Decreased serum brain-derived neurotrophic factor (BDNF) is associated with post-stroke depression but not with BDNF gene Val66Met polymorphism

Zhiming Zhou1,2, Tingting Lu1, Gelin Xu1, Xuanye Yue1,2, Wusheng Zhu1, Minmin Ma1, Wenhua Liu1, Shuanggen Zhu1,4 and Xinfeng Liu1,*

1 Department of Neurology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, Jiangsu Province, P.R. China
2 Department of Neurology, Yijishan Hospital, Wannan Medical College, Wuhu, Anhui Province, P.R. China
3 Department of Neurology, Shiyan People’s Hospital, Yunyang Medical College, Shiyan, Hubei Province, P.R. China
4 Department of Neurology, Third Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, P.R. China

Abstract

Background: Decreased brain-derived neurotrophic factor (BDNF) has been demonstrated in animal models and patients with depression. However, little is known about changes in BDNF in post-stroke depression (PSD). This study investigated the changes in serum BDNF in patients with PSD, and evaluated whether serum concentrations of BDNF were associated with BDNF gene Val66Met polymorphism.

Methods: PSD patients were diagnosed in accordance with DSM-IV criteria, and the severity of depression was evaluated with the Hamilton Rating Scale for depression. Serum BDNF was measured twice, first at 7 days after the onset of stroke and then at 3–6 months after stroke. Val66Met polymorphisms of the BDNF gene were determined using the polymerase chain reaction-restriction fragment length polymorphism method. BDNF concentrations and Val66Met polymorphisms were also measured in 30 healthy controls.

Results: A total of 93 patients admitted as a result of first time acute ischemic stroke were included. During the 6-month follow-up, 35 patients (37.6%) were diagnosed with PSD. Serum BDNF concentrations were decreased in PSD patients at 3–6 months after stroke (p<0.05). The serum BDNF concentrations were not associated with BDNF gene Val66Met polymorphisms in either patients or healthy controls.

Conclusions: Serum concentrations of BDNF decrease in PSD patients and BDNF may play an important role in the pathogenesis of PSD. However, Val66Met polymorphisms are not associated with serum concentrations of BDNF. The mechanism of decreased serum BDNF requires further study.

Keywords: brain-derived neurotrophic factor; neurotrophins; polymorphism; post-stroke depression; stroke.

Introduction

Post-stroke depression (PSD) is one of the most frequent neuropsychiatric complications of stroke, affecting 14%–60% of ischemic stroke survivors (1–5). Apart from contributing poor quality of life, PSD is associated with poor neurofunctional recovery and higher mortality (6–8).

Brain-derived neurotrophic factor (BDNF), an important member of the neurotrophic factor family, plays a significant role in regulating neuron plasticity and promoting cell survival (9, 10). In several animal models, decreased BDNF is associated with increased symptoms. Chronic stress decreased BDNF concentrations and lowered mRNA expression of BDNF and its high affinity receptors in rat hippocampus (11). BDNF expression was decreased in depressed patients, and antidepressant treatment was found to reverse this effect (12, 13). All these studies indicate that BDNF plays an important role in the onset and development of depression. High concentrations of BDNF have not only been found in the central nervous system, but also in non-neuronal cells, particularly in platelets. A positive correlation between serum and cortical BDNF concentrations has been observed in rats (14) and humans (15).

Polymorphisms in the gene encoding BDNF Val66Met alter proBDNF intracellular trafficking, as well as result in increased susceptibility to several psychiatric disorders (16). Recently, a study demonstrated that the Val66Met genotype might influence BDNF protein in amniotic fluid (17).

This study investigated the changes in serum BDNF concentrations in patients with PSD, and whether serum BDNF concentrations were associated with the Val66Met polymorphism.
Figure 1  Serum concentrations of brain-derived neurotrophic factor (BDNF) by BDNF Val66Met genotype in patients with and without depression at acute stage and follow-up, and in healthy controls. An analysis of variance indicated no significant differences between BDNF Val66Met genotypes.

Figure 2  Serum brain-derived neurotrophic factor (BDNF) by BDNF Val66Met genotypes in patients with and without depression at acute stage and follow-up, and in healthy controls. An analysis of variance (ANOVA) indicated no significant differences between BDNF Val66Met genotypes Met carriers and non-Met carriers.

pro-BDNF, and then regulate secretion of mature BDNF (16). Recently, a study showed evidence of an effect of the BDNF Val66Met polymorphism on protein levels during weeks 15–17 of pregnancy (17). BDNF protein concentrations were significantly lower in Met allele carriers compared to non-carriers. These results were found in adulthood by Ozan and colleagues (30). They found that serum BDNF concentrations were lower in Met allele carriers than Val homozygote subjects (23.08 ng/mL vs. 26.87 ng/mL; p < 0.002). However, the results were not consistent. Jiang et al. and Terracciano et al. (31, 32) noted that the Val66Met polymorphism does not affect BDNF concentrations in serum or plasma. On the contrary, another study showed that serum BDNF was higher in Met allele carriers than Val homozygote subjects (25). The authors think that there was a constitutive up-regulation of peripheral BDNF concentrations in carriers of the Met allele that might compensate for defective intracellular protein signaling.

In the present study, the results did not provide evidence that serum concentrations of BDNF were associated with the functional Val66Met variant. Until now, the exact cause of decreased serum or plasma BDNF is not clear. High concentrations of BDNF have not only been found in the central nervous system, but also in non-neuronal cells, particularly in platelets (33–35). Platelets do not produce BDNF, but large amounts of circulating BDNF proteins are stored within platelets. BDNF is released into the serum through platelet activation or clotting (33–35). It should be noted that BDNF concentrations cannot be seen in different genotypes due dilution in the blood. The exact cause of decrease serum BDNF in PSD patients remains to be determined.

Conclusions

Serum BDNF decreases in PSD patients 6 months after stroke. Our findings support the neurotrophic hypothesis of PSD. Factors other than Val66Met polymorphisms may affect serum BDNF concentrations in PSD patients.

Acknowledgments

This study was supported by Natural Science Foundation of China (NSFC 30870847 to XL and NSFC 30870848 to GX). The authors wish to thank Dr. Gengbao Feng for his valuable technical assistance.

Conflict of interest statement

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article. Research support played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

References


