Review Article

Neurotrophic factors and their effects in the treatment of multiple sclerosis

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Abstract

Neurotrophins are small molecules of polypeptides, which include nerve growth factor (NGF) family, glial cell line–derived neurotrophic factor (GDNF) family ligands, and neuropoietic cytokines. These factors have an important role in neural regeneration, remyelination, and regulating the development of the peripheral and central nervous systems (PNS and CNS, respectively) by intracellular signaling through specific receptors. It has been suggested that the pathogenesis of human neurodegenerative disorders may be due to an alteration in the neurotrophic factors and their receptors. The use of neurotrophic factors as therapeutic agents is a novel strategy for restoring and maintaining neuronal function during neurodegenerative disorders such as multiple sclerosis. Innate and adaptive immune responses contribute to pathology of neurodegenerative disorders. Furthermore, autoimmune and mesenchymal stem cells, by the release of neurotrophic factors, have the ability to protect neuronal population and can efficiently suppress the formation of new lesions. So, these cells may be an alternative source for delivering neurotrophic factors into the CNS.

Key Words: Glial cell line–derived neurotrophic factor family ligand, multiple sclerosis, neuropoietic cytokines, nerve growth factor family

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INTRODUCTION

Growth factors are a group of proteins that are able to stimulate the growth of specific tissues and are expressed in a wide range of organisms including humans.[1] These proteins play an important role in regulating various cellular processes including cell proliferation, differentiation, and maturation. Several kinds of growth factors were originally isolated from the tissues of animals.[1] These substances include insulin-like growth factors, epidermal growth factors (EGFs), platelet-derived growth factors, and nerve growth factors (NGFs). Moreover, cytokines are another type of growth factors that are released by a cell to regulate the function of another cell.

Neurotrophic factors include three families of growth factors: NGF family (also known as neurotrophins or NTs), glial cell line–derived

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neurotrophic factor (GDNF) family ligands, and a heterogeneous group of molecules that belong to the cytokine family.[2] Many studies have shown that neurotrophic factors regulate various cellular processes including calcium homeostasis and blood flow to the brain. Furthermore, they inhibit free radical formation by increasing the levels of antioxidant enzymes.[3,4] Significant increase in the secretion of NT occurs in specific conditions such as antigen activation,[5] inflammatory infiltration during neurodegenerative diseases, and during demyelinating process. Each of the neurotrophic factors exerts its biological activities through specific Trk family of tyrosine protein kinases[6,7] and p75 receptor that is a member of the tumor necrosis factor receptor superfamily.[8]

THE NGF FAMILY OF GROWTH FACTORS

This family of growth factors includes NGF, brain-derived neurotrophic factor (BDNF), NT-3, NT-4 (NT-4/5 or NT-5),[9] and NT-6.[10] In their biologically active form, these growth factors exhibit about 50% amino acid identity. The genes responsible for coding of these NTs are highly expressed not only during the development of nervous system but also in the adult organism. In addition, these genes are highly expressed in a variety of tissues including hippocampus, cerebral cortex, and other parts of central nervous system (CNS). The Trk family of tyrosine protein kinases including TrkA, TrkB, TrkC, and a member of the tumor necrosis factor receptor superfamily (p75) are responsible for the physiological activities of NGF.[11]

Nerve growth factor

NGF is the first member of the NT family to be discovered in 1952 by Levi-Montalcini.[12] High concentrations of NGF were detected in the mouse submandibulary glands. Moreover, under normal conditions, NGF is distributed in high levels in regions of the CNS that are innervated by the magnocellular cholinergic neurons, such as hippocampus, and regions containing the cell bodies of these neurons.[13,14] The level of NGF in the nervous system and cerebrospinal fluid has been found to decrease with age.[15] NGFs that have a high specific activity on neuronal cells are classified as neurotrophic factors. Structurally, neurotrophic factors are polypeptides and are necessary for the development and maintenance of the vertebrate nervous system, neural regeneration, and remyelination.[2] NGF is essential for the growth, differentiation, regeneration, neurotransmitter function, development, and phenotypic maintenance of neurons in the peripheral nervous system (PNS), and for the functional accuracy of cholinergic neurons in the CNS.[13,14] The three-dimensional structure of NGF is made up of three subunits, including α, β, and γ subunits, which interact to constitute a high-molecular-weight 7S complex that is about 130–140 kDa in weight.[9,16] The β subunit is responsible for the biological activity of NGF, but the γ subunit is an EGF binding protein that has a role in the functions of the β subunit. In addition, the role of the α subunit is not clear. The 2.5S form of NGF has a molecular weight of 26 kDa and is organized by non-covalent interactions of two different subunits.[9,16]

NGF's biological activity is mediated by a specific receptor, including two receptors, TrkA and p75 neurotrophin receptor (NTR), whose signaling pathways can be synergic, antagonistic, or independent of each other.[17] The p75NTR is a transmembrane glycoprotein that is able to bind to all NTs with different affinities. This receptor has been shown to act as a co-receptor which increases the production of ceramides. Moreover, it activates gene transcription and acts as a mediator in the apoptotic process that is induced by NGF.[17,18] Trk receptors are composed of three parts including transmembrane, extracellular, and intracellular domains. The cytosolic domain of the Trk receptor is responsible for the tyrosine kinase activity and signal transduction.[17,19]

TrkA is a 140-kDa transmembrane protein that encoded by proto-oncogenes on chromosome 1. This receptor has a high affinity for NGF. So, the most function of NGF has done by TrkA receptors. After binding of NGF to a TrkA receptor, tyrosine kinase receptor autophosphorylation takes place leading to gene transduction in cells.[17,19] Some studies show that TrkA receptor has significant effects on the development of the nervous system. Thus, the lack of these receptors can lead to loss of neurons.[17,19]

NGF has been demonstrated to promote the biosynthesis of myelin component sheaths by myelin forming cells in CNS and PNS,[20,21] as well as differentiation of oligodendrocytes in experimental autoimmune encephalomyelitis (EAE).[22] *In vivo and in vitro* studies suggested that because of the beneficial effects of NGF, this factor may be a new good therapeutic tool for the treatment of neurodegenerative diseases.[23,24]

Brain-derived neurotrophic factor

BDNF is the second member of the NT family that was discovered in 1982 due to its trophic effects in dorsal root ganglion cells[25] and hippocampal and cortical neurons.[26] It is a 27-kDa basic protein and is one of the most potent factors that support neuronal survival, regulating neurotransmitter release and dendritic growth.[27] Traditionally, neurons,[28]

activated astrocytes present in inflamed areas of neurodegenerative diseases,[29,30] and immune cells[30] have been considered the major cellular sources of BDNF. Moreover, the expression of NTs and their respective receptors has also been detected in the lymphoid organs such as thymus and spleen.[31] In line with the above, *in vitro* studies show that activated T cells, B cells, and monocytes express bioactive BDNF in neurodegenerative lesions.[27,30] BDNF mRNA and protein levels have a more widespread distribution than NGF since they have been detected in several regions of CNS, such as neocortex, entorhinal cortex, some of the basal ganglia, hippocampus, thalamus, and the superior colliculus.[32] So, BDNF provides trophic support for developing cholinergic, dopaminergic, serotonergic, and gamma-aminobutyric acid (GABA) ergic neurons, and may also have a potential role in promoting the function and survival of other neuronal populations.[33]

BDNF binds with two different types of receptors: TrkB and p75NTR.[34] TrkB receptor exists in two isoforms including gp 145 TrkB or full length receptor and gp 95 TrkB receptor or truncated receptor that lacks the tyrosine kinase domain.[35] BDNF has the ability to act through different mechanisms including trophic mechanisms, neurotransmitter-like axodendritic communication, and by paracrine interactions between neighboring cells.[36] Several studies have shown the therapeutic application of BDNF that it is able to prevent neuronal degeneration after experimental axotomy and other forms of neuronal injury.[37-40]

NT-3 and NT-4

NT-3 is the third neurotrophic factor that was characterized in 1990 after NGF and BDNF.[41] In humans, this growth factor is encoded by the NT-3 gene and has distinct biological activity. The mature NT-3 has different characteristics from both NGF and BDNF, but displays a structural homology (57–58% amino acid identity) with them. NT-3 was detected in glia and neuronal populations and the level of NT-3 mRNA in the CNS is higher during fetal development than in adult brain.[41] This may indicate that NT-3 has a major role in neuronal survival and differentiation during development.[41,42] In addition, NT-3 induces profuse neurotic outgrowth from dorsal root ganglion explants, promotes outgrowth from both nodose ganglion and sympathetic ganglion,[43,44] prevents the death of facial motor neurons,[45] and is essential for the survival of sympathetic and sensory neurons.[46]

The cellular responses to NT-3 are mediated by three receptors that are placed on the surface of cells.[13,17] TrkC or physiologic receptor is a tyrosine kinase receptor that binds with the greatest affinity to NT-3 and is activated only by NT-3. In contrast to TrkC, TrkB mediates the effects of NT-3 and other neurotrophic factors such as BDNF and neurotrophin-4 (NTF4). Finally, the other NT-3 receptor is a low-affinity nerve growth factor receptor (LNGFR) that plays a somewhat less clear role.

NTF4, also known as neurotrophin-5 (NTF5), was described in 1991.[47] This protein is encoded by the *NTF4* gene and signals predominantly through the TrkB and p75NTR receptors. In addition, NTF4 can also interact with TrkA receptor, but with low affinity. A number of recent studies have proposed that NTF4 is able to promote the survival of corticospinal motor neurons in neonatal rats, prevent atrophy of rat rubrospinal neurons after cervical axotomy, and promote axonal regeneration.[48,49]

NGF FAMILY OF GROWTH FACTORS AND MULTIPLE SCLEROSIS

Multiple sclerosis (MS) has been explained as a chronic autoimmune demyelinating disease of CNS. Multifocal regions of inflammation into CNS are the primary cause of damage in MS.[50] However, a number of recent studies have proposed that BDNF is the first member of the NGF family that is expressed in areas of inflammation.[2,27,30]

Prescription of BDNF protein or *BDNF* gene can rescue neurons from degeneration and induce axonal outgrowth and regeneration.[51] Many of the identified NT factors such as BDNF can be produced by neurons. These cells are considered to be the major targets for neurotrophic interactions in the CNS. Therefore, neuronal BDNF might also contribute to endogenous neurotrophic support in MS lesions.[52] In the early stages of lesion development, T cells and other immune cells by the release high level of neurotrophic factors have the ability to protect neuronal population (by BDNF and NT3 secretion), enhance neuronal survival (by BDNF, NGF, NT3, and NT4 secretion), promote axon regeneration, and support remyelination (by NGF, GDNF, NT3, and BDNF secretion).[2,5,24]

Results of a study on MS patients showed that BDNF production by peripheral blood mononuclear cells is higher during relapse and in the recovery phase, compared to the values detected in the stable phase of the disease.[53] NT factors have a short half-life, and when delivered peripherally, their efficacy is reduced due to the blood–brain barrier. So, autoimmune cells may be an ideal vehicle for delivering neurotrophic factors to the CNS.[54] Studies on patients with MS have shown that endogenous

BDNF may play a beneficial role in the pathogenesis of lesion. Moreover, this factor and its receptor were found in the areas of inflammation in the CNS of MS patients.[30] The use of immunosuppressing drugs such as interferon-beta (IFNβ) for MS treatment can stimulate BDNF production.[55] In addition, some studies show that T cells derived from MS patients treated with glatiramer acetate (GA) produce high level of BDNF.[56,57] In various studies on EAE model of MS was found an increased level of BDNF and its receptor,[58-60] that activated astrocytes and immune cells which are present in the lesion areas of EAE, are key factors.[27] It was reported that stem cell treatment improved neurological functional recovery in mice model of MS by increasing the production of BDNF.[61-63] The outcomes of a study with BDNF heterozygous knockout mice proved that BDNF also regulates the number of oligodendrocyte progenitors and myelin protein synthesis.[64] These results support the idea that endogenous BDNF can play a neuroprotective role in the pathogenesis of MS lesion.

GDNF FAMILY LIGANDS

This family of growth factors consisting of GDNF, neurturin (NTN), persephin (PSPN), and artemin (ARTN) belong to the transforming growth factor (TGF)-β superfamily because they have seven cysteine residues in the same relative spacing. The amino acid sequence homology between the members of the GDNF family ligands (GFLs) is between 40 and 50%, but less than 20% with other members of the TGF-β superfamily.[65] GFLs exert their biological activities by activating the transmembrane RET tyrosine kinase by binding with high affinity to different glycosyl phosphatidylinositol (GPI)–linked GFRα receptors that include GFRα1, GFRα2, GFRα3, and GFRα4.[66] Mammalian GFRα4 is shorter than other GFRα receptors. Binding of ligand–GFRα complex to Ret triggers its homodimerization, phosphorylation, and intracellular signaling, which regulate cell survival, differentiation, proliferation, migration, chemotaxis, branching morphogenesis, neurites outgrowth, and synaptic plasticity.[67]

Glial cell line–derived neurotrophic factor

GDNF was characterized in 1993 as the first member of the GFLs that promotes the survival of many types of neurons such as dopaminergic and motor neurons.[68] In addition, GDNF was able to prevent apoptosis of motor neurons (almost 100 times more efficient survival factor for spinal motor neurons than the NT) as well as regenerate sensory axons after spinal cord injury.[69] GDNF has several functions outside the nervous system. For example, GDNF signaling is an attractive target for the kidney development[65] and spermatogenesis.[70] In humans, this neurotrophic factor is encoded by the *GDNF* gene. *GDNF* gene encodes a highly conserved neurotrophic factor that is processed and secreted as a mature protein. Structurally, GDNF is a glycosylated and disulfide bonded homodimer and the molecular weight is approximately 33–45 kDa.[68] GDNF signaling is mediated via a multicomponent receptor complex consisting of two-component receptor: GFRα1 and a transmembrane RET receptor tyrosine. In addition, GDNF crosstalk is weak with other GFRα receptors and can trigger Ret-independent signaling through GFRα1.[71]

Neurturin

NTN is the second member of GFLs that was originally purified and cloned by virtue of its ability to promote the survival of sensorimotor, sympathetic, parasympathetic, and enteric neurons.[72] NTN shares a 40% homology with GDNF. In addition, NTN and GDNF use the same receptors and signaling pathways. Endogenously, NTN binds to a heterotetrameric complex of c-Ket tyrosine kinase receptor and glycosyl phosphatidylinositol–linked proteins, GFRα-2 (GDNFR-α) and GFRα-2, which are high expressed in the adult substantia nigra but not in the adult striatum.[73] *In vitro* and *in vivo* studies show that NTN promotes the survival of developing dopaminergic neurons.[74] One hypothesis for this event may be that NTN mRNA is expressed in the ventral midbrain and striatum.[74]

It has been illustrated in a study that immune cells produce NTN and can potentially improve the function and delay the rate of degeneration of neurons in neurodegenerative diseases.[75] Moreover, NTN can stimulate DNA synthesis in spermatogonia.[76]

Artemin

ARTN is the most recent member of GFLs that is able to promote the survival of peripheral ganglia and dopaminergic neurons[77] and regulate the differentiation of autonomic, sensorimotor, and enteric neurons in CNS and PNS.[72]

Similar to other members of GDNF family, such as NTN and PSPN, ARTN is also expressed in the developing kidney, but is less important than GDNF. Moreover, an *in vitro* study shows that ARTN and PSPN are capable of inducing ureteric branching.[78] ARTN exerts its biological action by a specific receptor including GFRα3. Moreover, it has the ability to crosstalk weakly with other GFRα receptors.[79]

Persephin

PSPN is the fourth member of well-characterized GFLs that could be a good alternative to GDNF

and NTN because it lacks affinity to the extracellular matrix and has better pharmacokinetics.[80] Although PSPN is apparently inactive on peripheral neurons, it has prominent neurotrophic activities, in particular for dopaminergic neurons, and can promote the survival and morphological differentiation of basal forebrain cholinergic neurons, motoneurons, and dopaminergic neurons.[81] PSPN is widely expressed in the embryonic and adult brain,[78] but its expression is low in many human tissues including the adrenal gland, newborn spleen, muscles, and testis.[82-84] An *in vitro* study has reported that high levels of PSPN increased the number of ureteric buds in kidney explants.[78] Moreover, it could protect the cortical neurons from hypoxia-induced cell death and motor neurons from excitotoxic neuronal death.[85,86] PSPN exert functions through GFRα4 that is smaller than other GFRα receptors. In addition, the ability of PSPN to interact with any co-receptor other than GFRα4 has never been shown before.[65]

GDNF FAMILY LIGANDS AND MS

GDNF and NTN are the two main members of the GFLs that have been commonly explored for use in the therapy of neurodegenerative diseases.

Studies show that these factors can rescue dopamine neurons in the animal models of Parkinson's disease, as well as motor neurons.[87,88] Moreover, GDNF can prevent motor neuron degeneration in animal models of amyotrophic lateral sclerosis (ALS), and also, is a highly potent trophic factor for spinal motor neurons[88,89] and central noradrenergic neurons.[90]

Immune cells and their products are involved in the pathogenesis of MS and are found in the CNS of MS patients. A study demonstrates that different immune cell subsets express the GDNF family ligand and different isoforms of the GFL receptors.[31] So, these data give great hope that GDNF family ligands may be effective as a therapeutic agent in the treatment of several neurodegenerative diseases such as MS.

NEUROPOIETIC CYTOKINES

Neuropoietic cytokines are small proteins that well known for their role in immune response and play a much greater role in diverse aspects of physiology. This group of growth factors consisting of ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor (LIF)[2] play an important role in the differentiation of astrocytes from neural progenitors and have differential effects on adult neurogenesis. Interestingly, it should be considered that any cell that responds to CNTF could also respond to LIF.[91]

Ciliary neurotrophic factor

CNTF is the first neurotrophic factor that has ability to support the survival of motor neurons and parasympathetic neurons from the chick ciliary ganglion.[92] In addition, CNTF can also promote cholinergic and astrocytic differentiation and enhance the survival of sensorimotor, preganglionic sympathetic, and hippocampal neurons.[93-95] Unlike the other members of the neuropoietic cytokines such as LIF, high concentrations of CNTF were detected in intact nerves.[96] The cellular responses to CNTF are mediated by a multimeric receptor complex that consists of two elements.[97] The specific binding subunit that anchors to the plasma membrane by gp13o (gp13o is a glycosyl phosphatidylinositol linkage) is found in all neuropoietic cytokine receptors. CNTF receptor complex apparently also includes signaling subunits that consist of LIFR–gp130 heterodimers.[98,99] The cytoplasmic domains of these molecules are responsible for the intracellular activation of the Janus-activated kinase–signal transducer and activator of transcription (JAK–STAT) and the mitogen-activated protein kinase (MAPK) pathways.[98,99]

Leukemia inhibitory factor

LIF is well known due to its biological role in augmenting totipotent embryonic stem cell (ESC) self-renewal by activation of the JAK–STAT pathway.[100] LIF has no effect on humans,[101] but is needed for the long-term growth of embryonic human neural stem cells (NSCs).[102,103] In addition, LIF may promote neurogenesis in the adult human olfactory bulb.[104,105] So, it has the ability to alter human NSC differentiation. An *in vitro* study shows that LIF signaling has an important role in promoting astrocyte-like cell formation,[106,107] myelinization of Schwann-like cells,[108] and stimulating the self-renewal and maintenance of adult NSCs. LIF signaling is mediated by binding to heterodimers of LIF receptor (LIFR) and gp130.[109] As noted above, these heterodimers can also associate with other receptor subunits to bind with other members of neuropoietic cytokines.

Neuropoietic cytokines and MS

Based on the aforementioned findings, CNTF and LIF might represent novel therapeutic agents for neurodegenerative disorders such as MS.[110] Some clinical studies report that an up-regulation of CNTF and LIF occurs in patients with MS,[111,112] as well as in EAE.[113] A recent report demonstrated that in a CNTF-knockout model of EAE or in the presence of anti-LIF antibodies, there is enhanced oligodendrocyte death that is followed by increased demyelination

and a significant increase in the severity of the clinical symptoms.[113] The exact mechanism by which exogenous LIF is able to enhance oligodendrocyte survival and inhibits oligodendrocyte apoptosis is not clear. So, the endogenous protective mechanism versus axonal injury and oligodendrocyte apoptosis depends on the up-regulation of LIF and CNTF in MS.[111,112] Previous studies suggest that although mutations in *LIF* and *CNTF* genes do not seem to be associated with the development of MS, patients with a null mutation in *CNTF* exhibit increased severity of the disease.[114]

CNTF stimulates myelination[115] process directly with increased proliferation of oligodendrocyte precursors that is signaled by MAP kinase. In addition, CNTF enhances oligodendrocyte precursor survival that is mediated by rapid tyrosine phosphorylation of JAK–STAT.[116] So, recent studies revealed that binding of CNTF to mature oligodendrocytes activates a different combination of JAK and STAT proteins, which enhances the coordinate expression of the subset of myelin-specific genes that are necessary for remyelination.[116] However, cytokines and the ability of these factors in differentiating oligodendrocyte precursor could be of therapeutic value of these factors in the treatment of MS. Salehi *et al.* showed that CNTF increases myelin oligodendrocyte glycoprotein (MOG) expression and may be important in the pathophysiology of MS. Moreover, CNTF may play a role in the process of remyelination by inducing MOG expression.[117] It is reported that CNTF acts on oligodendrocytes' maturation, and this effect is mediated through the 130-kDa glycoprotein receptor via Janus kinase pathway.[118] Stem cells via CNTF secretion are able reduce demyelination and induce clinical recovery in EAE model of MS through exerting their immunoregulatory activity, inhibiting inflammation, reducing demyelination, and stimulating oligodendrogenesis.[119,120]

CONCLUSION

Here, we explained various neurotrophic factors, their related receptors, and their clinical applications in MS. These factors are small proteins that provide trophic events in neural cells. Moreover, NTFs play an important role in the developing and mature nervous system. Neurotrophic factors act by binding to the specific cell surface receptors that signal the neuron to survive. Stem cells and immune cells are cellular sources of neurotrophic factors. So, these cells, through neurotrophic factor secretion, may have an important role in the treatment of neurodegenerative diseases such as MS.

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