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Associations of serum brain-derived neurotrophic factor with cognitive impairments and negative symptoms in schizophrenia

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) may be involved in the pathophysiology of schizophrenia. The aim of this study was to examine the associations of serum BDNF levels with the cognition and clinical characteristics in patients with schizophrenia. Sixty-three patients with schizophrenia and 52 age- and sex-matched healthy controls were examined with neuropsychological tests. Serum BDNF levels were determined by enzyme-linked immunosorbent assay (ELISA). There were no significant differences in serum BDNF levels between normal controls and patients with schizophrenia. Serum BDNF levels of normal controls showed negative correlations with verbal working memory, but this was not the case with schizophrenic patients. Meanwhile, serum BDNF levels of schizophrenic patients showed positive correlations with the scores of the Scale for the Assessment of Negative Symptoms (SANS) and the Information subtest scores of Wechsler Adult Intelligence Scale Revised (WAIS-R). Serum BDNF levels are related with the impairment of verbal working memory and negative symptoms in patients with schizophrenia.

1. Introduction

Schizophrenia is characterized by three distinct symptom clusters: positive symptoms, negative symptoms, and cognitive impairments. Negative symptoms, an important and enduring component of the psychopathology of schizophrenia (Stahl and Buckley, 2007), include blunted affect, alogia, asociality, anhedonia and avolition (Andreasen, 1982; Kirkpatrick et al., 2006). Negative symptoms predict quality of life, social functioning and overall outcome measures in patients with schizophrenia (Bow-Thomas et al., 1999; Dickerson et al., 1999; Milev et al., 2005). Negative symptoms and cognitive impairments are involved in the prefrontal cortex (Ingvar and Franzen, 1974; Weinberger, 1988) and share many features, but are separable domains of illness (Harvey et al., 2006). While positive symptoms are greatly improved with atypical antipsychotic medication, negative symptoms and cognitive impairments are not sufficiently improved (Erhart et al., 2006; Keefe et al., 2007).

The cognitive impairments are the core features of schizophrenia, with both working memory and attention being characteristically impaired in patients with schizophrenia (Elvevag and Goldberg, 2000; Reichenberg, 2010). Cognitive deficits are related to community outcome, social problem solving and skill acquisition (Green, 1996), and therefore might predict the functional outcome in schizophrenic patients (Green et al., 2004).

Accumulating evidence suggests that brain-derived neurotrophic factor (BDNF) plays a role in the pathophysiology of psychiatric diseases, including depression and schizophrenia (Angelucci et al., 2005). It is well documented that BDNF is involved in neuronal survival, differentiation and outgrowth during brain development (Numakawa et al., 2010). Recently, a meta-analysis study showed that blood levels of BDNF were reduced in medicated and drug-naïve patients with schizophrenia (Green et al., 2010). However, the significant heterogeneity across the study results remained unexplained.

Abbreviations: BDNF, Brain-derived neurotrophic factor; BMI, Body-mass index; BPRS, Brief psychiatry rating scale; DIEPSS, Drug induced extrapyramidal symptoms scale; DSDT, Digit span distraction test; ELISA, Enzyme-linked immunosorbent assay; IQ, Intelligence quotient; PANSS, Positive and negative syndrome scale; SANS, Scale for the assessment of negative symptoms; WAIS-R, Wechsler adult intelligence scale revised; WCST, Wisconsin card sorting test.

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In this study, we examined the associations of serum BDNF levels with negative symptoms and cognitive impairments in patients with schizophrenia. To assess the cognitive functioning of the prefrontal cortex, 5 neuropsychological tests, verbal fluency, Wisconsin card sorting test (WCST), Stroop test, digit span distraction test (DSDT), and trail making test were administered. The rationale for choosing these tests stems from the hypothesis that each test works on a region-dominant part (medial or dorsolateral portions) of the brain and could examine the region-related functions.

2. Methods

2.1. Subjects

Sixty-three Japanese patients with schizophrenia (age: mean, 35.9 [SD, 8.2]; education: mean, 13.8 [SD, 2.3]; 26 men and 37 women) were recruited from the outpatients of the Chiba University Hospital and its affiliated hospitals, Chiba, Japan. Fifty-two age- and sex-matched healthy Japanese subjects also participated in this study as normal controls. Characteristics of the subjects are shown in Table 1. All subjects provided written informed consent for participation in the study after the procedure had been fully explained. The ethics committee of Chiba University Graduate School of Medicine approved the present study.

All patients were diagnosed according to the DSM-IV criteria for schizophrenia, and had no other psychiatric disorders, assessed by two senior level psychiatrists. Of the patients, 44 were diagnosed as the residual type and 19 were the paranoid type. They had been clinically stable for at least 3 months. All patients had been receiving monotherapy with a stable dose of a second-generation antipsychotic drug for at least 8 weeks prior to entry into the study. The antipsychotic drugs were risperidone (n = 25), olanzapine (n = 18), quetiapine (n = 8), perospirone (n = 2), aripiprazole (n = 9), and bronanserine (n = 1). The chlorpromazine-equivalent dose was 306 ± 240 (means ± SD) mg/day (Woods, 2003). Normal controls were recruited from the local community around the Chiba University Hospital. None of the normal controls presented with a personal history of psychiatric or neurological disorder, assessed by two senior level psychiatrists.

2.2. Clinical assessments

Clinical symptoms were assessed by using the Brief Psychiatry Rating Scale (BPRS) (Overall and Gorham, 1962) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982). Drug-induced extrapyramidal symptoms were evaluated by using the Drug Induced Extrapyramidal Symptoms Scale (DIEPSS), because cognitive functions are influenced by extrapyramidal motor side effects (Inada et al., 2002). Intelligence quotient (IQ) scores were estimated by using the short version of the Japanese Wechsler Adult Intelligence Scale Revised (WAIS-R) (Misawa et al., 1993; Nakamura et al., 2000), which consisted of the Information, Digit Span, and the Picture Completion subtests. Age at onset, duration of illness and duration of untreated psychosis were evaluated.

2.3. Enzyme immunoassay

Blood samples of the participants were collected between 10:00 and 13:00 h. Serum was then separated by centrifugation at 3000 rpm for 7 min and stored at −80 °C until assay. Serum BDNF levels were measured by using a BDNF Emax Immunoassay System kit (Promega, Madison, WI).

2.4. Neuropsychological assessments

In the Verbal Fluency Test (letter, category), the number of words produced in 1 min for each trial was recorded for evaluation (Sumiyoshi et al., 2005). In the WCST, the number of achieved categories and perseverative errors were assessed (Shad et al., 2006). We used the short version of the WCST (Keio version; 48 cards) to shorten the procedural time (Hori et al., 2006; Igarashi et al., 2002). In the Trail Making Test Part A and Part B, the time taken to complete each part of the test was assessed in seconds (Reitan and Wolfson, 1993). In the Stroop Test, a list of 24 colored dots (Part D) and 24 colored words incongruent with the color (Part C) were used (Carter et al., 1995; Chan et al., 2004). The reaction time taken to complete each part of the test was assessed in seconds. In the DSDT, subjects were asked to remember a tape-recorded string of digits read by a female voice while ignoring the digits read by a male voice (distractor) (Green et al., 1997; Oltmanns and Neale, 1975). The percentages of digits correctly recalled under the condition with and without a distractor were assessed separately.

2.5. Statistical analysis

All statistical analyses were performed by using SPSS software (SPSS version 18.0J; SPSS, Tokyo, Japan). For the comparisons

Table 1
Demographic characteristics and serum BDNF levels of subjects.

	Controls	Patients				Controls vs patients
	n = 52	n = 63	Subtype		Residual vs paranoid	
			Residual	Paranoid		
			n = 44	n = 19	p	p
Gender (male/female)	25/27	26/37	19/25	7/12	NS [a]	NS [a]
Age, year	34.9 (7.3)	35.9 (8.2)	36.7 (8.3)	34.1 (8.1)	NS [b]	NS [c]
Education, year	14.7 (2.7)	13.8 (2.3)	13.8 (2.4)	13.7 (2.1)	NS [b]	NS [b]
Smoking (Non-smoker/smoker)	43/9	45/18	33/11	12/7	NS [a]	NS [a]
Age at onset of illness, year	–	26.8 (7.0)	27.5 (7.3)	25.2 (6.1)	NS [c]	–
Duration of illness, year	–	9.1 (7.3)	9.2 (6.8)	9.0 (8.6)	NS [b]	–
Duration of untreated psychosis, month	–	8.1 (13.4)	7.3 (9.6)	9.8 (19.9)	NS [b]	–
BPRS	–	25.5 (7.5)	23.7 (7.1)	29.6 (6.9)	< 0.05 [b]	–
SANS	–	70.4 (11.8)	68.1 (12.0)	75.7 (9.5)	< 0.05 [b]	–
DIEPSS	–	2.7 (2.7)	2.5 (2.5)	3.3 (3.3)	NS [b]	–
BDNF, ng/ml	14.6 (4.4)	15.3 (3.8)	14.9 (3.6)	16.2 (4.2)	NS [c]	NS [b]

Values represent mean (SD). NS, not significant.
Abbreviation: BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; DIEPSS, Drug Induced Extra-Pyramidal Symptoms Scale; BDNF, Brain-Derived Neurotrophic Factor.
[a] χ^2 test.
[b] Mann–Whitney *U*-test.
[c] Student's *t*-test.