage, since the pro-inflammatory cytokines are increased.

Regarding inflammatory events, excessive immune activation is considered a key process for cellular damage, leading to toxic responses, such as an increased secretion of cytokines with pro-inflammatory activity (IL-6). When there is an excessive disturbance of the immune system, there is a disruption in the balance of cytokines, which leads to the anti-inflammatory interleukins being unable to control the increased production of pro-inflammatory interleukins. Moreover, several studies have shown that as IL-6/IL-10 ratio is an indicative between TH1/TH2 balance (Sousa et al., 2015).

It is known that cocaine is able to induce the inflammatory cytokines release both in the peripheral organs and central nervous system, and this inflammatory status is presented in cocaine users as well the immunity in these subjects is compromised (Maes, 2008; Maes et al., 2009). In this paper, we postulate that users from a population sample have a decrease in immunity, and this substance abuse will reflect in a possible damage in several systems functions, including in the brain. Part of this hypothesis is based on the increase of serum inflammatory cytokines reaching the brain, crossing the blood-brain-barrier and leading to an increase of these cytokines in the cerebrospinal fluid (Miller et al., 2013; Rosenblat et al., 2015, 2014). In addition, the presence of functional lymphatic vessels lining the dural sinuses (Louveau et al., 2015) and the microglia activation in cocaine users (Little et al., 2009) are worth noting.

Limitations of our study include the lack of a control over quantity or time of cocaine use and a small sample size. However, in our study, the users are young individuals without medication use and identified from a population-based study. Most other studies utilize users admitted to psychiatric and psychological clinics, usually due to abuses of substances which may interfere with the inflammatory parameters. It is also important to note that in our study cocaine users had no psychiatric disorder and also did not use alcohol. Some of the individuals reported concomitant use of cannabis and tobacco, which is common among cocaine users, but did not interfere in the statistical analysis, therefore indicating that the results are reflecting the change caused by the use of cocaine.

In conclusion, this study demonstrates that cocaine users showed increased serum levels of IL-6 and decreased levels of IL-10 when compared to healthy subjects. These results suggest an activation of the immune system and consequent neuronal damage. Thus, peripheral cytokines may represent a putative biomarkers for cocaine users, contributing to the development of diagnosis and effective treatments. However, future studies are needed to elucidate the immune mechanism in cocaine users.

Conflict of interest

The authors declare that there is no conflict of interest.

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