



Plasma levels of mature brain-derived neurotrophic factor (BDNF) and matrix metalloproteinase-9 (MMP-9) in treatment-resistant schizophrenia treated with clozapine[☆]



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H I G H L I G H T S

- Plasma levels of mature BDNF in schizophrenia were measured for the first time.
- No significant difference was observed in mature BDNF levels in schizophrenia.
- MMP-9 plasma levels were significantly increased in patients with schizophrenia.
- Plasma mature BDNF levels were significantly correlated with plasma MMP-9 levels.

A R T I C L E I N F O

Article history:

Received 12 August 2013

Received in revised form 9 September 2013

Accepted 25 September 2013

Keywords:

Treatment-resistant schizophrenia
Brain-derived neurotrophic factor (BDNF)
Matrix metalloproteinase-9 (MMP-9)
Clozapine

A B S T R A C T

Brain-derived neurotrophic factor (BDNF) regulates the survival and growth of neurons, and influences synaptic efficiency and plasticity. Peripheral BDNF levels in patients with schizophrenia have been widely reported in the literature. However, it is still controversial whether peripheral levels of BDNF are altered in patients with schizophrenia. The peripheral BDNF levels previously reported in patients with schizophrenia were total BDNF (proBDNF and mature BDNF) as it was unable to specifically measure mature BDNF due to limited BDNF antibody specificity. In this study, we examined whether peripheral levels of mature BDNF were altered in patients with treatment-resistant schizophrenia. Matrix metalloproteinase-9 (MMP-9) levels were also measured, as MMP-9 plays a role in the conversion of proBDNF to mature BDNF. Twenty-two patients with treatment-resistant schizophrenia treated with clozapine and 22 age- and sex-matched healthy controls were enrolled. The plasma levels of mature BDNF and MMP-9 were measured using ELISA kits. No significant difference was observed for mature BDNF however, MMP-9 was significantly increased in patients with schizophrenia. The significant correlation was observed between mature BDNF and MMP-9 plasma levels. Neither mature BDNF nor MMP-9 plasma levels were associated clinical variables. Our results do not support the view that peripheral BDNF levels are associated with schizophrenia. MMP-9 may play a role in the pathophysiology of schizophrenia and serve as a biomarker for schizophrenia.

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Abbreviations: BDNF, brain-derived neurotrophic factor; MMP-9, matrix metalloproteinase-9; MDD, major depressive disorder; DSM-IV, diagnostic and statistical manual of mental disorders, fourth edition; PANSS, positive and negative syndrome scale.

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1. Introduction

Schizophrenia is a severe psychiatric disease characterized by delusions, hallucinations, impairment of cognitive function and incoherent behavior. It affects approximately 1% of the general population worldwide. Mounting evidence suggests that a deficit in neurotrophin supply to cortical neurons may be an underlying factor in the pathophysiology of schizophrenia as adequate neurotrophic support is required for normal brain development, maturation and function [3,4].

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that regulates neuronal survival, differentiation and growth during brain development, with important effects on neurogenesis and neuroplasticity. It is also important for hippocampal-related learning and memory [17]. A common single nucleotide polymorphism (SNP) of the BDNF gene has impact on episodic memory, hippocampal morphology and memory-related hippocampal activity in human [9,16]. Mature BDNF is initially synthesized as a precursor protein, proBDNF. Following cleavage of the signal peptide, proBDNF is converted to mature BDNF by extracellular proteases, such as matrix metalloproteinase-9 (MMP-9). Mature BDNF and proBDNF each plays important roles in several physiological functions. Recent studies show that mature BDNF and pro BDNF elicit opposing effects via the TrkB and p75^{NTR} receptors respectively. Mature BDNF preferentially binds to the TrkB receptor and plays an important role through BDNF-TrkB signaling which fulfills wide variety of functions such as cell survival, migration, outgrowth of neuritis and synaptic plasticity. In contrast, pro BDNF preferentially binds to the p75^{NTR} receptors and elicit apoptosis rather than cell survival [8,11]. Considering the important roles of mature BDNF, it would be informative to specifically measure mature BDNF. Although BDNF levels in human blood can be measured using commercially available human BDNF ELISA kits, due to the limited specificity of the BDNF antibody, it has not been possible to distinguish between proBDNF and mature BDNF. Recently, peripheral levels of mature BDNF have been reported to be measurable using newly available human BDNF ELISA kits [23].

It is of great interest to assess the potential contribution of BDNF to the pathophysiology of schizophrenia. Several studies report altered BDNF mRNA and protein in prefrontal cortical regions and hippocampus of post-mortem brain tissues [13,21,22]. Peripheral BDNF levels in patients with schizophrenia have also been widely reported in the literature. However, there is no widespread agreement on the degree of peripheral BDNF levels in patients with schizophrenia, as measured in blood serum or plasma. A recent meta-analysis reported that peripheral BDNF levels were reduced in schizophrenia. However, there was considerable heterogeneity in the results [5]. Considering the important roles of mature BDNF such as cell survival, migration, outgrowth of neuritis and synaptic plasticity, it would be informative to specifically measure mature BDNF in patients with schizophrenia because dysfunction

of these mature BDNF roles might be an underlying factor in the pathophysiology of schizophrenia. The peripheral BDNF levels previously reported in patients with schizophrenia were total BDNF (proBDNF and mature BDNF); peripheral levels of mature BDNF specifically have not been investigated in patients with schizophrenia. This study aimed to determine whether peripheral levels of mature BDNF were altered in patients with treatment-resistant schizophrenia. We also investigated Matrix metalloproteinase-9 (MMP-9) levels, as MMP-9 plays a role in the conversion of proBDNF to mature BDNF [8].

2. Materials and methods

2.1. Subjects

Twenty-two patients with treatment-resistant schizophrenia who were treated with clozapine were included in this study. Twenty-two age- and sex-matched healthy controls also participated in this study (Table 1). Cases were recruited at Osaka University hospitals. Each subject had been diagnosed and assessed by at least two trained psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria based on structured clinical interview. Treatment-resistant schizophrenia was defined according to the following criteria mentioned in clozapine drug information in Japan: (1) Non- or little response to treatment from at least two adequately dosed antipsychotic trials for at least 4 weeks (including at least one second-generation antipsychotic, >600 mg/day of chlorpromazine equivalent) and patients never had the Global Assessment of Functioning (GAF) scores that were higher than 40. (2) Intolerance to at least two second-generation antipsychotics because of uncontrolled extrapyramidal symptoms. All subjects included in this study met the criteria of non- or little response. Symptoms of schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS). Cases of schizophrenia with the comorbidities of substance-related disorders or mental retardation were excluded. Controls were recruited through local advertisements. Psychiatrically, medically and neurologically healthy controls were evaluated using the DSM-IV structured clinical interview, non-patient version. Subjects were excluded if they had neurological or medical conditions that could potentially affect the central nervous system, such as atypical headache, head trauma with loss of consciousness, chronic lung disease, kidney disease, chronic hepatic disease, thyroid disease, active stage cancer, cerebrovascular disease, epilepsy or seizures. Written informed consent was obtained for all subjects after the procedures had been fully explained. This study was carried out in accordance with the World Medical Association's Declaration of Helsinki and approved by the Research Ethical Committee of Osaka University and Chiba University.

2.2. Measurement of mature BDNF and MMP-9

Plasma levels of mature BDNF and MMP-9 were measured using the human BDNF ELISA Kit (Adipo Bioscience, Santa Clara, CA, USA), and the human MMP-9 ELISA Kit (R&D Systems, Minneapolis, MN, USA), respectively. To minimize assay variance, plasma levels of mature BDNF and MMP-9 were measured in each subject on the same day. All experiments were performed in duplicate. Protocols were performed according to the manufacturer's instructions. The optical density of each well was measured using an automated microplate reader (Emax; Molecular Devices, Sunnyvale, CA, USA). As plasma levels of proBDNF are not measurable by the newly available proBDNF ELISA kit due to low sensitivity, we measured only mature BDNF.

Table 1
Demographic variables for subjects.

Variables	Control n = 22	Patients with schizophrenia n = 22
Age (years)	38.1 ± 12.9	38.1 ± 13.2
Gender (male/female)	(12/10)	(12/10)
Age at onset	–	21.9 ± 8.4
Duration of illness	–	17.2 ± 11.1
PANSS positive	–	23.0 ± 4.6
PANSS negative	–	25.5 ± 5.5
PANSS general	–	52.9 ± 9.6
Clozapine dose (mg)	–	448.6 ± 130.0

Means ± SD are shown.

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