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Neurotrophins and Their Receptors—Current Concepts and Implications for Neurologic Disease

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Nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4/5 are members of a family of proteins (the neurotrophins) that promote the differentiation, growth, and survival of peripheral and central nervous system neurons. Recently, the trk family of proto-oncogenes has been found to encode signal-transducing receptors for these growth factors. This discovery has important implications for our understanding of the normal function of these factors in the developing and adult nervous system. In this review, we highlight recent advances in neurotrophin research and discuss their relevance to neurologic disease. © 1993 Academic Press, Inc.

INTRODUCTION

The neurotrophins are factors that regulate the growth and survival of selected peripheral and central nervous system neurons. As *trophic* (survival-promoting) and *tropic* (directing axon growth) factors, they have been investigated for use in treatment of several types of neurodegenerative disease, peripheral neuropathy, and nervous system cancer. In this paper, we discuss recent advances in neurotrophin research and review their therapeutic potential for human disease.

NERVE GROWTH FACTOR

Nerve growth factor (NGF) was discovered as a sarcoma-derived substance that stimulated the outgrowth of dorsal root ganglion neurons (118). It is now recognized to be a survival and differentiating factor for neural crest sensory neurons and sympathetic and basal forebrain cholinergic neurons (106, 142, 201). In addition, NGF is a proliferative factor for striatal neuroepithelial precursors (27) and possibly an activity-dependent organizer of the visual cortex (21, 39). As a target-derived trophic factor, NGF is released at innervation sites, where it is internalized at nerve terminals and retrogradely transported back to the cell body (77, 110, 178). By controlling survival at the time of target innervation, NGF can help regulate the size and connectivity of neuronal populations.

Biologically active NGF consists of two noncovalently linked peptide chains (5, 156). Each chain is comprised of 118 amino acids that includes 6 strictly conserved cysteines (4). In its crystal structure, the NGF dimer contains three antiparallel pairs of β-strands (125). Variable residues located in three hairpin loops are believed to contribute to different biological properties observed among members of the nerve growth factor family.

THE NEUROTROPHIN GROWTH FACTOR FAMILY

In 1982, Barde and colleagues isolated a trophic factor from pig brain that promoted the outgrowth of spinal sensory neurons (14). That protein, known as brain-derived neurotrophic factor (BDNF) was cloned in 1989 and found to share close sequence homology with NGF (50% sequence identity) (118). BDNF supports the survival and outgrowth of neural crest-derived and placode-derived sensory neurons, parasympathetic nodose ganglion neurons, dopaminergic striatal neurons, basal forebrain cholinergic neurons, retinal ganglion neurons, and cranial and spinal motoneurons, but not sympathetic neurons (118, 150, 163, 176, 215). In addition to its survival and outgrowth-promoting activities, BDNF may also play a role in the cell fate determination of primary sensory neurons (180) and the activity-dependent organization of visual cortex (26). Across species lines, BDNF appears to have a higher degree of sequence conservation than nerve growth factor (65).

In 1991, neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) were cloned using the polymerase chain reaction and sequence identities shared between BDNF and NGF (23, 44, 70, 79, 95, 96, 127, 164). Mature NT-3 shared 50 identical amino acids in common with NGF and BDNF, including 6 cysteine residues. Across species lines, NT-3 also shows remarkable conservation—the sequences for NT-3 are identical in rats, mice, and humans (96). Neurotrophin-4 and neurotrophin-5 were initially thought to be distinct growth factors (23, 70). However, recent evidence suggests they are homologues of a

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TABLE 1

Neuronal Selectivities of Neurotrophin Growth Factors

Neurotrophin	Responsive neurons	References
NGF		
PNS	Sympathetic neurons	(119, 142)
	Neural crest sensory neurons	
CNS	Basal forebrain cholinergic neurons	(30, 140, 141)
	Striatal cholinergic neurons	
	Cerebellar Purkinje cells	
BDNF		
PNS	Placode-derived sensory neurons	(22, 36, 150, 215)
	Neural crest sensory neurons	
	Nodose ganglion neurons	
	Spinal motoneurons	
CNS	Basal forebrain cholinergic neurons	(36, 86, 163, 176, 206)
	Proprioceptive trigeminal neurons	
	Substantia nigra dopaminergic neurons	
	Retinal ganglion neurons	
	Facial motoneurons	
NT-3		
PNS	Sympathetic neurons	(51, 79, 127, 164)
	Sensory neurons	
CNS	Basal forebrain cholinergic neurons	
	Locus coeruleus	
NT-4/5		
PNS	Sympathetic neurons	(23, 51, 70)
	Dorsal root ganglion neurons	
	Nodose ganglion neurons	
CNS	Basal forebrain cholinergic neurons	
	Locus coeruleus	

single factor expressed in different animal species (88). NT-4/5 appears to be less highly conserved across species lines, although it shares over 50% sequence homology with NGF, BDNF, and NT-3 (23, 69). All neurotrophins can support the growth and survival of subsets of dorsal root ganglion neurons; however, they differ in their sites of synthesis, developmental patterns of expression, and neuronal targets (see Table 1).

THE NEUROTROPHIN RECEPTORS

High- and Low-Affinity Receptors

Receptors for neurotrophin growth factors consist of two general types—the high-affinity or "slow-dissociating" receptors and the low-affinity or "fast-dissociating" receptors. High-affinity receptors ($K_d \sim 10^{-11}$) distinguish between members of the neurotrophin family and appear to transduce most, if not all, of these factors' biological effects (83, 169, 193). Low-affinity receptors bind all neurotrophins with comparable low affinity ($K_d \sim 10^{-9}$) (22) and have a largely undefined role in the signaling process (discussed further below). High-affinity receptors have molecular weights of 140 kDa (135) and low-affinity receptors have molecular weights of 75 kDa (93). High- and low-affinity receptors can also be distinguished on the basis of their ligand specificity, dissociation kinetics, protease sensitivity, and detergent solubility (24, 115, 193, 211).

The first indication that high-affinity receptors were responsible for most of the neurotrophins' biological effects came from the *in vitro* observation that the concentration of NGF required to elicit a biological response was consistent with high-affinity binding (66). Subsequent *in situ* NGF-binding studies showed that the biological responsiveness of a tissue correlated with the expression of high- but not low-affinity receptors (162). The low-affinity receptor is found in neuronal and nonneuronal tissues not clearly responsive to NGF (214).

Trk Proto-oncogenes Encode Receptors for Neurotrophin Signal Transduction

In 1991, investigators discovered that at least one subunit of the high-affinity receptor for NGF was encoded by the trk A proto-oncogene (98, 99, 103). Trk A was originally discovered in tissue obtained from a human colon carcinoma biopsy (130). In its malignant form, the catalytic and transmembrane domains of trk A were fused with nonmuscle tropomyosin, resulting in the constitutive activation of trk A (33). The trk A proto-oncogene showed preferential expression in the nervous system (129). However, no link to NGF was made until investigators demonstrated that nonneuronal cells transfected with trk A acquired NGF-binding sites and activated intracellular signal transduction pathways (92, 98, 102). Fibroblasts transfected with trk A bound ^{125}I-NGF with high affinity and became morphologically transformed (92), and *Xenopus* oocytes transfected with trk A underwent maturational changes following exposure to NGF (146). Trk receptors have now been detected in every major population of neurons known to respond to NGF (82, 129). Shooter and colleagues have also demonstrated that trk A receptors possess kinetic and chemical properties characteristic of slow-dissociating receptors (136).

It is now known that the trk family of proto-oncogenes encodes three closely related tyrosine kinases—trk A, trk B, and trk C (14, 131, 138). The trk proteins have a tripartite structure consisting of an extracellular

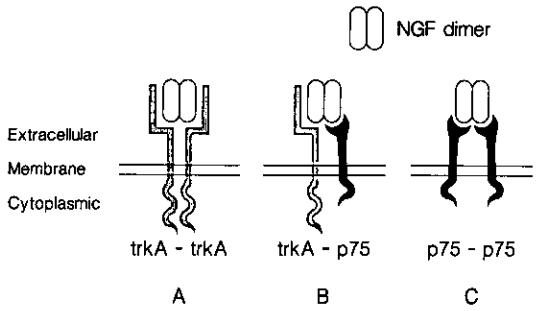

FIG. 1. Receptor models for nerve growth factor signal transduction. Three receptor models have been proposed for nerve growth factor signal transduction: (A) trk A–trkA homodimer; (B) trkA–p75 (low-affinity receptor) heterodimer; (C) p75–p75 homodimer.

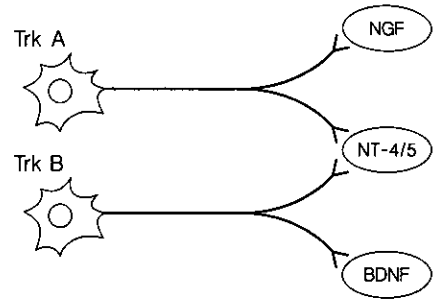

FIG. 2. Possible role for neurotrophin redundancy in the development of synaptic connectivity. The ability of a trk receptor to respond to multiple neurotrophins could have a role in the establishment of appropriate neuronal connections. For instance, a target tissue expressing NT-4/5 can support two distinct populations of neurons (one expressing trk A, the other expressing trk B). Although both trk A- and trk B-expressing neurons converge onto the NT-4/5 target, they are also able to form other divergent projections to NGF- or BDNF-expressing tissues. The redundancy in neurotrophins would also increase the availability of trophic support to a particular group of neurons.

domain for ligand recognition, a single transmembrane domain, and a cytoplasmic tail (containing the tyrosine kinase) for initiating the signaling cascade. The extracellular portion includes two immunoglobulin-like modules that may form a pocket for growth factor binding (174). Tyrosine kinase receptors are believed to be activated by a process of allosteric dimerization (207). In this model, growth factor binding causes tyrosine kinase receptors to pair (or form oligomers). When the cytoplasmic domains are brought into close proximity, they activate kinase domains. Figure 1 shows three hypothetical receptor dimers (trk A–trk A, trk A–p75, p75–p75) postulated in the signal transduction of NGF. The trk A receptor appears to be an essential mediator of the signaling response to NGF (87, 103, 204); the role of p75 is less clear (see discussion below).

A puzzling feature of neurotrophin signal transduction is the degree of redundancy that exists between the neurotrophin growth factors and their receptors. Trk A encodes a signal-transducing receptor for NGF (and NT-3 at lower efficacy) (31, 98, 99, 103, 146). Trk B is a signal-transducing receptor for BDNF (and NT-3 at lower efficacy) (186, 188). Trk C is a signal-transducing receptor for NT-3 (114). NT-4/5 is reportedly able to bind to and activate either trk A or trk B (23, 88) (Table 2). Because of restrictions in the timing and distribution of growth factors (and their receptors), functional redundancy may be rare *in vivo*. However, the presence of redundancy in other growth factor systems (200) suggests that the overlaps could have some biological significance. In some instances, differences in the temporal expression of factors (or their receptors) could allow a single factor to have multiple functions throughout the course of development. In addition, during embryonic development, the redundancy between neurotrophins and their receptors could be useful in the establishment of appropriate neuronal connections. As suggested in Fig. 2, the responsiveness of a single receptor to multiple neurotrophins would allow a tissue expressing different neurotrophins to establish divergent projections. By allowing a single factor to activate multiple receptors, different neuronal groups could share in trophic support. Also, during development, neurons could utilize different neurotrophins expressed along their pathways of growth.

TABLE 2

Redundancy of Neurotrophins and Their Receptors

Receptor	Neurotrophin
Trk A	NGF, NT-3, NT-4/5
Trk B	BDNF, NT-3, NT-4/5
Trk C	NT-3

Splice Variants

Splice variants of trk receptors represent another puzzling feature of neurotrophin signal transduction. Alternative transcripts for trk A, trk B, and trk C have been identified in the rat, mouse, and chick nervous systems (15, 59, 102, 138). The patterns of sequence divergence suggests that variants are generated by a differential splicing of alternative exons. The variants have included receptors that lack functional kinase sequences (truncated receptor) and receptors with either alternative 5′ terminals or kinase insertions. The truncated receptor appears identical to the full-length receptor in its extracellular and transmembrane domains, but lacks a cytoplasmic tyrosine kinase sequence. This receptor would bind neurotrophins normally, but fail to activate intracellular signal transduction pathways. Several putative functions for the truncated receptors have been proposed: (1) a role in ligand presentation (e.g.,

assisting in the presentation of neurotrophins to full-length receptors), (2) an activator of alternate signaling pathways (activating distinct signaling pathways from full-length receptors by stimulating cytoplasmic protein kinases), (3) a modulator of neurotrophin responsiveness (e.g., sequestering catalytic full-length receptors), and (4) a mediator of cell–cell interactions (e.g., having a role in axon guidance). Recently, Beck *et al.* found that truncated trk B receptors were induced in hippocampal pathways undergoing active synaptic reorganization (17). This group found that truncated trk B receptors were induced in reorganizing commissural/association pathways 6–14 days following perforant path–fimbria–fornix transections. In unlesioned mice, truncated trk B receptors have been found in choroid plexus and ependyma, consistent with clearance or active transport functions across the blood brain barrier (102).

p75: The Low-Affinity Receptor

When p75 was first isolated (93, 159), it was thought to be the signal-transducing receptor for NGF. It was named the low-affinity nerve growth factor receptor; however, it was later found to bind all neurotrophins with comparable affinity (70, 186, 188). p75 has a tripartite structure consisting of four cysteine-rich extracellular domains, a short serine- and threonine-rich spacer, and a cytoplasmic domain. The transmembrane and cytoplasmic domains of p75 are highly conserved between species, but share no known homology to signal-transducing proteins. p75's predicted tertiary structure is similar to that of mastoparan, an activator of GTP-binding regulatory proteins (46, 78), leading investigators to hypothesize that p75 may activate G proteins in its signal transduction pathway (16). The cysteine-rich extracellular domain of p75 shares sequence homology to genes encoding the receptors for tumor necrosis factor (184). T cell activation antigen OX-40 (128), B cell antigen CD40 (189), and Fas, a cell surface antigen that mediates apoptosis (90).

Although p75 is expressed in every neuronal tissue known to respond to NGF (43, 160), its role in the signaling process remains controversial. In membrane preparations, Chao and colleagues have reported that high-affinity NGF-binding sites were generated only if trk A was coexpressed with p75 (76). If membranes containing p75 and trk A were fused, high-affinity binding sites were generated *in vitro* (98). On the other hand, in whole cell preparations, Klein *et al.* (103) found that the expression of trk A (in the absence of p75) generated both high and low affinity sites for NGF. Chao and colleagues (216) have also reported that receptor chimeras, consisting of the extracellular domain of the epidermal growth factor receptor fused to the intracellular and transmembrane domains of p75, transduce NGF-like responses upon stimulation with epidermal growth factor. However, these results contradict the observation that BDNF (a ligand that binds p75 with similar affinity to NGF) fails to promote neurite outgrowth in p75-containing PC12 cells. In PC12 cells, transfection with trk B confers responsiveness to BDNF (186). In other studies, Chao and colleagues have reported that overexpression of the cytoplasmic domain of p75 in PC12 cells down-regulates trk A kinase activity (19). Despite the loss of high-affinity sites, transfected cells appeared to differentiate normally in response to NGF.

Persson and colleagues have examined the potential contribution of p75 by designing a mutant NGF molecule unable to bind p75 (87). This mutant retained its binding site for trk A and stimulated neurite outgrowth and dorsal root ganglion survival at physiological concentrations. Members of our group have also shown that polyclonal antibodies that block NGF–p75 binding have no effect on NGF's trophic effects (204). Recently, Barbacid *et al.* have reported that kinase-deficient trks can act as dominant negative mutants in NIH3T3 cells stably transfected with trk A (92). When kinase-deficient mutants are introduced into transfected cells, they form noncatalytic dimers with full-length receptors, blocking NGF-induced morphological transformation. The expression of p75 in these cells had no effect on high-affinity binding or transformation events.

Recently, Wheeler and Bothwell questioned whether functional assays such as neurite outgrowth or neuronal survival were adequate to detect biological functions of p75 (206). From *in situ* hybridization studies, they found that p75 expression in the developing limb bud, kidney, lung, and testes correlated better with sites of tissue induction than with innervation. In the developing limb bud, for example, NGF and p75 were expressed at sites of limb attachment and in the mesenchyme adjacent to the apical ectodermal ridge, rather than at sites of innervation. In the developing kidney, p75 was expressed in polarizing epithelium during glomerular morphogenesis. More direct evidence for p75's role in kidney morphogenesis is supported by the observation that antisense p75 oligonucleotides block glomerular formation in kidney explants (167). Recently Jaenisch and colleagues generated transgenic mice deficient in the gene encoding p75 (117). No kidney abnormalities in these animals were seen. However, sensory abnormalities and trophic ulcers developed by age 4 months. Immunohistochemical analyses of footpad skin revealed decreased innervation by calcitonin gene-related peptide- and substance P-immunoreactive fibers. When the human p75 gene was crossed into mutant animals, the phenotype was reversed. Although these findings support a role for p75 in the normal development and function of peripheral sensory neurons, the mutant phenotype could occur as a result of an indirect effect on Schwann cells. Schwann cells express p75 during and just prior to

cutaneous innervation (212). Their expression of p75 receptors may function in growth and guidance of developing axons (166).

IMPLICATIONS FOR NEUROLOGIC DISEASE

Alzheimer's Disease

Much of the initial clinical interest in NGF centered on its therapeutic potential in the treatment of Alzheimer's disease (AD). In AD, severe neuronal loss, neurofibrillary tangles, and neuritic plaques disrupt learning and memory pathways, resulting in the severe intellectual decline seen in AD (85). The cholinergic basal forebrain and septum (areas implicated in memory and learning) are severely affected by neuronal loss (37, 208). Since basal forebrain and septal cholinergic neurons are major central nervous system targets for NGF, NGF has been actively investigated for potential use as a therapy for AD. Over the past decade, several experimental paradigms have been used to address this potential application: (1) fimbria–fornix transection, (2) retrograde lesions of nucleus basalis magnocellularis (nbM), (3) the use of memory-impaired aged rats, and (4) a transplantation model of the trisomy 16 mouse.

If mammalian fimbria–fornix pathways are transected with a knife, 65–90% of medial septal neurons develop retrograde degenerative changes and die (10). However, if intraventricular NGF is administered at the time of lesioning, most cholinergic septal/diagonal band neurons will survive (54, 73, 108, 111, 199). Even with delayed administration of NGF, partial recovery of cholinergic neurons is seen (69).

Intraventricular NGF can also prevent lesion-induced atrophy in the nbM (71, 190). Following retrograde injury to the nbM, no decrease in neuronal number is seen, although choline acetyltransferase (ChAT) activity falls. If animals are treated with intraventricular NGF, levels of ChAT in the nucleus basalis and cortical areas spared by the lesion return to normal. NGF treatment has also been reported to ameliorate memory and learning deficits caused by fimbria–fornix or nucleus basalis lesions. However, these results are difficult to interpret because memory deficits created by septal lesions are exacerbated by NGF (152).

In experimental models of age-related memory impairment, NGF infusion improves the behavioral performance of impaired animals (49, 53). When aged rats were segregated on the basis of their performance on spatial memory tasks, impaired animals were found to have smaller cholinergic basal forebrain neurons (48). When impaired animals received intraventricular infusions of NGF, their basal forebrain neurons increased in size and their performance on the swimming maze improved (49). Using immunocytochemical methods, Koh and Loy (107) have reported an age-related decline in p75 immunoreactivity in the rat basal forebrain. In human tissue, Hefti and Mash (74) have also found age-related decreases in the NGF receptor. To date, one study has reported a decline in NGF protein and mRNA in the brains of aged rats (116).

Recently, the trisomy 16 (Ts16) mouse has provided a genetic model of basal forebrain abnormalities occurring in Down syndrome and Alzheimer's disease. A striking genetic homology exists between the distal long arm of human chromosome 21 and the distal end of mouse chromosome 16 (MMU16) (28, 34). At least six genes are shared between MMU16 and human chromosome 21, including the genes encoding amyloid precursor protein, superoxide dismutase, and markers linked to a familial form of AD. Ts16 mice share many of the phenotypic features of human Down syndrome, including basal forebrain cholinergic atrophy (34, 100, 195). Since trisomy 16 mice die at birth, experiments must be based on either *in vitro* or transplantation approaches.

The basal forebrains of Ts16 mice have fewer cholinergic neurons than euploid littermates and remaining neurons are small with short processes lacking varicosities (100, 195). If Ts16 neurons are cultured in the presence of NGF, they hypertrophy, extend processes (with varicosities), and increase their ChAT activity (32). In a transplantation model of the Ts16 mouse, Ts16 neurons integrate into normal mouse hippocampus and initially appear indistinguishable from euploid neurons. Six months later, however, Ts16 neurons atrophy and lower levels of ChAT activity are seen [81; D. M. Holtzman and W. C. Mobley, unpublished observations). If NGF is administered before the genetically programmed atrophy begins (at $5\frac{1}{2}$ months), basal forebrain cholinergic neurons retain their normal appearance and ChAT levels remain high.

Although NGF would appear to have therapeutic potential in the treatment of AD, critics have warned that available NGF models (fimbria–fornix transection, nbM lesioning, trisomy 16 mouse) do not replicate the essential findings of Alzheimer's disease. In fact, none of the animals in these paradigms develop β-amyloid plaques, neurofibrillary tangles, or amyloid angiopathy. Because point mutations in the βA4-amyloid precursor protein (β-APP) gene have been found to be responsible for certain kindreds of familial early-onset AD (61, 145, 202), it is important to consider the effect of NGF on normal and abnormal β-amyloid processes.

In hamster basal forebrain and SH-SY5Y neuroblastoma cells, NGF increases β-APP mRNA expression (109, 139). The β-APP gene generates at least five alternative translation products that include APP_{695}, APP_{751}, and APP_{770} (64, 97, 101, 158, 197). APP_{751} and APP_{770} are expressed predominantly in peripheral tissues; APP_{695} is expressed in developing and adult brain (101, 109, 147, 158, 197). In PC12 cells, NGF increases the expression of APP_{695}, decreases the expression of

APP_{770}, and increases β-APP release (161, 175, 185). Although the significance of these fluctuations is unclear regarding the pathogenesis of Alzheimer's disease, Yoshikawa *et al.* have recently shown that overexpression of APP_{695} or APP_{770} in P19 embryonal carcinoma cells results in the death of postmitotic neurons (218). They hypothesized that the overproduction of β-APP could overwhelm endogenous processing, leading to a generation of amyloidogenic fragments and the death of postmitotic neurons derived from these cells. β-APP expression has also been implicated in the aberrant sprouting responses seen in AD (133). In either instance the administration of NGF in this setting could exacerbate the pathological cascade of AD. In fact, Yankner *et al.* (1990) have reported that NGF treatment greatly increases the neurotoxicity of β-amyloid (10^5-fold) *in vitro* (217). β-amyloid also increased NGF receptor immunoreactivity in this study, leading investigators to hypothesize that pathological accumulations of β-amyloid could activate a positive feedback loop between β-amyloid and NGF, accelerating the death of NGF-responsive neurons.

Because many neuronal groups affected in AD are unresponsive to NGF, a primary defect in NGF-mediated pathways is not believed to underlie AD pathogenesis. Trk receptor expression has not been systematically examined in Alzheimer tissue. However, normal levels of NGF and p75 mRNA have been seen in AD brains at autopsy (62, 74). BDNF, NT-3, and NT-4/5 have recently been found to be survival-promoting factors for cholinergic basal forebrain neurons (51, 106). Their trophic effects *in vivo* are currently under investigation. Thus far, Knusel *et al.* (105) have demonstrated a slight, but significant, effect for BDNF on axotomized cholinergic septal and diagonal band neurons. BDNF appeared to rescue a portion of lesioned neurons, whereas NGF treatment rescued the entire population. Phillips *et al.* (155) have reported that the dentate gyri of AD patients express significantly lower levels of BDNF mRNA than those of nondemented controls. However, it is likely that these changes reflect secondary processes in the disease.

Parkinson's Disease

Parkinson's disease (PD) is a debilitating movement disorder caused by the selective death of dopamine-containing substantia nigra neurons (2). Until recently, acidic and basic fibroblast growth factor (aFGF, bFGF) were the only trophic factors known to promote the growth and survival of dopaminergic midbrain cells.

aFGF and bFGF are tyrosine kinase-mediated growth factors unrelated to the neurotrophin growth factor family. Other members of this family include INT2, HST, FGF5, FGF6, and KGF (20). If fetal dopamine-containing mesencephalic neurons are cultured in the presence of aFGF or bFGF, they show increased survival and neurite outgrowth (47). In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice, both aFGF and bFGF appear to prevent a loss of tyrosine hydroxlase (TH)-positive striatal neurons (151). However, a potential problem with mouse MPTP paradigms is that their dopaminergic neurons do not degenerate, despite the loss of TH immunoreactivity, and spontaneous regeneration is sometimes seen (179). In other studies, aFGF has been seen to have no effect on aged MPTP-exposed mice (35), and bFGF had no protective effect *in vitro* (72). Recently Engele and Bohn (41) have presented evidence that mesencephalic glia mediate the FGF's trophic effects on dopaminergic midbrain. Coincident with a rise in TH+ cells (in response to aFGF or bFGF) was a tripling of mesencephalic glia. If the glial proliferation was blocked by mitotic inhibitors, no neurotrophic effects were seen. Also, conditioned media from glial cultures supported dopaminergic neuron survival. In fact, the potent mitogenic effects of FGF's are likely to exclude their use in the treatment of neurodegenerative disease. bFGF stimulates the proliferation of human glioma cells (205) and elevated levels of bFGF have been reported in human glioma cell lines (168, 196).

BDNF has also been found to increase the survival, outgrowth, and dopamine uptake of embryonic dopaminergic midbrain neurons (86, 106). *In vitro,* BDNF is able to protect neurons from MPTP- or 6-hydroxydopamine-induced injury (106, 187); however, *in vivo* experiments with MPTP have not yet been reported. Hefti and colleagues have recently found no effect for BDNF on partially transected substantia nigra neurons (105). In other experiments nigral injections of BDNF have been found to stimulate rotational behavior and increase striatal levels of dopamine metabolites (3). To date, p75 and trk B have not been found in the substantia nigra (104, 157). An indirect action of BDNF on dopaminergic neurons cannot be excluded.

In adrenal transplantation approaches to PD, NGF has shown promise in increasing the process formation, differentiation, and survival of chromaffin grafts (40). In rodent models of Parkinson's disease, NGF treatment resulted in a longer graft survival and better functioning for the life of the animal (181, 192). Unfortunately, results in monkeys and humans have been disappointing. In man, adrenal graft survival has been poor and behavioral recovery slight (84, 153). Numerous groups have failed to reproduce the striking surgical successes of Madrazo and colleagues (1, 63, 126). In a single human case, murine NGF was administered intraputaminally to adrenal transplant recipient (148). NGF caused no apparent deleterious effects and appeared to prolong graft survival.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is a disease in which cranial and spinal motoneurons degenerate, resulting in a

debilitating syndrome of generalized weakness, wasting, fasciculation, and pyramidal tract dysfunction (210). The treatment is supportive, and most patients die within 4 years (25).

In 1990, Thoenen and colleagues discovered that ciliary neurotrophic factor (CNTF), a growth factor unrelated to the neurotrophins, could support the survival of cultured spinal motoneurons (9, 13). Although CNTF is not expressed in muscle (191), it rescues motoneurons from developmental or axotomy-induced death (150, 177). More recently, CNTF's trophic effects have been demonstrated in genetic animal models of motoneuron death (the wobbler, pmn, and mnd mouse) (75, 80, 176). In these studies, CNTF prevented motoneuron loss and slowed the progression of disease.

CNTF belongs to a class of neurotrophic molecules that transduce their biological signals on cytokine-like receptors (38, 113). Unlike the neurotrophins, CNTF lacks a signal sequence and glycosylation sites and is not secreted. Because rising levels of Schwann cell CNTF have correlated with an age-related increase in the survival of lesioned motoneurons (191), some investigators have hypothesized that CNTF acts as a "lesion factor" that is released under pathological conditions. Because of CNTF's promising performance in animal studies, it has entered Phase II trials for use in the treatment of human motoneuron disease.

In 1992, BDNF was also found to be a trophic factor for cranial and spinal motoneurons (150, 176, 215). In the neonatal rat, local applications of BDNF prevented the axotomy-induced death of spinal and facial motoneurons (176, 215). In the developing chick, BDNF prevented naturally-occurring motoneuron death (150). Because BDNF is expressed by developing muscle and retrogradely transported in spinal motoneurons (170, 215), it appears to be a normal regulator of motoneuron growth. Interestingly, Barbacid and colleagues have found that mice carrying a targeted mutation of trk B have obvious motor and sensory deficits (M. Barbacid, personal communication). Mice homozygous for the mutation have been found to have fewer facial and spinal motoneurons than wild-type or heterozygote siblings.

Peripheral Neuropathy

Since NGF is required for the normal survival of adult sympathetic and sensory neurons, it has also been investigated for use as a therapeutic agent in toxic and diabetic peripheral neuropathies. Disabling sensory neuropathies frequently limit the dosing of chemotherapeutic agents in cancer therapy. Taxol, a chemotherapeutic agent used in the treatment of melanoma and ovarian cancer (182), can disrupt axonal transport in peripheral neurons. This impairs the trophic supply of factors like NGF and causes painful sensory symptoms (123). When dorsal root ganglion explants are exposed to taxol *in vitro,* they accumulate abnormal aggregations of microtubules, disrupting the cytoskelton and resulting in cell death (172). If NGF is added to culture media, >90% of dorsal root ganglion neurons are rescued (154). In 1991, Apfel *et al.* developed an animal model of taxol neuropathy that reproduced changes in pain threshold, compound nerve action potentials, and dorsal root ganglion levels of substance P (8). When NGF was administered with taxol injections in this model, all three parameters improved. Similar findings have been reported for NGF treatment in a cisplatin model (7). However, two of the parameters used in this study (nerve conduction velocity, calcitonin gene-related peptide levels) have made the significance of these findings unclear. Again, it seems likely that other neurotrophins may be useful in maintaining sensory innervation and functions.

NGF has also been considered as a therapeutic factor in diabetic neuropathy because peripheral sensory and sympathetic neurons are affected early in the disease (45). In a streptozotocin model of diabetes, several groups have found decreased retrograde axonal transport of ^{125}I-NGF (137, 173). When NGF treatment was tested in this paradigm, it prevented some behavioral and biochemical manifestations of small fiber neuropathy, but failed to prevent nerve conduction velocity slowing (6).

Nervous System Cancer

The relationship between neurotrophin growth factors and primitive neuroectodermal tumors (PNETs) has been studied because members of the neurotrophin growth factor family affect the survival, proliferation, and differentiation of immature neural crest cells (121, 127). PNET tumors share a number of histological and functional similarities to immature neural crest cells, and it has been hypothesized that these cancers arise as a defect in normal differentiation (18). Neuroblastomas, medulloblastomas, ganglioneuromas, and Ewing's sarcomas have all been found to express the low-affinity neurotrophin receptor (165). Recently, Nakagawara *et al.* (144) noted an inverse relationship between the expression of trk A and n-myc amplification in a large number of human neuroblastoma cell lines. High levels of trk A expression correlated best with highly differentiated neuroblastomas and a favorable clinical prognosis; low levels of trk A correlated with poor differentiation and a poor prognosis. Tumors expressing high levels of trk A were more likely to differentiate, regress spontaneously, and respond to chemotherapy. Interestingly, treatment by NGF can cause responsive tumor cell lines to grow more slowly and acquire differentiated morphologies (91, 132, 134, 203). *In vivo,* NGF has been shown to slow the growth of intracerebrally implanted gliomas (203) and subcutaneous neurinomas

(213). In 1970, three children with disseminated neuroblastoma received five to eight intramuscular injections of murine NGF (10 mg/day) (112). Although no clear beneficial effects were noted, the treatment was tolerated with minimal side effects.

Epilepsy

The role of neurotrophins in epileptogenesis has also emerged as a promising area of scientific investigation. In the past few years, there has been a growing body of evidence that a reorganization of neural networks is an essential feature of certain forms of epilepsy. A consistent pathological finding in the temporal lobes of patients with intractable epilepsy is the mossy fiber sprouting of dentate granule cells (11, 194). In fact, quantitative histological and ultrastructural studies show that the extent of mossy fiber reorganization correlates with the occurrence of seizures. Although it is unclear whether this synaptic reorganization is maladaptive (60, 160, 198) or adaptive (183), it is an active area of investigation because it represents a potentially novel site for therapeutic intervention in epileptogenesis.

The association of abnormal electrical activity with synaptic reorganization led a number of investigators to study changes in neurotrophin expression following experimentally induced seizures. In 1989, Gall and Isackson (56) demonstrated that limbic seizures increased the expression of NGF mRNA in hippocampal pathways. Since then, seizures induced by intraventricular or intraperitoneal kainic acid have also been shown to increase NGF expression (42, 58, 89, 219). An increase in NGF expression can even be detected after a single epileptiform hippocampal discharge (57). More recently, BDNF expression has also been found to increase following the induction of limbic seizures (12, 89). No change in NT-3 expression was seen (42).

In vitro studies have confirmed that a rapid increase in neurotrophin synthesis can be induced by increased neuronal activity. Depolarizing stimuli such as high extracellular potassium, veratridine, or treatment with glutamate agonists cause prompt rises in NGF or BDNF expression in hippocampal neurons (124, 219). It is likely that the abnormal electrical activity that occurs in human epilepsy results in changes in neurotrophin expression. Although the functional significance of these changes remains unproven, it is interesting that Funibashi *et al.* (52) found that centrally administered antiserum to NGF delayed the onset of amygdaloid kindling.

FUTURE PROSPECTS

The past 5 years have seen great advances in our understanding of the normal biology and therapeutic potential of neurotrophin growth factors and their receptors. Since 1989, BDNF, NT-3, and NT-4/5 have been sequenced, trk proto-oncogenes have been found to encode neurotrophin signal transducing receptors, and the three-dimensional structure of NGF has been solved. Existing data have suggested that neurotrophin growth factors have therapeutic potential in the treatment of certain types of neurodegenerative disease, peripheral neuropathy, cancer, and epilepsy. With technical advances in gene and drug delivery, neural transplantation, and rational drug design, practical therapeutic hurdles are likely to be overcome in the near future.

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