

When Neurotrophic Factors Get on Your Nerves: Therapy for Neurodegenerative Disorders

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Issue: *Neurotrophic factors may rescue degenerating neurons and halt the progression of neurodegenerative disorders.*

In a previous BRAINSTORMS,¹ we reviewed how neurotrophic factors regulate neuronal survival as well as sprouting of axons to form new synaptic connections. Here we discuss the therapeutic potential for neurotrophic factors in disorders characterized by degeneration of neurons, loss of synapses, or both.

A growing number of neurotrophic factors have been characterized, many of which have overlapping function.² In addition, various neuronal cell populations are responsive to multiple neurotrophic factors.² This abundance of riches can make it difficult to decide how best to investigate the therapeutic potential of the different neurotrophic factors.

Hypothetically, the ideal cocktail of molecules could help nourish back to health all sorts of ailing neurons, ranging from peripheral motor and sensory nerves, to ascending and de-

scending spinal pathways, to brain stem monoamine neurons, to cortical cholinceptive neurons. Even cells in specialized sense organs such as the vestibular system, cochlea, and retina appear to be responsive to various neurotrophic factors.

No Thanks, We're Psychiatrists

Almost all of the research on neurotrophic factors has been conducted in animals, and most of the research targets are neurons involved in neurologic illnesses such as amyotrophic lateral sclerosis, various peripheral neuropathies, spinal cord trauma, Parkinson's disease, and Alzheimer's disease.²⁻⁵ The long-term therapeutic potential of neurotrophic factors should, nevertheless, be of interest to psychiatrists as well, because there

are hints that such molecules could regulate functions of neurons likely to be involved in the progressive course of schizophrenia, "kindling" in bipolar illness, and the development of treatment resistance in depression, panic, and various other disorders.^{2,6}

Although such clinical applications are a long way off, new understanding about how neurons survive and innervate their targets of communication is evolving at an ever-quicken pace. Applying knowledge of the actions of neurotrophic factors and recognition molecules that help guide sprouting axons^{7,8} might someday increase the odds that dysfunctional neurons in the mature nervous system will be salvaged, or even that desirable synaptic connections could be facilitated.²

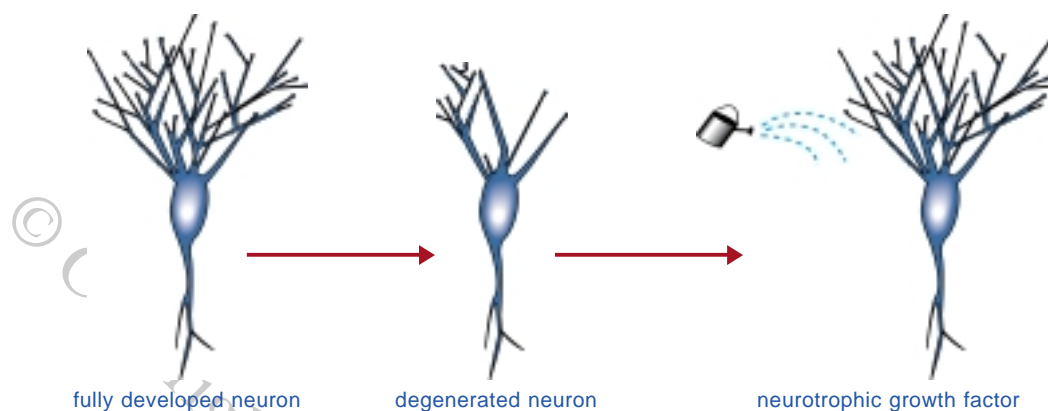
Take-Home Points

- ◆ Deficiencies in neurotrophic factors may cause neurons to degenerate
- ◆ Growth factors may get on your nerves by direct delivery of the growth factor itself, by stimulators of local production, or by delivery of genes for the growth factor
- ◆ Future psychiatric applications will encompass halting disease progress and treatment refractoriness in schizophrenia, bipolar, anxiety, and cognitive disorders

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You Can't Get There From Here

There are numerous problems in using neurotrophic factors as therapeutics. Such a large quantity of neurons are responsive to them that systemic administration may well activate all kinds of axonal sprouts that are not desired. Perhaps high doses or chronic use could be mitogenic, increasing the risk of cancer. When neurotrophic factors have been administered experimentally to both animals and humans, some unexpected consequences have been observed including appetite suppression, weight loss, increased pain perception, and muscle aches.² Thus, localized administration to the desired site of action, or site-selective actions of systemically administered neurotrophic factors, may be required if treatment is going to be safe.

To complicate application of this research, growth factors are large protein or peptide molecules unable to survive intact when orally administered and unable to cross the blood-brain barrier when administered intravenously. This has led to at least 5 approaches to delivering neurotrophic factors to their desired targets in the central nervous system. First, the protein itself can be infused directly into the cerebrospinal fluid or implanted in a biodegradable, slow-release preparation. Second, the active protein can

get a trip across the blood-brain barrier by hiding inside a "Trojan horse" molecule that is normally translocated across the barrier. Third, chemists might be able to make low molecular weight versions of trophic factors that can pass the blood-brain barrier. Fourth, a low molecular weight drug may be able to get into the brain and pharmacologically induce the formation of a trophic factor. This action, in fact, has been suggested for cholinesterase inhibitors, which not only increase acetylcholine levels, but subsequently increase nerve growth factor. Finally, a high-tech idea is to transfer genes that produce the trophic factor directly into the brain by grafting cells that normally make it, or by genetically engineering them to make it, or by delivering the gene in a carrier virus. All of these possibilities are under active investigation.

Ongoing Clinical Investigations

Some neurotrophic factors have actually been tested in man. Chemotherapy-induced peripheral neuropathy has been tested with a synthetic neurotrophic analogue and has shown promising results.² Nerve growth factor (NGF) is in early testing in diabetic neuropathy.² Ciliary neurotrophic factor (CNTF) has been studied in amyotrophic lateral sclerosis but failed to demonstrate efficacy and

caused excessive toxicity.² NGF infused intrathecally into one Alzheimer patient had no clear clinical effects, but changed cholinergic functioning and increased cerebral blood flow.²

Many more studies are planned, and a great many neurotrophic factors and chemically modified analogues are being developed. Someday it may be possible for neurotrophic factors to get on our nerves. ♦

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