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Comparison of serum BDNF levels in deficit and nondeficit chronic schizophrenia and healthy controls

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ABSTRACT

The aim of this study was to compare serum BDNF levels of chronic schizophrenic patients, with or without deficit syndrome, and healthy controls. A comparative study of serum BDNF levels, determined by ELISA, was performed in 47 chronic patients with schizophrenia matched with 47 healthy controls. A part of the chronic schizophrenic sample was further divided into patients with a deficit ($n=14$) and a nondeficit syndrome ($n=20$), according to the Proxy for the Deficit Syndrome Scale. A significant difference was observed in decreased serum BDNF levels between chronic schizophrenia and healthy controls. No statistical significant differences in BDNF levels between deficit and nondeficit chronic schizophrenic patients were found. Our study confirms differences of serum BDNF levels of chronic schizophrenia and healthy controls, which correspond to the clinical progression of the disease. Our results do not support a relation between deficit profile in chronic schizophrenia and lower serum BDNF levels.

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1. Introduction

Schizophrenia is a chronic and disabling mental disorder in which neurodevelopmental factors play a significant etiological role (Insel, 2010). The diagnosis is still mainly made on clinical grounds, typically using criterion-based approaches, such as DSM-IV and ICD-10 criteria. Biomarkers are currently being examined for diagnostic, prognostic or therapeutic usefulness, such as neurotrophins. They belong to a family of secretory proteins and are involved in the survival, development and function of neurons (Reichardt, 2006). This group includes nerve growth factor, neurotrophin-3, neurotrophin-4 and the brain-derived neurotrophic factor (BDNF) (Barde et al., 1982; Palomino et al., 2013). BDNF is known to be responsible for development, regeneration, survival and maintenance of neurons and their serum levels show a good correlation with cortical BDNF levels (Karege et al., 2002). Reduced serum BDNF levels have been implicated in the pathophysiology of various neuropsychiatric disorders, including schizophrenia (Binder and Scharfman, 2004; Durany and Thome, 2004; Autry and Monteggia, 2012; Martinotti et al., 2012). Several studies in schizophrenic patients established negative correlations between BDNF levels and positive and negative symptoms (Rizos et al., 2008), catatonia (Huang and Lee, 2006), and greater impairment in verbal working memory (Niitsu et al., 2011). Other studies in change suggested no differences in BDNF levels between schizophrenia patients and healthy controls, or even found increased BDNF levels in schizophrenia (Shimizu et al., 2003; Gama et al., 2007; Reis et al., 2008).

To clarify this inconsistency, a recent meta-analysis addressed BDNF levels in schizophrenia (Green et al., 2011). One main finding was that there was moderate quality evidence of reduced blood BDNF levels in acute and chronic schizophrenia.

From a clinical point of view, the subdivision of chronic schizophrenia into deficit and nondeficit types has been an influential and helpful recent clinical insight (Cohen et al., 2010). The deficit syndrome is characterized by a stable, at least one-year long presence of two or more negative symptoms, such as affective flattening, reduced emotional range, alogia, loss of interest, lack of

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focus or loss of interest in social activities (Carpenter et al., 1988). Patients with a deficit syndrome show a worse course of the disease and a poor response to treatment (Kirkpatrick et al., 2001), but no data of BDNF serum levels of this subtype have been published so far.

To the best of our knowledge, this is the first study which compared serum BDNF levels of chronic schizophrenia with or without a deficit syndrome with healthy controls.

2. Methods

2.1. Subjects

The sample size consisted of 47 chronic schizophrenic patients and 47 sex and age matched healthy controls. All patients were recruited in the Hospital Clinic of Barcelona, Spain, between 2009 and 2012 and met DSM-IV diagnosis criteria for schizophrenia. Exclusion criteria included a history of brain trauma or neurological disease, the presence of a current major medical disorder alcohol/substance abuse or dependence and electroconvulsive therapy within 6 months prior to participation. Nicotine dependence was allowed in both groups. All subjects had to be younger than 60 years to minimize possible aging effects on BDNF levels. Chronic schizophrenia was defined as duration of the illness of at least 1 year. All chronic schizophrenic patients were in treatment with an antipsychotic medication which they had been taking for at least 3 months before study entry. Patients used different antipsychotic drugs but all were converted into chlorpromazine equivalents, the international measure used to compare the medium dose of antipsychotics prescribed (Woods, 2003).

Patients were assessed with the Positive and Negative Syndrome Scale (PANSS) to quantify positive, negative and general psychotic symptoms (Kay et al., 1987). Inter-rater reliability for the PANSS was not calculated, but all raters received a specific training and a rater certification on the PANSS scale. A subgroup of chronic schizophrenic patients, were separated into those meeting criteria for the deficit and nondeficit syndrome, using the Proxy for Deficit Syndrome (PDS) based on the PANSS (Kirkpatrick et al., 1993). It is calculated by summing the following PANSS items: affective flattening (N1)+lack of spontaneity and fluency in conversation (N6) and subtracting others: (hostility (P7)+guilt (G3)+anxiety (G2)+depression (G6)). Scores in our sample ranged from −8 to 5. Patients with scores on the PDS of >0 are considered to reflect deficit schizophrenia ($n=14$), while PDS scores <-1 are considered as nondeficit schizophrenia ($n=20$). Subjects who scored 0 or −1 ($n=13$) were not included in this specific sub-analysis as they could not be determined to neither group (Kirkpatrick et al., 2009).

The chronic schizophrenic subjects had a mean duration of illness from 1 to 34 years (mean duration=6.80 years, S.D.=6.60).

The control group consisted of 47 healthy subjects who were recruited via mouth-to-mouth referrals in the hospital and local community. They were hospital staff, and persons of the local community that were recruited by advertisements. The controls met the same exclusion criteria as the patients. A complete medical history was taken and subjects excluded if they reported a history of mental illness and/or treatment with psychotropic medication. They were also excluded if they reported a history of psychosis in their first-degree relatives.

The study protocol was approved by the Ethics Committee of the Hospital Clinic of Barcelona, Spain. According to latest version of the Declaration of Helsinki, all subjects were informed in detail about the procedure and they gave written informed consent for their participation in the study.

2.2. Determination of BDNF levels and other analytical parameters

15 ml of blood was obtained from each subject between 8.30 a.m. and 10 a.m. in the morning to avoid fluctuations of hormones and therefore an influence on BDNF levels. The serum was extracted from the whole blood sample by centrifugation at 1100*g* for 15 min and frozen at −80 °C for a period from 6 to 12 months prior to processing, until the whole sample was collected. Using a sandwich-ELISA technique (EIA) BDNF serum levels were determined using a commercial kit (Chemicon Millipore, USA). Briefly, 96 flat bottom wells were incubated overnight at 2–8 °C with the samples diluted (as recommended by the kit) and the standard curve ranged from 7.8 to 500 pg of BDNF. The plates were washed four times with buffer; mouse anti-BDNF monoclonal antibody was added (diluted 1:1000 with sample diluent) and incubated for 3 h at room temperature. After washing, a second incubation was performed with peroxidase-conjugated anti-rabbit antibody (diluted 1:1000) for 1 h at room temperature. After addition of streptavidin enzyme, the amount of absorbance was determined (set at 450 nm). The standard curve showed a direct relationship between the optical density (OD) and the concentration of BDNF. Two determination of BDNF levels were made for each sample and the result was taken as the mean of both determinations.

Other serum parameters, including cortisol and prolactin levels, were also determined in blood sample using analytical standard methods. Biometric parameters such as weight, abdominal circumference and the index body mass index (BMI) were also measured.

2.3. Data analysis

A general linear model (GLM) was implemented to compare the serum BDNF levels in patients with schizophrenia and healthy controls. In a first analysis the comparison was carried out without covariates. In order to consider the possible influence of age and Body Mass Index (BMI) on BDNF levels (Lommatzsch et al., 2005; Pluchino et al., 2013) in a second analysis these two covariates were added to the GLM.

As stated before, the patients with schizophrenia were separated into two subgroups: deficit and non-deficit patients. Estimated serum BDNF levels between the two subgroups were compared using a GLM (with age and BMI as covariates). Moreover, correlation analyses were performed to detect any possible relationship between BDNF levels in the patients and clinical variables, including positive, negative, general and affective symptoms (i.e., items P4: excitation, P5: grandiosity, and G6: depression of the PANSS scale), and also the chlorpromazine equivalents dosage.

3. Results

Demographical and clinical details were comparable between the whole schizophrenia group and healthy controls (Table 1).

When comparing the deficit and nondeficit schizophrenic patients, no significant differences were found in any of the variables, except of PANSS scores of the positive and negative subscales. The positive subscale was significantly higher in nondeficit schizophrenia patients (13 vs 9.5, $p=0.044$) and the negative subscale was higher in deficit schizophrenia patients (23.7 vs 18.6 $p=0.015$). No significant differences in chlorpromazine equivalents were detected between deficit and nondeficit chronic patients. Forty-five patients received the following atypical antipsychotics: risperidone ($n=11$), aripiprazol ($n=8$), clozapine ($n=6$), olanzapine ($n=6$), paliperidone ($n=3$), quetiapine ($n=2$), and ziprasidone ($n=1$). Eight patients were treated with 2 atypical antipsychotics. One patient received a typical antipsychotic (flufenazine) and another patient was without antipsychotic treatment. Four schizophrenic patients received an antidepressive treatment (2 venlafaxine, 1 citalopram and 1 clomipramine) and one patient valproate as mood-stabilizer Table 2.

The chronic schizophrenic sample showed significantly lower serum BDNF levels compared to healthy controls (40.8 vs. 49.3 ng/ml; $p=0.020$) (Fig. 1).

As stated above, 14 subjects fulfilled criteria of the deficit syndrome and 20 subjects of the nondeficit syndrome. No significant differences in serum BDNF levels between both groups were detected (44.8 ng/ml vs. 39.1 ng/ml, $p=0.29$, respectively). No significant correlations were found either between serum BDNF levels and chlorpromazine equivalents (Pearson coefficient −0.039, $p=0.83$), duration of illness (partial correlation −0.017, $p=0.91$), cortisol (Pearson coefficient 0.11, $p=0.55$), prolactin (correlation

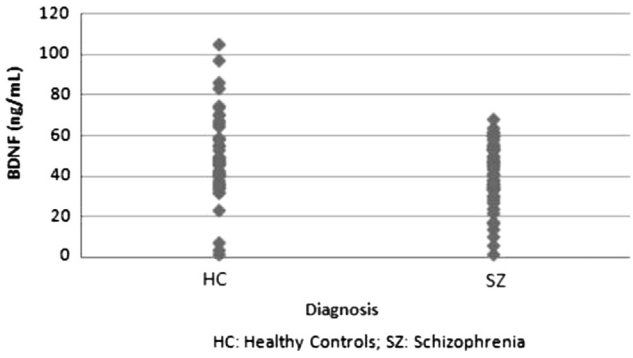

Fig. 1.. Comparison of serum BDNF levels between healthy controls (n=47) and chronic schizophrenia patients (n=47).

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