European Psychiatry 36 (2016) 23–28

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Increased serum brain-derived neurotrophic factor levels following electroconvulsive therapy or antipsychotic treatment in patients with schizophrenia

J. Li [a,b,c], F. Ye [b], W. Xiao [b], X. Tang [b], W. Sha [b], X. Zhang [b,1,*], J. Wang [a,c,1,**]

[a] Shanghai Key Laboratory of Psychotic Disorders (No. 13dz2260500), Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai 200030, PR China
[b] Department of Psychiatry, Affiliated WuTaiShan Hospital of Medical College of Yangzhou University, Yangzhou 225003, PR China
[c] Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders (Ministry of Education), Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai 200030, PR China

ARTICLE INFO

Article history:
Received 7 December 2015
Received in revised form 18 February 2016
Accepted 16 March 2016
Available online 13 June 2016

Keywords:
Electroconvulsive therapy
Serum brain-derived neurotrophic factor
Schizophrenia

ABSTRACT

Background: Many schizophrenia patients experience residual symptoms even after treatment. Electroconvulsive therapy (ECT) is often used in medication-resistant schizophrenia patients when pharmacologic interventions have failed; however, the mechanism of action is unclear. Brain-derived neurotrophic factor (BDNF) levels are reduced in drug-naive, first-episode schizophrenia and are increased by antipsychotic treatment. We tested the hypothesis that ECT increases serum BDNF levels by measuring BDNF concentrations in schizophrenia patients before and after they received ECT.
Methods: A total of 160 patients with schizophrenia were examined. The ECT group ($n = 80$) was treated with antipsychotics and ECT (eight to 10 sessions administered every other day). The drug therapy group ($n = 80$) received only antipsychotic treatment. A control group ($n = 77$) was recruited that served as the baseline for comparison.
Results: Baseline serum BDNF level in ECT group was lower than in controls (9.7 ± 2.1 vs. 12.4 ± 3.2 ng/ml; $P < 0.001$), but increased after ECT, such that there was no difference between the two groups (11.9 ± 3.3 vs. 12.4 ± 3.2 ng/ml; $P = 0.362$). There was no correlation between patients' Positive and Negative Syndrome Scale (PANSS) score and serum BDNF level before ECT; however, a negative correlation was observed after ECT (total: $r = -0.692$; $P < 0.01$). From baseline to remission after ECT, serum BDNF level increased ($P < 0.001$) and their PANSS score decreased ($P < 0.001$). Changes in BDNF level (2.21 ± 4.10 ng/ml) and PANSS score (28.69 ± 14.96) were positively correlated in the ECT group ($r = 0.630$; $P < 0.01$).
Conclusions: BDNF level was lower in schizophrenia patients relative to healthy controls before ECT and medication. BDNF level increased after ECT and medication, and its longitudinal change was associated with changes in patients' psychotic symptoms. These results indicate that BDNF mediates the antipsychotic effects of ECT.

1. Introduction

Schizophrenia is a chronic and serious mental disorder characterized by positive and negative symptoms, as well as cognitive impairment. Disease onset is typically between the ages of 15 and 35 years; in these individuals, social functioning and the ability to work are impaired. Schizophrenia is a global public health problem [1] as it requires repeated treatments, with many patients experiencing residual symptoms. Therefore, better strategies for the treatment of schizophrenia are urgently needed.

Despite substantial progress in the pharmacotherapy of schizophrenia, a subset of patients are treatment-resistant. Electroconvulsive therapy (ECT) can ameliorate schizophrenia and is typically administered under anesthetic along with a muscle relaxant; blood pressure is closely monitored, and an

* Corresponding author at: Department of Psychiatry, Affiliated WuTaiShan Hospital of Medical College of Yangzhou University, Yangzhou 225003, PR China.
** Corresponding author at: Shanghai Key Laboratory of Psychotic Disorders (No. 13dz2260500), Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai 200030, PR China.
E-mail addresses: zhangxiaobim@163.com (X. Zhang), jijunwang27@163.com (J. Wang).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.eurpsy.2016.03.005
0924-9338/

electrocardiogram is performed concomitantly. Under these conditions, there is no muscular response (convulsion) and the electroencephalogram is near normal. ECT is an effective treatment for various psychiatric illnesses and is the first-choice, non-pharmacological treatment after conventional pharmacologic interventions have failed; it is often used in treatment-resistant schizophrenia and recurrent refractory mania [2], and is safe and cost-effective [3].

Little is known about the etiology and pathogenesis of schizophrenia. One hypothesis posits that the disease is secondary to a dysregulation of neurotrophic factor levels during brain development, which could lead to disorganization of neuronal networks. Inadequate neurotrophic support in the adult brain may decrease its capacity to adapt to changes and increase vulnerability to neurotoxic damage. Brain-derived neurotrophic factor (BDNF) is a nerve growth factor that is widely expressed in the central and peripheral nervous systems and plays a major role in the survival and maintenance of dopaminergic neurons and synaptic plasticity [4]. Deficits in BDNF production and utilization have been implicated in the pathology of schizophrenia [5,6]; it has been shown that BDNF induces the short-term release of dopamine [7].

Human studies have reported reductions in BDNF levels in the serum [8] and dorsolateral prefrontal cortex [9] of patients with schizophrenia as compared to healthy controls; this was confirmed in a meta-analysis of medicated and drug-naive patients [10]. Reports on BDNF levels in schizophrenia are inconsistent. For instance, Gama et al. reported that chronically medicated schizophrenia patients exhibited higher BDNF levels than controls [11]. Peripheral BDNF levels in schizophrenia decreased with disease progression and were increased by treatment with antipsychotic medication [10]. Chronic administration of clozapine was shown to be effective in treating patients with schizophrenia; BDNF levels have been shown to be correlated with clozapine dose [12]. In addition, electroconvulsive seizures were reported to induce an increase of BDNF mRNA [13] and protein [14] levels in rat brain.

BDNF levels are reduced in drug-naïve first-episode schizophrenia and are increased by antipsychotic treatment [10], suggesting that they can be normalized by pharmacotherapy. We conjectured that ECT may also alter serum BDNF levels when improving clinical symptoms of schizophrenia. To test the hypothesis, we measured serum concentrations of BDNF in schizophrenia patients receiving ECT.

2. Methods

2.1. Study population

A total of 160 patients with schizophrenia were recruited for the study. Written, informed consent was obtained from participants or their caregivers. Diagnosis was based on DSM-IV criteria and all patients were interviewed in person by a trained psychiatrist. The ECT group consisted of 80 patients (38 female, 42 male; mean age: 38.1 ± 11.1 years, range: 17–60 years) who were referred for ECT at the Department of Psychiatry, WuTaiShan Hospital, Yangzhou, China; all of these patients were treated with antipsychotics. The drug therapy group included 80 patients (36 female, 44 male; mean age: 37.7 years, range: 16–65 years) who received only antipsychotic drug treatment at the hospital. The control group consisted of 77 healthy individuals without a history of psychiatric disorders. Exclusion criteria were as follows: hypothyroidism, epilepsy, diabetes, or cardiovascular disorders. The study protocol was approved by the local Institutional Ethics Committee.

2.2. ECT

All subjects underwent standard clinical evaluation prior to ECT. Pre-medication in all patients consisted of 0.05 mg atropine sulfate, 1.0 mg/kg propofol, and 1.0 mg/kg succinylcholine by intravenous injection. Patients underwent bilateral ECT between 07:00 and 09:00 h; a Thymatron TMDG instrument was used (Somatics, Lake Bluff, IL, USA). Two stimulus electrodes were placed on the left and right frontotemporal scalp. ECT conditions were similar for all patients (maximum charge delivered = 504 mC; output current = 0.9 A; frequency = 10–70 Hz; pulse width = 0.5 ms; and maximum stimulus duration = 8 s). Motor convulsions and induced tachycardia were monitored and electroencephalogram and electromyogram (when necessary) were recorded during ECT, which was administered 8–10 times every other day.

2.3. Symptom ratings

A trained research assistant or psychologist administered the Positive and Negative Syndrome Scale (PANSS) to all participants with schizophrenia to obtain a measure of current symptom severity. Patients recommended for ECT treatment were examined twice: before starting ECT and within 3 days after completing the sessions. Patients treated only with antipsychotic drugs were also examined twice: before starting antipsychotic treatment and after completing 8 weeks of treatment.

2.4. BDNF assay

After overnight fasting, pre-prandial blood samples were collected between 08:00 and 09:00 h on the same schedule as for symptom assessment. For healthy controls, a baseline blood sample was collected on the morning of the first visit. For patients receiving ECT, a baseline blood sample was collected on the morning of the first session and post-treatment serum was obtained within 3 days of the last session. Serum samples were separated by centrifugation (3000 rpm for 10 min at 20 °C) and stored at −80 °C. BDNF concentration was measured with an enzyme-linked immunosorbent assay (Emax Immunoassay System kit; Promega, Madison, WI, USA) according to the manufacturer's instructions.

2.5. Statistical analysis

Differences in continuous variables between groups were assessed by the independent samples *t*-test; the χ^2 test was applied to categorical data such as gender. The paired samples *t*-test was used to evaluate changes in PANSS score and BDNF level. The relationship between the two variables was examined using Spearman's correlation coefficient. *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Demographic data

Demographic and clinical characteristics of the study population are summarized in Table 1. There were no differences in demographic data (gender and age) between groups. Serum BDNF levels in patients are shown in Fig. 1 All patients included in the ECT group received antipsychotic treatment, including aripiprazole ($n = 32$), quetiapine ($n = 26$), olanzapine ($n = 4$), risperidone ($n = 3$), or a combination of antipsychotics ($n = 15$). Mean antipsychotic dose (chlorpromazine equivalent) was