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BDNF as a biomarker in the course and treatment of schizophrenia

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Summary

Many scientists agree that the genes involved in the aetiology and pathogenesis of psychiatric diseases could serve as biomarkers – biological indicators of the health status. Genetic markers may inform about general predispositions of a person to develop certain diseases, while other biochemical factors, such as concentrations of substances in body fluids, reflect the actual condition of the organism. Researchers involved in studies on schizophrenia are interested in the gene and protein of the brain-derived neurotrophic factor (BDNF) due to the role of this neurotrophin in the process of neurogenesis, synaptogenesis and its influence on the functioning of dopaminergic neurons.

Among patients diagnosed with schizophrenia, the BDNF gene polymorphisms and methylation in the promoter sequences were studied. The neurotrophin was also assayed in the blood of patients, also taking into account the effect of pharmacotherapy on the BDNF concentration, and post-mortem in the brains of the patients. The results of current studies are contradictory. The only systematically confirmed observation is the lowered concentration of BDNF in the serum of patients with schizophrenia compared to healthy controls. It seems that so far our knowledge about the BDNF gene expression and the functions of the protein is not sufficient to include BDNF analysis in the clinical assessment of patients with schizophrenia.

Key words: schizophrenia, BDNF, biomarkers

Introduction

Laboratory tests are used in current diagnostics of psychiatric disorders to a limited extent. Diagnostic tools commonly used by psychiatrists and clinical psychologists are prone to different types of bias. Clinical psychiatric examination and the observation of the patient's behaviour may turn out to be insufficient for the proper assessment of

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his/her personality or motivation. The patient and the diagnostician can be the source of mistakes, as they are limited by their subjective perception of the world. Using psychometric analyses can be biased as well, partly because they are constructed based on introspection, and thus the patient's insight into his mental state. Considering the above difficulties, efforts are made to improve the diagnostic outcome by the analyses of biomarkers. Many researchers share the thought that genes and proteins engaged in the pathogenesis of mental disorders could play such a role. Genetic markers may reflect the predispositions to develop mental illness, while other markers, such as proteins, could provide information about the current state of the organism. Perhaps in the future, with the development of psychiatry, genotyping and analysis of concentration of certain proteins in the body fluids will become an essential part in planning a personalised therapy.

Schizophrenia is a chronic disease of complex and not homogenous aetiology. During the course of the illness, a significant social, family and professional decline is observed and treatment rarely brings satisfactory results. Adequate pharmacotherapy, despite current standards of treatment, is still challenging. The goal is the reduction of psychopathologic symptoms as well as the side effects of drugs, as using neuroleptics is related to a diminution in the quality of life for many patients. The researchers involved in studies on the genetic background of schizophrenic psychoses have not yet found unequivocal answers to their questions. Currently there is a list of candidate genes, potentially related to the development of schizophrenia. The list is not closed yet, and there is no consensus as to which polymorphisms are likely to cause a patient to be predisposed to develop schizophrenia. One of the most examined genes is the *BDNF,* coding for the brain-derived neurotrophic factor (BDNF). The concentration of BDNF protein in the blood is considered a promising marker of the mental state of the patient.

BDNF: from gene to protein

The *BDNF* gene is located on the short arm of chromosome 11 (11p13) [1]. It contains 11 exons and 9 promoter sequences which are activated depending on the type of tissue and brain region [2], which results in the composition of several dozen transcripts. Therefore the regulation of *BDNF* transcription is very complicated. The following steps of gene expression, such as the polyadenylation of mRNA and modifications of the BDNF precursor protein, affect the final result [3]. Thanks to the progress in the techniques of molecular biology, more and more is known about these processes.

The BDNF protein was discovered over 30 years ago, and was the second neurotrophic factor, after the nerve growth factor (NGF) to be identified. BDNF dimers interact with the membrane receptor TrkB, which belongs to the group of receptors with tyrosine kinase activity. Binding of the neurotrophin causes the dimerisation of the receptor, followed by a cascade of protein phosphorylation inside the cell. This leads to diverse effects, such as changes in gene expression, which depend on the type of route activated [4, 5]. Recently it turned out that the role of proBDNF is not limited to biologically inactive precursor, secreted outside the cell only after the signalling sequence has been cut off. It was observed that the proneurotrophin affects the cells

and binds more strongly to the receptor $p75^{NTR}$ than to TrkB. The signal transduction via $p75^{NTR}$ in certain conditions leads to apoptosis [6]. Sustaining a balance between the two secreted forms: proBDNF and BDNF seems to be an important factor in the regulation of processes in the brain [3]

BDNF in the Central Nervous System

BDNF plays an important role in the development of the central nervous system. It has an impact on the serotonergic signalling, glial cells [7], hippocampus neurons and the brain cortex [8]. The concentration of BDNF remains high in the hippocampus and the cortex of a mature brain [2], which is related to the function of the neurotrophin. It has been shown many times, that BDNF affects the activity of synapses – it plays a key role in the mechanism of long-term potentiation (LTP) [9, 10] and allows proper memory function. On the other hand, proBDNF is related to long-term depression (LTD) phenomenon in the hippocampus [10, 11]. BDNF, in contrast to other neurotrophins, is secreted in response to neuron excitation [9, 12] and affects the release of dopamine and glutamate from the hippocampal cells [13]. BDNF expression in the frontal cortex, in turn, can be regulated via dopaminergic receptors [14]. Many studies also suggest the involvement of BDNF in the process of neurogenesis, although it is controversial whether the protein is responsible for the proliferation of the cells, their differentiation or promotion of their survival [10].

The involvement of BDNF in the development of the central nervous system (CNS), the activity of dopaminergic neurons, synapses and the neurogenesis process, suggests its role in the aetiology of schizophrenia – no matter to which of the popular hypotheses we refer to. On the other hand, such a broad function in the regulation of brain activity makes the changes in production and secretion of BDNF unspecific. They can be observed in the course of many psychiatric disturbances and neurological dysfunctions.

BDNF in the blood

The BDNF protein is present in many tissues outside of the nervous system, most is found in the blood platelets, but also in the plasma and serum plasma. It has been proven that BDNF particles cross the blood-brain barrier [15]. The degree of correlation between the BDNF concentration in the cerebral cortex and the serum of rat is about 0.8 [16], which suggests that the fluctuations of the neurotrophin in the blood reflect the changes in the nervous system. However, one must take into consideration that there are significant changes in the concentration of BDNF in different regions of the brain and that BDNF is secreted into the blood from other sources that the CNS, like the endothelium [17]. The processes of BDNF storage in the platelets and its secretion in response to activation have not yet been explained. One of the hypotheses suggests that in the case of vessel damage, BDNF serves as a regulator of the process of nerve regeneration [18].

BDNF: studies on patients with diagnosed schizophrenia

Genetic polymorphisms

The most commonly studied single nucleotide polymorphism (SNP) of the *BDNF* gene is the presence of guanine or adenine in the 196th position of the polynucleotide chain, which results in the presence of valine or methionine in the 66th position of the polypeptide. This polymorphism is described in the publications as rs6265, G196A and most frequently – Val66Met. It does not affect the amino acid sequence in a mature BNDF particle, as it is located in a part of the protein that is cut off from the propeptide. It was observed however, that Val66Met affects the release of neurotrophin depending on the excitation of the cell, with no effect on the constitutive BDNF secretion outside the cell [9].

Two of the studies showed that the Val allele is related to a higher risk of schizophrenia [19, 20]. It has been posed that the genotype Val/Val correlates with a lower volume of hippocampus and impaired memory [21]. A meta-analysis from 2007 that included a total of 12 studies, suggests that the other allele – Met, is present more often among people with schizophrenia than in the general population [22]. Many studies do not confirm the association between the Val66Met polymorphism and schizophrenia [23–30]. Some of the data suggests that the *BDNF* variability affects only the age at which the first symptoms of schizophrenia occur [28, 31, 32].

The C270T polymorphism analysis also did not bring consistent results. In one of the studies the rate of the genotype C/T and the allele T turned out to be higher among patients with schizophrenia compared to a healthy control group [33]. In another study, such correlation was not observed [34]. The cited data comes from studies that included groups of different ethnic origin, which should also be considered in the interpretation of the results.

Methylation of the BDNF promoter

It is currently stated that the underlying cause of mental diseases could be a faulty mechanism of epigenetic changes, such as DNA methylation (post-replication addition of methyl groups to cytosine residues within so called CpG sites). High levels of methylation of the promoter region cause a diminution in the gene expression, up to a complete suppression. Latest studies on the methylation of BDNF in the DNA isolated from peripheral blood cells of patients with schizophrenia brought inconsistent results. In 2012 a paper was published, suggesting that BDNF methylation diminished the risk of schizophrenia. A year later another study showed contrary results [35, 36]. Moreover, the authors of the latter publication observed that the level of methylation was correlated with the gender.

BDNF protein – post-mortem studies

Current diagnostic techniques allow for the evaluation of BDNF concentrations in the brain tissue only post-mortem. Such analyses are limited by a low group count. Comparing BDNF concentrations in the prefrontal cortex of patients with schizophrenia with a control group revealed differences in two independent studies. However, the observations were contrary. The first revealed an increased, and the second a decreased BDNF concentration in the tissue [37, 38]. Significantly, in the second study an increased level of the neurotrophin was observed in the cortex of the patients, but the BDNF level in the hippocampus was lower compared to the control group [38]. The diversified concentrations of BDNF in different parts of the brain suggest a cautious interpretation of BDNF levels in the peripheral blood, as they do not reflect the potential changes between certain regions of the CNS.

BDNF protein in the peripheral blood serum

Many studies have shown a lowered level of BDNF in the serum of people diagnosed with schizophrenia compared to control groups. This dependence was observed both in patients not undergoing pharmacological treatment [26, 39–41] and those treated with neuroleptics [39, 42–44]. One of the studies took into account the body mass index (BMI) and the difference between the groups turned out to be statistically insignificant [44]. According to the authors of the study, a low BDNF level could predispose women treated with neuroleptics to gain weight. This hypothesis is worth verification and seems probable considering the results of studies using animals. A phenotype of obesity is a characteristic for BDNF +/ – mice, lacking one copy of the gene, and thus producing less BDNF [45]. On the other hand, the latest studies suggest that there is no correlation between BMI and the BDNF level of patients with schizophrenia [46].

BDNF protein in the peripheral blood serum: isoforms

After using reagents specifically binding to mature BDNF, no differences in the BDNF concentration in the serum of patient with schizophrenia and patients treated with clozapine were observed [47]. In a publication from 2011, 3 isoforms of BDNF were assayed in the serum: precursor protein (pro-BDNF), mature form (mat-BDNF) and "short" form (truncated-BDNF – a result of splitting pro-BDNF within the signalling sequence). It turned out that people diagnosed with schizophrenia had a lower proportion of truncated-BDNF compared to other forms of the protein. Additionally, a lower concentration of the "short" form was correlated with more severe cognitive deficits and increased intensity of psychopathological symptoms [48]. The role of the "short" form of BDNF has not been explained. It seems that the disturbances in the CNS characteristic for schizophrenia can be related to impaired proteolytic processing of BDNF or abnormal secretion of different isoforms of the protein.

BDNF in the peripheral blood plasma

Results of the analyses of BDNF levels in the plasma of patients with schizophrenia and healthy control groups are less consistent compared to serum assays. In one of the studies a lower concentration of the neurotrophic factor was observed in patients before the treatment compared to the control group, but it is unknown whether the difference remained statistically significant after 11 weeks of treatment [49]. Two other analyses showed contrary results [50, 51], and the studies included patients undergoing pharmacological treatment. Interesting additions to these results are BDNF assays of the whole blood. In this case, no differences were observed between the patients and the control group [42]. Perhaps it is not the BDNF concentration in the blood that differentiates the ill from the healthy, but an impaired mechanism of collecting and releasing the neurotrophin from the platelets due to activation could take place in schizophrenia.

Pharmacological treatment and BDNF levels in the blood

Some researchers managed to observe the differences in BDNF concentrations during antipsychotic treatment. An increase in the concentration of the protein was observed after treatment with risperidone: after 11 weeks [49] and after 4 weeks (only in the subgroup of men) [52]. In two other publications, including a meta-analysis from 2012, in patients taking risperidone no effect on the BDNF concentration was observed [39, 53]. The same meta-analysis showed that the BDNF level increased after treatment with olanzapine [53]. It was also observed that treatment with clozapine did not cause changes in the concentration of the neurotrophin after 4 weeks [52]. The cited data do not allow explicit conclusions to be formulated. One must consider that antipsychotic medications, presenting different actions in the CNS, could also affect the production and secretion of BDNF in various ways.

BDNF level in the blood and other factors

In the population of patients with schizophrenia, the correlation of the BDNF levels with other factors was also studied. One obvious strategy is to look for associations between the concentration of the neurotrophin and the severity of symptoms. Some of the researchers confirmed a negative correlation between the BDNF concentration and scores in the PANSS scale (in the subscale of positive [34, 40] and negative symptoms [40, 54]). It was also observed that a higher level of the neurotrophin was related to better verbal skills [50] and a lower level of the "short" form was related to more severe cognitive deficits [48]. A positive correlation was observed between the BDNF concentration and tobacco smoking [46, 54]. Results of animal studies showed a stimulation of BDNF expression by nicotine, although not all authors confirm these observations [41, 52]. One of the publications revealed a positive correlation between the concentration of BDNF and the quality of life of the patients [55].

Recapitulation

Our knowledge about the BDNF gene, its products and processes in which they are involved is still limited. It seems that only recently we have begun to notice the complexity of the phenomena related to this neurotrophin.

Those who are searching for biomarkers useful in psychiatry are more and more frequently reaching for specific analyses, based on which no general conclusions can be stated. To this day psychiatric examination remains the most essential part of the diagnostic process.

References

1. Hanson IM, Seawright A, van Heyningen V. *The human BDNF gene maps between FSHB and HVBS1 at the boundary of 11p13-p14*. Genomics 1992; 13: 1331–1333.
2. Pruunsild P, Kazantseva A, Aid T, Palm K, Timmusk T. *Dissecting the human BDNF locus: Bidirectional transcription, complex splicing, and multiple promoters*. Genomics 2007; 90: 397–406.
3. Greenberg ME, Xu B, Lu B, Hempstead BL. *New insights in the biology of BDNF synthesis and release: implications in CNS function*. J. Neurosci. 2009; 29: 12764–12767.
4. Patapoutian A, Reichardt LF. *Trk receptors: mediators of neurotrophin action*. Curr. Opin. Neurobiol. 2001; 11: 272–280.
5. Barbacid M. *Neurotrophic factors and their receptors*. Curr. Opin. Cell Biol. 1995; 7: 148–155.
6. Teng HK, Teng KK, Lee R, Wright S, Tevar S, Almeida RD. et al. *ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin*. J. Neurosci. 2005; 25: 5455–5463.
7. Djalali S, Höltje M, Grosse G, Rothe T, Stroh T, Grosse J. et al. *Effects of brain-derived neurotrophic factor (BDNF) on glial cells and serotonergic neurones during development*. J. Neurochem. 2005; 92: 616–627.
8. Huang EJ1, Reichardt LF. *Neurotrophins: roles in neuronal development and function*. Ann. Rev. Neurosci. 2001; 24: 677–736.
9. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A. et al. *The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function*. Cell 2003; 112: 257–269.
10. Binder DK, Scharfman HE. *Brain-derived neurotrophic factor*. Growth Factors 2004; 22: 123–131.
11. Woo NH, Teng HK, Siao CJ, Chiaruttini C, Pang PT, Milner TA. et al. *Activation of p75NTR by proBDNF facilitates hippocampal long-term depression*. Nat. Neurosci. 2005; 8: 1069–1077.
12. Mowla SJ, Pareek S, Farhadi HF, Petrecca K, Fawcett JP, Seidah NG. et al. *Differential sorting of nerve growth factor and brain-derived neurotrophic factor in hippocampal neurons*. J. Neurosci. 1999; 19: 2069–2080.
13. Paredes D, Granholm AC, Bickford PC. *Effects of NGF and BDNF on baseline glutamate and dopamine release in the hippocampal formation of the adult rat*. Brain Res. 2007; 1141: 56–64.
14. Xing B, Guo J, Meng X, Wei SG, Li SB. *The dopamine D1 but not D3 receptor plays a fundamental role in spatial working memory and BDNF expression in prefrontal cortex of mice*. Behav. Brain Res. 2012; 235: 36–41.

15. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. *Transport of brain-derived neurotrophic factor across the blood–brain barrier*. Neuropharmacology 1998; 37: 1553–1561.
16. Karege F, Schwald M, Cisse M. *Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets*. Neurosci. Lett. 2002; 328: 261–264.
17. Nakahashi T, Fujimura H, Altar CA, Li J, Kambayashi J, Tandon NN. et al. *Vascular endothelial cells synthesize and secrete brain-derived neurotrophic factor*. FEBS Lett. 2000; 470: 113–117.
18. Fujimura H, Altar CA, Chen R, Nakamura T, Nakahashi T, Kambayashi J. et al. *Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation*. Thromb. Haemost. 2002; 87: 728–734.
19. Neves-Pereira M, Cheung JK, Pasdar A, Zhang F, Breen G, Yates P. et al. *BDNF gene is a risk factor for schizophrenia in a Scottish population*. Mol. Psychiatry 2005; 10: 208–212.
20. Rosa A, Cuesta MJ, Fatjó-Vilas M, Peralta V, Zarzuela A, Fañanás L. *The Val66Met polymorphism of the brain-derived neurotrophic factor gene is associated with risk for psychosis: evidence from a family-based association study*. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2006; 141B: 135–138.
21. Smith GN, Thornton AE, Lang DJ, MacEwan GW, Ehmann TS, Kopala LC. et al. *Hippocampal volume and the brain-derived neurotrophic factor Val66Met polymorphism in first episode psychosis*. Schizophr. Res. 2012; 134: 253–259.
22. Gratacòs M, González JR, Mercader JM, de Cid R, Urretavizcaya M, Estivill X. *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 2007; 61: 911–922.
23. Zhou DH, Yan QZ, Yan XM, Li CB, Fang H, Zheng YL. et al. *The study of BDNF Val66Met polymorphism in Chinese schizophrenic patients*. Prog. Neuropsychopharmacol. Biol. Psychiatry 2010; 34: 930–933.
24. Golimbet VE, Korovaĭtseva GI, Abramova LI, Kasparov SV, Uvarova LG. *Association between the Val66Met polymorphism of brain-derived neurotrophic factor gene and schizophrenia in Russians*. Mol. Biol. (Mosk.) 2008; 42: 599–603.
25. Hawi Z, Straub RE, O'Neill A, Kendler KS, Walsh D, Gill M. *No linkage or linkage disequilibrium between brain-derived neurotrophic factor (BDNF) dinucleotide repeat polymorphism and schizophrenia in Irish families*. Psychiatry Res. 1998; 81: 111–116.
26. Sotiropoulou M, Mantas C, Bozidis P, Marselos M, Mavreas V, Hyphantis T. et al. *BDNF serum concentrations in first psychotic episode drug-näive schizophrenic patients: Associations with personality and BDNF Val66Met polymorphism*. Life Sci. 2013; 92: 305–310.
27. Kawashima K, Ikeda M, Kishi T, Kitajima T, Yamanouchi Y, Kinoshita Y. et al. *BDNF is not associated with schizophrenia: data from a Japanese population study and meta-analysis*. Schizophr. Res. 2009; 112: 72–79.
28. Baig BJ, Whalley HC, Hall J, McIntosh AM, Job DE, Cunningham-Owens DG. et al. *Functional magnetic resonance imaging of BDNF val66met polymorphism in unmedicated subjects at high genetic risk of schizophrenia performing a verbal memory task*. Psychiatry Res. 2010; 183: 195–201.
29. Kayahan B, Kaymaz BT, Altıntoprak AE, Aktan Ç, Veznedaroğlu B, Kosova B. *The lack of association between catechol-O-methyltransferase (COMT) Val108/158Met and brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms and schizophrenia in a group of Turkish population*. Neurol. Psychiatry Brain Res. 2013; 19: 102–108.

30. Chen SL, Lee SY, Chang YH, Chen SH, Chu CH, Wang TY. et al. *The BDNF Val66Met polymorphism and plasma brain-derived neurotrophic factor levels in Han Chinese patients with bipolar disorder and schizophrenia*. Prog. Neuropsychopharmacol. Biol. Psychiatry 2014; 51: 99–104.
31. Numata S, Ueno S, Iga J, Yamauchi K, Hongwei S, Ohta K. et al. *Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism in schizophrenia is associated with age at onset and symptoms*. Neurosci. Lett. 2006; 401: 1–5.
32. Chao HM, Kao HT, Porton B. *BDNF Val66Met variant and age of onset in schizophrenia*. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2008; 147B: 505–506.
33. Szekeres G, Juhász A, Rimanóczy A, Kéri S, Janka Z. *The C270T polymorphism of the brain-derived neurotrophic factor gene is associated with schizophrenia*. Schizophr. Res. 2003; 6: 15–18.
34. Xiu MH, Hui L, Dang YF, Hou TD, Zhang CX, Zheng YL. et al. *Decreased serum BDNF levels in chronic institutionalized schizophrenia on long-term treatment with typical and atypical antipsychotics*. Prog. Neuropsychopharmacol. Biol. Psychiatry 2009; 33: 1508–1512.
35. Kordi-Tamandani DM, Sahranavard R, Torkamanzehi A. *DNA methylation and expression profiles of the brain-derived neurotrophic factor (BDNF) and dopamine transporter (DAT1) genes in patients with schizophrenia*. Mol. Biol. Rep. 2012; 39: 10889–10893.
36. Ikegame T, Bundo M, Sunaga F, Asai T, Nishimura F, Yoshikawa A. et al. *DNA methylation analysis of BDNF gene promoters in peripheral blood cells of schizophrenia patients*. Neurosci. Res. 2013; 77: 208–214.
37. Issa G, Wilson C, Terry AV Jr, Pillai A. *An inverse relationship between cortisol and BDNF level in schizophrenia: Data from human postmortem and animal studies*. Neurobiol. Dis. 2010; 39: 327–333.
38. Durany N, Michel T, Zöchling R, Boissl KW, Cruz-Sánchez FF, Riederer P. et al. *Brain-derived neurotrophic factor and neurotrophin 3 in schizophrenic psychoses*. Schizophr. Res. 2001; 52: 79–86.
39. Pırıldar Ş, Gönül AS, Taneli F, Akdeniz F. *Low serum levels of brain-derived neurotrophic factor in patients with schizophrenia do not elevate after antipsychotic treatment*. Prog. Neuropsychopharmacol. Biol. Psychiatry 2004; 28: 709–713.
40. Rizos EN, Rontos I, Laskos E, Arsenis G, Michalopoulou PG, Vasilopoulos D. et al. *Investigation of serum BDNF levels in drug-naive patients with schizophrenia*. Prog. Neuropsychopharmacol. Biol. Psychiatry 2008; 32: 1308–1311.
41. Jindal RD, Pillai AK, Mahadik SP, Eklund K, Montrose DM, Keshavan MS. *Decreased BDNF in patients with antipsychotic naïve first episode schizophrenia*. Schizophr. Res. 2010; 119: 47–51.
42. Toyooka K, Asama K, Watanabe Y, Muratake T, Takahashi M, Someya T. et al. *Decreased levels of brain-derived neurotrophic factor in serum of chronic schizophrenic patients*. Psychiatry Res. 2002; 110: 249–257.
43. Grillo RW, Ottoni GL, Leke R, Souza DO, Portela LV, Lara DR. *Reduced serum BDNF levels in schizophrenic patients on clozapine or typical antipsychotics*. J. Psychiatr. Res. 2007; 41: 31–35.
44. Zhang XY, Tan YL, Zhou DF, Cao LY, Wu GY, Xu Q. et al. *Serum BDNF levels and weight gain in schizophrenic patients on long-term treatment with antipsychotics*. J. Psychiatr. Res. 2007; 41: 997–1004.
45. Kernie SG, Liebl DJ, Parada LF. *BDNF regulates eating behavior and locomotor activity in mice*. EMBO J. 2000; 19: 1290–1300.
46. Nurjono M, Tay YH, Lee J. *The relationship between serum brain-derived neurotrophic factor (BDNF) and cardiometabolic indices in schizophrenia*. Schizophr. Res. 2014; 157: 244–248.

47. Yamamori H, Hashimoto R, Ishima T, Kishi F, Yasuda Y, Ohi K. et al. *Plasma levels of mature brain-derived neurotrophic factor (BDNF) and matrix metalloproteinase-9 (MMP-9) in treatment-resistant schizophrenia treated with clozapine*. Neurosci. Lett. 2013; 556: 37–41.
48. Carlino D, Leone E, Di Cola F, Baj G, Marin R, Dinelli G. et al. *Low serum truncated-BDNF isoform correlates with higher cognitive impairment in schizophrenia*. J. Psychiatr. Res. 2011; 45: 273–279.
49. Chen SL, Lee SY, Chang YH, Chen SH, Chu CH, Tzeng NS. et al. *Inflammation in patients with schizophrenia: the therapeutic benefits of risperidone plus add-on dextromethorphan*. J. Neuroimmune Pharmacol. 2012; 7: 656–664.
50. Asevedo E, Gadelha A, Noto C, Mansur RB, Zugman A, Belangero SI. et al. *Impact of peripheral levels of chemokines, BDNF and oxidative markers on cognition in individuals with schizophrenia*. J. Psychiatr. Res. 2013; 47: 1376–1382.
51. Domenici E, Wille DR, Tozzi F, Prokopenko I, Miller S, McKeown A. et al. *Plasma protein biomarkers for depression and schizophrenia by multi analyte profiling of case-control collections*. PLoS ONE 2010; 5: e9166.
52. Chen CC, Huang TL. *Effects of antipsychotics on the serum BDNF levels in schizophrenia*. Psychiatry Res. 2011; 189(3): 327–330.
53. Lin PY. *Increase in brain-derived factor in patients with schizophrenia treated with olanzapine: a systemic review and meta-analysis*. J. Exp. Clin. Med. 2012; 4(2): 119–124.
54. Zhang XY, Xiu MH, Chen DC, Yang FD, Wu GY, Lu L. et al. *Nicotine dependence and serum BDNF levels in male patients with schizophrenia*. Psychopharmacology 2010; 212: 302–307.
55. Vinogradov S, Fisher M, Holland C, Shelly W, Wolkowitz O, Mellon SH. *Is serum brain-derived neurotrophic factor a biomarker for cognitive enhancement in schizophrenia?* Biol. Psychiatry 2009; 66: 549–553.

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