Relationship between negative symptoms and plasma levels of insulin-like growth factor 1 in first-episode schizophrenia and bipolar disorder patients

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ABSTRACT

Previous studies have suggested that insulin-like growth factor-1 (IGF-1) is altered in schizophrenia. The objective of this study was to investigate whether plasma IGF-1 levels were altered at the onset of psychiatric disorders such as schizophrenia or bipolar disorder. We focused at the first psychotic episode (FPE) and during 1-year follow-up. We also studied if IGF-1 levels were related to clinical symptoms. 50 patients and 43 healthy controls matched by age, gender and educational level were selected from the Basque Country catchment area in Spain. Plasma IGF-1 levels were measured at FPE and 1 month, 6 months and one year later. Patient symptoms were assessed at the same disease stages using the Positive and Negative Symptoms Scale (PANSS), the Global Assessment of Functioning (GAF), the Hamilton Depression Rating Scale (HDRS21) and the Young Mania Rating Scale (YMRS). A statistically significant increase in the plasma levels of IGF-1 was found in the whole cohort of patients one month after FPE compared to matched controls (219.84 ng/ml vs 164.15 ng/ml; $p = 0.014$), as well as in schizophrenia patients alone at that stage (237.60 ng/ml vs 171.60 ng/ml; $p = 0.039$). In turn, negative symptoms in both groups of patients were positively correlated with IGF-1 levels both at FPE ($\beta = 0.521$; $p < 0.001$) and after 1 year ($\beta = 0.659$; $p = 0.001$), being patients diagnosed with schizophrenia the main contributors to this relationship. These results indicate that there is a significant change in the plasma levels of IGF-1 at the initial stages of schizophrenia but not in bipolar disorder, and suggest that IGF-1 could have role in the pathophysiology of negative symptoms.

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1. Introduction

Insulin-like growth factor 1 (IGF-1) is a 70-amino acid peptide, mainly produced by the liver, which plays an important role in human growth and development (Le, 2003). IGF-1 crosses the blood–brain barrier and is thought to influence human brain development with roles ranging from neuroprotection following neuronal damage to neurogenesis, myelination, synaptogenesis and dendritic branching (Aleman and Torres-Aleman, 2009; Gluckman et al., 1998; Niblock et al., 2000). Consequently, abnormal signaling of IGF-1 can influence neuronal differentiation and synaptic function leading to altered brain development and functioning. In addition, IGF-1 not only exerts its effects during neurodevelopment but also is an important antiapoptotic factor after brain damage (Gluckman et al., 1998). Furthermore, markers of low IGF-1 levels such as leanness and short stature, are associated with an increased risk of schizophrenia (Perrin et al., 2007; Walhbeck et al., 2001).

IGF-1 is essential for optimal insulin sensitivity, and deficient IGF-1 can lead to insulin resistance (Holt et al., 2003). Schizophrenia is associated with an increased risk to develop impaired glucose tolerance, insulin resistance, and type II diabetes mellitus (Ryan and Thakore, 2002). Notably, first-episode antipsychotic-naïve schizophrenia patients have impaired glucose tolerance and higher insulin resistance than healthy comparison subjects (Ryan et al., 2003). In addition, lower IGF-1 blood levels were reported in antipsychotic-naïve schizophrenics several years after the onset of disease (Venkatasubramanian et al., 2007) as well as in schizophrenic patients receiving clozapine (Melkersson et al., 1999). Thus, low levels of IGF-1 may underlie associations of markers of pre- and post-natal growth and development with schizophrenia (Gunnell and Holly, 2004).

Here, we have analyzed the plasma level of IGF-1 in patients who suffered a first psychotic episode (FPE) and during a 1-year follow-up when patients were re-diagnosed with schizophrenia or bipolar disorder. Finally, we also assessed putative correlations of IGF-1 levels with clinical symptoms using an ample array of relevant scales.

2. Methods

2.1. Patients

This study consisted of 50 patients (mean age ± S.E.M., 25.8 ± 0.96 years) from the health catchment area of Vitoria (Alava, Spain), who experienced a first psychotic episode during the period 2002–2006. The study was approved by the Basque Country Ethical Committee and patients were recruited only if they signed the written informed consent. FPE was defined as the first time a patient displayed positive psychotic symptoms of delusions or hallucinations. In this study, we only included the patients who were subsequently diagnosed with schizophrenia (27 patients) or bipolar disorder (23 patients). Patients were re-diagnosed at 12 months after FPE using the Structured Clinical Interview for DSM IV (SCID-I) and their symptoms assessed at all times by means of the Positive and Negative Syndrome Scale (PANSS; (Kay et al., 1987)) and the Global Assessment of Functioning (GAF; (Endicott et al., 1976)), the Hamilton Depression Rating Scale (HDRS21; (Hamilton, 1960)) and the Young Mania Rating Scale (YMRS; (Young et al., 1978)). The cohort examined consisted of all first-episode patients who required hospitalization, and represented 75% of the total population of patients who had been admitted to the psychiatric emergency care unit. Dropout from the study by the end of the 1-year follow-up was 11 patients with schizophrenia and 12 patients with bipolar disorder. There were no differences in age, gender, or clinical symptoms between patients included and patients that did not complete the one year follow-up. Patients with medical diseases included diabetes were excluded from the study.

2.2. Controls

Control samples were taken from 43 healthy volunteers who were matched for sex and age (mean age ± S.E.M., 25.7 ± 1 years). 25 of these controls were used for comparisons with patients diagnosed with schizophrenia (24.7 ± 1.3) and 20 controls for patients diagnosed with bipolar disorder (27 ± 1.4). We needed to repeat control subjects in order to complete every match. All subjects (case and controls) were recruited from the same community and included after written informed consent to participate in the study was obtained. Subjects with mental retardation, organic brain disorders, or drug abuse as a primary diagnosis were excluded. The exclusion criteria for controls consisted of absence of any Axis I disorder, as well as the exclusion criteria applied to the patients group.

2.3. Experimental procedures

All the blood extractions from patients and control subjects were done early in the morning after fasting overnight and at FPE, and at 1, 6, and 12 months later, using glass whole-blood tubes containing K3-EDTA. Plasma was isolated by centrifugation at 300 g for 10 min and frozen at −80 °C until the time of analysis. Plasma levels of IGF-1 were measured by ELISA, using a kit based on the sandwich technique according to the manufacturer's instructions (Quantikine Human IGF-1 Immunoassay SG100 from R&D Systems). Standard curves were constructed using data from duplicate plasma samples. Absorbance was determined using a microplate reader (BIO-TEK, Sinergy HT) subtracting readings at 540 nm from the readings at 450 nm in order to correct for optical imperfections in the plate.

2.4. Analysis

Comparisons of plasma IGF-1 levels between each patient group and controls were made between pairs matched for age and sex using one-way ANOVA. We used Mann–Whitney U test in schizophrenic patients because the sample does not fit to a normal distribution. Values are given as mean ± S.D. and differences were considered significant when p < 0.05. Correlations between IGF-1 levels and PANSS positive, negative, and general symptom scores as well as with GAF, HDRS21 and YMRS scores were obtained using Pearson's correlation and ordinary linear regression. In addition, the same statistical analysis was carried out for consumption of tobacco, alcohol and cannabis at the first psychotic episode and after 12 months of treatment.

3. Results

27 patients were diagnosed with schizophrenia and 23 with bipolar disorder. The demographic information and treatment of the patients is provided in Table 1. There were no differences in age between patients and controls. Total PANSS scores (mean ± S.D.) were 76.14 ± 18.92 at baseline, 57.10 ± 19.87 at one month, 51.88 ± 19.97 at six months, and 53.07 ± 18.49 at twelve months. GAF was 33.96 ± 11.07 at baseline, 51.70 ± 14.30 at one month, 55.31 ± 16.21 at six months, and 56.79 ± 15.95 at twelve months. YMRS was 21.83 ± 10.29 at baseline, 9.30 ± 6.05 at one month, 5.80 ± 6.04 at six months, and 7.19 ± 7.17 at twelve months. Finally, HDRS21 scores were 19.81 ± 8.83 at baseline, 11.24 ± 6.82 at one month, 9.97 ± 7.13 at six months and 7.19 ± 6.14 at twelve months.

We found no differences in IGF-1 levels between patients and controls at first psychotic episode. Interestingly, IGF-1 levels are higher in schizophrenia patients than in bipolar disorder patients at this stage (Table 2; p = 0.022). There were no changes in IGF-1 levels at baseline between dropouts and individual who completed the entire study (Schizophrenia: p = 0.36; Bipolar disorder: p = 0.94). Interestingly, we found a statistically significant increase of IGF-1 levels in schizophrenia patients alone one month after FPE (p = 0.039) but not at any of the other stages examined (Table 2). Higher IGF-1 levels at one month after FPE were also observed in the whole cohort of patients (Table 2; p = 0.014).

To assess the putative relationship between IGF-1 plasma levels and the severity of the disease symptoms, we evaluated GAF, PANSS, HDRS21 and YMRS ratings at the disease onset and a year later. There was a positive correlation between IGF-1 levels and negative symptoms (PANSSN) that was preserved during the first year of disease treatment (Table 4; Basal: $r^2 = 0.256$, p < 0.001 and 12 months: $r^2 = 0.407$, p = 0.001). In addition, we found a significant positive correlation for the PANSSGP ($r^2 = 0.397$, p < 0.001) and HDRS21 ($r^2 = 184$, p = 0.002) scales at FPE but not subsequently. Nicotine ($r^2 = 0.104$, p = 0.024) but not alcohol ($r^2 = −0.003$, p = 0.352) or cannabis ($r^2 = 0.022$, p = 0.940) negatively influenced IGF-1 levels at FPE (Table 4). Segmentation of the cohort of patients into those diagnosed with schizophrenia or bipolar disorder revealed that patients in the former group were the main contributors to the observed correlations (Table 3; PANSSN: Basal: $r^2 = 0.333$, p = 0.001 and 12 months:

Table 1
Subjects data.

Diagnosis	Patients		Controls
	Schizophrenia	Bipolar disorder	
Gender (M–F)	20–7	15–8	30–13
Age (years)	24.7	27	25.7
Primary academic level (11 years)	81.5%	78.3%	95.5%
Medium or higher socioeconomic level	34.8%	87%	88.8%
Smokers	67.5%		42.2%
Alcohol consumption	69.6%		64.4%
Alcohol abuse	10.9%		–
Cannabis consumption	45.8%		13.3%
Atypical antipsychotics	71.4%		
Atypical antipsych. and mood stabilizers	22.5%		
Typical antipsychotics	6.1%		