

Potential Therapeutic Effects of Neurotrophin on Acute and Chronic Urological Diseases

Abstract

Neurotrophin Nerve Growth Factor (NT) (NGF), Brain-Derived Neurotrophic Factor (BDNF), NT-3, and NT-4/5 are proteins that regulate proliferation, differentiation, and proliferation. Cell survival in the developing and mature Central Nervous System (CNS) by binding to two types of receptors, the Trk and p75 NTR receptors. Driven by the growth-promoting and survival-promoting effects of these proteins, many studies have attempted to use exogenous NT to prevent neuronal disease-associated cell death or promote regeneration of cells. The axon is broken due to mechanical trauma. . Indeed, such neurological effects have been demonstrated repeatedly in animal models of stroke, nerve damage, and neurodegenerative disease. However, limitations, including the short biological half-life and low blood-brain permeability of these proteins, preclude their conventional application to the treatment of human disease. In this report, we review the evidence for the neuroprotective effects of NT in animal models, highlight outstanding technical challenges, and discuss more recent attempts to exploit this potential. Neuroprotective effects of endogenous NT using small molecules and cell transplantation. Preclinical research over the past 3 decades has detailed the signaling pathways leading to neuronal cell death. In addition, numerous neuroprotective strategies have been developed to improve brain injury and preserve or restore neurological function in animal models of stroke, Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD) and other neurological disorders. These treatments include the use of neurotrophic factors, which are endogenous proteins required for proliferation, differentiation, and survival during development and neuroplasticity throughout life. Indeed, supplying the brain with exogenous neurotrophic factors, such as Neurotrophin Growth Factor (NGF) and Brain-Derived Neurotrophic Factor (BDNF), can 60-90% reduction in infarct volume with almost complete recovery stroke.

Keywords: Potential • Therapeutic • Neurotrophin • Mediators • Chronic Urological Diseases

Introduction

Despite this success in the laboratory, there are currently no widely effective treatments to reverse or halt the progression of these diseases in patients. Numerous theories have been advanced to explain the failure of neurotrophins in clinical trials, including limited access of peripherally administered neurotrophins to the Central Nervous System (CNS), the short biological half-lives of neurotrophins, the multimodal nature of disease progression, and the relatively short temporal window in which such treatments are effective (at least for acute neural insults such as stroke). For example, anti-stroke therapies must be instituted within 1-6 h of the event for significant efficacy, and few stroke patients can be treated within this timeframe. Thus, prophylactic strategies that upregulate endogenous protective capacity may be needed. In recent years, methods for delivery of neurotrophins across the Blood Brain Barrier (BBB) have advanced rapidly, as has the development of smaller Neurotrophin Receptor (Trk) agonists with significantly longer

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biological half-lives and BBB permeability than native neurotrophins like BDNF (serum half-life of 10 min). Perhaps the most difficult problem is that of delivering these molecules to appropriate targets, such as astrocyte cells, microglia cells, and vascular endothelial cells as well as neurons, while limiting exposure to undamaged brain tissue [1, 2].

Discussion

Despite these challenges, we may be about to develop neurotrophin receptor agonists and delivery systems that allow rapid brain penetration to protect vulnerable human neurons. Humans from cell death This goal may be supported by the fact that many distinct pathogenic processes involved in stroke, trauma, and neurodegenerative diseases seem to converge at some mutually reinforcing common endpoints: toxicity: excitability due to overstimulation of glutamate receptors, intracellular calcium overload, oxidative stress, mitochondrial failure, die programmed. Here, we review the evidence that neurotrophic factors can prevent neuronal cell death in acute and chronic encephalopathies, and highlight remaining issues for until now, it still prevents clinical application [3].

Numerous studies have demonstrated that neurotrophins, particularly BDNF, reduce infarct volume in rodents when administered before, during, and/or after experimental stroke. These studies have used various strategies to enhance the level of BDNF in brain. Intra ventricular injection of BDNF for 8 days at the beginning of 24 hours before permanent Middle Cerebral Artery Occlusion (MCAO) in Wistar rats was found to improve neurological deficits. Similarly, BDNF was delivered into the territory of the MCA by an osmotic minipump shortly after occlusion reduced cortical infarct volume by 37%. Infusion of recombinant BDNF into Sprague Dawley rat neocortex by an implanted osmotic minipump. 5-14 days before, during, and for 2 days following MCAO reduced infarct volume as measured 2 days after stroke without affecting cerebral blood flow [4].

Continuous infusion of BDNF immediately after 2h of right MCAO in rats reduced cortical and subcortical infarct volume as well as the number of ischemic twilight neurons expressing the pro apoptotic factor Bax, while increasing the number of anti-apoptotic Bcl-2-expressing neurons. The hippocampal CA1 pyramidal neurons were found to rescue by intra ventricular

injection of a viral vector encoding BDNF, as well as similar vectors encoding a neurotrophic factor derived from Glial Cells (GDNF), NGF, Insulin-Like Growth Factor-1 (IGF-1), or Vascular Endothelium Growth Factor (VEGF) 30 min after ischemia. Transplantation of fresh Bone Marrow (BM) with BDNF into the Ischemic Boundary Zone (IBZ) of the rat brain after MCAO facilitates rehabilitation of sensory and motor functions. The effect of BDNF on infarct size is synergistic with cerebral hypothermia, another well-described stroke treatment modality. Furthermore, glutamate levels in the early post-ischemic period were reduced to a greater extent with the combination of BDNF and hypothermia than with treatment alone. Choroidal Plexus (CP) transplantation, which is known to secrete multiple growth factors including BDNF, GDNF and NGF, reduces infarct volume in mice. Injection of neural progenitor cells into the hippocampus immediately after cerebral ischemia increases spatial memory performance in Morris Water Maze (MWM) 12-28 days after cerebral ischemia and decreases pain volume heart. Injection of Neural Progenitor Cells (NPCs) also reversed post-ischemic BDNF expression decline. Sodium orthovanadate protected cortical and hippocampal neurons after experimental subarachnoid hemorrhage by increasing BDNF and inhibiting inactivation of the BDNF receptor TrkB, effects that were abrogated by treatment with the TrkB inhibitor K252a [5, 6].

While most of these studies examined infarct formation or neurological recovery in the early post-ischemic period, a more recent study demonstrated that Neural Stem Cell Transplantation (NSC) BDNF overexpression improved neural function up to 12 weeks after MCAO. In addition to gray matter damage, BDNF may also reduce lacunar-type stroke injury in primates after occlusion of deep subcortical perforating arteries. Furthermore, BDNF expression is stimulated in the affected white matter following ischemic injury. In a similar study, BDNF did not reduce infarct volume, but still resulted in better functional recovery after ischemia compared with controls. In addition, this treatment reduces glial atresia, a process that can impede long-term recovery by preventing axonal regrowth [7].

In contrast, mice lacking one BDNF allele or both neurotrophin-4 alleles (nt4^{-/-}) experienced more severe cerebral infarction than their wild-type

counterparts. Transgenic mice overexpressing the predominant negative truncation variant of the BDNF receptor (TrkB.T1) specifically in cortical and hippocampal neurons showed greater damage in the cortex but not in the region (striated) that does not express the TrkB T1 transgene. Infusion of antisense BDNF oligonucleotides for 28 days after unilateral cortical ischemia suppressed BDNF mRNA expression and reversed the beneficial effects of motor rehabilitation on the dexterity post-traumatic recovery of BDNF. Contralateral limb, but did not affect the motor function of the ipsilateral limb [8].

Conclusion

While neurotrophins in general have been shown to have neuroprotective effects against stroke *in vitro*, several studies have shown a greater efficacy of a particular neurotrophin than others as well as a potential for superior protection against stroke dominant in specific regions of the brain. Transfusion of BDNF into the Substantia Nigra (SN) had no effect on the survival of nigrostriatal projection neurons after stroke and even exacerbated the death of some cholinergic and GABAergic neurons. In contrast, BDNF may be more effective than other neurostimulants in combating cortical stroke damage. Mesenchymal Stem Cells (MSCs) overexpressing BDNF or GDNF improved functional outcomes, as revealed by MRI one and two weeks after MCAO, unlike MSCs overexpressing neurotrophin NT-3. Thus, region-specific delivery may be required for full efficacy, which is a major obstacle to noninvasive peripheral delivery [9, 10].

Acknowledgement

None

Conflict of Interest

None

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