Cite as: Corominas-Roso, M., Roncero, C., Eiroa-Orosa, F. J., Ribasés, M., Barral, C., Daigre, C., … Casas, M. (2013). Serum Brain-Derived Neurotrophic Factor Levels and Cocaine-Induced Transient Psychotic Symptoms. *Neuropsychobiology*, *68*(3), 146–155. http://doi.org/10.1159/000353259

Serum BDNF levels and cocaine-induced transient psychotic symptoms

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Running title: BDNF in cocaine-induced psychosis

Abstract

Background: Cocaine-induced psychosis (CIP) is among the most serious adverse effects of cocaine. Reduced serum BDNF levels have been reported in schizophrenia and psychosis; however, studies assessing the involvement of BDNF in CIP are lacking.

Methods: Twenty-two cocaine-dependent patients (ages 33.65 ± 6.85) who had never experienced psychotic symptoms under the influence of cocaine (non-CIP) and eighteen patients (ages 34.18 ± 8.54) with a history of CIP completed a two-week detoxification program in an inpatient facility. Two serum samples were collected from each patient at baseline and at the end of the protocol. Demographic, consumption and clinical data were recorded for all patients. A paired group of healthy controls was also included.

Results: At the beginning of the detoxification treatment, serum BDNF levels were similar in the non-CIP and the CIP groups. During early abstinence, the non-CIP group exhibited a significant increase in serum BDNF levels (p=0.030), whereas the CIP group exhibited a decrease in serum BDNF levels. Improvements in depression (BDI, p = 0.003) and withdrawal symptoms (CSSA, p=0.013) show a significant positive correlation with serum BDNF levels in the non-CIP group, whereas no correlation between the same variables was found in the CIP group.

Conclusions: This study suggests that BDNF plays a role in the transient psychotic symptoms associated with cocaine consumption. In the non-CIP group, the increase in serum BDNF appears to be driven by the effects of chronic cocaine consumption and withdrawal. In contrast, patients with CIP share some of the neurotrophic deficiencies that characterize schizophrenia and psychosis.

Key words: addiction; cocaine; cocaine-induced psychosis; CIP, brain-derived neurotrophic factor; BDNF

Introduction

The term "cocaine-induced psychosis" (CIP) has been used to describe transient psychotic symptoms, such as paranoia, delusions or hallucinations, that usually resolve with abstinence (1). Psychotic symptoms are among the most serious adverse effects of cocaine use because they may lead to severe behavioral outcomes such as aggression and agitation and because patients experiencing such symptoms may be at a higher risk of developing psychosis (2). Despite the morbidity and mortality associated with CIP, risk factors for the trait are still not well known. In this context, it may be useful to find biological markers of vulnerability that may assist in the identification of those patients who are at risk of developing psychotic disorders and in the development of new therapeutic strategies. Psychotic symptoms have also been observed in the general population, and a clinical continuum from non-clinical to clinical psychosis has been reported (3–5). Among cocaine dependents, more than 50 % of patients report experiencing psychotic symptoms (2). Whereas some clinical studies have reported that subjects using higher cocaine doses have higher CIP scores (1,6,7), others have found no difference in lifetime cocaine abuse between CIP and non-CIP subjects in the month prior to admission (1). Other risk factors for psychotic experiences include an early age of onset of cocaine use (6) and being male (7). However, not all cocaine users develop psychotic symptoms despite prolonged or heavy exposure (2,8,9) and those users who do experience psychotic symptoms may be at a higher risk of developing psychosis than cocaine users who do not experience those symptoms (8,10). Early identification of patients at risk of developing psychosis may help prevent inappropriate diagnosis and treatment and may improve long-term outcome (11–13).

Genetic risk factors also appear to be involved in the interindividual variability in the probability of experiencing psychotic symptoms. A decrease in the activity of the enzyme dopamine beta-hydroxylase (DBH), which converts dopamine into adrenaline, has been observed in CIP (14,15). Reduced DBH activity has also been observed in individuals who exhibit impulsive and aggressive behaviors (16,17), which are also associated with CIP (2). The neurotrophin brain-derived neurotrophic factor (BDNF), which interacts with the dopaminergic system (18,19) and with other neurotransmitters involved in schizophrenia, such as glutamate (20–22), may be a risk factor for CIP. Low serum BDNF levels have been reported in schizophrenic patients under chronic treatment with antipsychotics (23–27) as well as in drug-naïve schizophrenic patients (28,29). Additionally, low serum BDNF levels are associated with cognitive impairment, especially immediate memory, in chronic schizophrenic patients (30), and BDNF levels increase in stable schizophrenic patients after cognitive training (31). In patients who experienced first-episode psychosis, low BDNF levels have also been reported (32,33), even in drug-naïve patients (34). Postnatal stress appears to mediate the BDNF decrease and its consequences on brain structure in these patients (33). Moreover, the most frequently studied single nucleotide polymorphism (SNP) of the *BDNF* gene, the Val66Met SNP (35), is associated with changes in intracellular trafficking and secretion of the protein (36) and affects serum BDNF levels (37) and hippocampal-dependent learning (38). This polymorphism has also been associated with cognitive impairment in schizophrenic patients (30) and with social stress-induced paranoia (39,40).

The objective of this study is to examine the involvement of BDNF in CIP. We evaluate whether serum BDNF levels in abstinent cocaine addicts may be capable of differentiating between patients with and without psychotic symptoms during cocaine consumption. We will measure serum BDNF levels in cocaine addicts immediately after cocaine consumption and after two weeks of withdrawal and compare them to serum BDNF levels in a group of healthy controls.

Materials and Methods

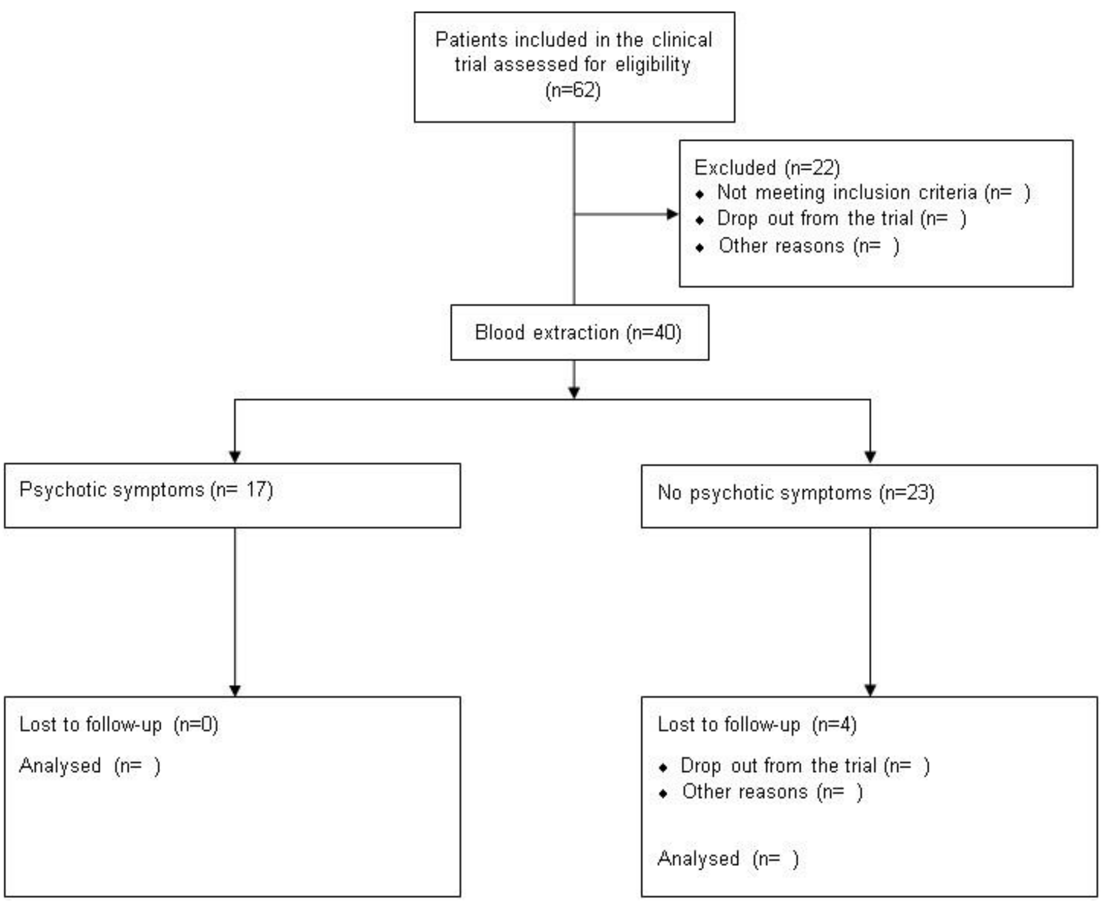
Subjects

Patients included in this study were selected from a group of participants in an independent clinical trial for inpatient cocaine detoxification conducted by the Psychiatry Department of the University Hospital Vall d'Hebron in which pharmacological treatment was effectuated with caffeine+Biperiden (Biperiden is an anticholingergic and antiparkinsonian agent), caffeine+placebo or placebo+placebo (ClinicalTrials.gov Identifier: NCT00495092). All patients were cocaine dependent according to the DSM-IV (41) criteria. Exclusion criteria included the following factors: 1) lifetime history of psychotic, bipolar, or substance abuse disorder except nicotine; 2) current history of mood, psychotic or anxiety disorder; 3) neurological illness; 4) history of cranial trauma; 5) being treated with psychotropic medication (antidepressants or antipsychotics) at least one month before joining the study; 6) being seropositive for HIV; 7) abnormal results on laboratory screening tests or physical examination; 8) having metabolic, cardiac or any medical illness that can interfere with the expression of BDNF; 9) being treated with chronic drug therapy using corticosteroids, thyroid hormones, allergy medication and/or analgesics.

Clinical diagnosis was performed by two independent and trained psychiatrists. Sixty-two cocaine-dependent patients were assessed for eligibility; of these, 40 met the diagnostic criteria for inclusion. A subgroup of 22 patients reported never having experienced psychotic symptoms while under the influence of cocaine throughout their lives, whereas a subgroup of 18 patients had experienced psychotic symptoms while using cocaine (Figure 1). A gender- and age-matched sample of 46 healthy controls met the same inclusion criteria. All participants were Caucasian and unrelated to one another.

This study was approved by the Clinical Research Ethics Committee of the University Hospital Vall d'Hebron. Written informed consent was obtained from all participants Subjects did not receive any financial compensation.

Figure 1. Flow Diagram of the study.



Inpatient Procedure

Patients included in this study underwent a 12-day detoxification treatment in an inpatient unit of the Department of Psychiatry, University Hospital Vall d'Hebron. This unit is a locked facility where patients have limited visitation privileges and no access to alcohol or drugs. During detoxification treatment, drug testing was conducted twice to ensure abstinence. A maximum of six breaks per day previously established by the medical team were allowed for smoking.

As part of the independent clinical study, patients received caffeine (starting dosage of 300 mg/d; dosage was increased by 300 mg/d; maximum dosage was 15 mg/kg/d up to 1200 mg/d) and Biperiden (4 to 8 mg/day) or matched placebo. Caffeine was administered to improve patients' comfort, and Biperiden was administered to prevent tolerance to caffeine. No additional psychotropic medication was administered except Lorazepam (up to 5 mg/d) for the treatment of insomnia.

Clinical Assessment

Diagnoses and cocaine dependence were evaluated using the Structured Clinical Interview for DSM-IV (SCID) Axis I (42) and Axis II (43). To assess psychotic symptoms under the influence of cocaine throughout their life, a structured interview was conducted. The questions used in previous studies (2) and based in DSM IV-TR, were as follows: 1) Have you ever heard, or thought you heard, something that wasn't really there? Did it happen while you were under the effects of cocaine? 2) Have you ever seen, or thought you saw something, that wasn't actually there? Did it happen under the effects of cocaine? 3) Have you ever felt anything unusual on your body or on your skin? Did it happen while you were under the effects of cocaine? 4) Have you believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? Did it happen while you were under the effects of cocaine? Patients were considered CIP positive by the psychiatrist if they were marked positively in any of the above questions.

Variables related to cocaine consumption, craving and abstinence were systematically registered. The Visual Analog Scale (VAS) Craving for cocaine scale (44), the Cocaine Craving Questionnaire (CCQ) (45) and the Cocaine Selective Severity Assessment (CSSA) (46) were utilized. Anxiety and depression were evaluated using the State-Trait Anxiety Inventory (47) and the Beck Depression Inventory (48), respectively.

Blood sample collection

For serum sampling, 8 ml of blood was collected from the antecubital vein in anticoagulant-free tubes and kept at 4ºC for 2 h. All samples were collected between 10 and 12 h to avoid circadian variations. The samples were refrigerated at 4ºC for 2 h and then centrifuged at 3500 rpm for 10 min at 4ºC. We carefully collected the serum and stored it at -80ºC until performing the BDNF assay.

Measurement of serum BDNF

Levels of human BDNF in serum samples were measured using the Aushon SearchLight Multiplex Array (Aushon BioSystems, Billerica, MA), a sandwich enzyme-linked immunosorbent system for quantitative protein measurement. In this assay, samples and standards were added to wells, and proteins within the samples bound to capture antibodies. The integrated values of known standards were used to generate standard curves. We analyzed each sample twice and used the mean of the two BDNF measurements. All mean intra-assay coefficients of variation were less than 20%.

Statistical analyses

Due to the low n in the three subsamples (controls, non-psychotic and psychotic), non-parametric statistics were used for all bivariate analyses. Categorical variables were compared between groups using chi-squared tests for independence. Continuous variables were compared using the Kruskal–Wallis one-way analysis of variance by ranks when comparing the three groups and the Mann–Whitney–Wilcoxon rank-sum test when comparing only the non-psychotic and psychotic subsamples. Pre and post detoxification BDNF serum levels were compared using the Wilcoxon signed-rank test for related samples. Correlations between psychometric scales and BDNF levels were performed using Spearman's rank correlation coefficient. Finally, for the variables with statistically significant correlations with changes in BDNF levels, a linear regression was used to assess if this change could predict symptomatology amelioration.

Results

Sociodemographic features of patients and control groups

Table 1 shows comparisons between the control, non-psychotic and psychotic subsamples. No gender or age differences were found among groups. As can be seen in Table 2, there were no baseline clinical differences between psychotic and non-psychotic patients beyond a small trend ($z=-1.743$, $p=.081$) on the scale of loss of control from cocaine withdrawal, as evaluated using the CCQ. Differences were neither found between treatment groups (caffeine, caffeine-biperiden or placebo) in any of these measures.

Table 1. Sociodemographic features by patients (with or without psychosis) and control groups.

	PATIENTS				CONTROLS		Significance	
	No psychotic symptoms (n=22)		Psychotic symptoms (n=18)		(n=46)			
Age	M	SD	M	SD	M	SD	χ^2	p
	33.77	6.98	34.00	8.32	35.52	9.37	1.302	.521
	N	%	N	%	N	%		
Gender (% female)	2	9.1	1	5.6	5	10.9	*	

*No statistical test was performed due to low n in the female subsample.

Table 2. Clinical information of patients. Includes consumption data, craving, depression and anxiety measures at detoxification treatment baseline. VAS: Visual Analogic Scale Craving for cocaine; CCQ: Cocaine Craving Questionnaire; CSSA: Cocaine Selective Severity Assessment; BDI: Beck Depression Inventory; STAI: State Trait Anxiety Inventory.

	Non psychotic symptoms		Psychotic symptoms			
Consumption variables	Mean	SD	Mean	SD	Z	P
Age of onset	24,05	13.65	23.38	8.54	-.492	.639
Days of consumption in the last month	13,00	7.55	19.06	9.13	-.560	.585
Consumption episodes in the last month	21,14	2.48	2.77	2.39	-.907	.404
Maximum quantity in 24 hours in the last month (g)	3,67	4.13	5.90	1.26	-1.506	.137
Baseline addiction measures						
VAS (1-10)	3,14	3.33	2.78	2.81	-.224	.827
CCQ			25.92	10.19	-1.003	.323
Desire	22,00	10.61	26.00	11.31	-.418	.698
Intention	23,63	9.23	23.00	11.27	-.326	.767
Anticipation	21,19	9.77	20.33	8.27	-.372	.732
Relief	21,44	7.79	55.42	35.42	-1.743	.082
Loss of control	42,88	17.03	17.67	10.59	-.953	.347
CSSA (18 symptoms)	13,21	9.56	2.78	2.81	-.224	.827
Baseline clinical measures						
BDI. (cut-off for moderate depression=7)	12,61	9.33	17.00	8.11	-1.344	.183
STAI. trait (Q3=28)	27.88	9.39	31.42	12.72	-.976	.347
STAI. state (Q3=25)	24.94	10.50	29.92	8.56	-1.115	.280

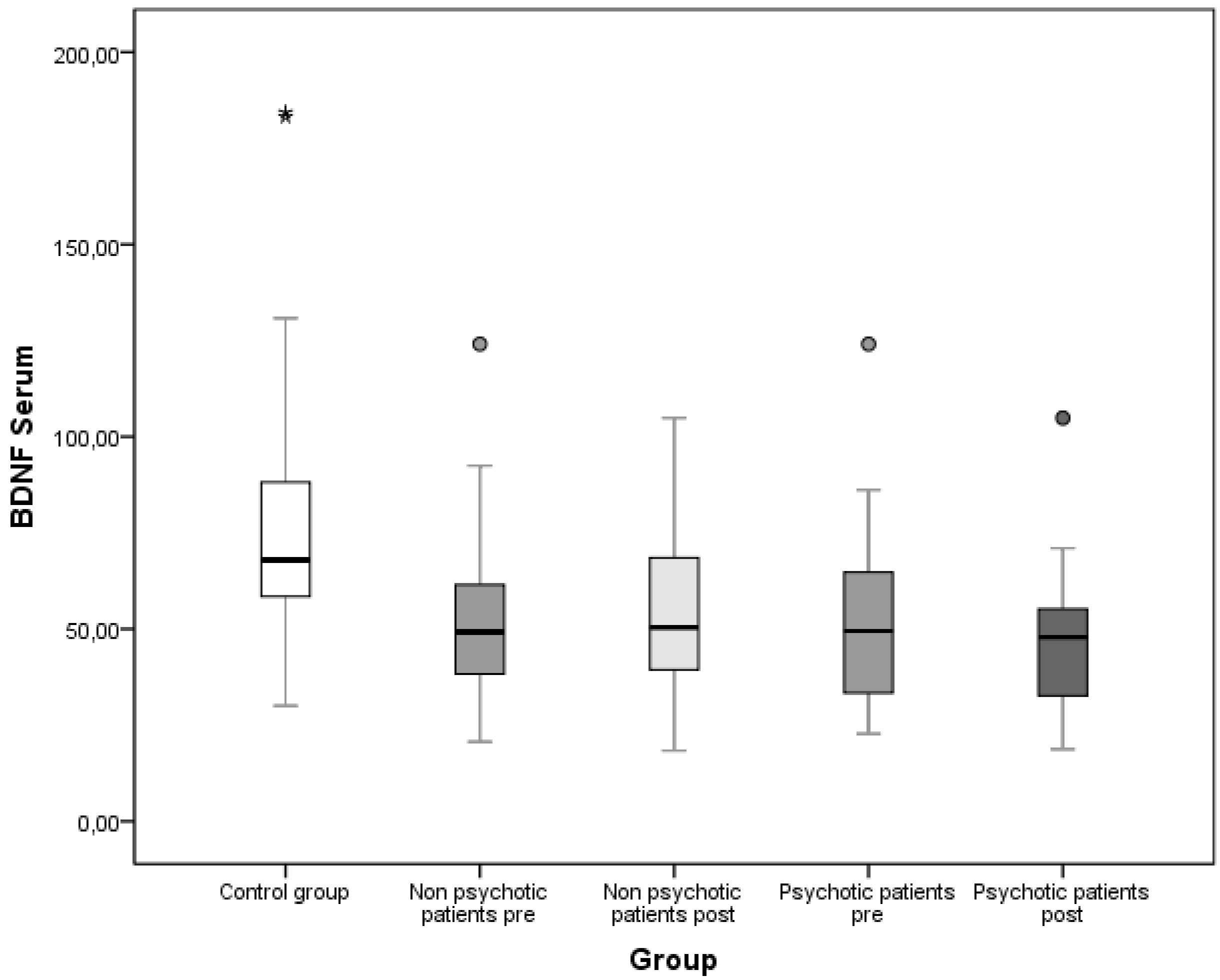
Baseline clinical characteristics by patient groups

Table 3 and Figure 2 show the evolution of BDNF serum levels in the two patient groups (CIP and non-CIP). There was a clear baseline difference between both treatment groups and the control group (total χ^2=15.835, p<.0001). There was a clear difference in the evolution of BDNF in both groups, but the pre-post difference was only statistically significant for the non-psychotic patient group (z=2.025, p=.43).

Table 3. Means (M) and standard deviations (SD) of Brain Derived Neurotrophic Factor (BDNF) among healthy controls and cocaine addicted patients with and without psychotic symptoms.

	PATIENTS						CONTROLS			
	No psychotic symptoms (n=23)		Psychotic symptoms (n=17)		Significance between patients with and without psychotic sypmtoms*		(n=46)		Total significance**	
	M	SD	M	SD	Z	p	M	SD	χ^2	p
BDNF pre	51.676	17.505	53.947	25.098	-.041	.978	76.044	32.661	15.420	<.0001
BDNF post detoxification	60.643	22.607	48.134	20.376	-1,69	.095				
Significance***	z=-2.173	p=.030	z=-1.086	p=.278						

Figure 2. Boxplot of serum BDNF levels. Se- rum BDNF levels (ng/ml median) repre- sented in order from left to right for: (1) the control group, (2) nonpsychotic patients at baseline, (3) nonpsychotic patients after 12 days of early detoxification treatment, (4) psychotic group of patients at baseline and (5) psychotic group of patients after 12 days of early detoxification treatment. Statistically significant differences in se- rum BDNF levels between groups are re- ported in table 3 .



Brain-derived neurotrophic factor evolution

Regarding the evolution of clinical characteristics no differences between patients with or without psychotic symptoms in clinical variables were found at the end of the detoxification process. As can be seen in table 4, both groups experienced a statistically significant improvement in all measures, except for relief from cocaine withdrawal, as evaluated using the

CCQ. No differences in BDNF parameters were found between treatment groups (caffeine, caffeine-biperiden or placebo).

Correlation of BDNF with symptom improvement during early abstinence

When the entire sample was taken, the evolution of BDNF levels did not correlate with the progression of symptoms. However, when stratifying the two patient groups, there were differences in evolution such that changes in BDNF levels were correlated with depression and abstinence in the non-psychotic group, whereas there was no correlation in patients who have experienced some type of psychotic symptoms

The change in serum BDNF levels was found to be a good predictor of depression (β=.690, $p<.005$; 44.1% of variance explained) but not abstinence, as measured by the CSSA among the non-psychotic patients; however, no predictive power of BDNF change was found for any variable among psychotic patients.

Table 4. Mean, standard deviations, statistical signification and non-parametric correlations with BDNF change of symptom improvement in patients with and without psychotic symptoms. Por coherencia conceptual, el cambio en BDNF se ha calculado teniendo en cuenta

	Symptoms change in non psychotic patients						**Symptoms change in psychotic patients**					
	Mean	**SD**	**Change signification**		**Correlation with BDNF change**		**Mean**	**SD**	**Change signification**		**Correlation with BDNF change**	
			t	p	ρ	p			t	p	ρ	p
VAS	2.25	2.79	-2.703	.007	.444	.111	2.56	2.14	-2.499	.012	.319	.339
CCQ												
Desire	8.00	10.63	-2.123	.034	.330	.322	11.55	9.50	-2.625	.009	-.005	.989
Intention	8.08	10.07	-2.277	.023	.483	.132	13.36	9.48	-2.803	.005	-.373	.259
Anticipation	7.42	12.59	-1.887	.059	.036	.915	6.73	10.50	-1.886	.059	.209	.537
Relief	5.25	10.57	-1.845	.065	-.173	.612	4.27	9.39	-1.336	.181	.132	.699
Loss of control	9.17	11.87	-2.237	.025	.300	.370	22.91	36.70	-2.848	.004	-.301	.368
CSSA	9.18	9.50	-2.490	.013	.657	.039	13.55	10.23	-2.936	.003	-.187	.582
Baseline clinical measures												
BDI	8.31	7.03	-2.945	.003	.683	.014	10.50	9.17	-2.449	.014	-.365	.300
STAI, state	13.36	8.09	-2.847	.004	.236	.511	14.55	8.45	-2.803	.005	-.136	.689

VAS: Visual Analogic Scale Craving for cocaine; CCQ: Cocaine Craving Questionnaire; CSSA: Cocaine Selective Severity Assessment; BDI: Beck Depression Inventory; STAI: State Trait Anxiety Inventory.

Discussion

To our knowledge, this is the first study to assess the evolution of serum BDNF levels during early abstinence in patients with cocaine-induced psychosis (CIP) compared with patients without cocaine-induced psychosis (non-CIP).

In this study comparing the CIP and non-CIP groups during early abstinence, both groups exhibited different serum BDNF response patterns. At the beginning of detoxification treatment, serum BDNF levels were similar in the CIP and the non-CIP groups of patients, but after 12 days of withdrawal, BDNF levels were higher in the non-CIP group than in the CIP group. That is, whereas the group of patients with no history of psychotic symptoms experienced a significant increase in serum BDNF levels, those patients with a history of psychotic symptoms experienced a decrease although it was not statistically significant, in BDNF levels. On the other hand, when compared to healthy controls, serum BDNF levels in the entire group of cocaine addicts were significantly lower both at the beginning and after 12 days of abstinence. The neurobiological significance of the decrease of serum BDNF levels in early abstinent cocaine addicts compared to healthy controls is discussed in more detail in a previous study (49).

The increase in serum BDNF levels during withdrawal in the non-CIP group of patients is consistent with previous studies. In animal models of addiction, it has been extensively demonstrated that after cocaine withdrawal BDNF levels rise significantly and progressively in different brain regions such as the nucleus accumbens, amygdala and prefrontal cortex (50–52). In human addicts, higher serum BDNF levels have been reported after three weeks of abstinence relative to healthy controls (53). The only study that provides data on the evolution of serum BDNF during the first weeks of cocaine detoxification was carried out by our group in which we found an increase in serum levels of BDNF during the first two weeks of withdrawal (49). BDNF is a neurotrophin (54) widely expressed in the adult mammalian brain and is a key factor in neuronal survival and neural plasticity in response to environmental stimuli and cognitive stimulation (55–57). BDNF also plays a role in cocaine-induced neuroplasticity in different brain regions, such as the prefrontal cortex, amygdala, striatum and ventral tegmental area (for a review of this topic, see (58). The reported increase of BDNF during cocaine withdrawal may mediate neuroplastic changes in brain regions that underlie enhanced responsiveness to cocaine-related cues and drug seeking in cocaine trained rats (50–52).

In contrast, in the CIP group, BDNF level showed a trend towards a decrease during early abstinence. This decrease occurs even though patients received caffeine, a stimulant drug, which has been reported to increase BDNF in rats (59) and in sleep-deprived rats (60). This response of BDNF in the CIP compared to the non-CIP group suggests the involvement of some additional factors that might mask the increase of BDNF during early abstinence. In this regard, reduced serum BDNF levels have been reported in schizophrenic patients (23–27,61) and in first-episode psychosis (32–34). Additionally, the most frequent single nucleotide polymorphism (SNP) of the *BDNF* gene, the Val66Met SNP (35), is associated with changes in intracellular trafficking and secretion of the protein (36) and affects serum BDNF levels (Lang et al., 2009) and hippocampal-dependent learning (38). This polymorphism has also been associated with cognitive impairment in schizophrenic patients (30) and with social stress-induced paranoia

(39,40). Together, these data suggest that patients with psychotic symptoms associated with cocaine consumption share some of the BDNF deficiencies that characterize psychosis

There is experimental evidence that BDNF crosses the blood-brain barrier in both directions (62,63) and serum or plasma BDNF may reflect brain BDNF levels (64–66) even in schizophrenic patients (67). In this context, the low serum BDNF levels found in the CIP group reported in the present study may reflect BDNF deficiencies in the brain. Throughout life, BDNF is involved in survival and repair in the central nervous system (68) and in long-term activity-dependent neuroplastic changes (69,70) that underlie normal learning and memory (71). Hence, lower than normal levels of BDNF would have profound consequences on the structure and function of the prefrontal cortex and other regions of the brain (72,73). Additionally, BDNF also mediates another form of activity-dependent plasticity that facilitates the maintenance of some degree of constancy and stability within neural networks. This process is known as homeostatic plasticity, and it contributes to the attenuation of neuronal excitability and activity, thereby allowing the neural network to restore its stability (74–76). For example, BDNF scales the quantal amplitude of excitatory synaptic inputs in cortical pyramidal neurons. This scaling stabilizes firing rates during periods of intense change in neural activity, thereby contributing to synaptic refinement and the regulation of cortical excitability (77,78). BDNF is synthesized and released in response to afferent activity (79,80), and dopaminergic, glutamatergic and serotoninergic activity considerably change during cocaine consumption and withdrawal (81). We hypothesize that the transient psychotic symptoms associated to CIP might be reflecting plasticity deficits associated to homeostatic plasticity. Longitudinal studies are necessary to assess whether low serum BDNF levels normalize with abstinence in the CIP group or whether BDNF deficiencies persist over time.

The possible role of social and clinical risk factors over the response of BDNF during abstinence was also analyzed. There were no significant differences between the CIP and non-CIP groups in consumption variables, such as age of first cocaine use, days of consumption per month, or maximum quantity of cocaine consumed in 24 hours in the last month before treatment. When considering clinical data, patients in the CIP and non-CIP groups exhibited no differences in craving, withdrawal symptoms, anxiety or depression, both at the beginning and after 12 days of detoxification. During inpatient period, the only drug treatment was caffeine with or without biperidene or placebo and there were no difference in BDNF levels between treatment groups. All patients received the same diet, performed the same physical exercise, and shared the same environmental conditions. Therefore, these data indicate that social and clinical risk factors do not explain the differences in the evolution of BDNF levels between the CIP and non-CIP groups.

The analysis of the correlation between the evolution of clinical symptoms and serum BDNF levels during detoxification treatment also shows differences between CIP and non-CIP patients. In the non-CIP group, there was a positive correlation between the improvement of depressive and withdrawal symptoms associated with withdrawal and the increase in BDNF levels during withdrawal which was not seen in the CIP group. Cocaine withdrawal characterizes by symptoms of depression (82) associated to a decreased functionality of the dopaminergic and serotoninergic system (83) that resemble those symptoms and deficits that characterizes major depression (84). Depressive disorders also characterize by a decrease of serum BDNF (85–87) that recovers with the improvement of clinical symptoms (88). These data suggest that changes in serum BDNF in the non-CIP group are driven by neurobiological consequences of repeated cocaine consumption and withdrawal. In contrast, in the CIP group no correlation was found between scores of depressive and withdrawal symptoms and serum BDNF levels. This contrast suggests the possibility of a different neurobiological background underlying the response of BDNF during early withdrawal that might result in vulnerability to develop psychotic symptoms associated with drug of abuse.

We are aware of the limitations of this study especially related with the limited number of patients included in the protocol. In this regard, it is important to mention the difficulty of recruiting patients for various reasons. First, patients addicted to cocaine usually have additional organic or psychiatric comorbidities and are also subject of poly drug abuse. Both factors were exclusion criteria of the study. Additionally, patients pre-recruited in our study were reluctant to enter an inpatient regime with very restricted admission conditions.

In summary, these data suggest a different evolution of serum BDNF during early abstinence depending on the fact of having had transient psychotic symptoms associated to cocaine consumption or not. The increase in serum BDNF in the non-CIP group appears to be driven by the effects of chronic cocaine consumption and withdrawal. In contrast, in the CIP group there was a trend towards a decrease of serum BDNF during withdrawal suggesting that these patients share some of the neurotrophic deficiencies that characterize schizophrenia and psychosis.

Therapeutic strategies that tend to activate and stabilize BDNF levels may have a beneficial effect in the treatment of CIP and in preventing its transition to psychosis.

Acknowledgements

We thank the Neurovascular Research Laboratory of the University Hospital Vall d'Hebron and, particularly, Ms. Anna Penalba for her assistance with the biochemical analyses. Dr. Marta Ribases is a recipient of a Miguel Servet contract from the "Instituto de Salud Carlos III", Spain.

Financial disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

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