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Review

Neurotrophins and their receptors: signaling trios in complex biological systems

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Abstract. The neurotrophins, a class of four related growth factors, utilize a dual receptor system consisting of Trk receptor tyrosine kinases and the structurally unrelated $p75^{NTR}$ to modulate diverse and sometimes opposing biological actions. The identification of novel ligands for $p75^{NTR}$, unconventional mechanisms for Trk activation and unique signaling intermediates further underscores the complex nature of neurotrophin: receptor interactions, as well as their functions within and outside of the nervous systems. This review summarizes recent surprises of how ligand-receptor pairing may affect diverse developmental events, regulate response to injury and extend their influence on memory and learning.

Key words. NGF; BDNF; NT-3; NT-4; $p75^{NTR}$; Trk; nervous system; vascular biology.

Introduction

Neurotrophins, including nerve growth factor (NGF), brain derived neurotrophic factor (BDNF) and neurotrophin (NT) 3–4, are a family of highly conserved polypeptide growth factors that regulate the generation and maintenance of diverse neuronal populations [1, 2]. More recent studies have revealed additional actions in mediating axonal guidance [3], synaptic plasticity [4] and injury protection [5]. Although initially characterized as a soluble survival factor for peripheral neurons [6], NGF has emerged as an important player with diverse roles in the fields of glial biology [7, 8], vascular biology [9, 10] and tumor biology [11, 12]. Likewise, following their identification as NGF homologues with neurotrophic activities, BDNF, NT-3 and NT-4 have all been implicated in a variety of biological processes in neuronal and nonneuronal populations [1, 13].

Similar to many other secreted growth factors, neurotrophins are synthesized as preproproteins, which are subsequently cleaved to smaller, mature forms that homodimerize. At the molecular level, mature neurotrophins exert their effects by interacting with two structurally unrelated receptors: $p75^{NTR}$, a member of the tumor necrosis factor (TNF) receptor superfamily, and the Trk receptor tyrosine kinases. The two receptors for neurotrophins also differ in terms of ligand binding specificity. While $p75^{NTR}$ is capable of binding to all mature neurotrophins with equivalent affinity but unique kinetics [14, 15], Trk family members exhibit ligand selectivity. Thus NGF is the preferred ligand for Trk A, BDNF and NT-4 for Trk B and NT-3 for Trk C [16]. The extracellular motifs of $p75^{NTR}$ and Trk receptors are unrelated, with neurotrophins interacting with the immunoglobulin-like C2 (IgGC2) domains of the Trk receptors, but with the cysteine-rich domains of the $p75^{NTR}$ receptor [17–19]. The intracellular portions of the two receptors also share no homology. Unlike full-length Trk receptors that possess signature tyrosine kinase motifs, the intracellular domain of $p75^{NTR}$ does not exhibit intrinsic ligand-inducible enzymatic activity [20–22].

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Historically $p75^{NTR}$ was the first neurotrophin receptor to be identified as a NGF-binding transmembrane protein [23, 24]. However, the lack of readily identifiable signal-transducing modules within its cytoplasmic sequence led to the hypothesis that $p75^{NTR}$ functions primarily to augment Trk signaling by enhancing the affinity and the specificity of neurotrophin-Trk interactions [20, 21]. Expression of $p75^{NTR}$ can promote the survival of Trk A-expressing neurons to limiting concentrations of endogenous neurotrophins, best exemplified in studies using $p75^{NTR}$ gene targeted mice where decreased responsiveness to NGF was observed in $p75^{NTR}$-null sympathetic neurons [25]. As other members of the TNF receptors were demonstrated to modulate apoptotic responses [26], a potential role for $p75^{NTR}$ as a mediator of cell death has rekindled interest in this receptor [27–30]. Indeed, large number of studies now establish neurotrophin-$p75^{NTR}$ interactions as a critical biological event that governs life and death decisions in neuronal and nonneuronal cells alike [20–22, 31] (table 1).

In contrast, survival signaling predominantly reflects Trk activation. Tyrosine phosphorylation of activated Trk recruits downstream signaling enzymes and adaptor proteins that contain protein interacting domains. The formation of receptor-adaptor-enzyme complexes ultimately mediates the trophic responses ascribed to the neurotrophins. Classic signaling modules, such as the Ras-mitogen-activated protein (MAP) kinase cascade and the phosphatidylinositol-3 (PI-3)-kinase-Akt pathway, have been identified as downstream cellular events induced by Trk activation. The latter in particular is considered pro-survival, as Akt-mediated phosphorylation of a number of proapoptotic proteins results in their inactivation [32, 33].

In numerous neuronal and noneuronal cells, ligand activation of $p75^{NTR}$ can initiate apoptosis when $p75^{NTR}$ is expressed independently of Trk. When $p75^{NTR}$ and Trk are expressed in the same cell, however, survival signaling dominates following addition of mature neurotrophins. This is due in part to enhanced affinity of neurotrophins to their cognate Trk receptor (a function of $p75^{NTR}$) and in part to the ability of Akt to suppress the apoptotic signaling cascade initiated by neurotrophin binding to $p75^{NTR}$. The 'Jekyll and Hyde' nature of $p75^{NTR}$ is perplexing, given the diametrically opposite roles this receptor plays in promoting death and augmenting survival. A recent study has shed light on this issue by identifying a high-affinity proapoptotic ligand for $p75^{NTR}$ as pro-NGF [34]. Surprisingly, pro-NGF neither binds to nor activates Trk A. Accordingly, pro-NGF and pro-BDNF can be differentially released as soluble proneurotrophins or processed as mature neurotrophins, each with distinct ligand-receptor interactions and biological consequences.

Recent studies have revealed additional levels of complexity within the neurotrophin-receptor trios. A number of $p75^{NTR}$ ligands, including β-amyloid and prion peptides can induce receptor clustering and signaling, leading to cell death. Novel actions for $p75^{NTR}$ in regulating glial differentiation and myelination have also been uncovered [35]. In exciting recent studies $p75^{NTR}$ appears to act as a signal-transducing component of the Nogo receptor complex to limit neuronal process extension by selective glial proteins [36, 37]. Lastly, a point mutation in the pro-domain of BDNF has been linked to memory loss in human [38]. The purpose of this review is to highlight the unusual modulation of neurotrophins and their receptors by diverse cellular mechanisms. In addition, we integrate the newly found identities for this ligand-receptor system with its traditional roles in neuronal differentiation and survival promotion.

Distinct domains and processing of neurotrophins

The neurotrophins are phylogenetically one of the oldest families of polypeptide growth factors, with members expressed in zebrafish and the lampry. Despite divergence of NGF and BDNF more than 600 million years ago [39], neurotrophins remain remarkably well conserved across species, as exhibited by the finding that zebrafish BDNF can provide trophic support to rodent Trk B-expressing neurons [40, 41]. Indeed, from lampry to humans, each neurotrophin is translated from a single coding exon to generate a preproneurotrophin of approximately 30 kDa,

Table 1. Selected examples of $p75^{NTR}$-modulated survival and death in the nervous system.

$p75^{NTR}$-dependent survival (Trk-independent)			$p75^{NTR}$-induced apoptosis		
Cell types	Ligand	Ref.	Cell types	Ligand	Ref.
Neocortical subplate neurons	BDNF, NT-3	[153]	oligodendrocytes	NGF	[28]
Sensory neurons	NGF	[154]	retinal ganglion cells	NGF	[27]
Schwann cells	NGF	[73]	sympathetic neurons	BDNF	[29–30]
			hippocampal neurons	all	[155–156]
			sympathetic neurons	pro-NGF	[34]
			oligodendrocytes	pro-NGF	[56]

which can be glycosylated in the N-terminal pro-domain. Proneurotrophins dimerize to yield approximately 60-kDa species [42]. They are cleaved intracellularly by furin and proconvertases to yield C-terminal mature proteins of 13.5 kDa that exist as 28-kDa dimers and have been considered the biologically active forms [2, 43, 44]. In comparing neurotrophin sequences, two regions are highly conserved across species: the distal 35 amino acids of the pro-domain of the neurotrophin as well as the amino acids within the mature portion of the protein. The degree of conservation in these regions is striking. For example, zebrafish and mammalian BDNF are 94% conserved in the distal 43 residues of the pro-region and 91% identical in the mature BDNF sequence. Past work has also established that one function for the highly conserved pro-domain of the neurotrophins is to enable proper folding of the mature neurotrophins [45]. Another is that the pro-domain is required for correctly sorting the mature neurotrophins to constitutive or regulated secretory pathways [46, 47].

Recently, Egan et al. [38] reported that a single nucleotide polymorphism (SNP) within the human BDNF gene results in an amino acid substitution (valine to methionine at position 66) within the pro-domain of BDNF. Consistent with the interpretations that the pro-domains of the neurotrophins are important for the processing and release of the mature isoforms, human met^{66}-BDNF appears mislocalized, and perhaps as a consequence is less efficiently processed for stimulated release when assessed in cultured rat hippocampal neurons [38]. The most intriguing aspect of this study, however, is the strong correlation between (i) episodic memory deficiency in humans with one or both copies of the val → met substitution, (ii) functional magnetic resonance imaging (MRI) evidence of decreased hippocampal activity and (iii) reduced activity-dependent release of mature BDNF from neurons. Thus, for the first time, neuronal functions in humans have been linked to the neurotrophins in a manner that is largely consistent with the role of BDNF in modulating synaptic plasticity [4], an area well described in animal models.

Analysis of adult tissue lysates reveals the presence of multiple NGF and BDNF isoforms with molecular masses that range from 13.5 kDa (mature neurotrophins) to 30 kDa (proneurotrophins) of the reduced proteins. The intermediate-size peptides correspond to a number of the predicted cleavage products by selective metalloproteases (MMPs) and plasmin within the pro-domain of NGF and BDNF [34]. These potential cleavage sites, some of which contain dibasic motifs, are conserved phylogenetically. While this study does not directly address whether the intermediate neurotrophin isoforms are released, it raises the possibility that mature neurotrophins may not be the only biologically active peptides from this growth factor family and that higher molecular isoforms of neurotrophins may exist with distinct functions. Indeed, proneurotrophins as well as mature neurotrophins are released from heterologous recipient cells in culture [46, 48, 49]. Although met^{66}-BDNF is processed and released, albeit less efficiently, as mature BDNF, currently available information does not indicate whether additional alternative isoforms might be concomitantly produced, and if so, whether these isoforms contribute to altered neuronal function.

Pro-NGF as an apoptotic ligand for p75^{NTR}

Several lines of evidence suggest that the mature neurotrophins are potent and selective ligands for Trk receptors. In nonneuronal paradigms, mature NGF is a more effective Trk ligand than the pro-domain of NGF in mediating cell survival [11, 50]. Comparable results have also been observed with BDNF and Trk B activation [48]. In addition, the mature NGF dimer and the portion of the Trk A extracellular domain which binds NGF (i.e. the $IgGC_2$ domain) have been cocrystallized [51], as have mature NT-4 and the Trk B IgGC2 domain [52]. The crystallographic structure confirms that the ligand : receptor interface is composed of two extended patches, but does not predict whether Trk A dimers can accommodate and effectively interact with the larger pro-NGF dimeric ligand.

Far less is known about the interaction of neurotrophins with the p75^{NTR} receptor. Structural/functional analysis of the p75^{NTR} receptor suggests that multiple regions of the extracellular domain contribute to NGF binding, with the second and third cysteine loop in the extracellular domain being most critical [17, 18]. Point mutagenesis of the four neurotrophins suggests that the variable loops are important for interaction with p75^{NTR} [53]. This is an unexpected finding, as these loops exhibit the highest degree of variation between neurotrophins, yet all neurotrophins bind specifically to p75^{NTR}. The kinetic analysis of NGF : p75^{NTR} binding is also unusual in that NGF binds and dissociates very rapidly, whereas most ligand: receptor interactions exhibit slow dissociation rates that reflect the close apposition of ligand and receptor binding domains [54]. Lastly, mature neurotrophins are relatively ineffective in inducing an apoptotic response via p75^{NTR}; high concentrations of neurotrophins (2–4 nM), significantly above the 1-nM binding constant, are required for apoptosis to be initiated (see [9, 28] for example). In contrast, activation of other proapoptotic TNF receptor family members occurs following receptor occupancy of 10–20% of the total binding sites [55].

Given these inconsistencies, the activity of pro-forms of neurotrophins as p75^{NTR} ligands was investigated. Indeed, recombinant pro-NGF, in which the conserved furin cleavage site has been mutated to impair proteolytic pro-

cessing to the mature form, is five times as effective as mature NGF in dissociating radiolabeled NGF from $p75^{NTR}$ but is ineffective in competing for Trk A binding. These results strongly suggest that pro-NGF is a high-affinity, specific ligand for $p75^{NTR}$ but that, unlike mature NGF, lacks the ability to activate Trk A. Results from in vivo comparison of the biological actions of pro-NGF and mature NGF are consistent with the receptor binding studies. In $p75^{NTR}$-expressing vascular smooth cells where Trk A is absent, pro-NGF is approximately 10 times as effective as mature NGF in inducing apoptosis. In cultured sympathetic neurons where Trk A is present, pro-NGF induces neuronal death where mature NGF promotes cell survival [34].

Further support for pro-NGF as a high-affinity apoptotic ligand comes from a recent study in which upregulation of pro-NGF is causally linked to $p75^{NTR}$-mediated oligodendrocyte death following spinal cord injury [56]. In this study, expression of pro-NGF, but not other proneurotrophins, was detected within 1–2 days of traumatic spinal cord injury in rodents. Pro-NGF was likely responsible in part for oligodendroglial apoptosis via $p75^{NTR}$, as cell death was significantly reduced in $p75^{NTR}$ gene-targeted animals, and the apoptotic actions of neurotrophins upon $p75^{NTR}$-expressing oligodendrocytes could be blocked by pro-NGF-specific antibody. As $p75^{NTR}$ is induced in other cell populations in the injured spinal cord, including motor and corticospinal neurons, future studies will be needed to assess the potential actions of proneurotrophins in these cells.

Modulating the role of $p75^{NTR}$ as a death receptor

The above studies are consistent with the limited extent of apoptosis observed in normal tissues that express both neurotrophins and $p75^{NTR}$, as they predict that pro-NGF actions are not only regulated by its secretion, but also governed by tissue-specific regulation of proteases such as plasmin and MMPs. These results further suggest that different neurotrophin isoforms can discriminate among distinct components of multimeric Trk-$p75^{NTR}$ receptor complexes: mature neurotrophins selectively bind Trk, whether it is expressed alone or complexed with $p75^{NTR}$ (fig. 1), while proneurotrophins bind selectively to $p75^{NTR}$ but not to Trk. Proteolytic processing of pro-NGF thus releases the molecule in its mature form, capable of activating Trk A for prosurvival signaling. In contrast, apoptotic events are triggered when pro-NGF is released as a result of protease inhibition. Clearly, this hypothesis will require the reevaluation of prior studies of neurotrophins and $p75^{NTR}$, which are highly expressed during development and reinduced post injury, to assess the ratio of proneurotrophin vs. mature neurotrophin that is re-

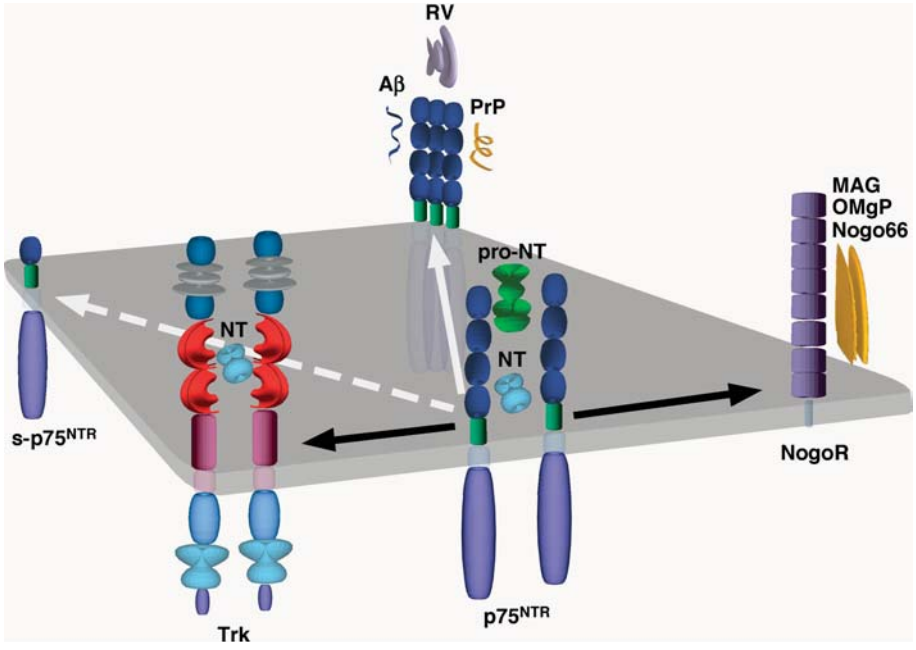

Figure 1. Distinct interactions of $p75^{NTR}$ with proneurotrophins, mature neurotrophins and other ligands. Dimeric $P75^{NTR}$ is depicted here to bind either mature neurotrophin (NT) or proneurotrophin (pro-NT), resulting in apoptosis. It also interacts with dimeric Trk receptor tyrosine kinase and modulates the specificity of mature neurotrophin actions. In addition, $p75^{NTR}$ interacts with the Nogo receptor (NogoR) for axonal growth inhibition mediated by MAG, OMgp and Nogo66. The binding of rabies virus (RV), prion protein (PrP) or a β-amyloid to $p75^{NTR}$ appears to induce receptor trimerization. Finally, the potential interaction between full length $p75^{NTR}$ and its naturally occurring short isoform s-$p75^{NTR}$ is denoted by dashed arrow. The signaling mechanisms and biological actions of $p75^{NTR}$ activation were recently reviewed [20–22].

leased from cells for differential receptor activation. In addition, a better understanding of the potential pathobiology of proneurotrophins requires the use of pro-domain-specific antisera to distinguish pro- from mature isoforms as well as in vivo approaches to misexpress cleavage-resistant proneurotrophins in models of neuronal and nonneuronal injury.

Although pro-NGF may bind $p75^{NTR}$ with higher affinity than mature NGF, the molecular mechanisms utilized by these two related ligands to trigger apoptosis have not yet been characterized in detail. Whether $p75^{NTR}$ activation by pro-NGF results in recruitment of novel adaptors to more efficiently induce cell death remains an open question. Towards this end, it is interesting to note that a truncated isoform of $p75^{NTR}$ (s-$p75^{NTR}$) has been reported to negatively regulate neuronal survival, but may promote the survival of vascular cells [10]. In addition, a gene related to *$p75^{NTR}$*, named *NRH* (neurotrophin receptor homolog), has been identified in lower vertebrates, and consists of a short extracellular domain, as well as transmembrane and cytoplasmic regions that are highly homologous to $p75^{NTR}$ [57]. As both s-$p75^{NTR}$ and NRH encode transmembrane and intracellular domains, signaling actions are possible through the binding of apoptotic adaptor proteins. It is interesting to note that other members of the tumor necrosis factor (TNF) receptor family exist as preformed trimeric receptor complexes and are activated by trimeric ligands [26]. Thus, one could postulate that an efficient means for dimeric pro-NGF to induce apoptosis is to induce complex formation between s-$p75^{NTR}$ or NRH with a dimeric $p75^{NTR}$, thereby enabling dimeric ligand : receptor interaction to induce trimeric $p75^{NTR}$ cytoplasmic complexes. In addition, full-length $p75^{NTR}$ can be cleaved by matrix metalloproteinases within the extracellular domain to yield a product that does not bind ligand, but could signal via the transmembrane and cytoplasmic domains [58]. Overexpression of recombinant $p75^{NTR}$ proteins that similarly lack the extracellular domain can promote apoptotic signaling in vivo [59]. Adding complexity, the generation of $p75^{NTR}$ (or $p75^{NTR}$-like) forms lacking most of the extracellular domain could potentially enhance Trk-mediated survival. As the transmembrane and cytoplasmic domain interactions between $p75^{NTR}$ and Trk A receptors appear important in dictating the formation of Trk A high-affinity sites [60], it is tempting to consider whether these 'short' forms of $p75^{NTR}$ or $p75^{NTR}$ homologs could modulate responsiveness of Trk A, B or C. Evidence suggests that this may occur in vivo, as gene-targeted animals that lack both s-$p75^{NTR}$ and full-length $p75^{NTR}$ exhibit impaired survival of vascular cell populations [10] known to express Trk B receptor and respond to BDNF [61]. In addition, overexpression of a short form of $p75^{NTR}$ that lacks a ligand binding domain can promote survival via activation of PI-3 kinase in in vitro systems [62]. Spatial and temporal regulation of these naturally occurring $p75^{NTR}$ related isoforms as well as the relevant proteases may clarify the roles of $p75^{NTR}$ in postnatal life and in pathologic states.

Novel biological actions of neurotrophin:$p75^{NTR}$-mediated induction of glial differentiation have recently been uncovered [35]. Although prior studies utilizing $p75^{NTR}$ null mice had described impaired Schwann cell migration and defective coverage of dorsal root ganglia axons [7], more recent evaluations implicate BDNF-mediated $p75^{NTR}$ activation as an important regulator of myelin formation by Schwann cells [35, 63]. These studies underscore the emerging, diverse biological responses observed upon $p75^{NTR}$ activation. Like other TNF receptors, $p75^{NTR}$ appears capable of mediating a range of responses from apoptosis, to migration, to differentiation. Consistent with this interpretation is the finding that pro-NGF activation of $p75^{NTR}$ in A875 melanoma cells results not in apoptosis but rather in enhanced chemotactic response via an interaction with the actin-bundling protein fascin [64]. Further characterization will be required to determine whether the spectrum of $p75^{NTR}$-dependent cellular responses reflects differences mediated by distinct ligands, or by recruitment and activation of cell-type-specific intracellular mediators.

Distinct signaling intermediates for $p75^{NTR}$

Structurally, $p75^{NTR}$ belongs to TNF-receptor superfamily, and like other members contains a death domain consisting of six α helices in a packed antiparallel conformation within its intracellular region [65]. Fas and TNFR1 encode a type I death domain, whereas $p75^{NTR}$ encodes a related domain that differs in reduced ability to self-associate in vitro. This domain is critical to recruit scaffolding proteins and additional mediators to promote the proapoptotic functions of the TNF receptors [26]. In contrast, although $p75^{NTR}$ has also been established to induce cell death in neuronal and nonneuronal paradigms, the molecular mechanism by which this occurs is less clear [20–22, 31]. In particular, one study reports that mature neurotrophin-induced $p75^{NTR}$-dependent apoptosis of an immortalized striatal neuron cell line requires the $p75^{NTR}$ death domain but not the apoptotic adaptor molecules FADD and TRADD, which are utilized by Fas or TNFR [66]; however, more recent studies in breast cancer cell lines suggest that TRADD/$p75^{NTR}$ interaction can occur [67]. The structural distinction between $p75^{NTR}$ and TNFR1 intracellular domains suggest a potential mechanistic divergence between $p75^{NTR}$ and other apoptotic receptors. Consistent with this possibility is the observation that of the many $p75^{NTR}$ interacting proapoptotic proteins thus far identified, including NRIF [68], NADE [69], members of the MAGE protein family [70, 71] and

TRAF-2 [72], only NADE interacts with the death domain of p75^{NTR}. Interestingly, RIP-2 also interacts with the p75^{NTR} death domain, but its engagement with the receptor is antiapoptotic [73]. The identification of prosurvival p75^{NTR} interacting proteins such as RIP-2 [73], IRAK [74] and TRAF-6 [75] suggests that the equilibrium between apoptotic and survival signaling cascades ultimately determines the cellular consequence of p75^{NTR} activation. This equilibrium may be dictated by cell-type-specific expression of critical signaling proteins, as has been proposed for other TNF receptor family members [76].

Other p75^{NTR}-binding molecules identified by biochemical means and by yeast two-hybrid analysis reveal potential functions of p75^{NTR} in cell cycle control and in cytoskeleton rearrangement. The former includes SC-1 [77], NRAGE [70] and NRIF [78], while the latter pathway is specified by an interaction between RhoA [79] and Rho-GDI [80]. Very recently, Higuchi et al. [81] reported that the β-catalytic subunit of protein kinase A (PKA) directly phosphorylates p75^{NTR} to induce p75^{NTR} migration into lipid rafts, events that support prior findings of an interaction between p75^{NTR} and caveolin [82]. Although serine/threonine phosphorylation of p75^{NTR} has been noted previously, this is the first study that integrates ligand-induced phosphorylation of p75^{NTR} with PKA-dependent inactivation of RhoA and axonal outgrowth.

The lack of ligand-induced enzymatic activity and the dual capability of p75^{NTR} to signal independently and together with Trk have made the study of this receptor a challenging endeavor. However, the identification of novel interacting proteins, newly described selective ligands and cell types in which p75^{NTR} activation, independent of Trk, can be probed should provide welcome tools to dissect this multifaceted receptor.

Novel ligands for p75^{NTR}

Recently a number of nonneurotrophin ligands for p75^{NTR} have been described. Two of these are the aggregated β-amyloid [83] and the aggregated prion peptide [84]. Both appear to bind p75^{NTR} with relatively low affinity, in the nanomolar ranges, and both are reported to induce apoptosis. Interestingly, β-amyloid binds monomeric p75^{NTR} and may induce its trimerization to activate c-jun transcription and c-jun N-terminal kinase (JNK) activity [83, 85]. Likewise, an aggregated prion protein fragment implicated in mediating neuronal apoptosis has also been proposed as a p75^{NTR} ligand [84]. This protein fragment competes poorly with mature NGF in kinetic analysis, suggesting that p75^{NTR} may have distinct binding domains for mature NGF or aggregated prion peptides. These aggregated prion peptides initiate apoptosis in a neural crest line, with concomitant caspase-8 activation. Although the concentrations of β-amyloid or aggregated prion peptide required for p75^{NTR} activation are as high or higher than those of mature neurotrophins, such local concentrations may be attained in pathologic states.

Two rabies/rabies-related viral encoded glycoproteins that form a trimeric transmembrane protein complex have also been reported to selectively bind p75^{NTR} in vitro [86, 87]. Again, this interaction utilizes regions of the p75^{NTR} extracellular domains that are distinct from those mediating mature neurotrophin binding. These extracellular sequences of p75^{NTR} are encoded in the alternatively spliced s-p75^{NTR} product, and evidence suggests that both full-length and s-p75^{NTR} bind to rabies virus. The biological consequence does not appear to involve apoptosis regulation but rather facilitation of viral entry in a p75^{NTR}-dependent manner [87].

Exciting new studies also suggest that p75^{NTR} may inhibit the elongation of axons that is mediated by specific myelin proteins. In a rapidly unfolding field, p75^{NTR} was initially identified as a coreceptor with the ganglioside GT1b to mediate the inhibitory actions of myelin-associated glycoprotein (MAG) on the migration of growth cones. Although MAG does not appear to bind directly to p75^{NTR}, it interacts with a GT1b: p75^{NTR} receptor complex, and can activate Rho in a p75^{NTR}-dependent manner, to inhibit process extension [88]. These actions contrast with mature neurotrophins, which impair p75^{NTR}-mediated Rho activation to promote axonal elongation [89]. These observations have been extended in mouse studies by the use of animals that lack expression of the full-length p75^{NTR}. Aberrant axonal elongation is detected in these gene-targeted animals into myelin-rich regions where these processes would otherwise not grow [90].

In addition to MAG, emerging evidence suggests that other myelin glycoproteins utilize multicomponent receptor complexes that include p75^{NTR} to mediate repulsive axonal signaling. The extracellular domains of Nogo-A, oligodendrocyte myelin glycoprotein (OMgp) and MAG can interact with the Nogo receptor present on axons to limit elongation [91]. Because the Nogo receptor is a glycosylphosphatidylinositol (GPI)-anchored protein and thus lacks an intracellular domain capable of signal transduction, additional members of a receptor complex had been sought to provide a molecular mechanism. In recent studies, p75^{NTR} has been identified as a component of the Nogo receptor complex, as Nogo and p75^{NTR} biochemically interact [36, 37] and as misexpression of p75^{NTR} lacking an intracellular domain permits extensive process outgrowth on inhibitory myelin substrates [36]. Interestingly, mature neurotrophins do not appear to compete with Nogo in biochemical assays of p75^{NTR} binding [36]. However, antibodies that induce clustering of the extracellular domain of p75^{NTR} can overcome the axonal repulsion mediated by MAG [37]. These surprising studies together illustrate the unique abilities of p75^{NTR} to

partner with numerous receptors to mediate diverse biological actions (fig. 1).

Neurotrophin signaling via Trk receptors

Amongst the neurotrophin-Trk interactions thus far characterized, that between NGF and Trk A remains the best-studied paradigm of how neurotrophins signal through their cognate receptors. NGF-induced Trk A activation in PC12 cells and BDNF-induced activation of Trk B in neurons is accompanied by a cascade of well-defined cellular events (recently reviewed in [32, 92]). In particular, activation of the small GTPases Ras and Rap1 has been linked to the Raf-1/B-Raf → MAPK/ERK kinase (MEK) → extracellular singal-related kinase (ERK) pathway for transcriptional regulation and differentiative signaling [93, 94], while the PI-3 kinase → PDK → Akt cassette targets and inactivates proapoptotic substrates [95–98]. Unlike the lipid enzyme phospholipase C-γ1 (PLC-γ) which binds directly to activated Trk A at Tyr^{785} residue [32, 33], both of these pathways interact indirectly with the autophosphorylated receptor on Tyr^{490} [99–101]. Indeed, both genetic and biochemical evidence indicates that adaptor proteins, including Grb-2 [102], Shc [101], FRS-2/SNT [99] and Gab-1 [103], link Trk A to the Ras pathway for Erk activation, and to the PI 3-kinase pathway for Akt activation. Perhaps paradoxically, a number of cytoplasmic SH2 domain-containing tyrosine phosphatases have been shown to positively regulate neuronal differentiation and survival [104–106]. Although the precise cellular mechanisms for these observations are unknown, they appear to involve interaction with the adaptor proteins FRS-2 and Gab-1 [107].

Unlike many other receptor tyrosine kinases which utilize multiple tyrosine-containing motifs to define distinct interaction sites for downstream signaling components [108], only two of the seven conserved (among Trk A, B and C) tyrosine residues that lie outside of the Trk kinase domain have been established to play critical roles in functional reconstitution studies (i.e. Y^{490} and Y^{785}; reviewed in [32, 92]). Thus the adaptor proteins FRS-2 and Shc, each of which has been associated with differentiative and survival signaling, compete for phosphorylated Y^{490} on activated Trk A [100]. Similarly, at least two molecules have been shown to interact with phosphorylated Y^{785}: PLC-γ, whose activation has been linked to intracellular Ca^{2+} mobilization, PKCδ activation and transcriptional regulation [32, 109–111], and a C-terminal SRC kinase (CSK) homolog kinase (CHK), implicated to modulate neurite outgrowth in PC12 cells via an as yet undefined mechanism [112].

A number of independent studies have also demonstrated that upon Trk activation, the activation loop tyrosine residues (Y^{670}, Y^{674} and Y^{675}) constitute binding sites for several SH2 domain-containing adaptor proteins. These include rAPS and the closely related SH2-B [113]; the latter has been characterized in terms of growth hormone signaling via JAK2 [114]. In neuronal cells, however, SH2-B has been implicated in the survival signaling of NGF-dependent sympathetic neurons [113] and differentiation of PC12 cells [115, 116]. This appears to occur, in part, via the MAP kinase cascade initiated by Grb-2 binding to tyrosine-phosphorylated SH-2B [113]. In addition, a direct SH2-B-independent interaction between the activation loop tyrosines of Trk A with Grb-2 has been reported [102]. As Grb-2 also interacts with FRS-2 and Shc, these studies suggest a highly redundant mechanism for modulating Grb-2-associated signaling events. Finally, an interaction between the cytoplasmic tyrosine kinase c-Abl with Y^{674} and Y^{675} of activated Trk A has been proposed based on in vitro binding analysis [117], while another study has proposed that the c-Abl interaction occurs within the juxtamembrane region of Trk A [118]. Although the precise mode of c-Abl : Trk interaction remains to be clarified, c-Abl and the c-Abl related gene product (Arg) have been implicated in early neurulation [119] and regulation of growth cone dynamics [120], cellular events in which Trk might potentially participate.

In additional to direct interactions with Trk as summarized above, a number of signaling proteins have been indirectly linked to neurotrophin responsiveness with only partially defined signal transduction pathways. Most notable is the Rap 1 → B-Raf-mediated prolonged MAP kinase activation cascade, which has been correlated with differentiative signaling in PC12 cells [93, 94]. Although it is generally recognized that upon NGF treatment, the small GTPase Rap1 is activated by the guanine exchange factor C3G via the adaptor c-Crk II (or the related CrkL) [121], direct interaction to connect ligand-activated Trk A to c-Crk II or CrkL remains to be delineated. However, an in vitro interaction between the SH2 domain of c-Crk II with FRS-2 has been reported [100]. Alternatively, the identification of additional Rap 1 exchange factors [122] might afford a C3G-independent means for modulating the B-Raf-directed MAP kinase activation. Members of the Src kinase family may also modulate distinct aspects of neurotrophin-induced cellular responses, but the molecular mechanisms await clarification [92]. In contrast to other growth factor receptors such as the PDGF receptor, which contains distinct SH2 domain binding motifs for c-Crk II/CrkL and c-Src [123], direct binding of these signaling modules to Trk has not been established. Although future analysis should identify whether these (and other) 'orphan' signaling proteins interact directly with Trk, it is interesting to note that in addition to Y^{490} and Y^{785}, other conserved tyrosine residues of Trk A have been posited to play synergistic roles in mediating NGF-induced neurite outgrowth [124].

Novel Trk substrates and modes of activation

Many of the downstream effectors of Trk are not unique to the neurotrophins, but are activated by other receptor tyrosine kinases to yield distinct biological endpoints. Although the duration (i.e. sustained vs. transient) of MAP kinase activation remains an important parameter in defining growth factor specificity [93, 94], recent advances suggest that additional mechanisms orchestrate the diversity and specificity of neurotrophin actions.

Initially described by Campenot more than 20 years ago, compartmentalized cultures of peripheral neurons can be used to evaluate the differential effects of Trk A activation in the cell body and in distal processes [125]. In these highly polarized cells, where sustained delivery of NGF at the axon in vivo is required for cell survival, the mechanisms that facilitate retrograde transport of distal Trk signaling are highly relevant [126]. Creative application of this tissue culture system by a number of investigators has begun to dissect the cellular consequences of distal Trk receptor activation. Although many of the molecular details remain unresolved (recently reviewed by [127, 128]), retrograde transport of activated Trk receptor itself [129–131] is a critical event in promoting CREB-mediated gene transcription [132] and neuronal survival [129]. Other studies also demonstrate that both PI-3 kinase and a member of the Erk family (ERK 5) are integral components of the retrograde neurotrophic signal [133–135]. In addition to its role in activating Akt [97], PI-3 kinase activity is required for the internalization of Trk-containing signaling endosomes [136, 137]. Equally intriguing, however, is the finding that direct application of NGF to the proximal cell body compartments results in local activation of both ERK1/2 and ERK5, while axonal exposure to NGF (confined within the distal compartment) leads to retrograde transport of only activated ERK5 [135]. Since ERK1/2 and ERK5 can mediate distinct transcriptional events, these results strongly suggest that unique signaling pathways can be generated by spatially limiting the exposure of neurotrophins in highly polarized neurons.

Interestingly, intrinsic mechanisms also exist to define spatially specific signals. Using fluorescent resonance energy transfer to detect activated Ras and Rap1, Mochizuki et al. have reported distinct cellular localization of these two GTPases [138]. Surprisingly, active Ras was detectable along the neurites of NGF-differentiated PC12 cells, while activated Rap1 remained only within the perinuclear region of the cells [138, 139], suggesting that even on cells that are uniformly exposed to NGF, biochemically redundant pathways for MAP kinase activation need not cross paths. Given the number of known downstream effectors that could modulate neurotrophin signaling, systematic analysis of localized activation of these molecules would be extremely informative.

Recent reports on the crosstalk between Trk and G-protein-coupled receptors (GPCRs) provide yet another mechanism by which activation of Trk results in selective utilization of downstream signaling pathways. In these studies, adenosine and the neuropeptide PACAP were shown to promote neuronal survival in a Trk-dependent manner [140, 141]. In contrast to similar observations with the EGF receptor, transactivation of Trk occurs with delayed kinetics, suggesting an alternative mechanism of activation than that which occurs on the plasma membrane. Interestingly, and unlike that reported for the EGF receptor, transactivated Trk A engages only the PI-3 kinase pathway to promote neuronal survival without concomitant activation of the MAP kinase cascade [140]. Although transactivation of Trk A (and Trk B) by GPCRs is still an emerging theme in receptor crosstalk, the preferential activation of PI-3 kinase but not of MAP kinase suggests the mode of Trk activation (i.e. ligand-induced vs. transactivated) may play a critical role in dictating downstream biological outcomes.

Of potential relevance with regard to specificity of Trk signaling, several novel Trk interacting proteins have been identified. These include Tctex-1, a 14-kDa cytoplasmic dynein light chain that might play an important role in retrograde transport of activated Trk [142], and GIPC, a PDZ domain-containing protein that modulates GPCR functions [143]. Interestingly, both of these proteins interact with Trk within the juxtamembrane portion but not the signal-transducing tyrosine Y^{490} or Y^{785}, a region which has previously been implicated in NGF-dependent neuritogenesis [144]. In the search of $p75^{NTR}$-interacting protein, an ankyrin rich membrane spanning protein (ARMS) was identified. Further characterization revealed that ARMS also interacts with Trk and that it is tyrosine phosphorylated in response to NGF and BDNF but not the mitogenic growth factor EGF [145]. A GTPase-activating protein (Grit) for Rho and CDC42 has also been reported to bind Trk A [146]. Although the region of interaction has not been clearly defined, Grit appears to complex with Trk A but not Trk B or C in in vitro analysis. This is a potentially important finding, as distinct Trk family members have been known to exhibit biological responses unique to the corresponding neurotrophins [147–149], and little is known of the molecular mechanism that might exist to account for such selectivity at the postreceptor level. Finally, the transcription cofactor MafK has been identified from serial analysis of gene expression (SAGE) of NGF-treated PC12 cells [150]. Its expression profile belongs to those of the immediate early genes (IEGs), but unlike other IEGs, MafK appears to be specifically induced by NGF. The additional finding that MafK expression is required for the differentiation of telencephalic neurons and PC12 cells [150] suggests that Trk-specific signaling is coupled to transcription responses unique for neuronal functions.

An additional level of complexity is encountered in cells which coexpress both $p75^{NTR}$ and Trk receptors. Although coexpression of both receptors can modulate the affinity of ligand binding, there is increasing evidence that crosstalk between $p75^{NTR}$ and Trk receptors occurs via modulation of intracellular signaling pathway (recently reviewed by [20]). For example, prior studies have suggested that $p75^{NTR}$ increases serine phosphorylation of Trk A via an unknown kinase [151]. Further study will be required to determine whether this results in attenuation or augmentation of specific signaling pathways downstream of Trk. In addition, Trk activation of PI-3 kinase can suppress $p75^{NTR}$-mediated ceramide production and may serve as a mechanism to impair $p75^{NTR}$-elicited apoptosis [152]. Thus, future studies that clarify the biologically relevant $p75^{NTR}$-signaling cascade will provide important targets that additionally may be regulated by Trk-induced intermediates to balance and modulate neurotrophin responsiveness (fig. 2).

Perspectives

Since the identification of NGF as a soluble factor with axonal growth-promoting activity more than 50 years ago [6], this small family of polypeptides has continued to fascinate the neuroscience community. This is due not only to the critical roles of the neurotrophins in maintaining neuronal survival, but also to an expanding list of equally important functions governed by the neurotrophins [1, 2]. At the molecular level, a dual-receptor system with unique and redundant signal transduction networks appears to have evolved to account for the complexity of neurotrophin actions. Recent findings of proneurotrophin-specific effects, alternative $p75^{NTR}$ ligands and spatially regulated Trk signaling have addressed some outstanding issues and uncovered new ones in terms of how neurotrophins and their receptors modulate basic cellular functions (e.g. survival/death and differentiation) and extending those influences to higher order mental activities (e.g. memory and behavior). On the other hand, these studies also hold promise for rational therapeutic approaches for diseases within and outside of the nervous systems. For example, once the molecular mechanism is better characterized, the apparently 'promiscuous' interaction of $p75^{NTR}$ with mature and proneurotrophins, myelin components and β-amyloid might be pivotal for selective blockade of one ligand-induced event over another. In summary, it appears that neurotrophin : receptor trios have expanded to include additional players, as has the repertoire of associated biological effects. Perhaps future studies will determine whether other growth factor : receptor systems are equal diverse in terms of ligand specificity, receptor signaling and functions.

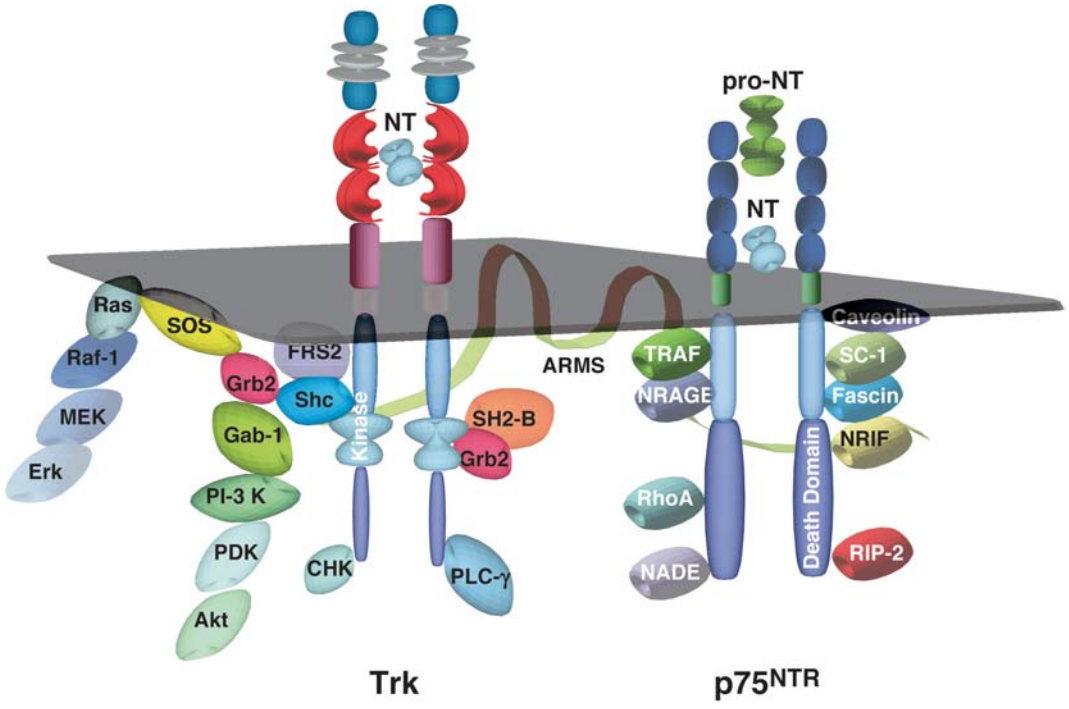

Figure 2. Schematic representation of $p75^{NTR}$ and Trk interacting proteins and selected downstream signaling cascades. The final biological outcomes of (pro)neurotrophin binding to $p75^{NTR}$ and/or Trk are ultimately determined by the equilibrium between downstream signaling components that maintain survival (i.e. Akt, TRAFs, FAP-1 and RIP2), or induce death (i.e. NRIF, NADE and NRAGE), or modulate cell cycle progression (i.e. NRAGE and SC-1) or promote neuronal differentiation (i.e. Erk, and RhoA). See main text for a detailed discussion.

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