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Effects of antipsychotics on the serum BDNF levels in schizophrenia

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) is active during a critical developmental period and likely influences the neuroplasticity of schizophrenia. This study longitudinally examined the effects of atypical antipsychotics on serum BDNF levels in schizophrenic patients. Specifically, this study measured serum BDNF levels in 53 patients with paranoid schizophrenia during a relapse and again 4 weeks following the administration of antipsychotic treatment (with risperidone in 32 cases, and clozapine in 21 cases). BDNF levels remained unchanged relative to study entry after 4 weeks of atypical antipsychotic treatment. However, serum BDNF was significantly increased in the subgroup receiving risperidone compared to that receiving clozapine, albeit only in the 15 male subjects and not in the 17 females. These results suggest that gender might significantly influence the antipsychotic treatment of schizophrenia from the perspective of BDNF. These findings may also indicate that the treatment with atypical antipsychotic agents differentially affects BDNF levels.

1. Introduction

Schizophrenia is a heterogeneous group of disorders with a pathogenesis resulting from multiple factors, including genetic, biological and environmental ones. Studies have examined the relationship between brain development and schizophrenia (Weinberger, 1995; Nawa et al., 2000; Ashe et al., 2001; Frost et al., 2004). Additionally, growth factors regulate specific phenotypic markers and influence the reorganization of brain circuitry. Schizophrenia is characterized by perturbed synaptic organization, and thus modifying synaptic connections with antipsychotics is important in its treatment.

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, is crucial in the development, regeneration, survival and maintenance of neuronal function (Karege et al., 2002). BDNF is active during a critical developmental period and likely influences the neuroplasticity of schizophrenia (Frost et al., 2004). BDNF has also been shown to modulate neurotransmitter synthesis, metabolism and release, regulate the long-term synaptic potentiation of neurons, and influence synaptic plasticity (Altar et al., 1997) . BDNF has also been suggested to interact with other neurotransmitter systems implicated in schizophrenia, such as dopamine, glutamate, serotonin and GABA (Shoval and Weizman, 2005). Our previous study also identified an association between the BDNF G196A gene polymorphism and suicide history in schizophrenic patients (Huang and Lee, 2007).

Previous studies have found changes in BDNF level in several brain regions and in serum of patients with schizophrenia, although the reported changes vary among these studies (Ikeda et al., 2008). Decreased BDNF levels have been found in the serum of treated patients (Toyooka et al., 2002; Pirildar et al., 2004; Tan et al., 2005; Grillo et al., 2007; Zhang et al., 2007). However, our previous, as well as other investigations, failed to identify any significant difference in serum BDNF level between schizophrenic patients and normal controls (Shimizu et al., 2003; Huang and Lee, 2006). Some studies identified differential regulation of BDNF mRNA expression in rat hippocampus and neocortex via typical and atypical antipsychotic administration (Bai et al., 2003), and cross-sectional survey of serum BDNF levels in chronic schizophrenic patients treated with clozapine exceeded that in those treated with risperidone, but the difference was not significant for those treated with typical antipsychotics (Tan et al., 2005; Xiu et al., 2009). Another cross-sectional study also identified a trend toward significantly higher BDNF levels in chronic schizophrenic patients treated with clozapine compared to those treated with typical antipsychotics (Grillo et al., 2007). However, few longitudinal human studies have explored the relationships between several antipsychotic agents and changes in BDNF levels (Pirildar et al., 2004; Rizos et al., 2010). The true influence of different antipsychotics on change in BDNF levels thus deserves further investigation.

This study attempted to determine the effects of antipsychotics on serum BDNF levels in schizophrenic patients. Furthermore, this study also tried to identify correlations between changes in serum BDNF levels and improvement of psychotic symptoms in schizophrenic patients, using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989).

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2. Methods

2.1. Subjects

Serum BDNF levels in 53 paranoid schizophrenia inpatients were collected from December 2006 to May 2008 at Chang Gung Memorial Hospital (CGMH)-Kaohsiung Medical Center, Taiwan. Institutional Review Board (IRB) approval was obtained from the CGMH Ethics Committee. The diagnoses of schizophrenic disorder, paranoid type were made based on DSM-IV (American Psychiatric Association, 1994) during initial patient visits to a single psychiatrist. The patient's symptoms were assessed with the PANSS at the baseline and after 4 weeks of treatment. All patients received monotherapy of antipsychotic drugs. The antipsychotic drugs administered to patients were risperidone ($N=32$) or clozapine ($N=21$). No participants had any systemic diseases, including heart, liver, and thyroid diseases. Age and body mass index (BMI, kg/m^2) data were collected. All patients underwent blood pressure, chest X-ray, electrocardiogram (EKG) examinations and routine blood tests to exclude subjects with chronic medical illnesses including heart, lung, liver, kidney and metabolic diseases. All patients were also free of acute infections or allergic reactions and did not take any medication for at least 1 week before study enrollment. All participants gave written informed consent after receiving a full explanation of the study purpose and procedures.

2.2. Laboratory data

Venous blood (5 ml) was collected from each patient at the baseline and after 4 weeks of antipsychotic treatment. Blood samples were collected into tubes without anticoagulant and allowed to clot at room temperature. Serum was separated by centrifugation at 3000 rpm for 7 min and then stored at −80 °C until use. Serum levels of BDNF were determined with an enzyme-linked immunosorbent assay (ELISA) method (BDNF Emax Immunoassay System, Promega, USA), according to the manufacturer's instructions. Briefly, 96-well flat bottom immunoplates (Nunc™, Thermo Fisher Scientific Inc., USA) were coated with Anti-BDNF monoclonal antibody and incubated at 4 °C overnight. After blocking by non-specific binding with Block & Sample Buffer, standards and samples were added to the plates and incubated and shaken for 2 h at room temperature. Subsequently, after washing with TBST (20 mM Tris-HCl [pH = 7.6], 150 mM NaCl and 0.005% Tween® 20) wash buffer, plates were incubated for 2 h with Anti-Human BDNF polyclonal antibody. The last incubation required the addition of Anti-immunoglobulin Y-horse-radish peroxidase conjugate. After another wash the plates were incubated with a TMB One Solution for 10 min, and HCl 1 N was added to the wells. The colorimetric reaction product was measured at 450 nm using a microplate reader (VICTOR™ *X*4 Multilabel Plate Reader, PerkinElmer Inc., USA). BDNF concentrations were determined from the regression line for the BDNF standard (ranging from 7.8 to 500 pg/ml of recombinant BDNF) incubated under similar conditions in each assay. As reported in the manufacture's instructions, the sensitivity of the assay is about 15.6 pg/ml of BDNF. All the samples were analyzed in duplicate in one session by an investigator blind to experimental set up. The intra-assay and inter-assay variations were less than 10%.

2.3. Statistical analysis

All results are presented as means ± standard deviation (SD). Within subject changes from the baseline to the endpoint for each treatment group were assessed using the paired *t*-test. The level of statistical significance was set at an alpha value of $p<0.05$. The relationship between BDNF levels and PANSS scores was assessed by Pearson Correlations. All statistical analyses were performed using SPSS, version 12.

3. Results

The sample comprised 53 schizophrenic patients. Table 1 lists the demographic data, and serum BDNF protein levels for all participants. Fifty-three schizophrenic patients took antipsychotics over a period of 4 weeks and underwent assessments of psychosis severity, including 32 patients treated with risperidone and 21 treated with clozapine. It has been reported that alterations in BDNF levels have also been associated with nicotine (Kim et al., 2007). In our study, the smoking status of the patients did not differ among the two drug groups ($p=1.0$, by Fisher's exact test).

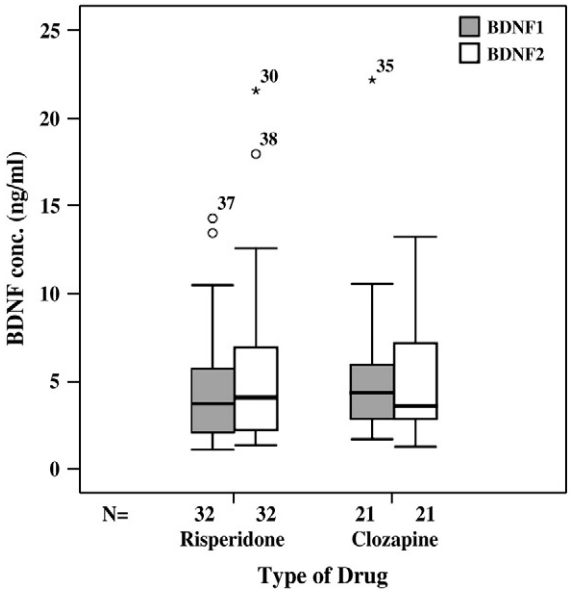

Fig. 1. Alteration of serum BDNF levels from patients medication free (BDNF1) and medicated (BDNF2).

All patients responded to risperidone and clozapine treatment, which was defined as an at least 30% decrease in the baseline total PANSS scores. Patients who did not meet these criteria were excluded from the study. Comparisons between BDNF1 (study entry) and BDNF2 (study endpoint after a period of 4 weeks of antipsychotic medication) in each drug group showed a significant effect of risperidone ($p=0.017$), whereas no significant effects were found for clozapine (Fig. 1).

The risperidone-treated group included 32 patients and the dose ranged from 3 to 6 mg/day (mean ± SD = 4.32 ± 0.91), and the clozapine-group included 21 patients and the dose ranged from 37.5 to 350 mg/day (190.34. ± 103.94). Patients were matched with respect to chlorpromazine equivalents of their antipsychotic medication (Table 2). Table 2 lists the effects of antipsychotics and serum BDNF protein levels. The paired *t* test revealed significant increases in serum BDNF protein levels in the patients taking risperidone over a period of 4 weeks ($t=-2.517$, $p=0.017$), especially in 15 men ($t=-2.201$, $p=0.045$), but not in women ($t=-1.447$, $p=0.167$).

4. Discussion

The main finding of this study was the significantly increased serum BDNF protein levels in 32 patients taking risperidone over a 4-week period, an increase that occurred in 15 males but not in 17 females. This finding suggests that short-term treatment with an atypical antipsychotic agent might prevent neurotrophin from decreasing. One recent study (Verhagen et al., 2010) revealed significant effects of gender-stratified analyses in both the allelic and genotypic analyses in depressive men but not depressive women. Another study also reported that BDNF levels showed tendencies to increase again in association with exercise in male depressive patients after 60 minutes of rest (Gustafsson et al., 2009).

Table 1
Demographic data and serum BDNF Levels of all participants (Mean ± S.D.).

	Age (years)	BMI (kg/ m^2)	Education (years)	Age of illness onset (years)	Duration of illness (years)	Serum BDNF levels (ng/dl)	PANSS(total score)
Schizophrenia ($n=53$)	35.4 ± 9.9	22.7 ± 4.0	11.9 ± 3.0	27.4. ± 10.1	8.0 ± 6.2	5.0 ± 3.9	134.9 ± 11.2
Men ($n=23$)	32.4 ± 6.5	23.9 ± 5.1	11.9 ± 1.8	22.2 ± 6.3	10.2 ± 6.2	5.1 ± 3.8	134.2 ± 8.4
Women ($n=30$)	37.7 ± 11.5	21.8 ± 2.6	11.9 ± 3.7	31.4 ± 10.7	6.4 ± 5.8	5.0 ± 4.0	135.5 ± 13.0