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Serum brain-derived neurotrophic factor levels and psychotic symptoms in heroin dependence

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Abstract

Objectives: Psychotic symptoms are commonly observed among heroin users. Low serum brain-derived neurotrophic factor (BDNF) levels have been reported in schizophrenia and psychosis; however, studies assessing the relationship between serum BDNF levels and psychotic symptoms in heroin dependence are lacking.

Method: A total of 31 heroin-dependent patients who had never experienced psychotic symptoms during heroin consumption and 21 patients with a history of psychotic symptoms were consecutively recruited. We measured by enzyme-linked immunosorbent assay (ELISA) serum BDNF levels during early abstinence. A gender- and age-matched sample of healthy controls was also recruited and underwent measurement of BDNF.

Results: BDNF levels were significantly lower in patients with psychotic symptoms than in those without psychotic symptoms ($P < 0.001$). BDNF levels were not found to be correlated with sex, age, age of onset, duration of heroin use, average daily dose of heroin use, frequency of heroin use, SDS scores, BAI scores and BDI scores in the psychotic subsamples (all $P > 0.05$).

Conclusions: Our findings suggest that heroin-dependent patients with psychotic symptoms share some of the neurotrophic insult that characterizes schizophrenia and psychosis.

1. Introduction

Coexisting psychotic symptoms in heroin users have been frequently mentioned in previous literatures [1–4]. The prevalence of psychotic symptoms associated with opiates consumption has been reported to range from 6.7% to 58.2% [4]. The presence of psychotic symptoms has been associated with increased severity of the substance use [4,5], greater psychosocial problems and lower quality of life. However, risk factors for the trait are unclear until now.

Brain-derived neurotrophic factor (BDNF) is the most broadly distributed neurotrophin in the human brain and it regulates neuronal development, survival and function and neural plasticity [6–8]. BDNF has also been shown to be involved in synaptic neurotransmission, with special effect on dopamine, GABA and glutamate, three neurotransmitter systems that play a critical role in the pathophysiology and treatment of schizophrenia [9,10]. Low serum BDNF levels have been reported in medicated and non-medicated patients with schizophrenia [11–13] while further studies focus on the involvement of BDNF in the pathophysiology and treatment of schizophrenia [9,14]. Moreover, the Val66Met single nucleotide polymorphism (SNP) of the BDNF gene has been associated with cognitive impairment in chronic schizophrenic patients [15]. The polymorphism may also contribute to the development of schizophrenia, regarding the pathophysiology, symptoms and medication [16–18]. Recently, Corominas-Roso et al. [19] found that cocaine-dependent patients with a history of cocaine-induced psychosis exhibited a significant decrease in serum BDNF levels during early abstinence.

Abbreviations: BDNF, brain-derived neurotrophic factor; SDS, Severity of Dependence Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory.

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However, to our best knowledge, no study has examined this association between serum BDNF levels and psychotic symptoms in heroin dependence. The objective of our study is to examine the involvement of BDNF in heroin-dependent patients with psychotic symptoms. We evaluate whether serum BDNF levels during early abstinence may be capable of differentiating between patients with and without psychotic symptoms during heroin consumption.

2. Method

2.1. Participants

Fifty-two heroin-dependent patients were consecutively recruited from Sanyang Detoxification Institute in Wenzhou city in the Zhejiang province. Recruited patients, with an average abstinent period of 4.62 ± 2.27 days, had no access to alcohol or drugs. The inclusion criteria were: (1) age 18 years or older; (2) fulfillment of the Diagnostics and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for heroin dependence; (3) positive urine test for opiates on admission; (4) heroin abstinence within 7 days; (5) signed informed consent. The exclusion criteria included: (1) history of psychotic, mood, anxiety or substance abuse disorder except heroin or nicotine; (2) neurological illness; (3) history of cranial trauma; (4) being seropositive for HIV; (5) metabolic, cardiac or any medical illness that can interfere with the serum levels of BDNF. To manage withdrawal symptoms, heroin-dependent subjects received initial dosages of methadone in the range of 30–40 mg/day and then slowly tapered by 5 mg/day. Methadone was administrated orally and once daily. All participants took no other medications during heroin abstinence.

Clinical diagnosis was performed by a trained psychiatrist. A subgroup of 31 subjects reported never having experienced psychotic symptoms during their heroin consumption, whereas a subgroup of 21 subjects had experienced psychotic symptoms while using heroin. A gender-and age-matched sample of 57 normal controls met the aforementioned inclusion criteria. Our study was approved by the Human Research and Ethics Committee of Wenzhou Medical University. Written informed consent was obtained from all participants.

2.2. Measures

To evaluate the psychotic symptoms associated with heroin consumption, a structured interview was performed. The questions based in DSM IV-TR were as follows: (1) Have you ever heard something that wasn't actually there? Did it happen while you were under the influence of heroin? (2) Have you ever seen something that wasn't really there? Did it happen under the influence of heroin? (3) Have you ever felt anything abnormal on your body or on your skin? Did it happen while you were under the influence of heroin? (4) Have you thought 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 influence of heroin? Patients were considered as having psychotic symptoms if they were marked positively in any of the above questions.

We interviewed heroin-dependent patients to gather variables related to heroin consumption, including age of onset, duration of heroin use, average daily dose of heroin use, and frequency of heroin use (<1 time per week; 2–5 times per week; 1–2 times per day; ≥3 times per day). The Severity of Dependence Scale (SDS) measured the degree of dependence. The Beck Depression Inventory (BDI-13) [20] and Beck Anxiety Inventory (BAI) [21] assessed depression and anxiety symptoms respectively.

2.3. Determination of BDNF concentrations in serum

For serum sampling, 5 ml of blood was collected from the antecubital vein in anticoagulant-free tubes. All samples were collected between 8 and 10 AM to limit a possible rhythm variance bias. The samples were allowed to clot at room temperature for 4 h and then centrifuged at 3500 rpm for 10 min immediately. We collected serum and then stored it at −80 °C until conducting the BDNF assay.

Serum levels of BDNF were measured using DuoSet ELISA Development System (Catalog number DY248, R&D Systems, USA). The measurements were performed by trained operators blind to our research design. All assays were performed in duplicate and expressed as pg/ml. The detection range of the assay was 20–4000 pg/ml. The intra-assay and inter-assay coefficients were <5% and <10% respectively.

2.4. Data analysis

The categorical variables were compared with the Pearson χ^2 test. If any of the expected counts were <5, Fisher's exact test was used instead. Kolmogorov–Smirnov test was used to analyze for normality, and then Levene test was used to verify homogeneity of group variances. Student *t* test and one-way analysis of variance (ANOVA) were employed for the normally distributed variables, while the Mann–Whitney *U* test was employed for variables that did not pass the test for normality. Post hoc tests were conducted to determine the difference between groups, followed by Fisher's least significant difference (LSD) test. The effect of age and sex was tested by adding these variables to the analysis model as covariates. Correlations between serum BDNF and demographic and clinical parameters were examined by bivariate correlation (Pearson or Spearman rank correlation). Bonferroni corrections were applied to each test to adjust for multiple testing. All analyses were performed with SPSS software (version 17.0, SPSS Inc., Chicago, IL.). A two-tailed *P* value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Demographic and clinical features of heroin-dependent patients and controls

The demographic features of the control, non-psychotic and psychotic subsamples are shown in Table 1. No gender