MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 397-402
DOI: 10.12659/MSM.895896

Received: 2015.09.07
Accepted: 2015.10.14
Published: 2016.02.06

DNA Methylation of BDNF Gene in Schizophrenia

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: Departmental sources

Background: Although genetic factors are risk factors for schizophrenia, some environmental factors are thought to be required for the manifestation of disease. Epigenetic mechanisms regulate gene functions without causing a change in the nucleotide sequence of DNA. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that regulates synaptic transmission and plasticity. It has been suggested that BDNF may play a role in the pathophysiology of schizophrenia. It is established that methylation status of the BDNF gene is associated with fear learning, memory, and stressful social interactions. In this study, we aimed to investigate the DNA methylation status of BDNF gene in patients with schizophrenia.

Material/Methods: The study included 49 patients (33 male and 16 female) with schizophrenia and 65 unrelated healthy controls (46 male and 19 female). Determination of methylation pattern of CpG islands was based on the principle that bisulfite treatment of DNA results in conversion of unmethylated cytosine residues into uracil, whereas methylated cytosine residues remain unmodified. Methylation-specific PCR was performed with primers specific for either methylated or unmethylated DNA.

Results: There was no significant difference in methylated or un-methylated status for BDNF promoters between schizophrenia patients and controls. The mean duration of illness was significantly lower in the hemi-methylated group compared to the non-methylated group for BDNF gene CpG island-1 in schizophrenia patients.

Conclusions: Although there were no differences in BDNF gene methylation status between schizophrenia patients and healthy controls, there was an association between duration of illness and DNA methylation.

MeSH Keywords: Brain-Derived Neurotrophic Factor • DNA Methylation • Epigenesis, Genetic • Schizophrenia and Disorders with Psychotic Features

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/895896

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Background

Schizophrenia is a multifactorial disorder, and genetic and environmental factors are involved in its etiology [1]. Although genetic factors are risk factors for schizophrenia, it is believed that some environmental factors are required for the manifestation of disease [2]. Epigenetic mechanisms regulate gene functions without changing the nucleotide sequence of DNA [3]. These regulations are reversible, and the most commonly studied epigenetic mechanisms are DNA methylation and histone modification [3,4]. DNA methylation and epigenetic mechanisms are associated with psychiatric disorders, such as depression, psychotic disorders, post-traumatic stress disorder, autism, eating disorders, and substance dependence [5–7]. Epigenetic factors have an important role in gene and environment interactions, and environmental factors influence the genomic expressions through epigenetic mechanisms [8]. Epigenetic mechanisms are associated with many environmental factors, including nutrition, maternal care and behavior, hormones and drugs, early life experiences, and environmental agents in early development stages [9,10]. DNA methylation is caused by coupling of a methyl group to CpG sites with the DNA methyltransferase enzyme [11]. A normal level of DNA methylation is required for controlling genomic expressions [12]. Disease-related hypermethylation is thought to be associated with decreased RNA levels and hypomethylation is associated with increased RNA levels [13].

An animal study reported that animals showed schizophrenia-like behaviors and molecular changes, such as significant decrease in BDNF mRNA variants, increase in DNA methyltransferase1 (DNMT1), and ten-eleven translocase methylcytosine dioxygenase1 (TET1), no changes in histone deacetylases, histone methyltransferases and demethylases, or methyl CpG binding protein 2 in mice exposed to prenatal stress. This and several other studies show that environmental factors, such as prenatal stress, influence brain development and cause schizophrenia by epigenetic mechanisms, especially in early stage of brain development [14–16].

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that regulates synaptic transmission and plasticity, and it has a role in proliferation, differentiation, survival, and death of neuronal and non-neuronal cells [17]. It has been suggested that BDNF plays a role in the pathophysiology of schizophrenia [18]. A schizophrenia animal model induced by prenatal stress showed increased DNA methylation of the BDNF gene and reduced BDNF transcription [14]. Genetic studies show an association between BDNF and schizophrenia [19]. Reduced BDNF levels in the prefrontal cortex, serum and CSF samples of patients with schizophrenia have been reported [20–23]. BDNF protein level and mRNA expression are lower in the prefrontal cortex of schizophrenia patients [20,24]. However, other studies showed higher BDNF levels in serum of schizophrenia patients [25,26] and there are conflicting results regarding BDNF levels in the hippocampus [27,28]. Postmortem studies have shown increased BDNF levels in the parietal cortex and frontal cortex, but decreased levels in the temporal cortex and occipital cortex [29]. Another post-mortem study showed abnormalities of DNA methylation in brains of patients with schizophrenia [30]. Methylation status of the BDNF gene is associated with fear learning, memory, and stressful social interactions. DNA methylation has a role in regulation of the BDNF gene in schizophrenia [31–33] and DNA methylation and demethylation may be used as targets for antipsychotic therapy [14].

In this study we aimed to investigate the DNA methylation status of the BDNF gene in patients with schizophrenia. We report the methylation status of 2 CpG islands of the BDNF gene that are located on the promoter region and intron 3-exon 4 boundary, as shown in Figure 1.

Material and Methods

The study included 49 patients (aged 35.31±10.35 years, 33 male and 16 female) with schizophrenia and 65 unrelated healthy controls (aged 35.18±9.05 years, 46 male and 19 female). Mean duration of illness was 11.6±8.7 (min: 1, max: 36) years, mean PANSS total score was 66.3±30.2 (min: 30, max: 129), and mean CGI-S score was 3.9±2.16 (min: 1, max: 7). All patients were on medication. Thirty-two patients received atypical antipsychotic, 1 patient received typical and atypical antipsychotic combination, 11 patients received RLAI and atypical antipsychotic combination, and 7 patients received zuclopenthixol or flupenthixol depot and atypical antipsychotic combination. Volunteers in the control group had no personal or familial history of schizophrenia. Individuals with known major health problems, including diabetes and malignancies, were excluded from the study. Patients were diagnosed with schizophrenia according to the 4th edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) [34]. Patients and controls were of the same ethnic origin and from the same geographical area (south-eastern Turkey). The severity

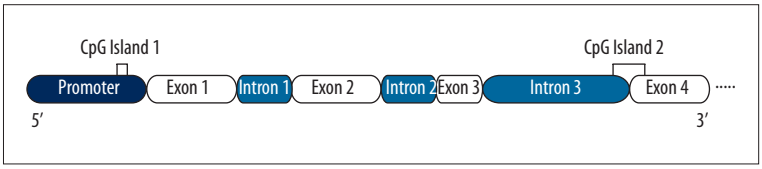

Figure 1. Schematic representation of BDNF gene. Only four exons are shown. The CpG islands amplified are idicated by orange lines.

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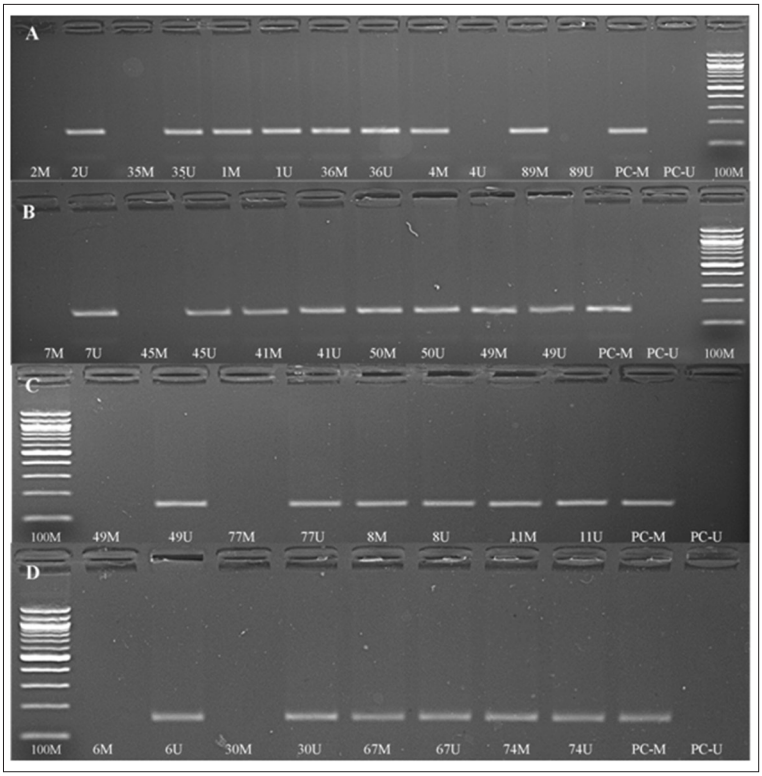

Figure 2. Methylation-specific PCR results of some randomly selected sample patients with schizophrenia and control groups, analyzed with 2% agarose gel electrophoresis followed by ethidium bromide staining. **A:** Methylation pattern of some patients in CpG island-1 from BDNF gene. **B:** Methylation pattern of some controls in CpG island-1 from BDNF gene. **C:** Methylation pattern of some patients in CpG island-2 from BDNF gene. **D:** Methylation pattern of some controls in CpG island-2 from BDNF gene. **PC:** Positive control; **M:** methylated; **U:** unmethylated; **100M**: 100 bp DNA ladder.

of schizophrenia symptoms in the patients was evaluated using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression Severity Scale (CGI-S) [35,36]. Physical and neurological examinations were performed in each of the patients and controls. The study was approved by the local ethics committee, informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

DNA was extracted from blood samples by using the salt-chloroform method. Determination of methylation pattern of CpG islands was based on the principle that bisulfite treatment of DNA results in conversion of unmethylated cytokine residues into uracil, whereas methylated cytokine residues remain unmodified. Methylation-specific PCR was performed with primers specific for either methylated or unmethylated DNA. The primers were designed for 2 different CpG islands in the BDNF promoter (Figure 1). We treated 100 ng DNA samples with EpiMark Bisulfite Conversion Kit (Catalog No. E3318, New England Biolabs), in accordance with the manufacturer's standard instructions. Primer sequences were: BDNF_1_MFw: 5'-GTAGTTTTCGTAGGATGAGGAAGC-3' and BDNF_1_MRv: 5'-AATATAAATTAACAACCCCGATACG-3' for the methylated (M) reaction and BDNF_1_UFw: 5'-GTAGTTTTTGTAGGATGAGGAAGTG-3' and BDNF_1_URv 5'-TATAAATTAACAACCCCAATACACA-3' for the unmethylated (U) reaction. BDNF_2_MFw: 5'-ATGATAGCGTACGTTAAGGTATCGT-3', BDNF_2_MRv: 5'-AACGAAAAACTCCATTTAATCTCG-3' and BDNF_2_UFw: 5'-ATATGATAGTGTATGTTAAGGTATTGT-3', BDNF_2_URv: 5'-ACAAAAAACTCCATTTAATCTCAAC-3'. PCR mixture contained 10 ng of modified DNA, 2.0 mmol each of dATP, dGTP, dCTP, and dTTP, 1.0 pmol each of primer, 2.0 mmol MgCl2, 1× reaction buffer, and 1.0 U Taq polymerase. The PCR conditions were: 1 cycle at 95°C for 1 min, 12 cycles at 95°C for 10 s, at 54°C to 48°C (touch-down) for 40 s, at 72°C for 60 s, then 25 cycles at 95°C for 10 s, at 52°C for 40 s, at 72°C for 60 s, and 1 cycle at 72°C for 5 min. Amplified PCR products were electrophoresed on 2% agarose gels, visualized by staining with ethidium bromide, and illuminated under UV light. Positive control sample (Fermentas, Cat. No: SD1131) was utilized as hypermethylated.

Statistical analyses

The collected data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Both descriptive and analytical statistics were used. Chi-square/Fisher's exact test was used to compare categorical variables. The *t* test was used to compare continuous variables.

Results

The mean ages (F=1.306, p=0.947) and the sex distribution (x^2=0.154, DF=1, p=0.695) of the study groups were similar. For BDNF gene CpG island-1, 3.9% (n=2) was methylated, 68.6%

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Table 1. Methylation status of BDNF gene with schizophrenia patients and healthy controls.

	Schizophrenia patients		Healthy controls (n= 65)		p
CpG island 1 (n=49)					0.669*
Hemi-methylated	35	(71.4%)	44	(67.7%)	
Unmethylated	14	(28.6%)	21	(32.3%)	
CpG island 2 (n=51)					1.00**
Hemi-methylated	2	(3.9%)	2	(3.1%)	
Unmethylated	49	(96.1%)	63	(96.9%)	

* Chi-square test; ** Fisher's exact test.

(n=35) was hemi-methylated, and 27.4% (n=14) was unmethylated in he patient group. There were no methylated subjects, 67.7% (n=44) were hemi-methylated, and 32.3% (n=21) were unmethylated in the control group (Figure 2). There were no significant difference in methylated or unmethylated status for each area between schizophrenia patients and controls (p>0.05). The comparisons of the methylated or unmethylated status for each area according to the study groups are presented in Table 1. When patients were compared with clinical parameters (duration of the illness, CGI-S, PANSS scores, BMI, and methylated or unmethylated status for each area) we did not find any significant difference (p>0.05). There were no differences in DNA methylation status of BDNF gene CpG island-1 and CpG island-2 regions with respect to sex or age between the schizophrenia patients and the control group (p>0.05). The mean duration of illness was significantly lower in the hemi-methylated group compared to non-methylated group for BDNF gene CpG island-1 in schizophrenia patients (p=0.017). However, there was no difference in mean duration of illness between the hemi-methylated group compared to the non-methylated group for BDNF gene CpG island-2 in schizophrenia patients (p>0.05). There were no differences in median CGI-S PANSS total and subscale scores between hemi-methylated group compared to non-methylated group for BDNF gene CpG island-1 and CpG island-2 regions in schizophrenia patients (p>0.05).

Discussion

We found that there was no difference in methylation status of 2 regions of the BNDF gene between schizophrenia patients and healthy controls, suggesting that the genetic component of schizophrenia is very complex. Genetic studies have reported that some genes are associated with schizophrenia. The most likely candidate genes are: GABAergic genes (RELN and GAD1), dopaminergic genes (DAT and DRD2, MB-COMT), 5-HT2A receptor (HTR2A) gene, and BDNF [33,37]. It is suggested that down-regulation of GABAergic genes such as RELN and GAD1 are related to hypermethylation of their gene promoters, causing GABAergic dysfunction; moreover, it plays a role in schizophrenia [38–40]. However, in another study, decreased methylation of the GAD1promoter and lower levels ofGAD1mRNA in schizophrenia patients were found [41]. A postmortem study performed in patients with schizophrenia showed increased methylation of RELN gene and decreased RELN gene expression [38]. However, another study shows no detectable DNA methylation in RELN promoter region [42]. Another study showed no or less methylation in RELN gene until puberty, while increased levels of methylation were found after puberty [43]. 5-HT2A receptor (HTR2A) gene is a serotonergic system gene and in a study it was found that methylation of the HTR2A gene promoter correlated with HTR2A expression levels. However, another study found no difference between schizophrenia patients compared to controls in HTR2A methylation [44,45]. Epigenetic regulations of genes influencing the dopaminergic system, such as COMT, DRD2, and DAT genes, have been investigated in schizophrenia. It was shown that there was a hypomethylation in MB-COMT gene and it was suggested that this methylation is a risk factor for schizophrenia [46]. However, another study was found no difference in COMT promoter methylation between schizophrenia patients and controls [47]. It was found that there were no differences in DRD2 and DAT gene methylation between schizophrenia patients and controls [48,49].

There are few studies about methylation status of the BNDF gene in schizophrenia patients. A postmortem study found that there were no differences in BDNF gene exon I, III, VI, and IX regions methylation status between schizophrenia patients and controls, but the same study fond reduced DNA methylation in the Val66Met SNP in exon IX [50]. There are 2 other studies on BDNF gene methylation with peripheral blood samples of schizophrenia patients – one study showed reduced BDNF promoter IV methylation, and the other one showed increased BDNF promoter I methylation in schizophrenia patients compared to controls [48]. Another study with peripheral blood samples of Japanese schizophrenia patients found

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that there was a small but significant increase in methylation in the BDNF 1 promoter, and the same study suggested that epigenetic differences in peripheral blood might be a potential biomarker and reflect the pathophysiology of schizophrenia [51]. A review by Mitchelmore and Gede suggested that BDNF had a central role in neuronal development and neuroplasticity, and dysregulation of the BDNF gene was associated with several psychiatric and neurologic disorders. In addition, epigenetic mechanisms that regulate BDNF gene expression could be used in diagnosis, prognoses, and as biomarkers of several psychiatric disorders [37]. In the present study we found that there were no associations between DNA methylation status of BDNF gene CpG island-1 and CpG island-2 regions with respect to sex or age. However, another study showed that the methylation status of BDNF promoter was associated with sex – there was more prominent methylation in male patients with schizophrenia.

The mean duration of illness was significantly shorter in the hemi-methylated group compared to the non-methylated group for BDNF gene CpG island-1 in schizophrenia patients. To the best of our knowledge there is no published data about the association between duration of illness and DNA methylation in schizophrenia. A review of DNA hypomethylation and human diseases showed that DNA methylation plays a role in neuronal cell survival and maturation; the balance of the methylation level is important for neuronal survival and hypomethylation causes abnormalities in neuronal function [52]. Although the mechanism is not clear, a study mentioned that DNA hypomethylation may cause cell death by apoptosis [53]. Considering these data, it appears that reduced methylation ratios with duration of disease may cause the neuronal dysfunction by altering neuronal survival, suggesting that there is an association between duration of illness and DNA methylation.

We hypothesized that there was a defect in the DNA methylation mechanisms that affect the BDNF gene, and that there is an association between DNA methylation and schizophrenia. However, there was only an association between duration of illness and DNA methylation. As mentioned above, there are inconsistent results in methylation studies. Several other factors, such as patients receiving antipsychotics and analyzing methylation in blood, may affect the methylation status. A study that examined the effect of antipsychotics on DNA methylation found that clozapine and quetiapine reduced the DNA methylation, but there are no similar effects of haloperidol and risperidone on DNA methylation status [54]. Another study in animals showed that clozapine reduces BDNF methylation and that this increases social interaction [55,56].

There are some limitations of this study. First, we analyzed DNA methylation in peripheral blood, which does not directly reflect the central nervous system. Second, this is a naturalistic and cross-sectional study and patients were continuing their medication. Therefore, receiving antipsychotics may have affected the methylation status. DNA methylation is a dynamic and reversible process, and many other environmental factors also affect methylation. BDNF methylation may be different in different populations and environments [57]. For these reasons, examining the methylation status and protein levels of BDNF gene at certain intervals throughout the treatment period in the same patients may be more valuable.

Conclusions

Although there were no differences in BDNF gene methylation status between schizophrenia patients and healthy controls, there was an association between duration of illness and DNA methylation. Further studies with more patients are necessary, and the limitations referred to in this paper should be considered.

Conflicting interests

The authors declare no conflicting interests.

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