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Review article

The role of brain-derived neurotrophic factor and its single nucleotide polymorphisms in stroke patients

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ABSTRACT

Stroke is the main cause of motoric and neuropsychological disability in adults. Recent advances in research into the role of the brain-derived neurotrophic factor in neuroplasticity, neuroprotection and neurogenesis might provide important information for the development of new poststroke-rehabilitation strategies. It plays a role as a mediator in motor learning and rehabilitation after stroke. Concentrations of BDNF are lower in acute ischemic-stroke patients compared to controls. Lower levels of BDNF are correlated with an increased risk of stroke, worse functional outcomes and higher mortality. BDNF signalling is dependent on the genetic variation which could affect an individual's response to recovery after stroke.

Several single nucleotide polymorphisms of the BDNF gene have been studied with regard to stroke patients, but most papers analyse the rs6265 which results in a change from valine to methionine in the precursor protein. Subsequently a reduction in BDNF activity is observed. There are studies indicating the role of this polymorphism in brain plasticity, functional and morphological changes in the brain. It may affect the risk of ischemic stroke, post-stroke outcomes and the efficacy of the rehabilitation process within physical exercise and transcranial magnetic stimulation. There is a consistent trend of Met alleles' being connected with worse outcomes and prognoses after stroke. However, there is no satisfactory data confirming the importance of Met allele in stroke epidemiology and the post-stroke rehabilitation process. We present the current data on the role of BDNF and polymorphisms of the BDNF gene in stroke patients, concentrating on human studies.

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1. Introduction

Stroke is the main cause of motoric disability in adults, especially after 60 years of age. There is specific treatment for stroke, such as the recombinant tissue-plasminogen activator, which decreases the risk of motoric impairment, but its efficacy is still not fully satisfactory. New studies have been published to search for neuroprotection and neuroplasticity in cerebrovascular disorders. Moreover, motoric, speech and cognitive rehabilitation relates to significant aspects of secondary-stroke management. The brain-derived neurotrophic factor (BDNF) is part of the neurotrophin family of growth factors, such as the nerve-growth factors (NGF) neurotrophins 3 and 4 (NT-3, NT-4) [1]. They are responsible for enhancing progenitor-cell proliferation and differentiation, cell growth, regeneration processes, neuronal survival, synaptic regulation and remodelling, the regulation of plasticity, and repair and connectivity in the brain [2,3]. The effects of neurotrophins are mediated by a family of specific transmembrane tyrosine-kinase receptors, of which TrkB is the primary signal-transduction receptor for BDNF [3].

Recent advances in research into the role of BDNF in neuroplasticity, neuroprotection and neurogenesis might provide important information for the development of new poststroke rehabilitation strategies. It plays a role as a mediator in motor learning and rehabilitation after stroke. This protein is involved in a number of brain functions, including neuroplastic changes which underly motor learning. It exerts its effects on neuroplasticity by facilitating long-term potentiation and a long-lasting increase in the strength of the connection between the two neurons which are repeatedly activated together. Dendritic growth and remodelling are also promoted [4]. This trophic factor has direct effects on oligodendroglia, promoting the proliferation and differentiation of oligodendrocyte-precursor cells (OPC) and myelination [5]. It promotes prostacyclin biosynthesis in cerebral arteries [6].

Unlike other growth factors, BDNF is secreted in the CNS (Central Nervous System) throughout both constitutive and activity-dependent pathways. BDNF production is boosted by activities such as learning, physical exercise, sensory stimulation and motor-cortex activation [7]. The 32 kDa pro form (proBDNF) is rapidly cleaved to the mature form after secretion. This activity-dependent secretion is crucial for the role of BDNF in promoting neuroplasticity in circuits activated in response to experience [8,9].

BDNF plays an essential role in the integration and optimisation of behavioural and metabolic responses to environments with limited energy resources and intense ''competition''. In particular, BDNF signalling mediates adaptive responses in the central, autonomic, and peripheral nervous systems from exercise and dietary-energy restriction (DER). In the hypothalamus, BDNF inhibits food intake and increases energy expenditure. By promoting synaptic plasticity and neurogenesis in the hippocampus, BDNF mediates exercise- and DER-induced improvements in cognitive function and neuroprotection. It also has the ability to regulate the peripheral-energy metabolism [10].

Besides the potential clinical use of BDNF in stroke patients, there are also reports of significant correlations between its level in autoimmune and neurodegeneration disorders. The conclusions reached in such studies can be used for scientific investigations into stroke. The level of circulating BDNF compared to healthy controls decreases, even at the early stages of multiple sclerosis (MS), and it is associated negatively with neurological impairment. This level is increased by immunomodulating treatment with the interferone-beta 1b [11,12]. The concentrations of BDNF are connected with selected factors (cognitive impairment, low educational level, advanced age) in Alzheimer's disease, and in patients with mild cognitive impairment [13]. In amyotrophic lateral sclerosis patients there were no beneficial effects within the primary endpoints (survival, retardation/loss of pulmonary function) of BDNF administration, neither in the subcutaneous injections nor in the intrathecal infusions used in various doses in 9-months follow-ups. In a subgroup of patients with respiratory impairment, and those who had developed secondary altered-bowel function, the results showed statistically significant benefits [14,15]. No effect of BDNF intrathecal administration on the functions of the autonomic sympathetic or the parasympathetic system was observed in 9-months follow-ups [16].

The therapeutic effect of BDNF administration on stroke patients needs further investigations, including the potential effect of improving the drug-delivery system throughout the brain–blood barrier (BBB) by nano-particles, or by optimising the pharmacokinetics of BDNF [17]. Previous studies of BDNF administration in stroke involved only experimental or animal models [17–19].

2. BDNF concentrations and stroke

There is occurring an emerging role of BDNF in cardiovascular-risk factors and disorders, especially in ischaemic-stroke patients. Lower plasma BDNF levels in physically active men were associated with a higher atherogenic index (TC/HDL), and higher levels of hsCRP and oxLDL. Increased levels of circulating BDNF were present in subjects with a high level of cardio-respiratory fitness, as reflected in VO2max in the Åstrand–Rhyming bike test. BDNF interacts with oxidative stress and inflammatory molecules, as its level can be raised by the administration of atorvastatin for ischaemic stroke [3,20]. The level of BDNF is associated with the occurrence of delirium in intensive-care-unit patients, but not in individuals with ischaemic stroke [21,22].

Concentrations of BDNF are lower in acute-ischaemic-stroke patients compared with controls, but BDNF has not been associated with 3-month outcomes. However, patients with BDNF in the lowest tertile had an increased risk of experiencing a poor outcome, at both the 2-year and 7-year follow-ups [23]. Similar results were presented by other authors, where the initial BDNF level at ischaemic-stroke onset significantly correlated with 3-months mortality, and functional outcomes measured with the modified Rankin Scale (mRS) – lower BDNF levels were connected with poor outcomes and higher mortality [24,25].

In the Framingham Study during a median follow-up lasting for 10 years, a lower BDNF level was associated with an

increased risk of stroke and TIA (HR Q1 versus Q2–Q4 1.47; 95% CI: 1.09–2.00, $p = 0.012$). Moreover, subjects with a higher BDNF level had less white-matter hyperintensity volume and better visual memory, which might demonstrate the protective properties of this protein [26]. Lower BDNF levels in a meta-analysis published in year 2013 proved to be a significant risk factor in developing post-stroke depression [27]. Further analyses confirmed this conclusion [28].

BDNF plays an important role in stroke incidence and outcome, but its use as a marker in the rehabilitation process needs to be established. BDNF has a direct role in promoting the migration of neuroblasts to ischaemic areas, and cells migrating in the ischaemic striatum display higher exploratory behaviour and longer stationary periods [29]. The systemic level of BDNF increases for approximately 10–60 min following aerobic exercise in humans, and the return to the baseline level is achieved 1 h after such exercise [30]. Such observations might suggest potential pathogenetic and clinical implications for BDNF in the rehabilitation process. Two-week-long combination therapy involving upper-limb rehabilitation and repetitive transcranial magnetic stimulation (rTMS) in post-stroke patients increased the level of the BDNF serum, but not of the proBDNF serum. Moreover, the BDNF-serum level did not correlate with motor-function improvement, but the baseline proBDNF-serum level correlated negatively and significantly with improvement [31]. Despite the analyses of functional outcomes in relation to BDNF levels, there are limited data on the clinical value and potential use of BDNF as a marker of the common neurorehabilitation process in stroke patients in relation to methods, time of initiation, intensity, and duration of rehabilitation.

Besides motoric rehabilitation, of note might be the use of BDNF measurements in cognitive therapy, but also limited studies have been performed in this field. It has been demonstrated that patients who underwent aerobic training achieved cognitive improvement in relation to BDNF level [32].

3. *BDNF* polymorphisms and stroke

BDNF signalling is dependent on the expression of genes. As a result, genetic variation could affect an individual's response to motor rehabilitation, training and motor recovery after stroke. The BDNF protein is coded by the *BDNF* gene located on the chromosome 11 (11p13) [4]. Several single nucleotide polymorphis of *BDNF* gene have been described, but the most promising as a clinically important polymorphism seems to be the rs6265 SNP [33].

4. Rs6265 polymorphism of the *BDNF* gene

In approximately 30%–50% of the human population, there is a single nucleotide polymorphism of the *BDNF* gene which results in an amino-acid substitution of valine (Val) for methionine (Met) at position 66 (val66met, rs6265, 196 G > A) of the precursor peptide proBDNF [33]. The presence of the Met allele results in a 25% reduction in the activity-dependent secretion of BDNF in the CNS [9,34].

The first study to demonstrate the effect of the rs6265 polymorphism of the *BDNF* gene on activity-dependent brain plasticity associated with movement was presented in 2006 [35].

There are not only functional, but also morphological, changes in the brain, depending on the rs6265 SNP. The authors detected a bilateral reduction in hippocampal grey-matter volumes in Met-allele carriers compared with Val/Val. In addition, a whole-brain analysis was performed on these subjects, indicating reduced grey-matter volume in the lateral convexity of the frontal lobes, with peak values bilaterally encompassing the dorsolateral prefrontal cortex [36]. In a small-sample-size study the Met allele was associated with an 11% reduction in the volume of hippocampal formation [37]. Besides the anatomical considerations, the functional effect of rs6265 polymorphism of the *BDNF* gene can also be observed. In a group of 42 ischaemic-stroke patients, decreased brain activation was detected in the fMRI in Val/Met participants compared to others [38]. Radiological correlates were also found in MRI diffusion-tensor imaging (DTI) scans, indicating an association between corticospinal degeneration, motor function and 196 G > A *BDNF* gene polymorphism [39].

The role of the rs6265 SNP of the *BDNF* gene has also been analysed in epidemiological and clinical studies in stroke patients. An analysis was presented of ischaemic-stroke occurrence in 206 stroke patients and 200 controls, but there was no significant association [40]. The risk of ischaemic stroke was also analysed in 494 patients and 337 controls, indicating a higher risk in Met/Met (AA) carriers of 196 G > A polymorphism of the *BDNF* gene (OR 1.541; 95%CI: 1.034–2.298, $p = 0.028$) [41].

Potential association between the rs6265 genotype and neurological deficit has been studied. 3-Months functional outcomes measured with mRS were poor in Met-allele patients [41]. Poor outcomes 2 weeks and 1 year after stroke were observed in Val/Met-genotype patients [42]. Ischaemic-stroke patients with Val/Met SNP had a median change in the NIHSS (National Institute of Health Stroke Scale) score within 1 month after the stroke of only 4 points, compared to 5 points amongst the rest, while no differences were found in the analysis of changes in the NIHSS and mRS scores at the 3-month interval [43]. There was also no impact on 30-day outcomes, but at the 3-months observation period a positive association was found [2,44].

Despite our prime interest in ischaemic stroke, there are interesting results of studies on outcomes and cognition in other types of stroke. There has also been a single analysis on the role of the rs6265 SNP of *BDNF* gene in intracerebral and subarachnoid haemorrhage patients. The Met carriers had poor outcomes compared with the Val/Val group in the assessment 3 months after the aneurysmal subarachnoid haemorrhage (SAH) (OR 8.40; 95% CI: 1.60–44.00; $p = 0.012$) [45]. In patients assessed 1 year after the SAH with the use of the neuropsychological test battery, the Val66Met polymorphism of the *BDNF* gene was not associated with learning and memory performance, but the Met carriers had poorer learning and memory performance than Val/Val homozygotes in a subgroup of patients without cerebral infarction [46]. In the intracerebral haemorrhage patients, the Val/Val carriers scored better in NIHSS on admission (14.23 versus 21.00,

$p = 0.0192$) and after 7 days (8.60 versus 15.00, $p = 0.0408$) after the onset. There was no impact on 30-day outcomes [2].

5. Neurorehabilitation and rs6265 polymorphism of the *BDNF* gene

The presented analyses were made irrespectively of the type of neurorehabilitation, which to a great extent affects the neurological outcome.

Several studies are available in which the authors presented rehabilitation characteristics, but generally no relationship between the BDNF genotype and the results was found. In the mean follow-up lasting for 21 months, post-stroke patients attending the upper-limb-rehabilitation programme were assessed, depending on the SNP status. There was no significant effect of the BDNF genotype on motor function at the baseline or following therapy. However, a significant interaction between the level of residual motor function and the BDNF genotype was identified. The post-therapy improvement was significantly less for Met-allele patients with moderate and high, but not low, motor function [47]. In an analysis of 67 ischaemic-stroke patients no correlation was detected between rs6265 SNP and both the 1- and 6-months motoric statuses after the inpatient rehabilitation [48]. In a study on the greater groups i.e. 600 ischaemic-stroke patients and 600 controls with follow-up until 7 years, there was again no association between the outcomes measured at 3 months, 2 years and 7 years [49]. There was also no significant difference within the SNP regarding the severity of the stroke and the functional disability in an average period of 202 days after the stroke [40].

The results presented above do not overall provide convincing data on the significant role of rs6265 SNP of the *BDNF* gene in epidemiology and the rehabilitation process for stroke patients. In addition to physical therapy, the rTMS (repetitive transcranial magnetic stimulation) proved to be effective in the neurorehabilitation process in stroke patients. The therapeutic results might be influenced by the BDNF genotype, in both the acute and chronic period from the onset [50]. The rTMS used 10 days after ischaemic stroke provoked greater excitability over the unaffected hemisphere in patients without the Met/Val genotype in a group of only 20 patients [51]. A worse response to rTMS in 44 post-stroke patients was also observed in Met-alle groups in comparison to the Val/Val group [52]. At least 6 months after both ischaemic-stroke and intracerebral haemorrhage, patients with Val/Met polymorphism were more likely to adapt to an aide, but this was tested in only 27 subjects [53]. The rTMS performed 6 months after the stroke onset in 22 patients with persistent paresis showed differences in their motor-evoked potentials, depending on their genotype status [50]. These potentially 'positive' studies were performed on small sample sizes, so have limited statistical weight and cannot be fully conclusive. There was no correlation between genotype and rTMS use in the rehabilitation of 26 ischaemic-stroke patients [54]. Even the outcome of the combination therapy of upper-limb rehabilitation and rTMS in post-stroke patients was not altered by any rs6265 *BDNF* gene polymorphism [31].

6. Neuropsychological dysfunctions and rs6265 polymorphism of the *BDNF* gene

In addition to motoric impairment due to stroke, neuropsychological dysfunctions such as cognitive impairment and depression also significantly affect social functioning. The rs6265 SNP of *BDNF* gene variations can be clinically important in cognitive dysfunctions. In the cohort of healthy subjects, the Met/Met homozygotes had lower scores in episodic memory measured by the Wechsler Memory Scale, and a revised version (WMS-R) compared to the other two genotype groups (Val/Val and Val/Met). The difference between the SNPs was also evident in the blood-oxygenation-level dependent (BOLD) functional MRI technique while performing the working-memory task in the area of the hippocampus [34]. Moreover, studies on post-stroke-dementia patients have been presented. In patients diagnosed with post-stroke dementia (PSD) at the mean 6-months period, Val/Met carriers were at greater risk of PSD (HR 2.280; 95% CI: 1.566–4.106, $p = 0.006$). However the risk ratio was insignificant after adjusting demographic, clinical, and vascular risk factors [55]. Therapy for cognitive impairment in post-stroke patients employed with the use of rTMS was not connected with any of the rs6265 SNP of the *BDNF* gene, but only 40 patients were assessed for this [56]. The Val-allele carriers had more cognitive impairment after IS assessed on average 202 days after stroke, which is partially inconsistent with the studies presented above, in which Val allele had beneficial effects on stroke patients [40]. The psychopathological effect, such as post-stroke depression, appeared not to be connected with this SNP status, but only with the level of BDNF [57]. On the other hand, rs6265 SNP of the *BDNF* gene is the only one which has potential clinical significance in the risk of depression in stroke-free patients [58].

The potential role of Met allele in the neurorehabilitation process presented above appears to be mainly explained by the difference in the susceptibility to plasticity. This effect takes place in the cortex and is less pronounced in Met carriers, who have instead spared global-recovery potential. Met carriers can benefit from different rehabilitation strategies from other genotypes, which should be considered and analysed in further studies. Genotyping can gain clinical significance through the individualisation of motoric and cognitive rehabilitation in stroke patients [7,59].

7. Other *BDNF* gene polymorphisms

The rs6265 SNP of the *BDNF* gene is a polymorphism of prime interest, but there have been other SNPs tested as well, though less frequently. There was a higher occurrence of the −270 CC genotype of the *BDNF* gene in patients with haemorrhagic than ischaemic stroke (96% versus 86%, $p = 0.0495$). None of the determined polymorphisms had any impact on the 30-day outcome in ischaemic and haemorrhagic strokes [2]. There was no correlation between this genotype and rTMS use in the rehabilitation of the 26 ischaemic-stroke patients [54].

A correlation was indicated between the rs11030119 SNP of the *BDNF* gene and favourable outcomes measured 7 years after the ischaemic stroke OR (0.6; 955CI: 0.42–0.86, $p = 0.01$) [49].

On the other hand, there was no effect of rs11030107 and rs2049046 polymorphisms of the *BDNF* gene on outcomes measured at 3 months, 2 and 7 years after the ischaemic stroke [49]. The latest SNP was connected with the risk of migraine and migraine with aura, which is an established risk factor of stroke [60].

8. Conclusions

BDNF and its polymorphisms appear to play an important role in ischaemic-stroke patients, with special attention being paid to motoric and neuropsychological rehabilitation. There are reliable results indicating the evident connection between the BDNF level and the risk of stroke, functional outcome and mortality in stroke patients. We conclude that there are no satisfactory data regarding the clinical utility of circulating BDNF and the neurorehabilitation process in the acute phase of stroke and in the post-stroke rehabilitation provided in neurorehabilitation departments, where most stroke patients should be referred in the event of no contra-indications. We also propose that further studies should be continued on the potentially beneficial effects of BDNF administration in stroke patients, as it can potentially penetrate the blood–brain-barrier [61]. As long as there is no such treatment proven to be safe and effective, other, non-invasive, methods of increasing BDNF could be of importance. These include intensive, early post-stroke rehabilitation, and probably rTMS.

Most of the available studies involve the rs6265 SNP of the *BDNF* gene. There is a consistent trend that the Met allele is connected with worse outcomes and prognoses after stroke, but there is no convincing evidence of its role in effective rehabilitation therapy for stroke epidemiology. However, this SNP should be of interest in clinical studies, especially as Met-inclusive allele is present in up to 66.2% of the population [62]. Despite the current pharmacotherapy for stroke, the rehabilitation process still remains an important and effective method of decreasing motoric and cognitive disability. The present data in human studies indicate weak or no significance of *BDNF* SNPs in post-stroke neurorehabilitation. However, the potential role of SNPs in the identification of special groups of stroke patients in the rehabilitation process needs to be established in further studies.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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