Serum Brain-Derived Neurotrophic Factor Levels and Cocaine-Induced Transient Psychotic Symptoms

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Key Words
Addiction · Cocaine · Cocaine-induced psychosis · Brain-derived neurotrophic factor

Abstract

Background: Cocaine-induced psychosis (CIP) is among the most serious adverse effects of cocaine. Reduced serum brain-derived neurotrophic factor (BDNF) levels have been reported in schizophrenia and psychosis; however, studies assessing the involvement of BDNF in CIP are lacking. Methods: A total of 22 cocaine-dependent patients (aged 33.65 ± 6.85) who had never experienced psychotic symptoms under the influence of cocaine (non-CIP) and 18 patients (aged 34.18 ± 8.54) with a history of CIP completed a 2-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 both 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. Improvements in depression (Beck Depression Inventory, BDI, p = 0.003) and withdrawal symptoms (Cocaine Selective Severity Assessment, 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.

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 nonclinical to clinical psychosis has been reported [3–5]. Among cocaine dependents, more than 50% of patients communicate 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 β-hydroxylase, which converts dopamine into adrenaline, has been observed in CIP [14, 15]. Reduced dopamine β-hydroxylase activity has also been found 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 schizoaffective patients under chronic treatment with antipsychotics [23–27] as well as in drug-naive 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-naive individuals [34]. In these patients, postnatal stress appears to mediate the BDNF decrease and its consequences on brain structure [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 measure serum BDNF levels in cocaine addicts immediately after cocaine consumption and after 2 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 anticholinergic 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 1 month before joining the study; (6) being seropositive for HIV; (7) abnormal results in laboratory screening tests or physical examination; (8) having metabolic, cardiac or any medical illness that can interfere with the expression of BDNF and (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. A total of 62 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 (fig. 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.

**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 6 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/day; dosage was increased by 300 mg/day; maximum dosage was 15 mg/kg/day up to 1,200 mg/day) and biperiden (4–8 mg/day) or matched placebo. Caffeine was administered to improve the comfort of patients, and biperiden was administered to prevent tolerance to caffeine. No additional psychotropic medication was administered except lorazepam (up to 5 mg/day) for the treatment of insomnia, if it was necessary.

**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 (STAI) [47] and the Beck Depression Inventory (BDI) [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 4 °C for 2 h. All samples were collected between 10 and 12 h to avoid circadian variations. The samples were refrigerated at 4 °C for 2 h and then centrifuged at 3,500 rpm for 10 min at 4 °C. We carefully collected the serum and stored it at −80 °C 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, Mass., USA), 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 were 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%.

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**Fig. 1. Flow diagram of the study.**
Due to the low numbers in the three subsamples (controls, non-psychotic and psychotic), nonparametric statistics were used for all bivariate analyses. Categorical variables were compared between groups using χ² 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 nonpsychotic and psychotic subsamples. Pre- and postdetoxification 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 nonpsychotic patients beyond a small trend (z = −1.743, p = 0.081) on the scale of loss of control from cocaine withdrawal, as evaluated using the CCQ. No differences were found between treatment groups (caffeine, caffeine-biperiden or placebo) in any of these measures.
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 $\chi^2 = 15.835$, $p < 0.0001$). There was a clear difference in the evolution of BDNF in both groups, but the pre-post difference was only statistically significant for the nonpsychotic patient group ($z = 2.025$, $p = 0.043$).

BDNF 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 had experienced some type of psychotic symptoms.

The change in serum BDNF levels was found to be a good predictor of depression ($\beta = 0.690$, $p < 0.005$; 44.1% of variance explained) but not abstinence among the non-psychotic patients, as measured by the CSSA; however, no predictive power of BDNF change was found for any variable among psychotic patients.

**Discussion**

To our knowledge, this is the first study to assess the evolution of serum BDNF levels during early abstinence in patients with CIP compared with patients without 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 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 was 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 3 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

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**Table 4.** Mean ± SD, statistical signification and nonparametric correlations with BDNF change of symptom improvement in patients with and without psychotic symptoms

| Symptoms change in nonpsychotic patients | Symptoms change in psychotic patients |
|-----------------------------------------|-------------------------------------|
| Mean ± SD | Change signification | Correlation with BDNF change | Mean ± SD | Change signification | Correlation with BDNF change |
| VAS 2.20±2.88 | –2.549 | 0.011 | 0.463 | 0.111 | 2.60±2.04 | –2.669 | 0.008 | 0.280 | 0.378 |
| CCQ Desire 8.00±10.63 | –2.123 | 0.034 | 0.330 | 0.322 | 11.55±9.50 | –2.625 | 0.009 | –0.005 | 0.989 |
| Intention 8.08±10.07 | –2.277 | 0.023 | 0.483 | 0.132 | 13.36±9.48 | –2.803 | 0.005 | –0.373 | 0.259 |
| Anticipation 7.42±12.59 | –1.887 | 0.059 | 0.306 | 0.915 | 6.73±10.50 | –1.886 | 0.059 | 0.209 | 0.537 |
| Relief 5.25±10.57 | –1.845 | 0.065 | –0.173 | 0.612 | 4.27±9.39 | –1.336 | 0.181 | 0.132 | 0.699 |
| Loss of control 11.17±11.87 | –2.237 | 0.025 | 0.300 | 0.370 | 22.91±36.70 | –2.848 | 0.004 | –0.301 | 0.368 |
| CSSA 9.18±9.50 | –2.490 | 0.013 | 0.657 | 0.039 | 13.55±10.23 | –2.936 | 0.003 | –0.187 | 0.582 |

Baseline clinical measures

| BDI 8.31±7.03 | –2.945 | 0.003 | 0.683 | 0.014 | 10.50±9.17 | –2.449 | 0.014 | –0.365 | 0.300 |
| STAI State 13.36±8.09 | –2.847 | 0.004 | 0.236 | 0.511 | 14.55±8.45 | –2.803 | 0.005 | –0.136 | 0.689 |

CCQ = Cocaine Craving Questionnaire; CSSA = Cocaine Selective Severity Assessment; VAS = Visual Analog Scale.
tion was carried out by our group, in which we found an increase in serum levels of BDNF during the first 2 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 review, 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 these patients.

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 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]. 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 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 with CIP might be reflecting plasticity deficits associated with 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 h 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 the inpatient period, the only drug treatment was caffeine with or without biperiden or placebo and there were no differences 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 is characterized by symptoms of depression [82] associated with a decreased functionality of the dopaminergic and serotoninergic system [83] that resemble those symptoms and deficits that characterize major depression [84]. Depressive disorders are also characterized
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 to 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 to polydrug abuse. Both factors were exclusion criteria of the study. Additionally, patients prerecruited 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 whether subjects had transient psychotic symptoms associated with 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.

Acknowledgments

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.

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