Is There Nicotinic Modulation of Nerve Growth Factor? Implications for Cholinergic Therapies in Alzheimer’s Disease

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Studies on the neurobiology of nerve growth factor (NGF) reveal a diverse range of actions. Through alterations in gene expression, NGF is important in maintaining and regulating the phenotype of neurons that express the high-affinity receptor, trkA. Nerve growth factor also has a rapid action, revealed by its role in pain signaling in bladder and in skin. In the central nervous system (CNS), NGF has an intimate relationship with the cholinergic system. It promotes cholinergic neuron survival after experimental injury but also maintains and regulates the phenotype of uninjured cholinergic neurons. In addition to these effects mediated by gene expression, NGF has a rapid neurotransmitter-like action to regulate cholinergic neurotransmission and neuronal excitability. Consistent with its actions on the cholinergic system, NGF can enhance function in animals with cholinergic lesions and has been proposed to be useful in humans with Alzheimer’s disease (AD); however, the problems of CNS delivery and of side effects (particularly pain) limit the clinical efficacy of NGF. Drug treatment strategies to enhance production of NGF in the CNS may be useful in the treatment of AD. Nicotine is one such agent, which, when administered directly to the hippocampus in rats, produces long-lasting elevation of NGF production. Biol Psychiatry 2001;49:185–193 © 2001 Society of Biological Psychiatry

Key Words: Neurotrophin, hippocampus, acetylcholine, glutamate, NGF, trkA

Introduction

Nerve growth factor (NGF) is the prototypic neurotrophic factor. In humans and other mammals, the neurotrophins comprise a family of four similar proteins named NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5) (Lindsay et al 1994). The first member of this family to be characterized was NGF, and it remains the best studied. This molecule exists as a dimer of two identical polypeptide chains, each of 118 amino acid residues (McDonald and Blundell 1991). All neurotrophins have a similar overall structure, with a small number of amino acid differences between the neurotrophins determining the specificity of receptor binding.

The best understood neurotrophin receptors are the family of proteins known as tyrosine receptor kinase (trk). Within this family are three distinct but closely related receptors known as trkA (p140^trk), trkB, and trkC. Each trk receptor subunit crosses the cell membrane a single time. The extracellular portion of each trk forms the neurotrophin-binding site, with differences in amino acid residues determining binding selectivity. NGF binds to trkA, BDNF, and NT-4/5 bind to trkB. Neurotrophin-3 binds relatively selectively to trkC but also can bind to trkA and trkB (Ultrech et al 1999). The intracellular portion of the receptor contains a tyrosine kinase (TK) domain and various sites that can dock with other proteins.

Binding of NGF to trkA causes receptor dimerization, enabling an active complex of two trk receptor subunits with the neurotrophin molecules to be formed. This change of shape results in phosphorylation of three tyrosine residues on each subunit within the TK domains. The activated TK domains catalyze the phosphorylation of several adjacent tyrosine residues within the intracellular regions of each receptor subunit. These phosphorylated regions are then able to dock with, and activate by phosphorylation, a number of enzymes and proteins in the nerve ending (Figure 1A). Docked proteins bind to additional proteins and activate them (Figure 1A). Thus, a large number of signaling proteins become recruited and activated as a consequence of NGF binding to the trk receptor. These include phospholipase C gamma, which mediates phospholipid hydrolysis, and a number of protein kinases (including PI3 kinase, S6 kinase, protein kinase C, and mitogen-activated protein [MAP] kinase), which are capable of phosphorylating a wide range of target proteins.
The complex cascade of intracellular signaling events underlies the biological effects of the neurotrophins (Friedman and Greene 1999).

The complex of NGF/trkA with docked proteins, including phospholipase C gamma, is endocytosed at the synapse to form signaling complexes that are retrogradely transported along the axon to the cell body (Grimes et al 1996). When the signaling complex reaches the neuronal cell body, it will phosphorylate transcription factors, including cAMP response element-binding protein (CREB), which can then enter the nucleus (Riccio et al 1997). In this manner, trk receptor activation is directly linked to alteration of gene expression. Alterations in the pattern of gene expression underlie the maintenance, survival, and plasticity effects of NGF and other neurotrophins on their target neurons. In addition to these events, which would be predicted to occur hours to days after neurotrophin binding to trk receptors, there is an increased awareness that NGF and other neurotrophins can exert more rapid effects on neurotransmitter synthesis, release, and the electrical activity of neurons by altering the activity of proteins involved in synaptic transmission (Figure 1B).

Another neurotrophin receptor exists, named p75<sup>NTR</sup>, a member of the TNF receptor/Fas/CD40 superfamily. p75<sup>NTR</sup> binds to NGF and other neurotrophins with approximately equal affinity (Chao 1994). Receptor activation stimulates several intracellular events that are quite distinct to those mediated by trk receptors. The p75<sup>NTR</sup> receptor does not contain tyrosine kinase activity but instead mediates several distinct biochemical effects including sphingolipid hydrolysis and activation of the c-Jun amino terminal protein kinase (JNK) signaling pathway (Friedman and Greene 1999).

Current evidence suggests that for cells that express p75<sup>NTR</sup> but not a trk receptor, the dominant effect of neurotrophin-mediated p75<sup>NTR</sup> signaling is cell death. Neurotrophin signaling through p75<sup>NTR</sup> plays an important role in programmed cell death during the development of the nervous system (Friedman and Greene 1999). In some cholinergic neurons of the central nervous system (CNS), and in all neurotrophin-sensitive sensory and sympathetic neurons in the peripheral nervous system, p75<sup>NTR</sup> is coexpressed with one or more trk receptors. For these neurons, the death signals from p75<sup>NTR</sup> activation are suppressed by interactions with trk or signals from trk.
In this case, cell death does not occur in response to neurotrophins; instead p75NTR signaling somehow modulates the effect of trk receptor activation to suppress the death signal.

**Models for NGF Effects: Lessons from the Peripheral Nervous System**

Until recently, our knowledge of the functions of NGF and the other neurotrophins has arisen from studies of the developing nervous system. The neurotrophic concept states that the tissue to be innervated by a particular group of neurons produces a limiting amount of a trophic factor that, during a critical stage in target innervation, binds to receptors, is internalized, and retrogradely transported to the cell bodies of these neurons. This supply of neurotrophin is critical to the development of an appropriate phenotype and connectivity of the target neuron. For developing neurons at least, a supply of the appropriate neurotrophins is essential for cell survival. These concepts have been extensively tested and refined, particularly in the peripheral nervous system.

In the adult, neurotrophin expression continues to be widespread, suggesting a role of these factors beyond that of neuronal development. For example, NGF is produced by many peripheral tissues, in particular, the skin and other tissues that receive a rich sensory or sympathetic innervation. Many sympathetic neurons in the adult express trkA (and p75NTR) receptors, as do a class of primary sensory neurons that are particularly important in acute and inflammatory pain (McMahon 1996; Snider and McMahon 1998). Although it is clear that subgroups of sensory neurons retain their sensitivity to neurotrophins, it is also clear that a supply of neurotrophins is not necessary for the survival of these responsive neurons. Therefore, a new appreciation of the roles of these factors is emerging that does not fit with the classical neurotrophic concept: NGF is now known to play a role in cell survival after injury, regeneration, collateral sprouting, neuronal size and complexity, expression of transmitters, and neuronal sensitivity (McMahon et al 1995; McMahon 1996; Woolf 1996).

In the context of the adult nervous system, NGF is the best studied of the neurotrophins. Numerous studies have tested in vivo the effects of either administering exogenous NGF or sequestering naturally produced NGF. These experiments show that it can alter neuronal gene expression in sensory neurons (e.g., Michael et al 1997; Woolf 1996). Inflammatory injuries cause increased levels of NGF in peripheral tissues and therefore increase the exposure of sensory neurons to NGF (McMahon et al 1995; Woolf et al 1994; Woolf 1996). Under these conditions, NGF-dependent changes occur in the excitability and in the responsiveness of neurons to stimuli. Underlying these effects are alterations in neurotransmitter and neuropeptide release and in the sensitivity of neurons by alterations in neurotransmitter receptors and ion channels (e.g.; Fjell et al 1999; Malcangio et al 1997; McMahon 1996; Woolf et al 1996). Furthermore, NGF can induce morphologic changes, such as sprouting and outgrowth in responsive sensory or sympathetic axons, particularly after injury (e.g., Ramer et al 2000). These effects are all consistent with increased retrograde transport of trkA signaling complexes that alter gene expression in the NGF-responsive neurons.

One of the unexpected discoveries from these experiments was that NGF could produce changes in neuronal excitability and behaviors that are inconsistent with the time course of receptor internalization, retrograde transport, and gene expression. One example of this phenomenon comes from a model of chemical inflammation of the rat bladder. About 30 min after exposure of the bladder to an irritant, there is a behavioral and electrophysiologic response corresponding to pain. This rapid response, analogous to pain in humans, is dependent on NGF, confined to the population of sensory nerve fibers that express trkA, and involves the rapid induction of NGF mRNA and protein in the inflamed tissue (Dmitrieva et al 1997; Oddiah et al 1998). These results strongly suggest that NGF has direct and rapid actions on neuronal excitability and that these effects occur too quickly to be mediated by retrograde transport of signaling complexes.

**NGF and the Basal Forebrain Cholinergic System**

In contrast to the periphery, NGF expression in the central nervous system is much more restricted; NGF mRNA and protein are expressed in a number of brain regions, with the hippocampus providing the single largest source of NGF in the entire CNS (Korsching et al 1985). In the hippocampus, NGF messenger RNA and protein is expressed by the principal excitatory (glutamate) neurons in the hippocampus, as well as by a subset of γ-aminobutyric acid-containing inhibitory neurons (Rocamora et al 1996). These hippocampal target cells receive rich innervation from ascending neurons with their cell bodies in the basal forebrain.

Numerous studies have demonstrated that cholinergic neurons are responsive to NGF. All cholinergic neurons express trkA (Holtzman et al 1995). The distribution of p75NTR is more restricted than trkA, being expressed by subsets of cholinergic cells, notably the cholinergic neurons of the basal forebrain (Batchelor et al 1989). Cholinergic neurons account for nearly all of the NGF-responsive neurons in the CNS, although there are groups of noncho-
linergic neurons that express trkA, including some of the principal cells of the hippocampus (Cellerino 1996; Holtzman et al 1995). There are no noncholinergic neurons known to express p75NTR, but this receptor is expressed by some hippocampal astrocytes (Dougherty and Milner 1999). The distribution of NGF and its receptors suggests an intimate and precise interrelationship between cholinergic neurons and their NGF-producing targets.

Given that NGF is expressed in the targets for cholinergic neurons and that cholinergic neurons are responsive to NGF, it may be expected that NGF would have a classic neurotrophic role to mediate cholinergic cell survival during development; however, studies using transgenic mice deficient in NGF or trkA suggest that in prenatal and early postnatal periods there is little, if any, cholinergic cell loss in the CNS (Chen et al 1997; Crowley et al 1994; Fagan et al 1997; Ruberti et al 2000). This absence of central cholinergic deficits contrasts with the notable absence of sensory neurons observed in the NGF knockout transgenic animals prenatally and postnatally (Crowley et al 1994). These results clearly show that NGF is not critical for basal forebrain cholinergic neuron survival during development. Although basal forebrain cholinergic neurons are responsive to NGF during their development, other trophic factors are required for their survival. The actual survival factors are unknown, but it is clear that developing cholinergic neurons are responsive to a number of trophic factors, particularly BDNF (Ward and Hagg 2000) and maintain this responsiveness in adult life (Koliatsos et al 1994).

To what extent NGF is necessary as a survival factor for adult cholinergic neurons remains controversial. It promotes the survival of cholinergic neurons after axotomy (Hefti 1986; Kromer 1987; Williams et al 1986). Measuring the effects of reduced availability of NGF to undamaged cholinergic neurons has been technically difficult. Partial removal in vivo of the NGF supply to cholinergic neurons in transgenic animals or near-complete removal by ablation of the hippocampus causes severe cholinergic neuronal atrophy, with little or no neuronal death (Chen et al 1997; Sofroniew et al 1993). These studies have been interpreted to mean that NGF is not a survival factor for cholinergic neurons in the adult; however, a more recent study using a transgenic mouse that lacks NGF and survives to adulthood suggests that a complete lack of NGF in vivo in the adult does cause cholinergic cell loss in the basal forebrain (Ruberti et al 2000).

As outlined above, reduction in the NGF supply to basal forebrain cholinergic neurons causes atrophy in cholinergic neurons. These changes are reminiscent of the cholinergic neuronal changes in Alzheimer’s disease (AD). In AD, however, there is no evidence that it is NGF deficiency that causes cholinergic cell loss. In fact, measurements in postmortem brains from AD patients show that there is no change in the capacity of the CNS to produce NGF (mRNA levels) with increased levels of NGF protein in the cortex and hippocampus (Fahnstock et al 1996; Hock et al 1998; Jette et al 1994; Scott et al 1995). Increased NGF levels are thought to reflect a decreased ability of cholinergic neurons to retrogradely transport NGF.

In the adult, NGF influences the messenger RNA levels, structural plasticity, response to injury, and maintenance of basal forebrain cholinergic neurons. Administration of NGF to the uninjured CNS causes a number of effects on cholinergic neurons, including hypertrophy, sprouting, upregulation of NGF receptors, increased levels of choline acetyltransferase (ChAT), and increased choline uptake (Heisenberg et al 1994; Higgins et al 1989; Lapchak et al 1992; Mobley et al 1985). These results are all consistent with a role of NGF to maintain the cholinergic phenotype through retrograde transport of the NGF/trkA signaling complex from cholinergic nerve terminals in the hippocampus to the cell bodies in the basal forebrain (Seiler et al 1984).

There are also rapid actions of NGF on cholinergic neurons. It can rapidly increase acetylcholine release and choline uptake in synaptosomes (Knipper et al 1994), an effect that cannot include effects via gene expression because the cell bodies are not present in these preparations. Similarly, in cultured septal neurons, NGF has been shown to produce rapid increases in intracellular calcium levels, a stimulus known to enhance neurotransmitter release (Nonner et al 2000). It has been shown to cause rapid increases in the firing rate of cholinergic neurons (Albeck et al 1999). In other types of neurons, NGF can cause rapid activation of calcium-dependent potassium channels (Holm et al 1997) and voltage-sensitive calcium channels (Jia et al 1999), actions that may underlie NGF effects on cholinergic neuronal excitability and acetylcholine release. These findings fit well with the emerging evidence that neurotrophins can behave as neurotransmitter-like molecules. In fact, in a similar manner to a neurotransmitter, NGF can be released by neurons upon depolarization (Blöchl and Thoenen 1995).

Altogether, these studies suggest that NGF does not have a classic neurotrophic role in cholinergic cell survival. Instead, it is an important regulator of cholinergic neuron morphology and function and would be predicted to maintain, or even improve, cholinergic function in AD in three ways. First, increases of NGF levels in appropriate regions of the CNS would be predicted to promote the survival of degenerating or damaged cholinergic neurons. Second, such increases would be predicted to promote sprouting and enhance neurotransmitter synthesis in uninjured cholinergic neurons. Third, they would be predicted to enhance cholinergic neuronal firing and transmitter release through actions independent of retrograde signaling and gene expression.
Nerve Growth Factor, Cognition, and Alzheimer’s Disease

On the basis of the data described above, NGF, through its effects on the cholinergic system, may be predicted to improve cognitive functions in AD. Animal studies strongly support this notion and have shown that NGF can enhance performance in behavioral cognitive tasks (Gustilo et al. 1999; Pellymounter et al. 1996) and slow cognitive decline in aged rats (Martinez-Serrano and Bjorklund 1998). It has been shown to have a role in physiologic correlates of memory acquisition in the hippocampus (Bergado et al. 1998). Conversely, reduction of NGF levels appears to have a detrimental effect on learning and cognitive behaviors. Animals with reduced levels of NGF (anti-NGF antibodies, transgenic animals) show impaired spatial learning (Chen et al. 1997; Van der Zee et al. 1995).

From the evidence outlined above, it is likely that increased exposure of NGF to cholinergic neurons will be beneficial in AD. Because NGF does not cross the blood–brain barrier, and there are no small molecule agonists available, at present NGF must be delivered directly to the central nervous system. Experimental methods include gene transfer, cell grafts, or direct administration of NGF through intracerebroventricular infusion (Eagle et al. 1995; Gustilo et al. 1999; Hefti 1986; Kromer 1987; Martinez-Serrano and Bjorklund 1998; Williams et al. 1986; Winkler et al. 2000; Wyman et al. 1999). In general, in animals with deafferentation lesions and impaired cognitive function, these approaches have been shown to enhance cholinergic neuron integrity and restore some behavioral functions.

In AD patients, there is limited evidence at present that NGF may be beneficial. Treatment with NGF was tested in three patients, with no clear improvement in cognitive function (Eriksdotter Jonhagen et al. 1998). In this study, the potential therapeutic benefits of NGF infusion were offset by severe pain. Large quantities of NGF administered over long periods are likely to diffuse to affect the peripheral nervous system and cause pain. These peripheral side effects at present limit the therapeutic use of intracerebroventricular NGF. In addition to the painful side effects in humans, recent animal studies document a number of adverse behavioral effects and Schwann cell proliferation after high doses of NGF administered by the intracerebroventricular route (Winkler et al. 2000). On this basis, alternative means of delivering NGF to the CNS must be considered. In the future, gene therapy and transplantation techniques may prove successful, but these strategies are confined to the laboratory at present.

It may be possible to use pharmacologic approaches to increase the production of NGF within the CNS. The potential advantages of this strategy are that NGF should be induced in the correct brain regions. In addition, this approach is likely to circumvent the peripheral side effects of NGF and would not require surgical procedures. Nerve growth factor mRNA expression and protein secretion are tightly linked and can be regulated by a variety of compounds in vitro, including known drugs that act on neurotransmitter receptors (reviewed in Bennett et al. 1999). Therefore, numerous agents have the potential to enhance NGF expression and secretion in the brain.

A number of nonclassic compounds have shown to increase synthesis of NGF in astrocytes. These drugs include a phosphodiesterase inhibitor, propentofylline (Rother et al. 1998) and various quinone derivatives, such as idebenone, pyrroloquinoline quinone, and 1,4-benzoquinone (Takeuchi et al. 1990; Yamada et al. 1999; Yamaguchi et al. 1993). It is argued that these drugs may improve cholinergic neuron survival and enhance cognitive performance via increasing astrocyte secretion of NGF. How these drugs modulate NGF levels is unknown, and it is not known whether their clinical or preclinical efficacy in AD (if any) resides specifically in the ability of these compounds to increase NGF levels.

Cholinergic and Glutamatergic Regulation of NGF Levels: Prospects for AD Treatment

In AD there is extensive loss of cholinergic and glutamatergic input into the hippocampus (reviewed in Francis et al. 1993, 1999). Loss of nicotinic acetylcholine receptors is a clear finding in AD (Court 2001; Nordberg 2001), suggesting that fast cholinergic transmission is particularly affected in the disease. In the hippocampus, nicotinic receptors effect multiple neurotransmitter systems, which may underlie the cognitive enhancing effects of nicotinic receptor agonists and opposite effects of nicotinic antagonists. In addition to effects on classical neurotransmitter systems, it is possible that the cholinergic and glutamatergic inputs may be endogenous regulators of NGF in the hippocampus—and therefore that hippocampal NGF can be regulated by conventional and novel drugs targeted to the cholinergic or glutamatergic systems.

Several studies have measured NGF mRNA or protein levels after deafferentation lesions, using chemical or surgical procedures to remove the cholinergic or glutamatergic input to the hippocampus (Table 1). Although these studies show that glutamate and acetylcholine neurons are regulators of NGF, the results are difficult to interpret. Selective deafferentation lesions of the cholinergic neurons of the septohippocampal system cause upregulation of NGF levels in the hippocampus that is most prominent weeks to months after experimental injury (Table 1); however, if a more destructive lesion (fimbria fornix...
transection) is used, which cuts the axons of both the cholinergic and noncholinergic septohippocampal neurons, there is a long-lasting downregulation of NGF mRNA in the hippocampus (Table 1). Surgery to reduce glutamate input into the hippocampus produces upregulation of NGF levels (Table 1). These studies broadly suggest that CNS lesions mimicking the hippocampal deafferentation in AD lead to upregulation of NGF levels in targets and that NGF levels are subject to complex control mechanisms. It is difficult to extrapolate these findings into AD, where there is little if any change in NGF mRNA, but rather enhanced levels of protein due to impaired retrograde transport of NGF.

Because the lesion studies suggest that cholinergic and glutamatergic afferents regulate NGF production in the hippocampus, cholinergic drugs, glutamatergic drugs, or both may be effective inducers of NGF. Nicotinic drugs, as well as drugs that enhance acetylcholine transmission, are effective in improving cognitive function in both normal humans and in AD patients (Francis et al 1999; Newhouse 2001), and there is the interesting possibility that they may influence NGF. Perhaps surprisingly, there are few studies to have looked at this possibility in vivo. A recent study has tested the effects of local administration of cholinergic drugs into the hippocampus on neurotrophin mRNA levels (French et al 1999). Drug doses were carefully chosen in relation to previous studies, and only doses that caused no hippocampal neuronal death and did not cause seizures were used.

Nicotine, when injected into the hippocampus, caused a persistent increase in NGF mRNA levels in the principal neurons of the hippocampus that emerged 2 to 4 hours after drug administration and was still apparent 72 hours after drug administration, the last time point analyzed in the study. This contrasted with the muscarinic receptor agonist pilocarpine, which produced a very transient increase in NGF mRNA levels (French et al 1999). The effect was also highly selective for NGF, because BDNF mRNA levels showed a rapid and transient increase after nicotine administration (French et al 1999). The nicotine-induced increase of NGF mRNA levels was blocked by N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate glutamate receptor antagonists, consistent with the increase being dependent on nicotine-induced release of glutamate within the hippocampus (Gray et al 1996). The study strongly suggests that quite large and long-lasting induction of NGF in appropriate

Table 1. Afferent Regulation of Nerve Growth Factor (NGF) Levels in the Hippocampus

<table>
<thead>
<tr>
<th>Deafferentation lesion</th>
<th>Effect</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>AF64A lesion of septohippocampal cholinergic neurons</td>
<td>↑ NGF protein and mRNA 7 weeks after lesion</td>
<td>Hellweg et al 1997</td>
</tr>
<tr>
<td>Ig92 saporin lesion of septohippocampal cholinergic neurons</td>
<td>↑ NGF protein, 3 months after lesion</td>
<td>Gu et al 1998</td>
</tr>
<tr>
<td></td>
<td>↑ NGF protein, 2 weeks after lesion</td>
<td>Rolfler et al 1997</td>
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<tr>
<td></td>
<td>No change NGF mRNA</td>
<td>Yu et al 1995</td>
</tr>
<tr>
<td></td>
<td>1 week–5 months after lesion</td>
<td></td>
</tr>
<tr>
<td>Fimbria fornix transection removing cholinergic and other inputs</td>
<td>↓ NGF mRNA</td>
<td>da Penha Berzaghi et al 1993</td>
</tr>
<tr>
<td></td>
<td>↑ NGF protein 10 d after lesion</td>
<td>Laphak et al 1992</td>
</tr>
<tr>
<td>Angular bundle transection and/or entorhinal cortex lesion</td>
<td>↑ NGF mRNA</td>
<td>Gasser et al 1986</td>
</tr>
<tr>
<td></td>
<td>↑ NGF mRNA (rapid)</td>
<td>Forster et al 1997</td>
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<tr>
<td></td>
<td>↑ NGF protein 3.8 d after lesion</td>
<td>Conner et al 1994</td>
</tr>
</tbody>
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Figure 2. Nicotinic–nerve growth factor (NGF) interactions in the hippocampus. Current evidence suggests that local infusions of nicotine into the hippocampus increases NGF messenger RNA levels. The results are consistent with the model whereby acetylcholine (ACh) is released from nerve terminals to activate nicotinic receptors on glutamatergic neurons. Glutamate is released and via α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), N-methyl-D-aspartate (NMDA) receptors, or both, it stimulates NGF production in cells intrinsic to the hippocampus. Nerve growth factor will activate trkA receptors on the cholinergic nerve terminals, providing trophic support and influencing the activity of these neurons to further enhance ACh release.
CNS regions can be achieved with drug doses that are pharmacologically relevant.

These findings suggest a model of reciprocal interaction between cholinergic afferents and NGF-producing principal neurons in the hippocampus (Figure 2), an idea developed by other researchers (e.g., Knipper et al 1994; Yu et al 1995), which provides a testable concept for future studies. The model shown in Figure 2 defines a reinforcing loop whereby acetylcholine release elevates NGF production, and then NGF affects acetylcholine neurons to provide trophic support and further enhance acetylcholine synthesis and release. The implications of this model are that some cholinergic drugs may have cognitive enhancing effects beyond their primary effects as cholinesterase inhibitors and receptor agonists. A number of cholinergic drugs, including nicotinic receptor agonists, are currently in development for use in AD (Francis et al 1999). It is possible that in addition to having direct effects on cognition (e.g., Newhouse 2001), this kind of drug may provide a positive neurotrophic influence to the cholinergic neurons that may help both to prevent their degeneration in AD and to enhance cholinergic neurotransmission.

Some of the work presented in this article was supported by the Wellcome Trust and the Medical Research Council of Great Britain.

I gratefully acknowledge my collaborators on these projects: Michael V. Sofroniew, John V. Priestley, and Stephen B. McMahon.

Aspects of this work were presented at the symposium "Nicotine Mechanisms in Alzheimer’s Disease," March 16–18, 2000, Fajardo, Puerto Rico. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted educational grant provided by Janssen Pharmaceutica LP.

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