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# Increased serum brain-derived neurotrophic factor levels during opiate withdrawal

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## HIGHLIGHTS

- We examined changes in the levels of serum BDNF during opiate withdrawal.
- Serum BDNF levels increased during opiate early withdrawal.
- Serum BDNF levels remained higher even after one month of abstinence.
- BDNF may play a critical role in the course of opiate addiction and withdrawal.

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## ABSTRACT

Brain-derived neurotrophic factor (BDNF) has been implicated in the pathophysiology of opiate addiction. Both increased and decreased serum BDNF levels have been reported in heroin addicts. Moreover, the role of BDNF in heroin-dependent patients during withdrawal has not been studied. This study aimed to explore the differences in serum BDNF levels of heroin addicts and healthy controls, and investigate the changes of serum BDNF levels in heroin addicts at baseline and at one month after heroin cessation. Seventy-two heroin-dependent patients and ninety age- and gender-matched healthy controls were enrolled in this study. We measured serum BDNF levels at baseline (both heroin addicts and healthy controls) and one month after heroin cessation (heroin addicts only). A total of 37 (51.4%) heroin addicts completed the one-month study. We found that baseline serum BDNF levels were significantly higher in heroin addicts compared to controls ($F = 36.5$, $p = 0.001$). There was no difference in serum BDNF levels among heroin addicts at baseline and one month after heroin cessation ($F = 1.101$, $p = 0.301$). These results indicate that BDNF may play a critical role in the course of opiate addiction and withdrawal.
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## 1. Introduction

The midbrain dopaminergic system is presumed to play a critical role in reward and addiction [28]. Opiates have been shown to indirectly activate (disinhibit) dopaminergic neurons in the ventral tegmental area (VTA) by inhibiting local GABAergic interneurons [18]. Brain-derived neurotrophic factor (BDNF) is one of the most abundant neurotrophic factors in the brain, and has a critical role in the survival and function of midbrain dopaminergic and cholinergic neurons [13,15]. BDNF has been reported to be involved in learning and memory, and synaptic plasticity [4,21,29]. Furthermore, several studies have demonstrated alterations of serum or

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plasma BDNF levels in drug abusers [8,19] and implicated BDNF in the development of addiction [12].

In preclinical studies, changes of BDNF expression in the VTA were found during chronic opiate administration or withdrawal [7,30]. Chronic morphine treatment leads to induction of tyrosine hydroxylase and reduction in the size of dopamine neurons in the VTA, both of which were prevented by intra-VTA infusion of BDNF [5,27]. There also appears to be a relationship between heroin dependence and BDNF genetic polymorphisms [16]. At this time, there have been two studies measuring levels of serum BDNF in opiate abusers; however, the results were contradictory [2,14]. In addition, there have been no studies of serum BDNF levels in heroin-dependent patients after cessation of heroin.

In the present study, we compared serum BDNF levels of heroin-dependent patients during withdrawal and healthy controls in order to understand the relationship of BDNF and heroin use.

## 2. Materials and methods

### 2.1. Subjects

Seventy-two Chinese heroin-dependent patients were recruited from Sanyang Detoxification Institute, which is located in Wenzhou city in the Zhejiang province. While in the institute, inpatients had no access to heroin, which allowed for rigid control of abstinence. Participants were included in the study based on the following criteria: age 18 years or older, fulfillment of the Diagnostics and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for current heroin dependence, positive urine test for opiates upon admission, heroin abstinence for 1–7 days (period between enrollment and last drug use), and signed informed consent. Subjects were excluded if they were seropositive for HIV, had serious medical illnesses that required pharmacological treatment, or met the DSM-IV criteria for axis I psychiatric disorder or drug dependence other than heroin or nicotine, which were assessed and ruled out by a clinical psychiatrist. In order to manage withdrawal symptoms, patients were given 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. The patients took no other medications during heroin withdrawal.

Ninety normal controls were randomly selected from healthy subjects who visited the first affiliated hospital of Wenzhou medical university for regular medical examination. Healthy subjects had no self-reported family psychiatric history and no medication history. This study was approved by the Human Research and Ethics Committee of Wenzhou Medical University. Written informed consent was obtained from all subjects after a detailed description of the study.

### 2.2. Measures

We collected all participants' socio-demographic data (age, gender, educational years, height, and weight). Then, we interviewed heroin-dependent subjects to gather information about their drug use, including age at onset, duration of drug use (the period between the first-ever heroin use and most recent use), average daily dose (in the past week), and route of drug administration. In addition, depression and anxiety symptoms were examined at baseline using Beck Depression Inventory (BDI-13) [3] and Beck Anxiety Inventory (BAI) [25] respectively.

### 2.3. Determination of BDNF concentrations in serum

Serum BDNF levels were examined at baseline (both heroin group and control group) and at the one-month endpoint (heroin group only, 48.6% of heroin users dropped out from the study). All blood samples were collected between 8 and 10 AM in order to limit a possible rhythm variance bias. At baseline (recruited heroin subjects were abstinent for less than 7 days, with an average abstinent period of $4.28 \pm 1.7$ days), all 72 heroin subjects completed the measurement. However, at the end of the one-month endpoint, only 37(51.4%) heroin patients (with an average abstinent period of $29.2 \pm 2.1$ days) completed the measurement. 35(48.6%) heroin users dropped out due to discharge or referral. 5 ml of blood was collected and allowed to clot at room temperature, and the blood was centrifuged at 3500 rpm for 10 min immediately. Serum was obtained, and then stored at −80 °C until it was thawed for assay.

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

**Table 1**
Characteristics of heroin users and normal controls.

| Characteristics | Heroin users ($n = 72$) | Normal controls ($n = 90$) | Statistic ($p$ value) |
|---|---|---|---|
| Age (years) | $35.3 \pm 7.9$ | $32.9 \pm 9.9$ | −1.72 (0.087) |
| Male/female ($n$) | 65/7 | 77/13 | 0.82 (0.36) |
| Education (years) | $7.1 \pm 2.3$ | $13.9 \pm 1.9$ | −10.59 (**0.01**) |
| BMI (kg/m$^2$) | $20.8 \pm 2.4$ | $21.4 \pm 2.3$ | 1.55 (0.124) |

*Note*: BMI = body mass index.
Bold value indicates $p < 0.05$.

### 2.4. Statistical analysis

We compared serum BDNF levels between the healthy controls and heroin-dependent group at baseline or one-month endpoint using one-way analysis of variance (ANOVA). When there was a significant ANOVA, the effects of age, gender, education and body mass index (BMI) were tested by adding these variables to the analysis model as covariates. With repeated-measures, we analyzed the differences of serum BDNF levels at baseline and one month after heroin withdrawal. Depending on the data distribution, Pearson correlation analysis or Spearman correlation analysis was used to examine the relationships between serum BDNF levels and variables. Stepwise multiple regression analysis was used to examine the effect of some potential factors on BDNF values. All data were analyzed using SPSS software. A two-tailed $p$ value of less than 0.05 was considered to be statistically significant.

## 3. Results

### 3.1. Characteristics of heroin users and healthy controls

The demographics of heroin users and healthy controls are summarized in Table 1. Seventy-two heroin users (65 male and 7 female) and ninety healthy controls (77 male and 13 female) were recruited. Educational years in heroin users were lower than that of healthy controls ($p < 0.01$). There was no significant difference in any other variables between heroin users and healthy controls (all $p > 0.05$). In heroin users, the average age at onset of heroin use was $25.9 \pm 6.8$ years. The duration of heroin use ranged from 1 month to 244 months, with an average duration of heroin use of $97.2 \pm 77.6$ months. The dose of heroin use per day in the past week ranged from 0.1 to 2.0 g/day, with the average dose of heroin use of $0.42 \pm 0.45$ g/day. The primary routes of heroin administration were smoking (58.3%), intravenous injection (33.3%), intramuscular or subcutaneous injection (4.2%), oral administration (2.8%) and

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