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Brain-derived neurotrophic factor serum levels in heroin-dependent patients after 26 weeks of withdrawal

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Abstract

Background: Brain-derived neurotrophic factor (BDNF) has been implicated in the pathophysiology of heroin dependence. BDNF expression is dramatically changed during drug withdrawal, and is associated with drug withdrawal syndrome. This study aimed to explore (1) alterations of BDNF serum levels in heroin-dependent patients after long term abstinence; and (2) the association between BDNF serum levels and protracted withdrawal syndrome.
Method: Fifty-three male heroin-dependent patients and fifty-two gender-matched healthy controls were enrolled in this study. We measured BDNF serum levels at baseline and 26 weeks after heroin abstinence. Moreover, protracted withdrawal symptoms, depression and anxiety symptoms were measured by Protracted Withdrawal Symptoms of Heroin-dependent patients (PWSHA), Self-rating Depression Scale (SDS) and Self-rating Anxiety Scale (SAS), respectively.
Result: We found that baseline BDNF serum levels were significantly lower in heroin-dependent patients compared to controls ($p < 0.01$). There was also a significantly difference in BDNF serum levels among heroin-dependent patients at baseline and 26-week follow-up ($p < 0.01$). The BDNF serum levels were not associated with age, BMI, years of education, age of initial use, or duration of use. Of the clinical symptoms measured, the change in BDNF serum levels from baseline to 26-week follow-up was negatively associated with the change in PWSHA scores ($r = -0.44$, $p < 0.01$, see Table 2 and Figure 2 for details).
Conclusion: The results show that the BDNF serum levels in heroin-dependent patients are lower than those of healthy controls at baseline and increased after 26 weeks of abstinence, although the BDNF serum levels are still lower than those of the healthy controls. A negative correlation between the change in BDNF serum levels and protracted withdrawal symptoms was found but needs to be confirmed in further study. The results revealed that BDNF serum level is worth paying attention to in order to further investigate the possibility of it being a biomarker of treatment outcome for opiate dependence.

1. Introduction

Drug dependence, especially heroin dependence, causes many problems for individuals and society [1]. By the end of 2014, there were almost 2.96 million registered drug abusers in China, and more than 49.3% of them were individuals with heroin dependence [2]. Heroin dependence is a chronic, relapsing brain disease that can cause acute and protracted withdrawal symptoms when drug use is discontinued [3,4]. For some individuals with heroin dependence, withdrawal symptoms may last for weeks, months or even years. These symptoms may lead patients to seek relief by returning to drug use, resulting in a pattern of repeated relapse and return to treatment [5].

The current literature supports a close relationship between withdrawal symptoms and brain-derived neurotrophic factor (BDNF) [6–8]. BDNF is a neurotrophic neuropeptide that is well known to stimulate neuronal growth and differentiation and to facilitate survival in developing neurons [9]. BDNF ensures the trophic support of adult dopaminergic neurons and has been reported to be involved in the regulation of dopamine release from the midbrain [10].

The results of preclinical studies indicate that chronic exposure to opiates increases the BDNF levels in neurons of the ventral tegmental area (VTA) [11]. In another

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experiment, enzyme-linked immunosorbent assay (ELISA) reconfirmed a significant up-regulation of BDNF protein levels in the VTA of rats after opiate abstinence [12]. However, previous studies on the association between BDNF serum levels and drug withdrawal have revealed mixed results. Some researchers have shown that BDNF serum levels are decreased in heroin addicts after short-term abstinence (less than one month) [13], whereas other studies have declared that BDNF serum levels do not change or actually increase during withdrawal [14,8]. Relationship between BDNF serum levels and drug withdrawal was also understudied among heroin dependent population in Asia. Thus, studies on the BDNF serum levels and drug withdrawal, especially in long-term abstinence settings and cultural backgrounds, are still in need.

With the goal of advancing the understanding of alterations of BDNF serum levels in heroin-dependent patients after long-term abstinence and the association between BDNF serum levels and protracted withdrawal symptoms, this study obtained longitudinal data on a group of heroin-dependent patients who were maintained in a compulsory treatment facility in Shanghai. We hope that better understanding of relationship between BDNF serum levels and protracted withdrawal symptoms during long-term recovery can contribute to improving recovery strategies.

2. Methods

2.1. Sample

Science gender differences regarding the regulation of neurotrophic neuropeptides [15,16], only males were recruited to participate in this study. Fifty-three male Han Chinese heroin-dependent individuals were recruited from a compulsory rehabilitation center in Shanghai. Male participants were included in our study if they met the following criteria: (1) between 18 and 65 years old; (2) current opiate dependence according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV); (3) urine test positive for opiate upon admission; and (4) heroin abstinence for 1 to 7 days (the period between enrolment and the last drug use).

Patients were excluded if they met any of following exclusion criteria: (1) seropositive for HIV; (2) had serious mental illnesses (schizophrenia, manic episodes, mental retardation); (3) a recent (in the last 3 months) serious organic disease; or (4) met the DSM-IV criteria for drug dependence other than opiate, which was assessed and ruled out by two clinical psychiatrists. Abstinence from heroin lasted for twenty-six weeks. At the 26-week endpoint, two patients had dropped out from the study. Patients with severe insomnia were allowed to take 2 mg/day benzodiazepine tablets during the first two weeks of therapy but were asked to stop using benzodiazepine after two weeks.

Fifty-two male controls were recruited from healthy subjects who visited the Shanghai Mental Health Center for regular medical examination. The healthy controls had no self-reported family history of psychiatric conditions or history of drug use. This study was approved by the Human Research and Ethics Committee of Shanghai Mental Health Center. Written informed consent was obtained from all individuals after a detailed description of the study.

2.2. Clinical assessment

All participants' general demographic data, such as age, gender, years of education, height, and weight were collected. Then individuals in the patient group were interviewed heroin-dependent to obtain more information, including age of initial use and most recent use. In addition, we examined the protracted withdrawal symptoms, depressive and anxiety symptoms at baseline and at the 26-week follow-up using the Protracted Withdrawal Symptoms of Heroin-Dependent Patients (PWSHA), the Self-Rating Depression Scale (SDS) and the Self-Rating Anxiety Scale (SAS), respectively. Shi and colleagues edited the PWSHA, which consists of four factors (somatization, negative moods, cravings and dyssomnia) ranked on a 19-point rating scale [17]. The PWSHA has good internal and construct validity and reliability. The results of previous studies have indicated that the SDS and SAS are valid, sensitive measures of clinical severity in patients, supporting their continued use as research instruments [18,19].

2.3. Blood sample collection and BDNF measurements

Blood samples were taken upon admission between 08:00 and 10:00 to minimize a possible rhythm variance bias. 10 ml of blood was collected, and the blood was immediately centrifuged at 3500 rpm for 10 min. The serum was obtained and was stored at −80 °C until it was thawed for use in the assay. The BDNF serum levels were investigated at baseline and at the 26-week follow-up and were compared to the serum levels of the healthy control group. The BDNF serum levels were assessed using the DuoSet ELISA Development System (Catalog number DY248, R&D Systems, USA). All assays were performed according to the manufacturer's directions and were performed in duplicate and expressed as pg/ml. The lower thresholds of determination were 21 pg/ml. The intra-assay and inter-assay coefficients of variation were 5.0% and 8.7%, respectively.

2.4. Statistical analysis

The BDNF serum levels were normally distributed according to the Kolmogorov–Smirnov test. We compared the BDNF serum levels between the patients and the healthy controls at baseline and at 26 weeks using two-way analysis of variance (ANOVA). The between-subjects factor of group (patients vs. healthy controls) and the within-subjects factor of time (baseline vs. 26-week follow-up) were analyzed as