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NERVE GROWTH FACTOR: AN IMPORTANT TARGET FOR NEUROPROTECTION

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ABSTRACT

Protection of neurons i.e. Neuroprotection is the only and important way to stop neurodegeneration. Neurodegeneration is slowly, progressive and irreversible mechanism if remained untreated. Now-a-days there are many strategies are present to overcome with the problem of neurodegeneration. Nerve growth factor is one of the important factor to target neuroprotection. Nerve growth factor is neurotrophin which helps neurons for their survival and differentitaion. NGF,BDNF,GDNF,NT-3,NT-4 seems to play crucial role in diseases like Parkinson's and Hypoxic ischemic brain injury. Therefore in this review, wesummarize recent literature focusing on neuroprotection through various nerve growth factor.

KEYWORDS: Neurodegeration, Neuroprotection, Prakinsons Disease, HIBI, NGF, GDNF.

INTRODUCTION NEURODEGENRATION

Neuro means the neurons/nerve cells & degeneration means a mechanism of stopped its functioning or losing its structure. Therefor neurodegeneration collectively summarized as loss/ stoppage of functioning of neurons. Neurodegeneration is very slow and progressive disease and also it is irreversible if unnoticed. The family of neurodegeneration includes diseases as members of family viz. Alzimers disease, Parkinson's disease, Huntingtondisease, and amyotrophic lateral Sclerosis.

Asneurodegeneration is slowly and progressive, age is most important factor for neurodegeration, but apart from age there are certain environmental factors which may

termed as causative agents for neurodegeneration like lead exposure air pollution, pesticides, wrong food habitat, physicalinactivity, stress etc.

NEUROPROTECTION

Neuroprotection means protection for neurons. Neuroprotection refers to the relative preservation of neuronal structure and/or function. In the case of an ongoing insult (a neurodegenerative insult) the relative preservation of neuronal integrity implies a reduction in the rate of neuronal loss over time, which can be expressed as a differential equation.[1] It is a widely explored treatment option for many central nervous system (CNS) disorders including neurodegenerative diseases, stroke, traumatic brain injury, spinal cord injury, and acute management of neurotoxin consumption (i.e. methamphetamine overdoses). Neuroprotection aims to prevent or slow disease progression and secondary injuries by halting or at least slowing the loss of neurons.[2] Despite differences in symptoms or injuries associated with CNS disorders, many of the mechanisms behind neurodegeneration are the same. Common mechanisms include increased levels in oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammatory changes, iron accumulation, and protein aggregation.[2,3,4] Of these mechanisms, neuroprotective treatments often target oxidative stress and excitotoxicity—both of which are highly associated with CNS disorders. Not only can oxidative stress and excitotoxicity trigger neuron cell death but when combined they have synergistic effects that cause even more degradation than on their own.[5] Thus limiting excitotoxicity and oxidative stress is a very important aspect of neuroprotection. Common neuroprotective treatments are glutamate antagonists and antioxidants, which aim to limit excitotoxicity and oxidative stress respectively.

By definition, neuroprotectionis an effect that may result in salvage, recovery or regeneration of the nervous system, its cells, structure and function[6]

Neurotrophic factors

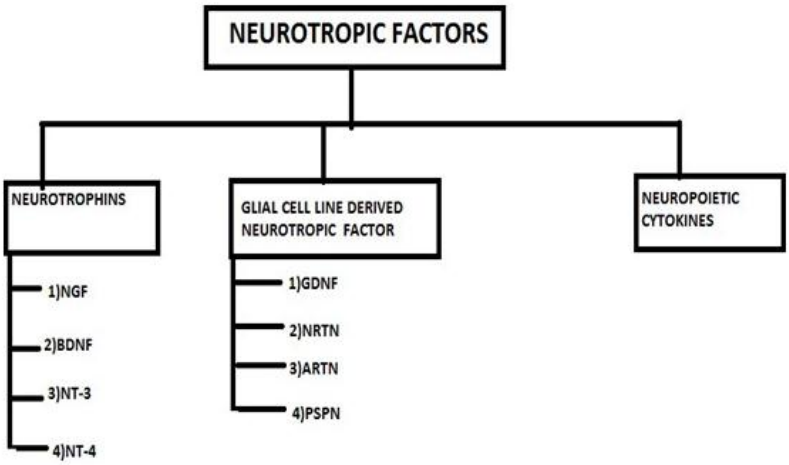
Neurotrophic factors (NTFs) are a family of Biomolecules

Nearly all of which are peptides or small proteins – that support the growth, survival, and differentiation of both developing and mature neurons. Most NTFs exert their trophic effects on neurons by signaling through tyrosine kinases, usually a receptor tyrosine kinase. In the mature nervous system, they promote neuronal survival, induce synaptic plasticity, and modulate the formation of long-term memories. Neurotrophic factors also promote the initial growth and development of neurons in the central nervous andperipheral nervous system and

that they are capable of regrowing damaged neurons in test tubes and animal models.[7]

Most neurotrophic factors belong to one of three families

1. neurotrophins,
2. glial cell-line derived neurotrophic factor family ligands (GFLs),and
3. neuropoietic cytokines.



Each family has its own distinct cell signaling mechanisms, although the cellular responses elicited often do overlap.[8]

(1) Neurotrophins

Neurotrophins are a family of proteins that induce the survival[9], development, and function[10] of neurons. They belong to a class of growth factors, secreted proteins that are capable of signaling particular cells to survive, differentiate, or grow[11] Growth factors such as neurotrophins are responsible to promote the survival of neurons are known as neurotrophic factors.

TYPES

Nerve growth factor

NGF the prototypical growth factor, is a protein secreted by a neuron's target cell. NGF is criticalforthesurvivalandmaintenanceofsympatheticandsensoryneurons. NGFisreleasedfrom the target cells, binds to and activates its high affinity receptor TrkA on the neuron, and is internalized into the responsive neuron. The NGF/TrkA complex is subsequently trafficked back to the neuron's cell body. This movement of NGF from axon tip to soma is thought to be involved in the long-distance signaling of neurons.[12]

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor found originally in the brain, but also found in the periphery. To be specific, it is a protein that has activity on certain neurons of the central nervous system and the peripheral nervous system; it helps to support the survival of existing neurons, and encourage the growth and differentiation of new neurons and synapses through axonal and dendritic sprouting. In the brain, it is active in the hippocampus, cortex, cerebellum, and basal forebrain — areas vital to learning, memory, and higher thinking. BDNF was the second neurotrophic factor to be characterized, after NGF and before neurotrophin-3.BDNF is one of the most active substances to stimulate neurogenesis.[12]

Neurotrophin-3

Neurotrophin-3, or NT-3, is a neurotrophic factor, in the NGF-family of neurotrophins. It is a protein growth factor that has activity on certain neurons of the peripheral and central nervous system; it helps to support the survival and differentiation of existing neurons, and encourages the growth and differentiation of new neurons and synapses. NT-3 is the third neurotrophic factor to be characterized, after NGF andBDNF.NT-3 is unique among the neurotrophins in the number of neurons it has potential to stimulate, given its ability to activate two of the receptor tyrosine kinase neurotrophin receptors (TrkC and TrkB). Mice born without the ability to make NT-3 have loss of proprioceptive and subsets of mechanoreceptive sensory neurons.[12]

Neurotrophin-4

Neurotrophin-4 (NT-4) is a neurotrophic factor that signals predominantly through the TrkB receptor tyrosine kinase. It is also known as NT4, NT5, NTF4, and NT-4/5.[12]

(1) Glial cell-derived neurotrophic factor (**GDNF**)

Glial cell-derived neurotrophic factor (GDNF) isa protein that, in humans, is encoded by the *GDNF* gene.[13]

GDNF is a small protein that potently promotes the survival of many types of neurons. It signals through GFRα receptors, particularlyGFRα1.

The GDNF family of ligands (GFL) consists of four neurotrophic factors: glial cell line-derived neurotrophic factor (GDNF), Neurturin(NRTN), Artemin(ARTN), and

persephin(PSPN).[14]

Nerve growth factor

Nerve growth factor (**NGF**) is a neurotrophic factor and neuropeptide primarily involved in the regulation of growth, maintenance, proliferation, and survival of certain target neurons.

Structure

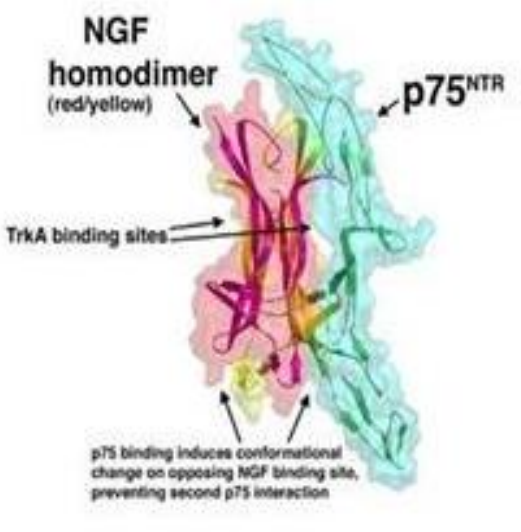
The NGF gene is located on human chromosome 1 and is expressed as two major splice variants (Edwards et al 1986, 1988). The mature, fully processed form ofbiologically active NGF appears to be similar in all tissues and consists of a dimer of 13-kDa polypeptide chains, each of which has three intrachain disulfide bridges. The crystal structure of NGF has been resolved (McDonald et al 1991). The NGFdimer has an elongated shape with a core, or "waist," that is formed by twisted beta sheets; the molecule also features a cysteine-knot motif, a reverse turn at one end (loop 3) and three beta-hairpin loops at the other (loops 1, 2, and 3). The amino terminus of NGF is not defined in the crystal structure. An octapeptide derived from the NGF amino terminus has potent bradykinin-like activity (Taiwo et al 1991) and is normally produced in the mouse submandibular gland in response to stress, but whether it is found under physiological conditions in other tissues is unknown (Fahnestock et al 1991). NGF is part of the neurotrophin family of molecules, which share a high degree of structural homology and includes brain- derived neurotrophic factors (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) (Butte et al 1998; Ibanez 1994; Robinson et al 1995, 1999). Neurotrophins are found in both mammals and lower vertebrates, and the neurotrophin homologues NT-6 and NT-7 were recently cloned in fish (Gotz et al 1994, Lai et al 1998). NGF has two known receptors, TrkA and p75NTR (Bothwell 1995, Kaplan & Miller 1997). TrkA is a single-pass transmembrane protein that serves as a receptor tyrosine kinase (RTK) for NGF. NGF signaling through TrkA elicits many of the classical neurotrophic actions ascribed to NGF(Loeb et al 1991). TrkA is a member of the Trk gene family, which includes TrkB, the receptor for BDNF and NT-4, and TrkC, the receptor for NT-3 (Kaplan & Miller 1997). NGF activates only TrkA; NT-3 activatesTrkA but only does so at much higher concentrations than does NGF. Two isoforms for TrkA exist that differ in their extracellular domain through the inclusion of six additional amino acids near the transmembrane domain of one of the variants (TrkAII). Inclusion of the insert appears to relax the specificity of TrkAactivation;NT-3mediatedsignalingismarkedlyenhancedthroughthisreceptorisoform(Clary & Reichardt 1994). p75NTR is a transmembrane glycoprotein that binds all members of the

neurotrophin family with approximately equal nanomolar affinity. p75NTR regulates signaling through TrkA; in addition, as discussed below, NGF binding to p75NTR activates signaling pathways that are characteristic for this receptor (Casaccia-Bonnefil et al 1999; Dobrowsky et al 1994, 1995; Friedman & Greene 1999).

Recent findings for the three-dimensional structure of NGF bound to its TrkA receptor provide a structural explanation for many of the results provided by mutagenesis studies (Wiesmann et al 1999). They show that NGF engages the TrkA second immunoglobulin (Ig)-like domain through two distinct patches (Wiesmann et al 1999). The first patch involves the four beta sheets that form the "waist" of the NGF molecule together with the first loop (residues 29–33); it includes NGF domains that show considerable homology with the other neurotrophins (Wiesmann et al 1999). It is likely that NGF and its neurotrophin family members engage each of their Trk receptors through this patch. The second patch is formed by the amino terminus of NGF, which in the NGF-TrkA structure is well defined (Wiesmannet al 1999). The lack of homology of the NGF amino terminus with that of other neurotrophins suggests that the second patch serves to specify NGF binding to TrkA. As yet there is no three-dimensional structure for NGF binding to p75NTR.

Mutagenesis studies for NGF binding to p75NTR point to the importance of mostly different domains (i.e. the first, third, and fourth loops and the carboxy-terminus) (Ibanez et al 1992, Ryden & Ibanez 1997, Urfer et al 1994) than those identified for binding to TrkA. The findings suggest that NGF could bind to both TrkA and p75NTR simultaneously (Wiesmann et al 1999). Both NGF and its receptors are produced during development, adult life, and aging by many cell types in the CNS and PNS, immune and inflammatory system, and various tissues. Given the wide range of neuronal and nonneuronal cells that have the potential to produce and/or respond to NGF, clues to the different functions that might be played by NGF signaling have been obtained by examining the expression of NGF and its receptors. During development, expression of NGF by target cells is compatible with its role as a survival and maturation factor for afferent neurons. In addition, as discussed in this section, a large body of evidence demonstrates that in response to numerous stimuli there is dynamic regulation of NGF and NGF receptor expression. It is interesting that NGF and/or its receptors are markedly upregulated by many cell types after tissue injury or insult. Documenting the patterns for NGF and NGF receptor gene expressioninspecific cells and tissues is required for documenting the plurality of NGF actions and for interpreting their

physiological significance.[15]



Neurotrophic factor receptor

Neurotrophic factor receptors or neurotrophin receptors are a group of growth factor receptors which specifically bind to neurotrophins (neurotrophic factors). Two classes of neurotrophic factor receptors are the p75 and the "Trk" families of Tyrosine kinases receptors.p75 is a low affinity neurotrophin receptor, to which all neurotrophins bind. It is a member of the tumour necrosis super family. In some contexts, the phrase "x" only applies to this receptor. The Trk family includes TrkA, TrkB, and TrkC, and will only bind with specific neurotrophins, but with a much higher affinity. The Trks mediate the functional signals of the neurotrophins. NGF binds to TrkA, BDNF and NT-4 bind to TrkB and NT-3 binds to TrkC. In addition NT-3 also binds to and activates TrkA and TrkB but it does so less efficiently. Whilst the Trk receptors have a clearly defined trophic role, p75 receptors activate signalling pathways which can also result in apoptosis.[16]

TrkA, B, and C receptors

TrkA is a nuclear receptor (meaning it mediates its actions by causing the addition of phosphate molecules on certain tyrosines in the cell, activating cellular signaling).

There are other related Trk receptors (TrkB and TrkC), and there are other neurotrophic factors structurally related to NGF (BDNF, NT-3, and NT-4) TrkA mediates the effects of NGF TrkB binds and is activated by BDNF, NT-4, and NT-3 TrkC binds and is activated

only by NT3.[16]

LNGFR RECEPTORS

The other NGF receptor, the LNGFR, (for Low affinity nerve growth factor receptor, commonly known as "p75", plays a less clear role.

LNGFR binds and serves as a "sink" for neurotrophins. Cells which express both the LNGFR and the Trk receptors might therefore have a greater activity - since they have a higher "microconcentration" of theneurotrophin.

However, although NGF has been classically described as promoting neuron survival and differentiation, research performed in the early 2000s suggest that NGF with its prodomain attached (proNGF) can elicit apoptosis of cells that are positive for the LNGFR and negative for TrkA.

Secreted proNGF has been demonstrated in a variety of neuronal and non-neuronal cell populations. It has been proposed that secreted proNGF can elicit neuron death in a variety of neurodegenerative conditions, including Alzheimer's disease, following the observation of an increase of proNGF in the nucleus basalis of postmortem Alzheimer's brains.[16]

FUNCTIONS OF NERVE GROWTHFACTOR

Neuronal proliferation

NGF can drive the expression of genes such as bcl-2 by binding to the TrkA receptor, which stimulates the proliferation and survival of the target neuron, High affinity binding between proNGF, sortilin, and p75NTR can result in either survival or programmed cell death (PCD). Study results indicate that superior cervical ganglia neurons that express both p75NTR and TrkAdie when treated with proNGF.[17]

Proliferation of pancreatic beta cells

There is evidence that pancreatic beta cells express both the TrkA and p75NTR receptors of NGF. It has been shown that the withdrawal of NGF induces apoptosis in pancreatic beta cells, signifying that NGF may play a critical role in the maintenance and survival of pancreatic beta cells.[18]

Regulation of the immune system

NGF plays a critical role in the regulation of both innate and acquired immunity. In the

process of inflammation, NGF is released in high concentrations by mast cells, and induce axonal outgrowth in nearby pain neurons. This leads to increased pain perception in areas under inflammation. In acquired immunity, NGF is produced by the Thymus as well as CD4+ T cell clones, inducing a cascade of maturation of T cells underinfection.[19]

Ovulation

NGF is abundant in seminal plasma. Recent studies have found that it induces ovulation in some mammals e.g. "induced" ovulators, such as llamas. Surprisingly, research showed that these induced animals will also ovulate when semen from on-schedule or "spontaneous" ovulators, such as cattle is used. Its significance in humans is unknown. It was previously dubbed ovulation-inducing factor (OIF) in semen before it was identified as beta-NGF in 2012.[20]

MECHANISM OF ACTION

NGF binds with at least two classes of receptors: the tropomyosine receptor kinase A (TrkA) and low-affinity NGF receptor (LNGFR/p75NTR). Both are associated with neurodegenerative disorders.

When NGF binds to the TrkA receptor, it drives the homodimerization of the receptor, which in turn causes the autophosphorylation of the tyrosine kinase segment. This leads to the activation of PI 3-kinase, ras, and PLC signaling pathways. Alternatively, the p75NTR receptor can form a heterodimer with TrkA, which has higher affinity and specificity forNGF.

Studies suggest that NGF circulates throughout the entire body via the blood plasma, and is important for the overall maintenance of homeostasis.[21,22]

OVERALL PART OF NGF IN VARIOUS DISEASES

Nerve growth factor prevents or reduces neuronal degeneration in animal models of neurodegenerative diseases and these encouraging results in animals have led to several clinical trials in humans[23] NGF promotes peripheral nerve regeneration in rats.[24] The expression of NGF is increased in inflammatory diseases where it suppresses inflammation.[25] NGF appears to promote myelin repair.[26] Hence NGF may be useful for the treatment of multiple sclerosis. NGF could also be involved in various psychiatric disorders, such as dementia, depression, schizophrenia, autism, Rett syndrome, anorexia nervosa, and

bulimia.[27]

Dysregulation of NGF signaling has also been linked to Alzheimer's disease.[28,29,30,31,32,33] Connective tissue cells genetically engineered to synthesize and secrete NGF and implanted in patients' basalforebrains reliably pumped out NGF, which enhanced the cells' size and their ability to sprout new neural fibers. The treatment also rescued vulnerable cells, even if they already showed the trademark signs of Alzheimer's pathology.

In some patients, these beneficial effects lasted almost 10year safterthetreatment. Evenpatientswhodied responded positively tothetherapy Even pathological cells with protein clumps in their cell bodies and surroundings extended their fibers toward the NGF source, maintained a healthy size and activated pro-survival signals that boosted their stress resilience. Two other patients received direct injections of modified viruses containing the NGF gene directly to their basal forebrains. This allowed the gene to express longer in the brain.[34,35]

Neurotrophins, including NGF, have been shown to affect many areas of the brain, including areas that are related to Rett syndrome, bipolar disorder, and Alzheimer's disease. Stress and/or anxiety are usually a precipitating factor in these disorders and affects levels of NGF, leading to impaired cognitive functioning.

This impaired cognitive functioning can be seen in patients with Schizophrenia. In treatment of schizophrenia, NGF levels are increased in patients using atypical antipsychoticmedication, but not in patients using typical antipsychotic medications. Patients using atypical medications usually report improved cognitive performance compared to those using typical antipsychotics. In addition, these higher NGF levels from the atypical antipsychotic medications lead to a reduction in negative symptoms of Schizophrenia.[36,37] Rett syndrome and Autism often show similar signs early in life, such as slowing development and intellectual disability. One distinguishing factor is that low levels of NGF have been found in the cerebral spinal fluid of children with Rett syndrome compared to children with Autism who have relatively normal to high levels.[38] Pharmaceutical therapies with NGF-like activity can be effective in treating Rett syndrome, including better motor and cortical functioning as well as increased social communication.[39]

NGF AS NEUROPROTECTION IN HIBI (HYPOXIC ISCHEMIC BRAIN INJURY)

INTRODUCTION

Hypoxic-ischemic brain injuries (HIBI) are frequently associated with poor clinical and neurological outcome in survivors, who can suffer from mental retardation, seizures, motor impairment and cerebral palsy. Unfortunately, there is currently no effective therapy which can restore neuronal loss and produce substantial clinical improvement. Several neurotrophins have a multifunctional role both in the central and peripheral nervous system. These neurotrophic factors are important regulators of neuronal development, proliferation, differentiation and maturation of the peripheral and central nervous system. Among them, Nerve Growth Factor (NGF), Brain- Derived Neurotrophic Factor (BDNF), Glial cell line-Derived Neurotrophic Factor (GDNF), Neurotrophin-3 (NT3) and Neurotrophin-4 (NT4) seem to play crucial roles in HIBI. Experimental animal models showed that these neurotrophins could be effective in restoring neuronal cells after brain ischemia, suggesting that they might be used as therapeutic agents for treating this kind of brain damage. NGF is a neurotrophin which supports the survival and differentiation of neurons during brain development. It has been shown that NGF reduces neural degeneration and promotes peripheral nerve regeneration in rats. It appears globally neuroprotective to the developing brain in a neonatal model of cerebral hypoxia-ischemia. NGF protects against neuronal death and exogenous NGF administration has been shown to prevent or significantly reduce acute cholinergic cell loss and severe neurological deficits following HIBI. It has been reported that also BDNF increases in the cerebrospinal fluid (CSF) of children following HIBI. Intraventricular infusion of BDNF in neonatal rodent models, who received unilateral carotid ligation, resulted in significant protection against both hypoxic-ischemic-induced brain tissue loss and also in spatial memory impairment. GDNF has been shown to have trophic activity on dopaminergic neurons and its endogeneous neuroprotective effect after brain ischemia has been proven. NT3 and NT4 participate in the early development of the brain and have been linked to the survival and functioning of multiple neuronal populations. Furthermore, it is also important to consider that glial cells manufacture neurotrophinreceptorsand NGF playsaroleinnormal glial functions. Basedon these previous experimental and clinical findings, we report our experience by intraventricular NGF administration in two children suffering from severe HIBI and prolonged comatose state after cardio-respiratory arrest. We hypothesize that NGF infusion after HIBI in pediatric patients could improve neurological outcomes and cerebral perfusion.[40]

Experimental Section

The patients, aged 8 and 13 months were admitted to our pediatric intensive care unit (PICU) after prolonged cardio-respiratory arrest and abrupt-onset coma. They were clinically unstable, with a heart rate of about 30 beats/min, small pulses and reduced peripheral perfusion. Mechanical ventilation was started and the haemodynamic stabilization was aimed toward maintaining a normal cerebral perfusion pressure. Because of severe intracranial hypertension, secondary to cerebral edema, the patients underwent external CSF diversion. Persisting severe comatose state and lacking any other feasible Brain Sci. 2013, 3 1015 therapeutic approach two months after the brain injury, treatment with intraventricular NGF infusion was taken into consideration. A total of 2.5S NGF was purified and lyophilized from male mouse submandibular glands and prepared according to the method of Bocchini and Angeletti. We utilized 1 mg of NGF diluted in 10 ml of saline solution and administered once a day for 10 days consecutively. NGF was infused via the external drainage catheter about two months after the HIBI when the patients continued to exhibit a poor response to conventional and standardized treatment. The treatment with NGF was approved by the University's institutional review and ethical board, and by the parents of the infants who provided written informed consent. Neurological evaluation before intraventricular NGF infusion revealed a comatose state and asymmetrical tetraparesis with GCS of 4 and 5, respectively. Both the patients presented a global aphasia and no response to environment. After NFG infusion, the infants showed progressive arousal with recovery of awareness, they regained postural control and a significant improvement of limb weakness with spontaneous and finalistic movements; they grasped objects. Moreover, they became expressive with a good level of understanding and able to communicate by significant amelioration of communicative skills. The first child (8 months of age) regained vocalization, the second patient (13 months of age) restarted to pronounce some words he acquired before the cardio-respiratoryarrest. Finally, whenthepatientsweredischargedfromthePICU, one month after the NGF treatment, their GCS scores were 8 and 9, respectively. SPECT images obtained in the first patient before NGF therapy, showed multiple cerebral areas with severe perfusion impairment. In the second SPECT scan carried out one month after NGF treatment, an important improvement of regional cerebral perfusion was visually observed in the right temporal and occipital cortices, with an increase in radiotracer uptake (20.5% and 17.5% in right temporal and occipital regions, respectively). In the second patient, the first SPECT study performed before intraventricular NGF infusion showed absent 99mTc-ECD uptake in left frontal, temporal, parietal and occipital regions. A severe hypoperfusion was also

observed in left basal ganglia, right thalamus and left cerebellar hemisphere. One month after NGF treatment, the patient underwent a second SPECT scan, showing a marked increase in radiotracer uptake (21% in right superior frontal area and 90% in right occipital region) (Figure 1A,B). We did not observe side effects after NGF infusion, such as pain and weight loss. At the two year follow-up, these children are still alive but have some neurological disorders: they have not acquired the equivalent motor and language development as other children of their age, their gait is rather uncoordinated and ataxic, the fine motor skills of their hands are not entirely certain, but they are improving with physiotherapy and speechtherapy.[40]

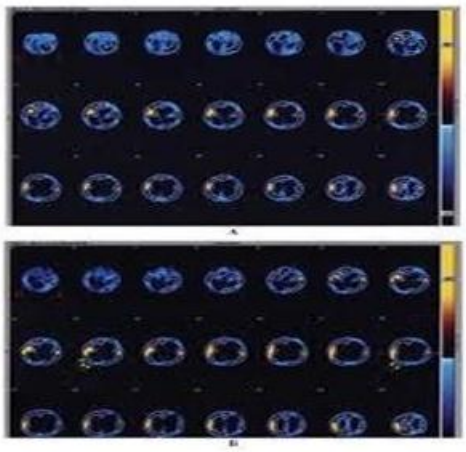


Figure. Single-photon emission computed tomography (SPECT) study showing the brain perfusion pattern in the second infant affected by severe hypoxic-ischemic injury. (A) Before treatment. (B) After intraventricular NGF infusion. The arrows in highlight the sites of improvement of cerebral perfusion in right temporal and occipitalcortices.

Glial cell-derived neurotrophic factor as neuroprotection in parkinsons

INTRODUCTION

Parkinson's disease (PD), a disease of the human CNS, is a neurodegenerative disorder that is characterized by the progressive degeneration of the nigrostriatal dopaminergic pathway resulting in the loss of dopamine (DA) in the basal ganglia. The basal ganglia is composed of a set of subcortical nuclei including the putamen and caudate nucleus that constitute the striatum, globus pallidus (both internal and external segments), subthalamic nucleus (STN) and substantia nigra (SN), which are interconnected by a complex network of projections and together plays an important role in the regulation of motorfunction.

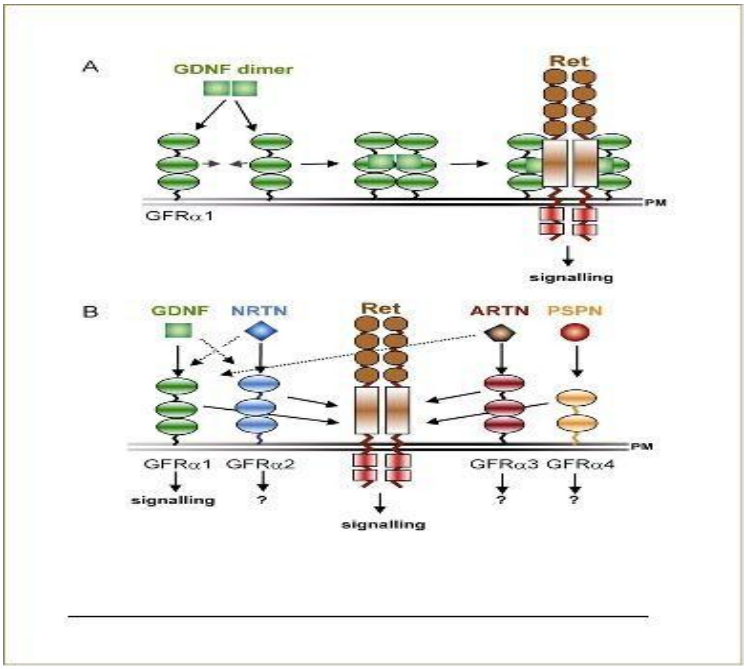
Although the underlying cause of PD remains unknown, parkinsonian-like symptoms can

result following exposure to various environmen- tal toxins, viruses, inflammation, brain injury, or may have a genetic basis. By contrast, the neuropathology of PD has been well character- ized. In addition to the loss of DA neurons in the SN, there is also an accumulation of protein (-synuclein) aggregates that form Lewy bodies in the pigmented (melanin-containing) DA neu- rons in the SN. Whether this accumulation of protein contributes to the loss of DA neurons remains unclear; other factors, including oxida- tive stress, apoptosis, mitochondrial dysfunction and excitotoxicity, likely contribute in the neurodegenerative process.

The age of disease onset is generally over the age of 45 years, with males being affected slightly more than females. With an increase inthe aging population, the prevalence of indiviuals affected by PD is on the rise and estimates suggest that at least 1% of the population over the age of 65 years is affected by PD. There is presently no cure for PD and current therapy is symptomatic.[41]

Effects of GDNF on the nigrostriatal DA system

The interest in GDNF as a potential therapeutic for PD stems from initial *in vitro* studies examining survival of embryonic mes-encephalic cell cultures, where it was found that GDNF enhanced DA cell survival and differentiation. Subsequent studies revealed that GDNF possesses potent dopaminotrophic effects that are both neuroprotective and neuroregenerative, and growth stimulating by influencing the neurite outgrowth of DA neurons to promote reinnervation. *In vivo* studies investigating the therapeutic potential of GDNF have primarily focused on the rodent 6-hydroxydopamine (6-OHDA) partial lesion model and to a lesser extent on the nonhuman primate (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine[MPTP]) model ofPD.[42]



Neurotrophic factors: neuroprotection &/or neuroregenerative effects

Over the past 15 years, research efforts have focused on pro-moting neuronal survival with the use of neurotrophic factors to rescue neurons affected in PD. Despite this considerable effort, translating their use from experimental studies in animal models of PD to clinical studies in PD patients to improve function and slow disease progression has resulted in less than favorable outcomes. Given the progressive nature of PD, the slow degeneration of thedopaminergic neurons of the SN pars compacta offers a window of opportunity to reverse, or at least halt, the neurodegenerative process, making PD a good candi-date for potential therapeutic agents that can improve cell sur-vival by neuroprotection or reinnervation by promoting neurite outgrowth of surviving DAneurons.

A number of neurotrophic factors have been investigated in PD including basic FGF (bFGF), EGF, BDNF and sonic hedgehog. Although many *in vitro* studies exploring the potential benefits of neurotrophic factors have demonstrated a reduction in neuronal cell loss following chemical insult or injury, and in some cases enhancement of neurite outgrowth of cultured cells, similar findings in experimental studies in animal models of PD have been more variable. By far the most widely studied neurotrophic factor in PD has been GDNF.

GDNF is a member of the GDNF family of trophic factors that also includes neurturin, artemin and persephin. The GDNF family interacts with a two-component receptor complex which dimerizes to form a receptor structure that is functionally active. GDNF has affinity for

both the GDNF receptor α-subunit and with the proto-oncogene c-*ret* receptor of the tyrosine kinase family to create a hetero-oligomeric receptor complex. Once this complex is formed, tyrosine kinase is enzymatically activated to initiate intracellular signaling.[41]

GDNF approaches towards PARKINSONS Direct infusion of GDNF into the brain

In the rodent 6-OHDA partial lesion model, cell death of the DA neurons in the SN pars compacta is slow and protracted over a period of weeks following infusion of the neurotoxin 6- OHDA into the striatum, the terminal field of the DA cell projections where the toxin is selectively taken up by the DA nerve terminal causing oxidative damage and retraction of the axons. Thus, this model is well suited to investigate both the neuroprotective and neuroregenerative effects of GDNF. Since cell death occurs in a slow and protracted manner, there is opportunity to study the neuroprotective effects on GDNF on degenerating neurons damaged by the 6-OHDA during the acute cell death stage that generally occurs within 2–4 weeks following 6-OHDA infusion. In addition, the restorative (regeneration and rescue) effects on the remaining spared DA neurons that may be atrophic and dysfunctional can be studied during the chronic phase of the lesion. Using this model, direct injection of GDNF into the region of the SN beginning on day 1 of 6-OHDA administration and given repeatedly every second day for 4 weeks prevented DA cell death in the SN, thus demonstrating a GDNF neuroprotective effect. A single injection of GDNF over the SN at 7 days following 6-OHDA administration afforded protection to approximately half of the DA cells that would have otherwise undergone cell death by 4 weeks. Similarly, injection of GDNF over the SN at 1 day prior to 6-OHDA infusion into the striatum resulted in partial protection of DA neurons. Injection of GDNF into the striatum before and after 6-OHDA adminis-tration has also been shown to result in sparing of DA cells in the SN and to a lesser extent tyrosine hydroxylase (TH)-positive innervation of the striatum itself. To date, sub-sequent studies in the partial 6- OHDA rodent model of PD using various GDNF infusion regimens have confirmed the neuroprotective effects of GDNF on DA cells in the SN and suggests that the neuroprotective effects of GDNF may result from a reduction in oxidative stress.

A single injection of GDNF in the 6-OHDA-lesioned animal has also been shown to attenuate DA agonist-induced rotational asymmetry in addition to increasing DA turnover and cell.[42]

Number, thus demonstrating GDNF neuroregenerative actions. The neuroregenerative effects of GDNF have also been confirmed using various administration regimens. However, these studies have consistently shown that injection of GDNF over the SN does not promote axonal

growth or reinnervation of the DA denervated striatum.

Studies in the nonhuman primate model of PD have also demonstrated the neuroregenerative effects of GDNF. Recovery of behavioral deficits in the MPTP-lesioned nonhuman pri-mate was observed following infusion of GDNF into the SN. In addition, histological examination revealed an increase in mean cell size and fiber density in the SN. An increase in DA levels was also observed. Similar histological findings have been observed following intraputaminal infusion of GDNF. Despite the beneficial effects of GDNF administration in the nonhuman primate model of PD, benefits were not sustained following discontinuation of GDNF infusion. Withdrawal of GDNF induced a slow deterioration in animals to the point that they returned to behavioral deficit baselines, thus suggesting a need for continuous GDNF infusion to maintain dopaminotrophic effects.

GDNF gene therapy in PD

Since direct infusion of GDNF into the brain has limitations in the long term, an alternative is to apply gene therapy with the use of various viral vector systems, including adenovirus, lentivirus and adeno-associated virus (AAV). Consistent with direct infusion studies of GDNF in animal models of PD, viral delivery of GDNF into the brain has been shown to produce beneficial anatomical and functional effects.[89] Infusion of adenoviral vectors for GDNF to the brain region adjacent to the DA cell bodies in the SN or directly into the striatum prevented cell death in the 6-OHDA rodent model of PD. Further study suggests that introduction of GDNF-viral vectors into the striatum, the site of neurotoxin infusion, as opposed to the SN, produces greater protection against cell death, a reduction in behavioral deficits and greater preservation of the TH-positive innervation of the striatum. Despite the potential benefits of using adenoviral vectors to introduce GDNF into the brain, the potential for the development of an inflammatory response or a downregulation in transgene levels over time following injection into the brain may be problematic in the longterm.

One manner in which to improve long-term expression of the GDNF transgene is to utilize AAV or lentiviral vectors. In the rodent model of PD, introduction of AAV or lentiviral vectors bearing the GDNF transgene into the brain has been shown to protect DA cells from damage, and attenuate behavioral deficits and induce fiber outgrowth. Under these conditions, maximal levels of expression of the GDNF transgene were sustained even at 6 months after gene transfer. In the nonhuman primate model of PD, AVV or lentiviral GDNF transgene transfer to both the striatum and SN pre-vents neurodegeneration and promotes

behavioral recovery. Surprisingly, an increase in the number of TH-positive cells in the striatum of nonhuman PD primates has been reported following striatal transgene expression of GDNF, raising the possibility that GDNF has the ability to pro-mote conversion of striatal neurons to a DA phenotype, or that GDNF influences both neurogenesis and migration of neural progenitors from the adjacent subependymal region of the sub ventricular zone. By contrast, lentiviral delivery of GDNF to the SN failed to prevent neuronal degeneration of the SN DA cells in a rodent genetic model of PD overexpressing α-synuclein, thus suggesting that GDNF lacks the ability to modulate metabolic cell death due to abnormal protein accumulation. However, the majority of experimental studies support the benefits of neuroprotection and functional improvement, but the long-term effects of long-term expres-sion of striatal GDNF remain unknown. Overexpression of striatal GDNF has been found to produce aberrant sprouting of fibers in the globus pallidus and entopeduncular nucleus, as well as a downregulation of TH expression over time despite preservation of TH- positive fibers of the nigrostriatal DApathway.

Regardless of the method used to transduce GDNF expression in the brain, viral vectors have the ability to transduce both neurons and non-neuronal cells in the brain target. Recently, it was reported that neurons are less suitable targets than glial cells or astrocytes to express GDNF. Using an adeno-viral vector for GDNF under the control of the neuron-specific enolase promotor, neuronal expression of GDNF produced significant protection against 6-OHDA damage, but failed to promote functional recovery. Since the aim of using GDNF as a therapeutic option in PD is to prevent cell degeneration and promote functional recovery, it would appear that cellular targets for GDNF expression and promo-tor activity of the transducing vector may be critical factors in providing a viable therapeuticoption.[42]

KEYISSUES

Treatments for Parkinson's disease (PD), whose motor symptoms are predominantly due to the selective degeneration of nigrostriatal dopaminergic neurons, are currently primarily symptomatic and focus on either restoring basal ganglia dopamine pharmacologically using L- DOPA or by electrical stimulation of basal ganglia circuitries using deep brainstimulation.

GDNF is a neurotrophic factor whose selective effects on dopaminergic neurons may be utilized therapeutically to address the underlying cause of PD by either protecting endogenous dopaminergic neurons from neurodegeneration, supporting the survival of remaining dopaminergic neurons, or adjunctively in cell restoration strategies that aim to

replace those dopaminergic neurons lost todisease.

Direct intracerebral injection of GDNF into the substantia nigra in animal models of PD has been shown to protect endogenous dopaminergic neurons from dopaminergic neurotoxin-mediated cell death and so attenuate the development of parkinsonian symptomatology.

An alternative manner of delivering GDNF to the parkinsonian brain has been performed using gene therapy in which viral vector systems are used to deliver the neurotrophic factor either directly to dopaminergic neurons in the substantia nigra or to their target area, thestriatum.

Clinical trials involving intraventricular infusion of GDNF failed to produce symptomatic benefits in parkinsonian patients and were associated with a number of deleterious side effects. Infusion of GDNF into the striatum instead in an open-label study was associated with significant clinical benefits, but these results could not be confirmed in a double-blind, placebo-controlled trial.

In cell restoration strategies for PD, exposure of fetal dopaminergic neurons to GDNF has enhanced their survival and neuritic outgrowth both *in vitro* and *in vivo* in animal models of PD. These results were also associated with significant recovery of motor function. An open-label clinical trial of transplantation of human fetal ventral mesencephalic cells in which the cells were hibernated in the presence of GDNF for several days prior to transplantation has shownpromise.[42]

CONCLUSION

With the study of this review now we are able to know that neuroprotection against neurodegeneration can be achieved by neurotropic factors such as NERVE GROWTH FACTOR, GLIAL CELL DERIVED NERVE FACTOR with deferent mechanisms explained in this report. The neurotrophic factors represent a complex array of pathways that influence many aspects ofneuronal function and survival during development as well as in the adult central nervous system.

Diseases like HYPOXIC ISCHEMIC BRAIN INJURY (HIBI) & PARKINSONS DISEASE caused due to ageing and a number of other factors. Research has been carried out thoroughly for neuroprotection against these diseases with this neurotropic factors.

Various other neurotropic factors are currently undergoing clinical trials for their neuroprotective activity.

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