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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