HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2012; **27**: 33–38.
Published online 30 December 2011 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.1257

Aripiprazole altered plasma levels of brain-derived neurotrophic factor and catecholamine metabolites in first-episode untreated Japanese schizophrenia patients

Reiji Yoshimura[1]*, Hikaru Hori[1], Atsuko Ikenouchi-Sugita[1], Wakako Umene-Nakano[1], Asuka Katsuki[1], Kenji Hayashi[1], Kiyokazu Atake[1], Masaru Tomita[2] and Jun Nakamura[1]

[1]*Department of Psychiatry, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan*
[2]*Department of Neuropsychiatry, Kurume University School of Medicine, Kurume, Japan*

Objective We investigated the effects of aripiprazole on plasma levels of brain-derived neurotrophic factor (BDNF) and catecholamine metabolites in first-episode untreated schizophrenia patients.
Methods The subjects were 50 Japanese first-episode untreated schizophrenia patients who met the Diagnostic and Statistical Manual of Mental Disorders Text Revision criteria and were treated with aripiprazole monotherapy. Twenty-nine were males, and 21 were females. The age ranged from 21 to 42 years (mean ± SD; 30.8 ± 5.3 years). Plasma BDNF and catecholamine metabolites were measured by ELISA and HPLC, respectively. Psychiatric symptoms were evaluated using by Positive and Negative Syndrome Scale.
Results Treatment with aripiprazole for 8 weeks significantly increased plasma BDNF levels. It also changed plasma levels of homovanillic acid and 3-methoxy-4-hydroxyphenylglycol. A negative correlation was also observed between duration of psychosis and plasma BDNF levels. No correlation was observed however between plasma BDNF levels and the dose of aripiprazole.
Conclusions To the best of our knowledge, this is the first report showing that aripiprazole increases plasma BDNF levels in first-episode untreated schizophrenia patients. Furthermore, the BDNF Val66Met polymorphism was independent of the response to aripiprazole.

KEY WORDS—schizophrenia; aripiprazole; brain-derived neurotrophic factor; homovanillic acid; 3-methoxy-4-hydroxyphenylglycol

ABBREVIATIONS—BDNF, brain-derived neurotrophic factor; DUP, duration of psychosis; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol

INTRODUCTION

Aripiprazole is a new antipsychotic drug with a pharmacologically unique receptor binding profile that combines partial agonism at D_2 and 5-HT_{1A} with potent antagonism at 5-HT_{2A} (Sparshatt *et al*., 2010). Aripiprazole is an effective treatment for schizophrenia, is well tolerated, and has a low tendency to cause clinically significant weight gain, hyperprolactinemia, and parkinsonism. One major neurotrophic factor, brain-derived neurotrophic factor (BDNF), has been found to play a critical role in long-term potentiation, a cellular mechanism of learning and memory, suggesting that this neurotrophic factor can influence neuroplasticity (Korte *et al*., 1995; Figurov *et al*., 1996). In addition, BDNF is required for the survival and guidance of neurons during development and for the survival and function of neurons during adulthood (Thoenen, 1995; McAllister *et al*., 1999; Duman *et al*., 2000). Atrophy and loss of hippocampal or cerebral cortical neurons or glia can be the result of stress-induced loss of neurotrophic factors, or could be caused by other processes and/or insults that compromise neuronal function and activity, such as deleterious factors in the patient's genetic background (Sapolsky, 2000; Shelton, 2000). There is growing evidence indicating that BDNF may play a crucial role in the development of mental disorders such as depression (Durman *et al*., 1997) and schizophrenia (Shoval and Weizman, 2005). The BDNF gene is an important candidate for elucidating the mechanism of action of antidepressants because BDNF plays a significant role in the functioning of the serotonin system. The human BDNF gene maps to chromosome 11p13 and contains a functional 196 G/A single nucleotide polymorphism

*Correspondence to: R. Yoshimura, Department of Psychiatry, University of Occupational and Environmental Health, Kitakyushu, Japan. Tel: +81936917253; Fax: +81936924894. E-mail: yoshi621@med.uoeh-u.ac.jp

Received 11 April 2011
Accepted 7 November 2011

(rs6265) known to cause an amino acid substitution from valine to methionine in exon 1 (Val66Met). The BDNF gene encodes a precursor peptide that is proteolytically cleaved to form the mature protein BDNF (Mowla *et al*., 2001). Recently, Green *et al*. (2011) performed a systematic review including data from 17 case-control studies assessing 1144 schizophrenia patients and 970 healthy subjects. Using a meta-analytic approach, the authors compared BDNF blood levels between schizophrenia patients and healthy controls; they found medium-quality evidence of a moderate reduction in peripheral BDNF levels in people with schizophrenia. Our hypotheses are the following: (i) aripiprazole increases serum BDNF levels; (ii) the BDNF Val/Met polymorphism is associated with the response to aripiprazole treatment; and (iii) a significant correlation is found between the increase of serum BDNF levels and the dose of aripiprazole. In the present study, we focused on how aripiprazole influences serum BDNF levels or how the BDNF Val66Met polymorphism predicts response to aripiprazole treatment.

METHODS

Subjects

The subjects were 50 Japanese first-episode untreated schizophrenia patients who met the Diagnostic and Statistical Manual of Mental Disorders Text Revision (American Psychiatric Association, 2000) criteria and who were treated with aripiprazole monotherapy. All patients were screened by using the Structured Clinical Interview for DSM-IV Disorders (First *et al*., 1995), and exclusion criteria for all groups included current or past serious medical or neurological illness, or dependence on alcohol or illicit substances. Twenty-nine were males, and 21 were females. The age ranged from 21 to 42 years (mean $\pm$ SD; 30.8 ± 5.3 years). The dose of aripiprazole was not fixed based on ethical consideration. The daily dose of aripiprazole at 8 weeks ranged from 6 to 30 mg (mean $\pm$ SD; 20.1 ± 6.3 mg). We prepared age-matched (mean SD; 32.3 ± 7.1 years) and sex-matched (male/female; 25/25) 50 healthy control subjects without current or past psychiatric disorders. Use of lorazepam and biperiden was permitted when necessary. Clinical improvement of the patients was evaluated by using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al*., 1987) before and 8 weeks after treatment with aripiprazole. The patients whose total scores of PANSS reduced 30% or more after administration of aripiprazole for 8 weeks were defined as responders, whereas below 30 % as non-responders.

Experimental procedures

All blood samples were obtained between 7:00 and 10:00 AM before and 8 weeks after sertraline administration. Fifteen milliliters of venous blood was drawn with subjects in the supine position, after the patients had been lying at rest overnight.

The plasma was quickly separated in a centrifuge and stored at $-80\,^{\circ}C$ until assayed. Plasma concentrations of homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) were analyzed by using high-performance liquid chromatography with electrochemical detection (HPLC-ECD) according to our previous methods (Yoshimura *et al*., 2007). In brief, each cyano-bonded solid-phase extraction cartridge was preconditioned with methanol, followed by preconditioning with glass-distilled water. Each cartridge was added 0.3 ml of plasma sample or standard, and then 0.1 ml of working internal standard solution (5 ng of 5-hydroxyindolecarboxylic acid in 0.01 M KH_2PO_4, pH 7.2) was added to each group. The samples were deproteinized with 1 ml of acetonitrile. After mixture of the samples by vortexing and centrifugation (1760 *g*, 4 °C for 10 min), an aliquot (5 µl) of supernatant was allowed to pass through the cartridge slowly under a mild vacuum (15 mmHg). The cartridge was washed with 0.2 ml of distilled water and extracted with solution containing 1 ml of ethylacetate, and then an aliquot was evaporated to dryness under nitrogen gas. After dissolving the sample in the mobile phase (200 µl), a 10-µl portion of the solution was injected into the HPLC apparatus. The detection limit was 0.5 ng/ml, and the calibration curve was linear up to 40 ng/ml. The intra-assay and inter-assay coefficients of variation were 6% and 8%, respectively. The recovery rate exceeded 80%.

The plasma MHPG levels were also analyzed by using HPLC-ECD. In brief, the plasma was separated by centrifugation at 600 *g* at 4 °C. Extraction was performed under a vacuum by using Bond-Elut columns prepacked with 100 mg of C18-bonded silica (40 µm) in a 1-ml capacity disposable syringe. The columns, which were inserted into a vacuum chamber connected to an aspirator, were prepared by a wash in 1 ml of methanol followed by 1 ml of water. After the addition of 50 µl of a solution of vanillyl alcohol (internal standard equivalent to 5 ng/ml) to 1 ml of plasma, the samples were passed through the columns, followed by the addition of 0.75 ml of water, which was used to rinse off any residual sample and easily

DOI: 10.1002/hup

eluted hydrophilic compounds. The adsorbed materials were eluted with 200 µl of methanol to a 0.1 M phosphate buffer (pH 4.8) mixture (40:60, v/v). A 20-µl portion of this solution was injected into the HPLC system. The detection limit was 0.5 ng/ml, and the calibration curve was linear up to 40 ng/ml. The intra-assay and inter-assay coefficients of variation were 6% and 8%, respectively. The recovery rate exceeded 80%.

Plasma BDNF levels were measured by using a BDNF Emax Immunoassay Kit (Promega, Madison, WI, USA) according to the manufacturer's instructions. In short, 96-well microplates were coated with anti-BDNF monoclonal antibody and were incubated at 4 °C for 18 h. The plates were incubated in a blocking buffer for 1 h at room temperature. The samples were diluted 100-fold with assay buffer, and the BDNF standards were kept at room temperature under conditions of horizontal shaking for 2 h, after which the samples were washed using the appropriate washing buffer. Then, the plates were incubated with antihuman BDNF polyclonal antibody at room temperature for 2 h and washed with the washing buffer. The plates were then incubated with anti-IgY antibody conjugated to horseradish peroxidase for 1 h at room temperature and were incubated again in peroxidase substrate and tetramethylbenzidine solution to induce a color reaction. The reaction was stopped with 1 mol/L hydrochloric acid. The absorbance at 450 nm was measured with an Emax automated microplate reader. Measurements were performed in duplicate. The standard curve was linear from 5 to 5000 pg/ml, and the detection limit was 10 pg/ml. Cross-reactivity to related neurotrophins (NT-3, NT-4, NGF) was less than 3%. Intra-assay and inter-assay coefficients of variation were 5% and 7%, respectively. The recovery rate of exogenously added BDNF in the measured plasma samples exceeded 95%. Genomic DNA was extracted from peripheral blood mononuclear cells and diluted to a concentration of 10 ng/ml. We performed direct sequencing to determine the polymorphism of BDNF (Val/Met). All the assays were measured by the investigators who did not know the clinical information of each patient. This study was approved by the ethics committee of the University of Occupational and Environmental Health, and written informed consent was obtained from all participants.

Statistical analysis

Statistical analysis was performed with the use of paired *t*-test to compare plasma levels of BDNF, MHPG, and HVA before and 8 weeks after treatment with aripiprazole in schizophrenia patients. A paired *t*-test was used to compare plasma BDNF levels between schizophrenia patients and healthy control subjects. Chi-square test was used to examine the association between each genotype and the response to aripiprazole. The relationship between two variables was examined by using Pearson correlation analysis. The level of significance for the results was set at $p < .05$. Statistical procedures were performed by using the Japanese version of SPSS v15.1 (SPSS Japan, Tokyo, Japan).

RESULTS

Treatment with aripiprazole for 8 weeks reduced the PANSS scores of the subjects (positive, negative, general pathology, and total) (Table 1). Plasma levels of BDNF were significantly lower in schizophrenic patients than those in healthy controls (Figure 1). Plasma levels of MHPG were significantly increased after 8 weeks of aripiprazole treatment. In contrast, plasma HVA levels had significantly decreased after 8 weeks of treatment with aripiprazole. A trend for positive correlation was found between the changes in plasma MHPG and the changes in the negative scores in PANSS. A trend for negative correlation was found between the changes in plasma HVA levels and the changes in positive scores in PANSS (Table 3). Furthermore, treatment with aripiprazole for 8 weeks significantly increased plasma BDNF levels (Table 2).

Table 1. Changes in Positive and Negative Syndrome Scale scores

Positive and Negative Syndrome Scale	Week 0	Week 8	*p*-value
Positive	21.8 ± 3.1	15.2 ± 3.2	<.001
Negative	22.7 ± 2.7	16.5 ± 3.3	<.001
General pathology	30.8 ± 6.0	22.2 ± 5.3	<.001
Total	75.0 ± 8.1	54.0 ± 9.6	<.001

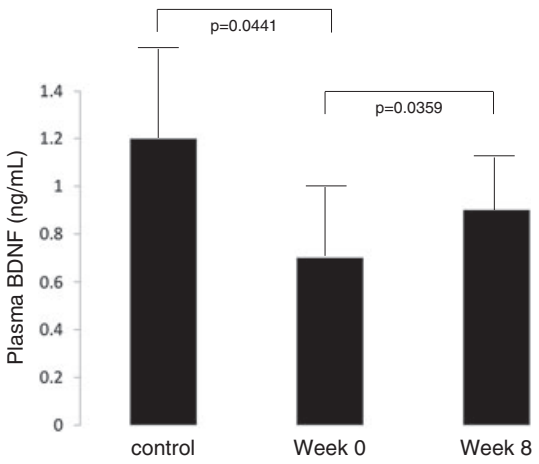

Figure 1. Plasma BDNF levels in controls and schizophrenia patients

DOI: 10.1002/hup

Table 2. Changes in plasma levels of brain-derived neurotrophic factor and catecholamine metabolites

	Week 0	Week 8	*p*-value
*p*MHPG (ng/ml)	4.3 ± 1.5	4.7 ± 1.2	$p = 0.0212$
*p*HVA (ng/ml)	6.6 ± 2.0	4.9 ± 1.7	$p < .0001$
*p*BDNF (ng/ml)	0.7 ± 0.4	0.9 ± 0.3	$p = 0.0359$

MHPG, 3-methoxy-4-hydroxyphenylglycol; HVA, homovanillic acid; BDNF, brain-derived neurotrophic factor.

Table 3. *R*-value and *p*-value of correlation in two variables

Positive and Negative Syndrome Scale	*p*BDNF	*p*MHPG	*p*HVA
Positive	0.121/0.714	0.161/0.899	−0.173/0.094
Negative	0.189/0.091	0.223/0.061	−0.162/0.148
General pathology	0.103/0.866	0.245/0.552	−0.203/0.217
Total	0.117/0.611	0.193/0.443	−0.181/0.228
Dose of aripiprazole	0.884/0.799	0.117/0.912	−0.913/0.338

BDNF, brain-derived neurotrophic factor; MHPG, 3-methoxy-4-hydroxyphenylglycol; HVA, homovanillic acid.

A significantly negative correlation was also found between the duration of psychosis and plasma BDNF levels (-0.656, $p < .0001$) (Figure 2).The distribution of BDNF (Val66Met) polymorphism was Val66-Val (18; 36%), Val66Met (28; 56%), and Met66Met (4; 8%). No difference was found between the responders and the non-responders with regard to Val66Val and Met carriers (d.f. = 1, $X_2 = 0.112$, $p = 0.7382$) (Table 3). A trend for negative correlation was found between the changes in plasma BDNF levels and the negative scores, but not positive, general pathology scores, total scores of PANSS, or dose of aripiprazole (Table 4). Eleven or eight subjects of 50 patients were administered lorazepam or biperiden, respectively. No differences were found in plasma BDNF levels in subjects with or without lorazepam or biperiden (Figure 2, Table 4).

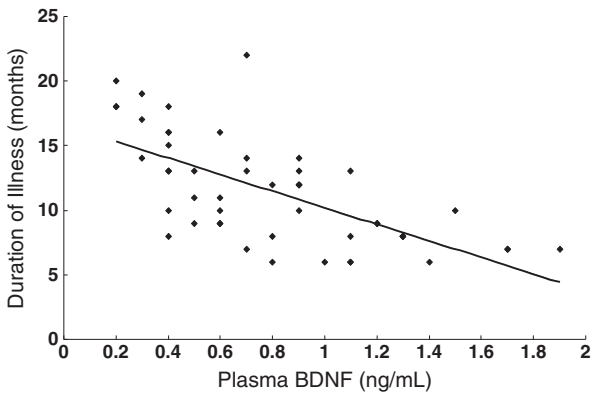

Figure 2. Duration of illness and plasma BDNF ($r = -0.656$, $p < 0.001$)

Table 4. The polymorphism of brain-derived neurotrophic factor and the response to aripiprazole

	BDNF (Val/Val)	BDNF (Met carriers)
Responders	7 (33.3%)	14 (66.6%)
Non-responders	11 (37.9%)	18 (62.0%)

BDNF, brain-derived neurotrophic factor; Val, valine; Met, methionine.

DISCUSSION

The most important finding of the present study was that 8 weeks of treatment with aripiprazole significantly increased plasma BDNF levels in patients with schizophrenia. To the best of our knowledge, this is the first report of increased plasma BDNF levels associated with aripiprazole treatment of patients with schizophrenia. Rizos *et al*. (2010) reported that olanzapine significantly increased serum BDNF levels in patients with chronic schizophrenia, indicating a differential effect of olanzapine on BDNF levels compared with that of haloperidol, risperidone, or amisulpiride. We previously reported that treatment with aripiprazole for 8 weeks did not increase plasma BDNF levels in only nine schizophrenic patients. In addition, neither treatment with risperidone ($n = 32$) or olanzapine ($n = 18$) altered plasma BDNF levels. Park *et al*. (2009) recently reported that treatment with aripiprazole at 10 μM increased levels of BDNF in SH-SY5Y cells by 85% as compared with control levels, whereas haloperidol had no such effect. The increase in BDNF levels achieved with aripiprazole might have been related to neuroprotective effects in human neuronal cells. Moreover, Park *et al*. (2009) speculated that the protective efficacy of aripiprazole in human neuroblastoma SH-SY5Y cells might involve an inactivation of GSK-3β via the BDNF-mediated activation of the transcription factor cAMP response element-binding, resulting in an increased expression of its survival target, Bcl-2. Another important finding of the present study was that of a significantly negative association between plasma BDNF levels and duration of psychosis in people with schizophrenia. Rizos *et al*. (2010) recently reported finding a negative correlation between serum BDNF levels and duration of psychosis in a group of patients, suggesting that low serum BDNF levels at the onset of schizophrenia were associated with a long duration of illness, which could reflect an acute neurodegenerative reaction during the untreated phase of psychosis. The results of the present study were basically in accord with those of Rizos *et al*. Recently, BDNF has emerged as a key contributor to brain plasticity and cognition, and it has become a focus of intense research on the psychopathology

DOI: 10.1002/hup

of schizophrenia (Pillai *et al*., 2010). Furthermore, neurodevelopmental models of schizophrenia have implicated reduced BDNF in the central nervous system. Specifically, it has been suggested that reduced BDNF might affect the synaptic efficacy and connectivity believed to underlie core behavioral signs and symptoms in people with schizophrenia. It has been speculated that a lack of pharmacological intervention could lead to a progression of schizophrenia. In fact, Lappin *et al*. (2006) demonstrated that temporal gray matter reductions are more marked in patients with a long duration of illness. Takahashi *et al*. (2007) also reported decreased gray matter volume in the left planum temporale in association with the initial untreated phase of schizophrenia. When taken together, these findings suggest that plasma BDNF levels reflect the progression of schizophrenia. We previously reported finding no difference in serum BDNF levels between patients with early-stage psychosis and age-matched and sex-matched healthy subjects. We have also demonstrated that there is no difference between first-episode schizophrenia patients and healthy controls in terms of frontal-lobe *N*-acetylaspartate levels (Goto *et al*., 2011). It was already known that *N*-acetylaspartate plays a role in myelin lipid synthesis, the control of osmolality, energy metabolism, and neurotransmission (Brugger *et al*., 2010). Therefore, it is likely that the observed reduction in blood BDNF and brain *N*-acetylaspartate levels could only have been detected in subjects with advanced stages of the illness. The most important finding of the present study was that treatment with aripiprazole for 8 weeks significantly increased plasma BDNF levels, and this increase was associated with improvements in negative symptoms of schizophrenia, which was not statistically significant but only the trend was observed These results indicate that aripiprazole might protect against micro-neuronal degeneration and/or aid recovery from such degeneration; however, such protection would be independent from any improvements in clinical symptoms of schizophrenia. In other words, aripiprazole might be specifically preventive against neurodegeneration. We previously demonstrated that risperidone, olanzapine, or aripiprazole treatment increased plasma MHPG levels, whereas these three atypical antipsychotic drugs decreased plasma HVA levels. We reconfirmed our preliminary results that aripiprazole altered plasma levels of MHPG and HVA in same manners as our preliminary results. The important finding in the present study was that a trend for association was observed between the PANSS scores and plasma levels of MHPG or HVA. In that study, we could not find the increase in plasma BDNF after treatment with aripiprazole for 8 weeks (Yoshimura *et al*., 2010). The discrepancy between the results in the present and our previous study remains unknown. The difference of the sample size and enrolled subjects might affect the differences in the results. In other words, subjects in the present study were first-episode untreated schizophrenia, and most of those in our previous study were changed from other antipsychotic drugs to aripiprazole. Finally, we demonstrated that no association was found between the polymorphism of BDNF (Val66Met) and the response to aripiprazole. To the best of our knowledge, this is the first study demonstrating that the response to aripiprazole was independent of the polymorphism of BDNF (Val66Met). Gratacos *et al*. (2007) performed meta-analysis and demonstrated that the homozygous carriers Met66Met showed a 19% increased risk of schizophrenia with respect to the heterozygous state. Ho *et al*. (2007) speculated that the Met carriers might be one of several factors affecting progressive brain volume changes in schizophrenia. Hong *et al*. (2003) reported that the BDNF gene Val66Met polymorphism might be associated with the response to clozapine. Furthermore, Xu *et al*. (2010) demonstrated that the individual and combinational genetic variants in the BDNF gene might have a role in the therapeutic response to risperidone in the Han Chinese population. In contrast, Anttila *et al*. (2005) showed that the BDNF G194A and C270T polymorphisms are not associated with treatment response to conventional antipsychotic drugs at first hospitalization for schizophrenia. From these findings, the BDNF gene might play a role in the pathogenesis of schizophrenia; it is however controversial the correlation between BDNF (Val66Met) and the response to antipsychotic drugs. It should be noted that the present study has several limitations. First, the sample size was small and heterogeneous, and the dosage of aripiprazole was not fixed. We only examine the association between the polymorphism of BDNF (Val66Met). The source of circulating BDNF remains unknown. Platelets, brain neurons, and vascular endothelial cells are currently considered to be putative sources. Thus, it may be a poor index to measure brain BDNF levels. Therefore, further study using a larger sample, a fixed-dosage regimen, and other polymorphisms of BDNF genes including haplotype analysis would be needed to reconfirm the present results. In conclusion, aripiprazole increased plasma levels of BDNF in first-episode schizophrenia patients, and the response to aripiprazole was independent of the polymorphism of BDNF (Val66Met).

In conclusion, we first reported that treatment with aripiprazole increased plasma BDNF levels in

DOI: 10.1002/hup

first-episode schizophrenia patients, which might be associated with the improvement of negative symptoms of schizophrenia.

CONFLICT OF INTEREST

No conflict of interest declared.

ACKNOWLEDGEMENT

We thank Ms Kazuko Shimizu for her great help for the experiment.

REFERENCES

American Psychiatric Association. 2000. *Diagnosis and Statistical Manual of Mental Disorders Text Revision (DSM-IV-TR)*. American Psychiatric Association: Washington, D.C.

Anttila S, Illi A, Kampman O, Mattila KM, Lehtimaki T, Leinonen E. 2005. Lack of association between two polymorphisms of brain-derived neurotrophic factor and response to typical neuroleptics. *J Neural Transm* **112**: 885–890.

Brugger S, Davis JM, Leucht S, Stone JM. 2010. Proton magnetic resonance spectroscopy and illness stage in schizophrenia–a systematic review and meta-analysis. *Biol Psychiatry* **69**: 495–503.

Duman RS, Malberg J, Nakagawa S, D'Sa C. 2000. Neuronal plasticity and survival in mood disorders. *Biol Psychiatry* **48**: 732–739.

Durman RS, Heninger GR, Nestler EJ. 1997. A molecular and cellular theory of depression. *Arch Gen Psychiatry* **54**: 597–605.

Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B. 1996. Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. *Nature* **381**: 706–709.

First MB, Spitzer RL, Gibbon M, Williams JBW. 1995. *Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), Version 2*. New York State Psychiatric Institute, Biometrics Research: New York.

Goto N, Yoshimura R, Kakeda S, *et al*. 2011. Comparison of brain N-acetylaspartate levels and serum brain-derived neurotrophic factor (BDNF) levels between patients with first-episode schizophrenia psychosis and healthy controls. *Eur Psychiatry* **26**: 57–63.

Gratacos M, Gonzalez JR, Mercader JM, de Cid R, Urretavizcaya M, Estivill X. 2007. Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. *Biol Psychiatry* **61**: 911–922.

Green MJ, Matheson SL, Shepherd A, Weickert CS, Cart VJ. 2011. Brain-derived neurotrophic factor levels in schizophrenia: a systematic review. *Mol Psychiatry* **16**: 960–972.

Ho BC, Andreasen NC, Dawson JD, Wassink TH. 2007. Association between brain-derived neurotrophic factor Val66Met gene polymorphism and progressive brain volume changes in schizophrenia. *Am J Psychiatry* **164**: 1890–1899.

Hong CJ, Yu YWY, Lin CH, Tsai SJ. 2003. An association study of a brain-derived neurotrophic factor Val66Met polymorphism and clozapine response of schizophrenic patients. *Neurosci Lett* **349**: 206–208.

Kay SR, Fiszbein A, Opler LA. 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* **13**: 261–276.

Korte M, Carroll P, Wolf E, Brem G, Thoenen H, Bonhoeffer T. 1995. Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. *Proc Natl Acad Sci USA* **92**: 8856–8860.

Lappin JM, Morgan K, Morgan C, *et al*. 2006. Gray matter abnormalities associated with duration of untreated psychosis. *Schizophr Res* **83**: 145–153.

McAllister AK. 1999. Subplate neurons: a missing link among neurotrophins activity, and ocular dominance plasticity? *Proc Natl Acad Sci USA* **96**: 13600–13602.

Mowla SJ, Farhadi HF, Pareek S, *et al*. 2001. Biosynthesis and post-translational processing of the precursor to brain-derived neurotrophic factor. *J Biol Chem* **296**: 12660–12666.

Park SW, Lee JG, Ha EK, *et al*. 2009. Differential effects of aripiprazole and haloperidol on BDNF-mediated signal changes in SH-SY5Y cells. *Eur Neuropsychopharmacol* **19**: 356–362.

Pillai A, Kale A, Joshi S, *et al*. 2010. Decreased BDNF levels in CSF of drug-naïve first-episode psychotic subjects: correlation with plasma BDNF and psychopathology. *Int J Neuropsychopharmacol* **13**: 535–539.

Rizos EN, Papadopoulou A, Laskos E, *et al*. 2010. Reduced serum BDNF levels in patients with chronic schizophrenic disorder in relapse, who were treated with typical or atypical antipsychotics. *World J Biol Psychiatry* **11**: 251–255.

Sapolsky RM. 2000. The possibility of neurotoxicity in the hippocampus in major depression. *Biol Psychiatry* **48**: 755–765.

Shelton RC. 2000. Cellular mechanisms in the vulnerability to depression and response to antidepressants. *Psychiatr Clin North Am* **23**: 713–729.

Shoval G, Weizman A. 2005. The possible role of neurotrophins in the pathogenesis and therapy of schizophrenia. *Eur Neuropsychopharmacol* **15**: 319–329.

Sparshatt A, Taylor D, Patel MX, Kapur S. 2010. A systematic review of aripiprazole-dose, plasma concentration, receptor occupancy, and response: implications for therapeutic drug monitoring. *J Clin Psychiatry* **71**: 1447–1456.

Takahashi T, Suzuki M, Tanino R, *et al*. 2007. Volume reduction of the left planum temporale gray matter associated with long duration of untreated psychosis in schizophrenia: a preliminary report. *Psychiatry Res* **154**: 209–219.

Thoenen H. 1995. Neurotrophins and neuronal plasticity. *Science* **270**: 593–598.

Xu M, Li S, Xing Q, *et al*. 2010. Genetic variants in the BDNF gene and therapeutic response to risperidone in schizophrenia patients: a pharmacogenetic study. *Eur J Hum Genet* **18**: 707–712.

Yoshimura R, Hori H, Sugita A, *et al*. 2007. Treatment with risperidone for 4 weeks increased plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) levels, but did not alter plasma brain-derived neurotrophic factor (BDNF) levels in schizophrenic patients. *Prog Neuropsychopharmacol Biol Psychiatry* **31**: 1072–1077.

Yoshimura R, Ueda N, Hori H, Ikenouchi-Sugita A, Umene-Nakano W, Nakamura J. 2010. Differential patterns of longitudinal changes in plasma levels of catecholamine metabolites and brain-derived neurotrophic factor after administration of atypical antipsychotics in first-episode untreated schizophrenic patients. *World J Biol Psychiatry* **11**: 256–261.