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Neurotrophic Factors and Their Potential Applications in Tissue Regeneration

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Abstract

Neurotrophic factors are growth factors that can nourish neurons and promote neuron survival and regeneration. They have been studied as potential drug candidates for treating neurodegenerative diseases. Since their identification, there are more and more evidences to indicate that neurotrophic factors are also expressed in non-neuronal tissues and regulate the survival, anti-inflammation, proliferation and differentiation in these tissues. This mini review summarizes the characteristics of the neurotrophic factors and their potential clinical applications in the regeneration of neuronal and non-neuronal tissues.

Keywords

Neurotrophic factor; Tissue regeneration

Introduction

Neurotrophic factors are growth factors that can promote the survival and regeneration of the neurons. They are sometimes referred as neurotrophins (NTs). The nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), other NTs all belong to the group. The glial cell derived neurotrophic factors (GDNF) family and neuropoietic cytokines, such as ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor, are also considered members of neurotrophic factor family (Kerschensteiner et al. 2003; Saarma 2000; Stolp 2013).

The neurotrophic factors have long been extensively investigated for their roles in supporting the survival, proliferation and maturation of certain neurons. They have been shown to improve neural regeneration in neurodegerative diseases, such as Alzheimer's (Heese et al. 2006–2007), Parkinson's (de Munter et al. 2014) and Huntington's disease (Rosser and Svendsen 2014). Recent researches have indicated that neurotrophic factors can be found in the tissue-specific adult stem cell niche and promote tissue regeneration outside

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of the nervous system. These works suggest that neurotrophic factors can serve as potential therapeutic candidates in adult tissue regeneration.

Nerve Growth Factor

The first neurotrophic factor identified is the NGF. It was originally found to enhance the growth of sensory and sympathetic neurons in the chicken embryo (Levi-Montalcini and Hamburger 1951). NGF is enriched in the brain, with the highest level in the hippocampus (Shelton and Reichardt 1986). NGF elevation is related to the nervous system development, and it is found to reduce the degeneration of the cholinergic neurons (Hefti and Will 1987; Korsching et al. 1986).

NGF knockout mice are born alive, but are smaller than the wild type littermates. Their lifespan is less than 4 weeks postnatal. There is a marked reduction in the number of lumbar dorsal root ganglia as well as cholinergic neurons in the knockout mice, which exhibit severe impairment in spatial learning and motor coordination (Ruberti et al. 2000). The NGF receptor p75 and tyrosine kinase A receptor (TrkA) are critical in mediating the NGF effect. Reduction of either receptors leads to severe loss of sympathetic neurons and cholinergic neurons in mice, which is similar to reducing NGF expression (Lee et al. 1992; Smeyne et al. 1994).

Transplanting immortalized NGF secreting neural progenitors into the rat brain significantly enhance the spatial memory, as verified by the Morris water maze test 7 weeks after the transplantation (Martinez-Serrano et al. 1996). Recombinant NGF can reduce the death of sympathetic ganglionic neurons and cholinergic neurons in mice, as well as in humans. Recombinant human NGF has been introduced into the brain of patients with Alzheimer's disease via either viral mediated infection or implantable devices on clinical trials. There has not been any sign of significant toxicity and patients showed improved cognition, reduced death of cholinergic neurons, and less brain shrinkage (Aloe et al. 2012; Eriksdotter-Jonhagen et al. 2012; Ferreira et al. 2015; Mandel 2010; Petty et al. 1994; Sofroniew et al. 2001; Tuszynski et al. 2005). NGF delivery or the p75 receptor overexpression has been shown to improve survival and neurite growth of basal ganglia cells, and reduce the bradykinesia in patients (Olson et al. 1991) or animal (Pezzoli et al. 1988) with Parkinson's disease. It can also stimulate cerebral perfusion and the neurogenesis in hypoxic–ischemic brain injury in infants (Chiaretti et al. 2008). The molecular mechanism downstream of NGF may be related to inhibition of apoptosis (Nguyen et al. 2009) by down regulating the Bcl-2 pathway (Lu et al. 2013), and promoting the survival (Ji et al. 2014), proliferation (Moscatelli et al. 2009) and differentiation of the neural stem cells by upregulating the AKT and MAPK pathway (Yuan et al. 2013).

Besides the nervous system, NGF has been noted to be highly expressed in the hematopoietic stem cells (Durand et al. 2007). NGF increases the colony formation unit of the granulocytes and monocytes in a dose-dependent manner both in cell culture (Matsuda et al. 1988) and in injured mice model (Huang and Zhu 2008; Huang et al. 2008). NGF over expression in the bone marrow stem cells (BMSCs) has a stronger rescue effect on rat models with vascular dementia by increasing BMSCs proliferation (Wang et al. 2014a).

NGF and its receptor TrkA are also highly expressed in the rat neonatal cardiac myocytes (Caporali et al. 2008) as well as in the adult human myocardium (Meloni et al. 2010). Blocking NGF signal pathway increases the apoptosis of the cardiomyocyte, while NGF gene transfer facilitates cardiomyocyte survival and regeneration in mice by inhibiting apoptosis (Caporali et al. 2008; Lavasani et al. 2006; Mahmoud et al. 2015; Meloni et al. 2010).

NGF and its receptor TrkA, co-receptor p75 are found highly expressed in the rat pancreas during both embryonic and adult stage (Miralles et al. 1998; Oberg-Welsh and Welsh 1996). Lesion of pancreas significantly increases the level of NGF in both islet and the exocrine cells (Larrieta et al. 2006; Teitelman et al. 1998). This might be related to the endogenous mechanism to repair the damage. NGF treatment significantly improves the viability of the isolated mice pancreatic islets (Hata et al. 2015; Miao et al. 2006). Interestingly, NGF treatment also increases insulin secretion in cultured islet (Rosenbaum et al. 2001), as well as in transplanted islet (Miao et al. 2005). Injection of 6 μg NGF can restore the glucose tolerance in male Balb/c mice to the level that is comparable to that of islet transplanted mice (Miao et al. 2005), or the non-diabetic control mice (Hussey et al. 2010).

In human salivary glands duct, NGF and its receptors are also found expressed at high levels. The signals overlap with stem cell marker CD49f and Thy-1 (Sato et al. 2007), indicating that NGF may potentially involved regulating in salivary gland stem cell activities.

The evidences show that NGF pathway is important for the development of sympathetic and cholinergic neurons. It also improves survival and recovery of neurons post damage, most likely through inhibiting apoptosis. High expression of NGF can be found in stem cells in several non-neuronal tissues, where it also promotes the tissue regeneration. Besides inhibiting apoptosis, NGF also enhances proliferation and functional recovery of the non-neuronal tissues, the mechanism of which still needs further investigation.

Brain Derived Neurotrophic Factor

Brain derived neurotrophic factor (BDNF) was first purified from the pig brain as a growth factor that can increase the survival of cultured embryonic chicken spinal sensory neurons (Barde et al. 1982). Later, BDNF was found to be a pro-survival factor for many different neurons, including sensory neurons in the dorsal root ganglia (Acheson et al. 1995), hippocampal neurons, and cortical neurons (Huang and Reichardt 2001). BDNF has primarily an excitatory effect at the synapse by enhancing the excitatory postsynaptic potential (Kang and Schuman 1995; Kang et al. 1997; Patterson et al. 1996) and reducing the inhibitory postsynaptic potential (Marty et al. 1996). Because of its high expression in the hippocampus (Hall et al. 2000) and its role in long-term potential, BDNF is thought to play an important role in learning and memory. The signal is mainly through the TrkB pathway (Howells et al. 2000; Kang and Schuman 1995; Kang et al. 1997; Minichiello 2009; Patterson et al. 1996; Yamada and Nabeshima 2003). By activating the receptor TrkB (Drake et al. 1999), BDNF can inhibit the phosphorylation of the GABA receptor (Jovanovic et al. 2004), thereby reducing the conductance of these receptors (Rivera et al.

2002). The MAPK pathway has also been shown to be downstream of the TrkB activation, and mediates neuronal survival and differentiation (Criscuolo et al. 2015; Liu et al. 2013). BDNF also activates PI3 K pathway and upregulate the phosphorylation of the transcription factor CREB (cAMP response element-binding protein), which inhibits apoptosis and prevents neurodegeneration (Chen et al. 2015; Jain et al. 2013).

Most of BDNF knockout mice die within a couple of days. Some survive for a few weeks after birth. There is a reduction of sensory neurons, but not motor neurons (Conover et al. 1995; Erickson et al. 1996; Ernfors et al. 1994a; Jones et al. 1994). The long-term potential is impaired in BDNF knockout mice (Frerking et al. 1998; Korte et al. 1995; Wardle and Poo 2003), which can be rescued by adding recombinant BDNF (Korte et al. 1996; Patterson et al. 1996). Heterozygous BDNF mice are generally smaller than normal mice, and characterized by defects in movement, poor coordination, and obesity (Kernie et al. 2000; Lyons et al. 1999). Their spacial learning capability is reduced (Linnarsson et al. 1997). Reduction of BDNF expression has been associated with several neurodegenerative diseases including Parkinson's (Howells et al. 2000), Alzheimer's (Ferrer et al. 1999; Phillips et al. 1991) and more recently Huntington's disease (Zuccato et al. 2001, 2003). A drastic drop of BDNF expression in the brain has become a feature of the Hunt-ington's disease (Zuccato et al. 2008). The underlying mechanism may be related to lower transcription of the protein in the Huntington's patients (Zuccato et al. 2001). These evidences indicate that BDNF is critical in neuron development and prevents the sensory neuron from degeneration.

Co-injection of BDNF and CNTF subcutaneously improves regeneration of motor neurons (Mitsumoto et al. 1994). Virus mediated delivery of BDNF into the hippocampal neurons in normal rats (Jeon et al. 2015) or the striatum of quinolinic acid-induced Huntington rats (Kells et al. 2004) significantly improves neuronal regeneration. One time injection of 50 μg BDNF could successfully improve the morphology and rescue the electrophysiological properties of injured optic nerve in rabbits. BDNF was also shown to enhance regeneration after injury of the cervical spinal cord (Gransee et al. 2015), cavernous sinus nerve of the penis (Kim et al. 2012), sciatic nerve (Dadon-Nachum et al. 2012), optic nerve (Zhang et al. 2015), and olfactory epithelium (Frontera et al. 2015; Uranagase et al. 2012) in animal models.

Because the blood–brain barrier filters many substances from the plasma, including the neurotrophic factors, substances that regulate BDNF level are being tested in patients with neurodegenerative diseases. Citalopram (Celexa), which is a selective serotonin reuptake inhibitor used as an antidepressant, can efficiently increase BDNF level in the plasma (Goekint et al. 2011; Haghighi et al. 2013; Ladea and Bran 2013) and has been shown to enhance neuronal regeneration in a murine ischemic stroke model (Espinera et al. 2013). Ampakines, recently used as a compound to enhance learning and memory, also increases BDNF level (Lauterborn et al. 2009). Another substance that can increase BDNF level and potentially be used to treat Huntington's disease is Cystamine, which is a transglutaminase inhibitor (Borrell-Pages et al. 2006).

Besides the neuronal tissues, BDNF can be secreted by mesenchymal stem cells, such as BMSCs. There are many reports on the ability of BDNF to induce differentiation of BMSCs

to neuron like cells, as verified by electrophysiological properties and neuronal specific markers (Han et al. 2015; Long et al. 2005; Sanchez-Ramos et al. 2000; Zhao et al. 2004). Transplantation of adipose tissue derived marrow stem cells significantly increases BDNF level in the brain, and is capable of reducing neuron damage in animal models (Berg et al. 2015; Han et al. 2014; Schwerk et al. 2015). Moreover, transplantation of marrow stem cells that overexpress BDNF or GDNF significantly improves the limb placement behavior in focal cerebral ischemia rats (Kurozumi et al. 2005). BDNF also enhances the proliferation and vascularization of the hematopoietic stem cells (Shmelkov et al. 2005).

There are not many reports of BDNF's function outside of the nervous system and the mesenchymal stem cells. However, when the BDNF signaling pathway is over activated, it promotes the growth of malignant gliomas (Lawn et al. 2015), breast cancer (Yin et al. 2015) and lung cancer (Sinkevicius et al. 2014), indicating BDNF can enhance the cell proliferation in certain types of cancer cells. Whether the effect is through cancer stem cell would require more evidences.

Other Neurotrophins

Neurotrophin (NT)-3 was the third neurotrophic factors identified based on the sequence identities to NGF and BDNF (Hohn et al. 1990; Maisonpierre et al. 1990). Another neurotrophic factor being investigated is NT-4 (Ip et al. 1992), also known as NT-5 in mice (Berkemeier et al. 1991). Similar to NGF and BDNF, NTs are required for the survival of sensory neurons isolated from the rat dorsal root ganglia, and promote the proliferation of the sensory neurons (Memberg and Hall 1995). NTs also promote chicken motor neuron survival (Becker et al. 1998). Similar to NGF and BDNF, NTs bind to the neurotrophin receptor p75 at low affinity. The binding between NGF, BDNF, NTs and the receptor tyrosine kinase are stronger and more specific. As mentioned above, NGF specifically binds to TrkA while BDNF preferentially binds to TrkB. NT-3 preferentially binds to TrkC, but can also activate the TrkA and TrkB, while NT-4/5 preferentially binds to TrkB (Berkemeier et al. 1991; Klein et al. 1992; Reichardt 2006). The PI3K/ AKT, MEK/ERK are reported to be downstream of the neurotrophin activation (Skaper 2012). During cerebral cortex development, NT-3 increases BrdU incorporation and the differentiation of phenotype specific neurons in the laminar formation through the MAPK pathway (Ohtsuka et al. 2013).

Similar to other neurotrophic factors, NT-3 is important in embryonic neuron development. NT-3 knockout mice die within a couple of weeks after birth. Peripheral sensory and sympathetic neurons are diminished (Ernfors et al. 1994b; Fox et al. 2013; Gacek and Khetarpal 1998), and motor neuron apoptosis increases (Usui et al. 2012; Woolley et al. 2005). NT-3 mutation leads to reduced number of muscle sensory neuron (Tessarollo et al. 1994) and fewer myenteric and submucosal neuron plexus in the enteric nervous system (Chalazonitis 2004). NT-4 knockout mice are viable but showed reduction in sensory neurons and long term memory (Liu et al. 1995; Smith et al. 2003; Xie et al. 2000).

Neurotrophins are required to maintain the neural stem cell niche. In the mouse sub-ependymal region, NT-3 can be secreted by the ependymal endothelia. It can slow down the cell proliferation through activation of the TrkC pathway, which induces the synthesis of the

nitric oxide and promotes quiescence of the neural stem cells (Delgado et al. 2014). Virus-mediated overexpression or sustained delivery through conduit of NT-3 improves neuron stem cell survival, proliferation and differentiation in vitro (Lu et al. 2011; Tang et al. 2014; Zhu et al. 2012), as well as in the injured spinal cord of animal (Elliott Donaghue et al. 2015). NT-3 has a distinct effect in the cochlear nerve terminals and the inner hair cells by promoting synaptic regeneration post noise damage (Wan et al. 2014).

NT-3 is showed to facilitate BMSC survival and neuronal differentiation. Bone marrow cells co-cultured on poly lactic-acid-*co*-glycolic acid with NT-3 (Zhang et al. 2012), or with pharmacologically active microcarriers releasing NT-3 (Daviaud et al. 2015), have a significant increase of survival and neuronal differentiation. Moreover, transplantation of NT-3 overexpressed fibroblast into injured spinal cord improves the motor neuron response to electric stimuli (Arvanian et al. 2003). Overexpression of NT-3 also increases the survival and differentiation of BMSCs into neuron like cells (Dong et al. 2014; Gong et al. 2015; Yang et al. 2014). NT-3 transfected BMSCs or fibroblasts show stronger motor neuron axon regeneration, synaptic regeneration and remyelination after spinal cord injury in rodents (Arvanian et al. 2003; Liu et al. 2015; Thomas et al. 2014; Wang et al. 2014c). NT-3 and its receptor TrkC are found in the ovarian follicles and play a role in the follicle transition (Nilsson et al. 2009), indicating that NT-3 promotes germ cell differentiation.

NT-4/5 is less well studied compared to other neurotrophic factors. It has overlapping effect as BDNF in taste sensory neuron development (Huang and Krimm 2014). It also has synergistic effect with GDNF in promoting neuron survival in cultured embryonic rat brain slice (Meyer et al. 2001). NT-4/5 is reported to promote the oligodendrocyte precursors proliferation in culture (Scarisbrick et al. 2000). It also increases embryonic neural stem cell differentiation through inhibiting STAT3 phosphorylation (Shen et al. 2010). Overexpression of NT-4/5 protects the cochlear hair cell from by kanamycin toxicity and improves auditory function in guinea pig (Zheng et al. 2013). NT-4/5 and BDNF are found enriched in the umbilical cord blood, and may play a role in the hematopoietic stem cell proliferation (Fan et al. 2005).

GDNF Family

GDNF belongs to the GDNF family of ligands (GFL), which also includes neuturin (NRTN), artemin (ARTN) and persephin (PSPN). GFL binds to the GDNF family receptors (GFR). GDNF preferentially binds GFRα1, NRTN preferentially binds GFRα2, ARTN binds GFRα3, and PSPN binds GFRα4 (Airaksinen and Saarma 2002; Sariola and Saarma 2003).

GDNF is the most well-studied member of the family. GDNF was first purified as a potent neurotrophic factor that can enhance the survival of the dopaminergic neurons in the midbrain (Lin et al. 1993). It is reported to improve dopaminergic and enteric neuron survival, proliferation and migration (Airaksinen and Saarma 2002; Granholm et al. 2000; Sariola and Saarma 2003). GDNF preferentially binds to the GFRα1, which then activates the receptor tyrosine kinase RET or the neural cell adhesion molecule (Zhou et al. 2003). The PI3K/AKT, MEK/ERK, SRC/c-Jun kinase, FYN/focal adhesion kinase pathways have

all been reported to be downstream of the GDNF signal (Charoy et al. 2012; Euteneuer et al. 2013; McAlhany et al. 2000; Oatley et al. 2007; Paratcha et al. 2003; Tang et al. 2002; Villegas et al. 2006).

GDNF knockout mice die soon after birth. There is renal agenesis due to undeveloped ureteric bud, early sequester of kidney development and complete absence of the enteric neurons (Costantini 2010; Pichel et al. 1996; Sanchez et al. 1996). The RET signaling pathway and the ETS transcription factors ETV4 and ETV5 have been demonstrated to be directly involved in the embryonic kidney development downstream of GDNF stimulation (Jain et al. 2006; Lu et al. 2009; Tang et al. 2002).

Recombinant human GDNF promotes the survival of the dopaminergic neurons in the midbrain, and has been tested for the treatment of Parkinson's disease in clinical trials (Lin et al. 1993). Amgen conducted a phase I clinical trial of monthly intraputamental injection of 15 μg/day recombinant human GDNF (Liatermin) in 34 Parkinson's patients. Based on the Unified Parkinson Disease Rating Scale and motor tests, it is inconclusive that GDNF application shows a clinical benefit in patients within 6 months of treatment (Lang et al. 2006). Another phase I trial was performed in the United Kingdom. GDNF (14.4–28.8 μg/day) was delivered to five patients by a pump imbedded in the abdomen and continuously infused into the putamen through a catheter for 6 months. There was fewer side effects compared to the direct injection route, and there was a substantial improvement in symptoms and Dopa influx up to 1 year of treatment in some patients (Gill et al. 2003; Love et al. 2005). Another Phase I trial conducted at the University of Kentucky also showed significant improvement of bilateral motor balance and gait in ten patients, who received unilateral intraputaminal infusion of up to 30 μg/day GDNF for 8 weeks through a catheter (Slevin et al. 2005). Several preclinical studies performed on rodents and primates indicated that delivery of sufficient GDNF to the lesion improved neuronal regeneration and reduces the symptoms (Bartus et al. 2011; Gasmi et al. 2007; Richardson et al. 2011). In addition, over expression of GNDF through virus (Kells et al. 2004) or stable cell line (Pineda et al. 2007) has been shown to improve the neuronal survival in the animal models of Huntington's disease.

Outside of the nervous system and renal development, GDNF maintains the sperm stem cell pool by promoting spermatogonial self-renewal. It also regulates spermatogenesis and sperm differentiation (Chen et al. 2005; Meng et al. 2000). Similar to the ureteric bud generation pathway, RET signal is essential in mediating spermatogenesis (Jijiwa et al. 2008; Oatley et al. 2007). GDNF also protects the salivary gland from radiation induced damage by promoting the salivary gland stem cell regeneration and proliferation (Xiao et al. 2014). Human mesenchymal stem cells also release GDNF, which in turn facilitates the motor neuron regeneration in rats (Krakora et al. 2013).

GDNF family member NRTN induces dopaminergic neuron regeneration (Liu et al. 2009; Vourc'h et al. 2005). NRTN is also reported to support enteric neuron survival and proliferation through RET pathway (Heuckeroth et al. 1998). It is also involved in mouse embryonic salivary gland development and regeneration after radiation damage (Hai et al. 2014; Knox et al. 2013).

Another GDNF family member PSPN has very similar function as GDNF, such as supporting motor neuron survival (Milbrandt et al. 1998). It is known to increase the survival of both dopaminergic neurons (Akerud et al. 2002; Roussa et al. 2008) and mesenchymal stem cells (Yin et al. 2014).

GDNF family members and their signaling pathways have been associated with cancer cell growth, invasion, metastasis and resistance to therapy (Poteriaev and Saarma 2001). Specifically they have been linked to the growth of neuroblastoma (Komminoth et al. 1996), breast cancer (Banerjee et al. 2012; Ding et al. 2014), small cell lung cancer (Rudin et al. 2014), thyroid cancer (Hong et al. 2008; Wells and Santoro 2009), pancreatic cancer (Donahue and Hines 2009) and testicular cancer (Sariola and Meng 2003). GDNF promotes perineural invasion and metastasis of brain tumor (Ilhan-Mutlu et al. 2013), head and neck squamous cell carcinoma (Roh et al. 2015), glioma (Shabtay-Orbach et al. 2014), pancreatic cancer (He et al. 2014; Wang et al. 2014b) and colon cancer (Huang et al. 2014). GDNF family members also increase resistance to the chemotherapy in the prostate (Huber et al. 2015) and breast cancer (Ding et al. 2014; Morandi et al. 2013), while reduction of GDNF level decreased metastasis of mammary gland cancer and related pain in the bone of rat (Meng et al. 2015). These research works suggest that GDNF level is also important in regulating the cancer cell proliferation in multiple non-neuronal tissues.

Conclusion

Here, we reviewed different neurotrophic factors and their potential clinical applications in tissue regeneration. The neurotrophic factors not only nourish neurons during development, they are also critical in regulating survival, proliferation and differentiation of neuronal and non-neuronal cells. Some are also reported to be involved in abnormal cell behavior that leads to neoplasms. Further investigation on the role of these neurotrophic factors and the mechanism of actions will help to exploit their function for future functional restoration of organs in patients.

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