Brain Tonics for Brain Sprouts: How Neurotrophic Factors Fertilize Neurons

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Issue: *Numerous neurotrophic growth factors help determine which neurons develop in the immature brain and which are retained in the adult brain. Neurotrophic factors can also induce neurons to sprout axons capable of growing into new locations and forming new synaptic connections, a process that continues in the mature brain.*

Brain Tonics

Neurotrophic factors regulate both the survival and growth of various populations of neurons in the central and peripheral nervous systems.[1,2] Recent research has generated a virtual explosion of information on dozens of different neurotrophic factors and their effects on various types of neurons (see Table).

Some growth factors act not only on numerous populations of neurons, but also on non-neuronal cells as well.[1] Furthermore, individual neurons do not necessarily respond only to a single neurotrophic factor. Sorting out the effects of different combinations of growth factors on various CNS neurons, and the molecular mechanisms of their actions is an exciting chapter in contemporary neurobiology.

What Are Neurotrophic Factors?

A vast array of molecules are now known to exert neurotrophic actions on various neuronal populations (Table).[1–3] A veritable alphabet soup of neurotrophic factors contributes to the brain broth of chemicals that bathe and nourish nerve cells. Many of this ever-expanding list appear in the Table and include not only those related to nerve growth factor (NGF), but also another important family of neurotrophic factors called glial cell line–derived neurotrophic factor (GDNF). Still others are part of an ever-expanding list.

This Neuron Stays, That Neuron Goes

The brain first produces a vast oversupply of neurons in early development, but turns right around and removes most of them even before birth, in part through the actions of neurotrophic factors that help determine which are preserved and which are removed. A key mechanism for removing seemingly unwanted "extra" neurons is a process called apoptosis, discussed in an earlier BRAINSTORMS.[4] Neurotrophic factors, in fact, can trigger neurons to commit apoptotic cellular suicide.

Why the brain makes so many neurons only to kill them off later may be to ensure that enough neurons are deposited in the brain bank so that the fittest survivors can be used for a lifetime. Recall that neurons probably cannot replicate in the mature brain, so the ones drafted into service better be able to last a lifetime. The brain seems to choose which nerves live or die partially by whether a neurotrophic factor nourishes them or chokes them to death.[1–3] That is, certain molecules (like NGF) can interact at pro-apoptotic "grim reaper" receptors (such as p75) to trigger apoptotic neuronal demise. However, if NGF decides to act on a neuroprotective "bodyguard" receptor (such as Trk A), the neuron prospers.

These processes continue in the mature brain and may help determine

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Take-Home Points

Neurotrophic growth factors can

- act as molecular bodyguards that stimulate anti-apoptotic receptors on neurons to help ensure their survival
- select neurons for apoptotic demise by targeting pro-apoptotic receptors, thus helping to eliminate neurons
- signal axons to sprout and then cause various guidance molecules to be released in order to direct the sprouts to appropriate targets

whether a neuron stays or is destroyed. Apoptotic neuronal removal may still be beneficial in the adult brain, but chances are that this is an even more prominent factor in pathologic conditions such as neurodegenerative disorders. Using neurotrophic factors to salvage degenerating neurons is a new treatment strategy and will be featured in the June edition of BRAINSTORMS.

Brain Sprouts

Neurotrophic factors can also cause axons to sprout,[1–3] and specific factors may encourage formation of a motile tip, called a growth cone, on the axon. Axonal migration in the immature brain is characterized by spurts of axonal growth interrupted by growth cone collapse. As development progresses, cellular migration and the distance that axons can travel is greatly impeded, but this capacity is not completely lost.[2,3]

Neurotrophic factors may help direct axonal growth cones to grow toward their targets by signaling neurons and glia along the desired pathway to secrete a variety of recognition molecules.[1–3] These guidance molecules repel or attract growing axons, directing axonal journeys like a traffic cop. (Recognition molecules will be featured next month in BRAINSTORMS.)

Table
Neurotrophic Factors:
An Alphabet Soup of Brain Tonics

NGF	nerve growth factor
p75	pro-apoptotic receptors
Trk A	anti-apoptotic receptors
GDNF	glial cell line–derived neurotrophic factor, which includes neurturin, c-Ref, and R-alpha
BDNF	brain-derived neurotrophic factor
NT-3, 4, & 5	neurotrophins 3, 4, and 5
CNTF	ciliary neurotrophic factor
ILGF I & II	insulin-like growth factors
FGF	fibroblast growth factor, which comes in both acidic and basic forms
EGF	epidermal growth factor

Use It or Lose It

It is not clear how the brain dispenses its neurotrophic factors endogenously during normal adult physiologic functioning. Presumably, demand to use neurons is met by keeping them fit and ready to function—a task accomplished by salting the brain broth with neurotrophic factors that keep the neurons healthy.[2,3] Do thinking and learning provoke the release of neurotrophic factors? Are neurons preserved and new connections made if the brain stays active? Can the brain lose its strength without mental exercise? Does long-term lack of use signal apoptotic demise due to neuronal inactivity? Could psychotherapy induce neurotrophic factors to preserve critical cells and innervate new therapeutic targets to alter emotions and behaviors? Only future research will teach us how to balance seasonings in the tender stew of the brain. ◆

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