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Neurotrophic factors for treatment of neurotrauma

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Introduction

Overview

This article starts with a review of experimental evidence for the role of **neurotrophic factors** in the pathomechanisms of CNS injury at the molecular level. The developing brain responds to a mild injury by modifying factors related to synaptic plasticity, and regions remote from the site of injury express neurotrophic signals potentially needed for compensatory responses. Various studies of neurotrophic factors in traumatic brain injury have shown that they have a neuroprotective action and enhance cellular systems involved in the maintenance of Ca(2+) homeostasis and free radical metabolism. The levels of neurotrophic factors are increased following injury, indicating that this has something to do with repair mechanisms following spinal cord injury. Implantation of encapsulated genetically engineered fibroblasts producing neurotrophic factors has been shown to accelerate recovery from traumatic spinal cord injury in an adult rat. Neurotrophic factors also have well-documented abilities to support neuron survival and stimulate neurite outgrowth, making them excellent candidates for use in repairing injured nerves.

Key points

- There are changes in neurotrophic factors in the brain and the spinal cord following acute trauma.

- Reductions in neurotrophic factor concentration in tissues are reflected in CSF examination and may possibly be detected by examination of serum.

- Beneficial effects of stem cells in traumatic injuries of the central nervous system are attributed to release of neurotrophic factors.

- These findings form the basis of the investigative use of neurotrophic factors for neuroprotection and neuroregeneration in management of central nervous system trauma.

Historical note and terminology

A trophic factor can be generally defined as any molecule that supports the survival of neurons. Nerve growth factors are polypeptides that regulate the proliferation, survival, migration, and differentiation of cells in the nervous system. Most of the studies have focused on the effect of growth factors on neuronal survival and maintenance, hence, the term "neurotrophic factors." A neurotrophic factor is synthesized by, and released from, target cells of the neurons, bound to specific receptors, then internalized and transported by retrograde axonal transport to the cell soma where multiple survival-promoting effects are initiated.

Growth factors termed "cytokines" have also been found to modulate neuronal processes. Originally, cytokines were described as derived solely from the cells of the immune system, but now they are known to be produced by the cells of the CNS also. In this article, the term "neurotrophic factors" will be used in a broad sense to cover neurotrophins (nerve growth factor, brain-derived neurotrophic factor, neurotrophins), growth factors, and other substances that promote survival and repair of the cells of the nervous system.

Neurotrophic factors are the most important of all the factors influencing regeneration of CNS following trauma by facilitating cell survival, axon growth-cone stimulation, and synapse regeneration (17). The role of neurotrophic factors in injuries to the nervous system will be described according to the involvement of the brain, the spinal cord, or the

peripheral nerves. "Traumatic brain injury" is the term applied to a brain injury caused by external physical trauma, and "spinal cord injury" is the term applied to an injury to the spinal cord induced by physical trauma.

Clinical aspects

Description

Role of neurotrophic factors in the management of traumatic brain injury. Injured neurons may suffer 3 potential fates: (1) death, (2) persistent atrophy, or (3) recovery. The ability of injured neurons in the adult brain to recover from injury depends on the expression of growth-related genes and the responsiveness to survival and growth signals in the environment. These signals include neurotrophic factors and substrate molecules that promote neurite growth. The specificity of neurotrophic responsiveness parallels patterns observed during development of the nervous system.

Destructive multiple mediators of the secondary injury process ultimately dominate over a few intrinsic protective measures, leading to activation of cysteine proteases such as calpain that cleave key cellular substrates and cause cell death. Experimental studies in rodent models of traumatic brain injury suggest that treatment with calpain inhibitors and neurotrophic factors such as nerve growth factor and brain-derived neurotrophic factor can prevent neuronal death and dysfunction in traumatic brain injury.

Use of neurotrophic factors as neuroregenerative agents. The poor ability of the CNS to cause axons to regenerate after injury has been partly attributed to astrocyte behavior after injury, which is manifested by their limited ability to migrate and repopulate the injury site. Astrocyte migration is promoted by neurotrophic factors such as basic fibroblast growth factor, transforming growth factor-beta-1, and epidermal growth factor. This observation suggests that the appropriate choice of growth factors at the appropriate postinjury period may compensate for the glial support deficiency or the presence of glial inhibitory factors in CNS.

Neurotrophic factors have also been investigated for repair of the defects caused after injury to the brain. The regrowth of axons within tissue defects in the CNS is promoted by implanted hydrogel matrices that contain brain-derived neurotrophic factor and ciliary neurotrophic factor-producing fibroblasts. Neural stem cells that have been retrovirally

transduced to produce nerve growth factor can markedly improve cognitive and neuromotor function and rescue hippocampal CA3 neurons when transplanted into the injured brain during the acute posttraumatic period.

In newborn mice with traumatic brain injury, long-term treatment with Peptide 6, which corresponds to an active region of human ciliary neurotrophic factor, has been shown to enhance the pool of neural progenitor cells in the hippocampus and increased the numbers of neurons (08). Further studies are needed to understand its role in developing potential therapy for severe traumatic brain injury.

Study in a mouse model of severe traumatic brain injury has shown that the neurorestorative efficacy of repeated treatments with stem cell factor (SCF) and granulocyte colony-stimulating factor (G-CSF) initiated at 3 months in the chronic phase are superior to a single treatment with combination of 2 factors (32). Microglial degeneration in the cortex and hippocampus in the chronic phase of traumatic brain injury is ameliorated by combined stem cell factor and granulocyte colony-stimulating factor treatment.

One of the problems with neurotrophic factor administration is the penetration of the **blood-brain barrier**. Breach of blood-brain barrier follows cortical contusions. The data indicate that regions not initially destroyed by cortical impact, but evidencing blood-brain barrier breach, may be accessible to neurotrophic factors administered intravenously both immediately and days after brain trauma.

Use of neurotrophic factors as neuroprotective agents. Various studies of neurotrophic factors in traumatic brain injury have shown that they have a neuroprotective action and enhance cellular systems involved in the maintenance of Ca(2+) homeostasis and free radical metabolism. Beneficial effects of neural stem cell grafting in traumatic brain injury that are mediated through modulation of aberrant postinjury hippocampal plasticity include secretion of a variety of neurotrophic factors by astrocytes (36).

Nerve growth factor (*NGF*). The neuroprotective efficacy of intracerebral nerve growth factor infusion has been demonstrated during the acute phase of experimental head injury. This beneficial effect of nerve growth factor may be related to its ability to attenuate traumatically induced apoptotic cell death.

Insulin-like growth factor-1 (*IGF-1*). Intravenous insulin-like growth factor-1 has been evaluated for the treatment of moderate-to-**severe head injury** in a phase 2 safety and efficacy trial. Nitrogen utilization and clinical outcome improved in these patients. Glypromate, an N-terminal cleavage product of human insulin-like growth factor-1, has shown neuroprotective effects in models of brain injury. NNZ-2566, a structural analogue

of glypromate, was in clinical trials for the treatment of cognitive deficits following traumatic brain injury in 2009 (04). This trial was completed in 2018, but the results have not been published.

Cerebrolysin. It is a neuropeptide preparation that mimics the properties of neurotrophic factors. A preclinical randomized, placebo-controlled, and blinded study in a rat model of **mild traumatic brain injury** revealed that cerebrolysin administered 4 hours after injury and then once daily for a total of 10 consecutive days improved functional outcomes 3 months after injury (41).

Neurotrophic factors as mediators of beneficial effects of other agents. Some examples of these are as follows:

Glucocorticoids. Experimental evidence indicates that the neuroprotective effect of glucocorticoids in acute traumatic brain injury is mediated by modulation of expression of brain-derived neurotrophic factor (BDNF). Following intraventricular injection of bone marrow stromal cells secreting brain-derived neurotrophic factor, levels of this neurotrophic factor were significantly increased in cerebrospinal fluid of an animal model of traumatic brain injury and could promote the survival of neurons (39).

Δ9-tetrahydrocannabinol (Δ9THC). Administration of the phytocannabinoid Δ9THC promotes significant recovery from traumatic brain injury in mice and is associated with upregulation of brain granulocyte colony-stimulating factor, brain-derived neurotrophic factor , and glial cell line-derived neurotrophic factor—neurotrophic factors that have been shown to mediate brain self-repair following injury (38). Results of another study by these authors suggest that effects of granulocyte colony-stimulating factor do not depend on activation of cannabinoid 1 (CB1) or cannabinoid 2 (CB2) receptors (37). Investigation of the role of cannabinoid receptors in this traumatic brain injury model will require studies with CB1-receptor and in CB2-receptor knockout mice to avoid nonspecific interaction of cannabinoid receptor agents with other receptors.

Neurotrophic factor adjunct to hypothermia. Significant morbidity and mortality of patients with traumatic brain injury is associated with posttraumatic inflammatory complications. Hypothermia has been suggested as a treatment to lessen these inflammatory reactions. Hypothermia, applied immediately after the traumatic brain injury, reduces the posttraumatic increase in interleukin-1 beta-mediated nerve growth factor production. Thus, hypothermia, although reducing the inflammatory response, may also hinder the brain's intrinsic repair mechanism. This would justify the use of supplemental administration of neurotrophic factors along with hypothermia.

Delivery of neurotrophic factors to the injured brain. Because large molecule neurotrophic factors cannot cross the blood-brain barrier, other strategies such as cell and gene therapies are used for endogenous production of neurotrophic factors. In rats subjected to traumatic brain injury, direct and single dose hippocampal injection of beta-Ngf (nerve growth factor) fusion gene carried by a pseudo lentivirus vector is able to rescue the hippocampus function (27). However, this method of delivery is not practical in human patients. In 2017, a phase 2 randomized clinical trial (NCT01212679) was completed in China to test the effect of transnasal nerve growth factor, which can bypass the blood-brain barrier to enter the brain when administered between 24 to 72 hours after injury and treatment continues for 2 weeks. The rationale was that upregulation of nerve growth factor in the brain following injury correlates with better neurologic outcomes. The results of this trial have not been published.

*Stem **cell transplantation** as a source of neurotrophic factors*. Treatment with human mesenchymal stem cells during the acute phase of traumatic brain injury in experimental animals can improve neurologic functional outcome, and increased levels of neurotrophic factors in the injured hemisphere leading to decreased neuronal apoptosis is an explanation of this beneficial effect (21). Neural stem cells, genetically modified to encode brain-derived neurotrophic factor gene, were shown to improve neurologic motor function following traumatic brain injury in a rat model more than simple transplantation of naive neural stem cells (28).

Transplantation of bone marrow-derived mesenchymal stem cells (MSCs) that release neurotrophic factors has been used for treating CNS injuries and other diseases, but clinical applications are limited. An experimental study showed that dermal papilla cells from rat vibrissae, particularly those forming spheres, may be a more promising source of glial cell line-derived neurotrophic factor for treating CNS injuries as compared to MSCs (24).

Role of neurotrophic factors in the management of spinal cord injuries. Neurotrophic factors are excellent candidates for enhancing regeneration after spinal cord injury as they mediate neuronal plasticity throughout development by affecting proliferation of neuronal precursors, neuronal survival, axonal growth, dendritic arborization, and synapse formation (16). The factors involved are as follows.

Basic fibroblast growth factor (bFGF). Various studies show the administration of basic fibroblast growth factor for experimental severe spinal cord injuries in rats, either by continuous intramedullary infusion or intrathecal infusion, reduces the area of injury and leads to functional recovery that may or may not correlate with structural recovery. These findings indicate that yet-undefined mechanisms contribute to the functional recovery.

Brain-derived neurotrophic factor and neurotrophins. In a rat models of spinal cord injury, neurotrophin-3 has been shown to promote motor recovery. Clinical studies are necessary to define the role of neurotrophin-3 as a therapeutic option for patients suffering from spinal cord trauma. Neurotrophin-4/5 and brain-derived neurotrophic factor appear to be interchangeable to elicit substantial axonal growth in the injured spinal cord. The early antiinflammatory and antioxidant effects of local brain-derived neurotrophic factor-application into the lesioned spinal cord may contribute to the observed decreased loss of locomotor function. In the rat spinal cord crush injury model, a single intrathecal injection of brain-derived neurotrophic factor fused with collagen-binding domain was shown to result in prolonged retention at the injury site to improve chances of neural regeneration and locomotion recovery (25).

Transplantation of human mesenchymal stem cells hypersecreting brain-derived neurotrophic factor results in structural changes in the spinal cord, which are associated with improved functional outcome in **acute spinal cord injury** in experimental animals (34). Localized delivery of mesenchymal stem cells expressing brain-derived neurotrophic factor promotes neuroplasticity and enhances functional recovery of diaphragm muscle activity following cervical spinal cord injury in rat models (13).

Further knowledge of the effects of neurotrophins on specific populations of neurons will enable the most efficient targeting and receptor interaction for fine tuning of dosage and avoidance of off-target effects (20). In combination with measures to improve lesion environments such as stem cell grafts or nerve bridges, neurotrophic factors have the potential to facilitate meaningful recovery after spinal cord injury.

Glial cell line-derived neurotrophic factor (GDNF). Glial cell line-derived neurotrophic factor may play a novel therapeutic role in promoting propriospinal axonal regeneration, enhancing myelin formation. Glial cell line-derived neurotrophic factor has a strong neuroprotective effect on white matter sparing and the sparing of a subset of proprio- and supraspinal axons following spinal cord injury.

Granulocyte colony-stimulating factor (G-CSF). This is a cytokine approved for the treatment of chemotherapy-induced neutropenia. Evidence from experimental studies indicates that in acute, subacute, and chronic CNS lesions, granulocyte colony-stimulating factor has strong anti-inflammatory, antiapoptotic, antioxidative, myelin-protective, and axon-regenerative activities. Additional effects result in the stimulation of angiogenesis and neurogenesis, as well as in bone marrow stem cell mobilization to the CNS. There are emerging preclinical and clinical data indicating that granulocyte colony-stimulating factor is a safe and effective drug for the treatment of acute and chronic traumatic spinal cord injury (02). In a randomized trial of granulocyte colony-stimulating factor for spinal cord injury conducted in Japan, G-SPIRIT, patients aged

over 65 years showed a strong trend towards a better motor recovery in the granulocyte colony-stimulating factor treated group 6 months after drug administration compared with the control group (23). However, the trial failed to show a significant effect of granulocyte colony-stimulating factor in primary end point, ie, changes in American Spinal Injury Association motor scores from baseline to 3 months after drug administration, although the subanalyses of the trial suggested potential granulocyte colony-stimulating factor benefits for a specific population.

Combination of neurotrophic factors with other approaches for spinal cord regeneration. Neurotrophic factors will likely need to be combined with other treatment approaches to exploit the full potential of therapy for axonal regeneration (29).

Delivery of neurotrophic factors for the treatment of spinal cord injury. Neurotrophic factors are large molecules and do not penetrate the spinal cord after systemic administration. The following methods have been used to facilitate delivery of neurotrophic factors:

- Fibrin glue or gel foam containing neurotrophic factors can be applied locally to bridge the gap in the spinal cord. In animal models of spinal cord injury, bioavailability of epidermal growth factor and basic fibroblast growth factor released from injected alginate biomaterial to the central lesion site significantly enhanced the sparing of spinal cord tissue and increased the number of surviving neurons and sensory fibres (14).

- Continuous intramedullary infusion of brain-derived neurotrophic factor provides neuroprotection and enhances some regenerative activity after spinal cord injury.

- Tissue transplantation and exogenous neurotrophin support lead to improvements in supraspinal and propriospinal input across the transplant into the host caudal cord and a concomitant improvement in locomotor function in experimental spinal cord injury.

- Platelet-rich plasma (PRP) is an abundant source of growth factors, such as platelet-derived growth factor, transforming growth factor beta, insulin-like growth factor 1, and epithelial growth factor. Intrathecal injection of platelet-rich plasma stimulates angiogenesis and enhances neuronal regeneration after spinal cord injury in rats (07). As an autologous, biocompatible, nontoxic material that does not result in a

major immune response, platelet-rich plasma is a promising therapeutic agent for spinal cord injury in humans.

Local injection into the spinal cord is not practical, as neurotrophic factors need to be administered for extended periods of time. Genetically modified cells can deliver neurotrophic factors for longer durations. This method of delivery of neurotrophic factors is a form of **gene therapy** and is discussed in more detail in the MedLink clinical summaries on gene therapy. Grafts of genetically modified cells can be useful for characterizing neurotrophic factor responsiveness in the adult spinal cord and for designing strategies to promote axonal regeneration after injury. Some examples of delivery of neurotrophic factors to the injured spinal cord by genetically modified cells are as follows:

- Primary rat fibroblasts have been genetically modified to produce and secrete human nerve growth factor and then grafted to nonlesioned or lesioned adult rat spinal cords for periods of up to 1 year in vivo.

- Treatment with genetically engineered fibroblasts producing nerve growth factor or brain-derived neurotrophic factor can accelerate recovery from traumatic spinal cord injury in an adult rat.

- Intraspinal delivery of neurotrophin-3 using neural stem cells, genetically modified by recombinant retrovirus, has the potential to induce spinal cord repair.

There is a need for development of delivery methods that enable adequate supply of growth factors while restricting their distribution to target sites (03). A study in an animal model of spinal cord injury has shown that local delivery of IGF-1 and BDNF immobilized to PLGA/GO nanofibers significantly improves functional locomotor recovery, reduces cavity formation, and increases the number of neurons at the injury site (30). This method has potential as a nerve implant for spinal cord injury patients.

Clinical trials of neurotrophic factors for spinal cord injury. Currently, there are no controlled clinical trials of neurotrophic factors for spinal cord injury in the United States. Some of the clinical trials done in other countries are not listed in the U.S. Government registry. Stem cell transplantation is being done on spinal cord injury patients in some

countries outside of USA with the assumption that neurotrophic factors are released to promote regeneration, but there is no scientific documentation for this.

Concluding remarks on the use of neurotrophic factors for spinal cord injury. A review of experimental studies of use of various neurotrophic factors for repair of spinal cord injury reveals that most of these report favorable outcomes, but results are not consistent (15). The outcome depends on a number of variables such as the type of neurotrophic factor, method of delivery, site of application, dose, and whether the injury is acute or chronic. Assessment of the role of neurotrophic factors is difficult as they are often used in combination with cell or tissue grafts and/or other pharmacotherapeutic agents.

Role of neurotrophic factors in management of peripheral nerve injuries. Neurotrophic factors have well-documented abilities to support neuron survival and stimulate neurite outgrowth, making them excellent candidates for use in repairing injured nerves. A fibrin sealant containing nerve growth factor, glial cell line-derived neurotrophic factor, or acidic fibroblast growth factor has beneficial effects of repairing the transected rat sciatic nerve by local application.

Channels for releasing neurotrophic factors. Polymer channels can be loaded with various factors that enhance nerve regeneration. Basic fibroblast growth factor released from such a channel has been shown to facilitate peripheral nerve regeneration across long nerve gaps after rat sciatic nerve lesion. The release of an appropriate growth factor can enhance a specific subset of axons (eg, ciliary neurotrophic factor or brain-derived neurotrophic factor for motor neurons, and neurotrophin-3 or nerve growth factor for sensory neurons).

Combined delivery of nerve growth factor and glial cell line-derived neurotrophic factor through nerve conduits made of collagen and/or silk fibroin, with individually controlled release kinetics, facilitates synergistic activity of both on nerve regeneration (06).

Prolonged delivery of neurotrophic factors by encapsulation in microspheres. Polylactic/glycolic acid microspheres have been used for local release of various encapsulated neurotrophic factors and have shown to maintain longer bioactivity for enhancing regeneration of both sensory and motor neurons in severed rat sciatic nerves compared with administration of free neurotrophic factors (33).

Acute electrical stimulation. Acute electrical stimulation is useful for increasing axonal regeneration as well as functional recovery after nerve lesions. In an experimental study following nerve section and suture repair, electrical stimulation sped up expression of BDNF and GDNF in the dorsal root ganglia, and of BDNF and NT3 in the ventral horn (09). A combination of electrical stimulation with recombinant adenoviral vector-mediated brain-derived neurotrophic factor transfer has been shown to have a synergistic

effect in enhancing peripheral nerve regeneration in a rat model with crush-injured sciatic nerve (01).

Indications

- Acute traumatic brain injury with neurologic deficits
- Spinal cord injury with neurologic deficits
- Peripheral nerve injury
- Neural regeneration as an aid to the recovery of function
- Neuroprotection

Contraindications

No contraindications are known at present.

Outcomes

Most of the studies of neurotrophic factors are experimental, and their release is implicated in clinical trials of various methods such as mesenchymal stem cell transplantation and functional electrical stimulation. Some neurotrophic factors have already been tested in patients with spinal cord injury and have only shown partial recovery, but it is possible that administration of neurotrophic factors along with physical rehabilitation may act synergistically with significant improvement of the results (12).

Adverse effects

Adverse effects of neurotrophic factors are described in the preceding topics of this article.

Excessive concentrations of nerve growth factor may inhibit axonal growth from sensory neurons.

Special considerations

There is no experience with the use of neurotrophic factors during pregnancy.

Scientific basis

Pathophysiology of brain injuries as a basis for use of neurotrophic factors. For the discussion of the role of neurotrophic factors, relevant information for damage resulting from brain injury is as follows:

Immediate damage. Traumatic brain injury has long been thought to evoke immediate and irreversible damage to the brain. One major event taking place at the onset of traumatic brain injury is the massive ionic influx referred to as traumatic depolarization. Excitatory amino acids may play a vital role in this depolarization. This represents one of the most important mechanisms of diffuse neuronal cell dysfunction and damage associated with traumatic brain injury.

Delayed damage. There are at least 2 kinds of delayed and progressive pathobiological changes induced by traumatic brain injury. One of these is axonal damage that is not the direct consequence of traumatic tissue tearing. Rather, it results from complex axolemmal changes, cytoskeletal changes, or both, which lead to cytoskeletal collapse and impairment of axoplasmic transport. The other change is the traumatized brain's increased sensitivity to secondary ischemic insult that is triggered by a neurotransmitter storm evoked by traumatic brain injury. This relatively prolonged (greater than 24 hours) brain hypersensitivity offers a potential window for therapeutic intervention.

Delayed sequelae of traumatic brain injury include neuropsychiatric disorders and **cognitive impairment**, and even mild brain injury is recognized as a significant risk factor for the later development of **dementia**. Pathomechanisms include alterations in glucose metabolism, excitotoxicity, calcium influx, mitochondrial dysfunction, oxidative stress, and neuroinflammation. Of the neurotrophic factors, granulocyte-colony stimulating factor (G-CSF) may be particularly effective for preventing the long-term complications of traumatic brain injury because of its ability to reduce apoptosis, stimulate neurogenesis, and increase neuroplasticity (11).

Molecular events in traumatic brain injury**.** Important changes that occur at the molecular level are as follows:

- Induction of immediate early genes c-**fos** and c-jun.
- Increased levels of mRNA for inducible heat shock protein (**Hsp** 72).

- Expression of basic fibroblast growth factor gene.

- Elevations of cytokines: interleukin-1 beta, interleukin-3, interleukin-6, interferon-gamma, transforming growth factor-beta, and tumor necrosis factor. This is associated with an inflammatory response and results in **cerebral edema**. The production of interleukin-6 within the injured brain may contribute to the release of neurotrophic factors by astrocytes. Thus, the cytokines are involved in nerve regeneration by modulating the synthesis of neurotrophic factors.

Changes in neurotrophic factors in traumatic brain injury**.** Insulin-like growth factors (IGFs) and their associated binding proteins are increased following brain injury. IGF-1 not only counteracts injury-induced changes in neurotrophins but can also further increase their levels, which indicates that this growth factor could mediate repair and protective processes following brain trauma. Immunoaffinity capillary electrophoresis of serum from patients with traumatic head injury showed a marked decrease in concentration neurotrophin-3, brain-derived neurotrophic factor, ciliary neurotrophic factor, and nerve growth factor as the severity of the head injury increased (18). In a study using controlled cortical impact in rat pups, traumatic brain injury did not increase expression of brain-derived neurotrophic factor in the first 2 days after injury but decreased it later (35).

The brain has developed several strategies to protect itself against environmental insults. These include signals released from injured cells that can initiate a cascade of events in neurons and glia designed to prevent further damage. Increased oxidative stress following injury is due to the production of reactive oxygen species regulated by antioxidant enzyme activity that in turn can be influenced by nerve growth factor. Moderate hypothermia suppresses both the nerve growth factor and the antioxidant response.

Mechanisms of action of neurotrophic factors in traumatic brain injury**.** Even a mild traumatic brain injury can alter neurotrophin and neurotrophin receptor levels in the hippocampus. This may have important implications for neural plasticity and recovery of function following injury. The developing brain responds to a mild injury by modifying factors related to synaptic plasticity, and regions remote from the site of injury express neurotrophic signals potentially needed for compensatory responses. Voluntary exercise can endogenously upregulate brain-derived neurotrophic factor and enhance recovery when it is delayed after traumatic brain injury. Activity-induced enhancement of neuroplasticity may be considered for the treatment of traumatic brain injury.

Results of aerobic exercise for improving cognition, mood, and fatigue after animal experimental studies have shown that neurotrophins administered into ventricular CSF can attenuate blood-brain barrier damage following traumatic brain injury as well as examine the roles, and thereby confer neuroprotection.

NNZ-2566, a structural analog of brain-derived neurotropic glypromate (derivative of IGF-1), is an antiinflammatory and neuroprotective drug, which increases levels of both mRNA and activating transcription factor-3 (ATF3) to modulate neuroinflammation following penetrating ballistic-like brain injury (05).

Role of neurotrophic factors in mediating effect of other neuroprotective agents. Experimental studies suggest that the higher increase of nerve and peripheral vascular endothelial growth factor as mediators of response expression mediated by erythropoietin soon after the injury might explain, at least partially, better recovery of motor functions produced by erythropoietin compared to methylprednisolone and saline.

A study on a rat model of traumatic brain injury has shown that transplantation of umbilical cord-derived mesenchymal stem cells might play an important role in recovery through increasing the expression of GDNF and brain-derived neurotrophic factor (31). Transplantation of bone marrow-derived mesenchymal stem cells has been shown to improve neurologic function recovery after traumatic brain injury. However, the survival of bone marrow-derived mesenchymal stem cells after transplantation in early-stage traumatic brain injury is limited, and secretion of neurotrophic factors including neurotrophin 3 (NT3) mediate recovery of neurologic function. A mutation of NT3 gene enhances the biological function of NT3 via the reduction of the activation of the P75 signal pathway. Results of a study in mice demonstrate that administration of NT3P75-2 gene-modified bone marrow-derived mesenchymal stem cells dramatically improves neurologic function recovery after traumatic brain injury by increasing the survival of bone marrow-derived mesenchymal stem cells and ameliorating the inflammatory environment (40).

A systematic review of clinical trials that analyzed the effect of physical exercise on the peripheral levels of brain-derived neurotrophic factor in elderly individuals showed that moderate-intensity exercises increase the peripheral levels of brain-derived neurotrophic factor, but no protocol could be recommended for the type and intensity of physical exercise (NCT00619463). The results were not published. An ongoing required to produce this increase (10). A "proof-of-principle" study examined the safety and feasibility of implementing a 1-week aerobic exercise program in the postacute phase after mild traumatic brain injury (NCT02276079). The study sought to define the extent to which the exercise program improves recovery from mild traumatic brain injury in terms of relevant functional outcomes (cognition, mood, and physical status) and biomarkers

(peripheral brain-derived neurotrophic factor concentration). The study was completed in 2016, but the results have not been published.

Pathophysiology of spinal cord injury as a basis for use of neurotrophic factors. In both experimental and clinical spinal cord injury, the appearance of the lesion changes dramatically during the first few days after injury. Primary injury occurs due to mechanical factors such as impact and compression. Various secondary injury mechanisms include the following:

- Local microvascular damage
- Biochemical changes
    - Glutamate release
    - Free radical production
    - Accumulation of neurotransmitters
    - Arachidonic acid release
    - Cytokine release
- Trauma-induced autoimmune reactions
- Edema
- Loss of energy metabolism
- Electrolyte shifts

Local spinal cord lesions are often greatly enlarged by secondary damage that is accompanied by additional massive cell death.

Evolution of various biochemical changes that occurs in edema associated with spinal cord injury is like that in the brain.

Changes in neurotrophic factors following spinal injury**.** The concentration of neurotrophic factors is increased following injury, reinforcing the speculation that this has something to do with repair following injury. Some of the changes are as follows:

Basic fibroblast growth factor. An increase in the content of basic fibroblast growth factor mRNA at the injury site has been observed following contusive spinal cord injury in experimental animals. This suggests that basic fibroblast growth factor may play a role in the partial recovery of function seen following incomplete spinal cord injury.

Brain-derived neurotrophic factor and neurotrophin-3. Following spinal cord injury, the biosynthesis of brain-derived neurotrophic factor is upregulated in a different manner from that of neurotrophin-3, but both are involved in the repair mechanisms, directing the amelioration of the spinal cord injury.

Mechanisms of action of neurotrophic factors in spinal cord injury**.** Major challenges in the management of spinal cord injuries are to assure survival of damaged cells and to encourage regrowth of severed axons. Neurotrophic factors are among various new approaches that show promise for neurologic recovery and functional restoration after spinal cord injury. Neurotrophic factors can fulfill these needs by:

- Inhibition of apoptosis
- Reduction of degeneration
- Vascular proliferation
- Regeneration of transected axons
- Sprouting from intact axons

Nerve growth factor can protect the injured nerve tissues by stimulating the expression of bcl-2 protein, inhibiting the expression of Bax protein, and inhibiting the neuronal apoptosis after spinal cord injury. Neurotrophins can reduce axonal degeneration in the spinal cord after traumatic axonal injury. The delayed pattern of secondary neuronal cell loss after spinal cord injury can be ameliorated by treatment with neurotrophic factors.

Experimental studies of administration of neurotrophic factors in spinal cord injury models indicate that neurotrophic factors play a crucial role in the survival of CNS neurons in vivo during development and after injury. These observations also show that certain populations of CNS neurons depend on specific neurotrophic support after injury. Some of the effects of neural transplants in the spinal cord (embryonic tissue or Schwann cells) can be due to synthesis of neurotrophic factors by the transplanted cells. Neurotrophic factors, when combined with Schwann cell grafts, can further amplify axonal extension after injury.

In an experimental study, allogenic mesenchymal stem cells (MSCs) were transplanted intravenously or intralesionally in rats on day 1 following injury 1 (19). Regardless of the route of delivery, the MSCs transplantation following spinal cord injuries presented better behavioral improvement. The expression levels of neurotrophic factors were significantly higher in the intralesion group than those in the control group.

Neurite outgrowth has been shown to significantly increase in spinal motor neurons after co-cultured with bone marrow stem cells, whereas the secretion level of BDNF, GDNF, and NGF is significantly elevated in co-culture (26).

Continuous prolonged delivery of neurotrophic factors is not essential, and even transient delivery is enough for sustaining regenerated axons for prolonged time periods within spinal cord lesion sites. This effect is attributed to the persistence of Schwann cells in lesion or graft sites.

Role of neurotrophic factors in peripheral nerve injuries. The lesion of a peripheral nerve induces the production of factors that exert direct or indirect neurotrophic effects on CNS neurons. Neurotrophic factors are synthesized by nonneuronal cells, Schwann cells, and fibroblasts in the nerve trunk and promote axon regeneration. Neurotrophic factors that are involved in peripheral nerve regeneration include nerve growth factor, neurotrophin-3, brain-derived neurotrophic factor, ciliary neurotrophic factor, glial cell line-derived neurotrophic factor, fibroblast growth factor, and interleukin-6. Neurotrophic factors that have therapeutic potential are as follows:

- Neurotrophin-3, when infused directly over the cut sciatic nerve stump, prevents the axotomy-induced decline in conduction velocity of the sensory fibers.

- Ciliary neurotrophic factor may serve as an important neurocytokine for axonal regrowth during peripheral nerve regeneration.

- Brain-derived neurotrophic factor, infused intrathecally, promotes long-term survival of axotomized spinal motor neurons.

- Exogenously applied basic fibroblast growth factor mediates rescue effects on injured sensory neurons and supports neurite outgrowth of transected nerves. It is a promising candidate as part of various strategies for inducing regeneration of injured peripheral nerves.

- Results of animal experimental studies indicate that hepatocyte growth factor (HGF) and c-met play important roles in Schwann cell-mediated nerve repair; therefore, HGF gene transfer may be a useful method for treating traumatic **peripheral neuropathy** (22).

Neurite outgrowth promoting factors. Following nerve injury, neurotrophic factors are synthesized by nonneuronal cells (Schwann cells and fibroblasts) in the nerve trunk, thereby supporting the outgrowth of axons. Neurite-outgrowth-promoting factors on cell surfaces or in the extracellular matrix promote the extension of the axons by providing an appropriate "adhesiveness" in the substrate. Both neurotrophic and neurite-outgrowth-promoting factors are essential for axonal growth after injury.

Dorsal nerve root avulsion. Arrest of dorsal root axonal regeneration occurs following dorsal nerve root avulsion at the transitional zone between the peripheral and central nervous system. In adult rats with injured dorsal roots, treatment with nerve growth factor, neurotrophin-3, and glial cell line-derived neurotrophic factor, but not brain-derived neurotrophic factor, has been shown to result in selective regeneration of damaged axons across the dorsal root entry zone and into the spinal cord.

Pain following peripheral nerve injuries. Studies suggest that rearrangement of the synaptic circuitry of primary afferent neurons in the spinal cord may contribute, in part, to hyperalgesia, which is often associated with peripheral nerve injury. Peptides such as vasoactive intestinal polypeptide and neuropeptide Y may contribute indirectly to the nerve injury-induced increase in neurite outgrowth of sensory neurons via separate spinally derived neurotrophic factors and may provide further insight into the possible mechanisms underlying hyperalgesia associated with nerve injury.

Nerve growth factor also plays a part in painful conditions following nerve injury. After peripheral nerve crush injuries, nerve growth factor production increases dramatically. Nerve growth factor encourages the growth of sympathetic neurons and may cause them to form synapses where they do not belong. Therapeutic strategy to treat sympathetically maintained pain may be to develop compounds that neutralize nerve growth factor. Nerve growth factor is also considered to play a role in the pathogenesis of neuroma formation and in the development of **neuropathic pain**. Inhibition of nerve growth factor would, thus, be an important strategy to prevent the development of neuropathic pain due to neuroma formation.

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Dr. Jain was a consultant in neurology and had no relevant financial relationships to disclose.

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