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Review

p75^{NTR}: A study in contrasts

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Abstract

The p75 neurotrophin receptor (p75^{NTR}) and trkA, trkB and trkC mediate the physiological effects of the neurotrophins. The trk receptors are responsible for the stereotypical survival and growth properties of the neurotrophins but defining the physiological function of the p75^{NTR} has proven difficult. The p75^{NTR} binds each of the neurotrophins with low nanomolar affinity whereas the three trk receptors show strong binding preferences for individual neurotrophins; in some cell types, p75^{NTR} is the only neurotrophin receptor whereas in others it is co-expressed with the trks. The analysis of p75^{NTR} function has been complicated by the fact that the predominant physiological role of p75^{NTR} changes dramatically depending on cell context. Available data suggests that in cells where p75^{NTR} is co-expressed with trk receptors, p75^{NTR} functionally collaborates with the trks to either *enhance* responses to preferred trk ligands, to *reduce* neurotrophin-mediated trk receptor activation resulting from non-preferred ligands or to facilitate apoptosis resulting from neurotrophin withdrawal. In cells lacking trk expression, p75^{NTR} can act autonomously to activate ligand-dependent signaling cascades that may in some circumstances result in apoptosis but probably not through pathways utilized by its apoptotic brethren in the TNF receptor superfamily. Potential mechanisms for each of these functions of p75^{NTR} are considered and the physiological implications of this unique signaling system are discussed.

Keywords: nerve growth factor; neurotrophins; ceramide; tumor necrosis factor; apoptosis

Abbreviations: NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT-3, neurotrophin-3; NT-4, neurotrophin-4/5; p75^{NTR}, p75 neurotrophin receptor; TNF-R1, tumor necrosis factor receptor type 1; TNF-R2, tumor necrosis factor receptor type 2; TNF, tumor necrosis factor; JNK, jun kinase

Introduction

The classic *in vivo* and *in vitro* experiments which demonstrated that nerve growth factor (NGF) plays critical roles in the development of mammalian neurons set the stage for dramatic expansion of our knowledge of neurotrophic interactions in the nervous system in the past decade (Levi-Montalcini, 1987). The identification of sequence homology between NGF and brain-derived neurotrophic factor (BDNF; Leibrock *et al*, 1989) spurred cloning experiments which led to identification of neurotrophin-3 (NT-3; Ernfors *et al*, 1990; Hohn, 1990; Jones and Reichardt, 1990; Maisonpierre *et al*, 1990; Rosenthal *et al*, 1990) and neurotrophin-4/5 (NT-4/5; Berkemeier *et al*, 1991; Hallbook *et al*, 1991; Ip *et al*, 1992), each of which promotes survival of specific populations of mammalian neurons. These effects of the neurotrophins are mediated by interaction with two types of cell surface receptors. The trk receptors are highly related transmembrane receptor tyrosine kinases which preferentially bind different members of the neurotrophin family (Berkemeier *et al*, 1991; Ip *et al*, 1992, 1993; Klein *et al*, 1991, 1992; Lamballe *et al*, 1991; Soppet *et al*, 1991; Squinto *et al*, 1991). The preferential binding of the neutrophins to trk receptors has allowed them to be grouped as preferred ligands which bind with high affinity, non-preferred ligands which show weaker binding or non-ligands which do not bind or activate the receptor. Activation of trk receptors with preferred ligands results in the stereotypical effects typically associated with neurotrophin action (Clary *et al*, 1994; Ibanez *et al*, 1992; Rovelli *et al*, 1993; Weskamp and Reichardt, 1991). The physiological importance of the trks in neuronal survival has been clearly demonstrated in mice where trk receptor genes have been rendered null by homologous recombination (Klein et al, 1993, 1994; Smeyne et al, 1994).

Unlike the trks, the p75 neurotrophin receptor (p75^{NTR}) binds all the neurotrophins (Rodriguez-Tebar *et al*, 1990, 1992; Squinto *et al*, 1991). In contrast to the rapid progress made in elucidating the mechanism of action of the trk receptors (reviewed in Kaplan and Stevens, 1994), the physiological roles of the p75^{NTR} are complex and have been more difficult to discern. However, the available data on p75^{NTR} suggests that its actions fall into two categories. First, p75^{NTR} can functionally collaborate with trk receptors to either enhance (Barker and Shooter, 1994; Hantzopoulos *et al*, 1994; Verdi *et al*, 1994) or reduce (Benedetti *et al*, 1994; Ip *et al*, 1993; MacPhee and Barker, 1997) neurotrophin-mediated trk receptor activation. Second, p75^{NTR} acts autonomously to activate signaling cascades that may be involved in apoptosis, possibly in a manner similar to that utilized by its brethren in the TNF receptor superfamily (Casaccia-Bonnefil *et al*, 1996; Frade *et al*, 1996). However, the role of p75^{NTR} *in vivo* remains controversial and some caution in assigning physiological function is warranted. Nonetheless, common themes and complementary findings are beginning to coalesce to allow us to develop a more comprehensive view of the actions of

this enigmatic receptor. In this review, we will discuss the various actions of p75^{NTR} and suggest how these disparate roles may together contribute to common biological aims.

Structural features and expression of p75^{NTR}

The p75^{NTR} was the first-identified member of the TNF receptor superfamily, an expanding group of Type I membrane proteins (reviewed in Baker and Reddy, 1996; Smith *et al*, 1994). The distinguishing feature of the superfamily is the presence of tandem arrays of an extracellular motif which contains six cysteines and functions as the ligand binding domain. The crystal structure of the TNF-R1 receptor extracellular domain revealed that within each tandem array, cysteines are linked to produce a rigid, elongated structure (Banner *et al*, 1993). None of the receptors within this family have intrinsic enzymatic activity but intracellular domain sequences provide some clues to potential signaling mechanisms. The intracellular domain of p75^{NTR} has a 90 amino acid region that bears homology to the 'death domain' sequence present in other TNF receptor family members (Boldin *et al*, 1995; Chapman, 1995). In fas and TNF-R1, this region is critically required to mediate interactions with downstream signaling elements necessary for activation of the apoptotic proteolytic cascade (Takahashi *et al*, 1994; Tartaglia *et al*, 1993) and it has been suggested that this domain may subserve a similar function in p75^{NTR} (Carter and Lewin, 1997; Chapman, 1995). Sequence alignments have revealed death domains in a wide variety of proteins, including several with no apparent apoptotic role and it would appear that this structure may act as a general protein-protein association domain that in some proteins is specialized for a role in programmed cell death (Feinstein *et al*, 1995; Hofmann and Tschopp, 1995). Sequence alignments have placed death domains from various proteins into two groups on the basis of the homology within the first α-helix and in spacing between putative helices, with TNF-R1, fas and TRADD falling into subtype I and p75^{NTR} placed within subtype II (Feinstein *et al*, 1995). This subdivision likely reflects important structural differences between these types of death domains; unlike fas- and TNF-R1 death domains, the death domain in p75^{NTR} does not aggregate or self-associate (Barker *et al*, 1995). Recent NMR analyses has shown that the α-helix required for self-association of the fas death domain is shifted to an almost perpendicular position in p75^{NTR} (Huang *et al*, 1996; Liepinsh *et al*, 1997). Although most subtype I death domains show a propensity for death domain hetero-oligomerization, there is no indication that p75^{NTR} associates directly or indirectly with any other death domain-containing protein. Since oligomerization of TNF-R1 and fas death domains is critical for their apoptotic function (Boldin *et al*, 1995), it is likely that signaling mechanisms activated by p75^{NTR} death domain interactions differ considerably from those mediated by apoptotic receptors such as fas and TNF-R1.

Embedded within the fifth helix of the p75^{NTR} death domain is another region of interest which was identified through its similarity to a Gα activating domain present within some G-protein coupled receptors and to mastoparan, a wasp venom peptide that can directly activate G proteins (Feinstein and Larhammer, 1990; Myers *et al*, 1994; Liepinsh *et al*, 1997). Peptides representing this region are relatively poor G-protein activators (Barker, Ross, Shooter, unpublished observations) yet when added exogenously, they have been reported by one group to potentiate NGF-dependent neuronal process outgrowth from PC12 cells, embryo chick primary sensory neurons and fetal rat primary sensory neurons but have no affect on apoptosis (Dostaler et al, 1996) and by another to elicit apoptosis of neuroblastoma cells (Hileman *et al*, 1997). Whether these effects reflect bona fide physiological actions of p75^{NTR} remains unknown but caution is warranted since such amphiphilic peptides can exert a wide array of non-physiological effects. Other motifs that are present within the p75^{NTR} intracellular domain include a consensus sequence for binding of PSD-like proteins at the carboxy terminus (Kornau *et al*, 1995) and a weak homology to a region within TNF-RII, CD30 and CD40 which mediates interactions with the TRAF family of proteins but the physiological significance of these homologies remains to be demonstrated.

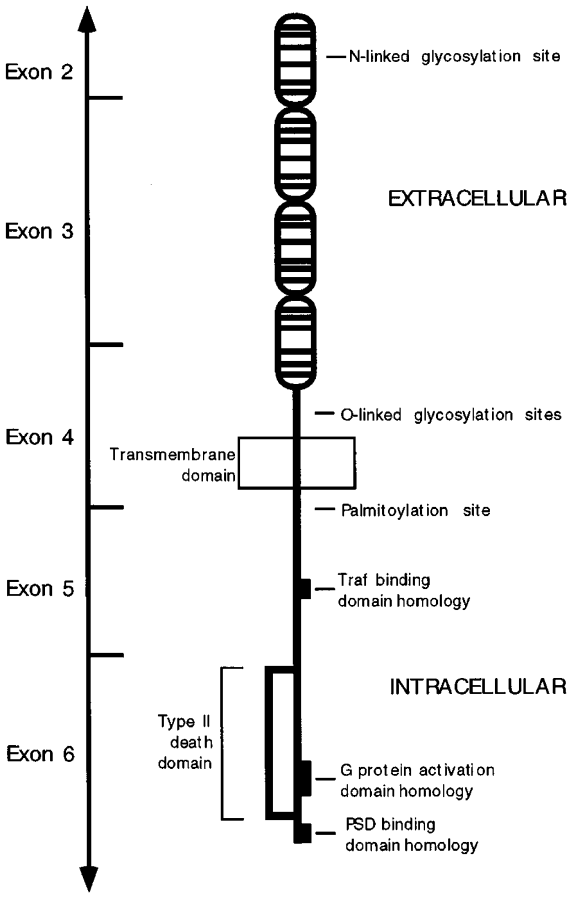

Figure 1 Schematic diagram of structural features of p75^{NTR}. The mature, cleaved form of p75^{NTR} is shown with exon boundaries indicated. Exon 1 (not shown) includes 5′ untranslated sequence and most of the signal peptide and exon 6 includes greater than 2 kb of 3′ untranslated sequence. Cysteine-rich domains 1–4 are indicated as ovals. See text for details of indicated features

An interesting feature of the p75^{NTR} intracellular domain is the degree to which it is conserved between species (Heuer *et al*, 1990a,b; Large *et al*, 1989). The transmembrane and intracellular and extracellular juxtamembrane region of chick, rat and human p75^{NTR} are almost completely homologous; the selective pressure exerted to maintain this degree of conservation indicates that these regions are likely to subserve important roles in p75^{NTR} function. Indeed, although NMR analysis indicates that the intracellular juxtamembrane region of p75^{NTR} is highly flexible (Liepinsh *et al*, 1997), the strong conservation of this region suggests that it is likely stabilized *in vivo* through protein-protein interactions.

Finally, although most functional assays of p75^{NTR} physiology have been limited to the full length receptor, other forms of p75^{NTR} are also produced. A mRNA splice variant of p75^{NTR} which lacks exon 3, which encodes the ligand binding domain, has recently been discovered by Barde and colleagues (Dechant and Barde, 1997). Intriguingly, this alternatively spliced form is apparently still expressed in the original p75 knockout mouse where exon 3 was deleted by homologous recombination (Dechant and Barde, 1997). If confirmed, the presence of this alternate transcript may require a re-evaluation of conclusions drawn from the analysis of the original p75^{NTR} knockout mouse (Lee *et al*, 1992). Other p75^{NTR} isoforms are produced by proteolysis. A constitutively active metalloprotease which appears ubiquitously expressed cleaves p75^{NTR} and produces a soluble extracellular domain and a receptor fragment containing transmembrane and intracellular domains (Barker *et al*, 1991; DiStefano *et al*, 1993; Zupan *et al*, 1989). This cleaved, soluble p75^{NTR} extracellular domain is produced at very high levels during development and following peripheral nerve injury (DiStefano *et al*, 1991). The biological roles subserved by p75^{NTR} isoforms produced by alternative splicing or proteolytic processing remain completely unknown but the possibility that they may interfere with normal signaling or even generate constitutive signals is currently under investigation.

A final important structural point on the p75^{NTR} receptors regards the nature of its ligands. Most members of the TNF receptor superfamily bind trimeric ligands that are produced as cell surface Type II transmembrane proteins (reviewed in Cosman, 1994) but the neurotrophins are soluble, dimeric ligands which are processed through the secretory pathway. Thus, the oligomeric, ligand-bound structure of the p75^{NTR} is likely very different from other members of the TNF receptor superfamily. On transformed cells expressing p75^{NTR}, each of the neurotrophins bind p75^{NTR} with approximately equal affinity with a single dissociation constant in the low nanomolar range but kinetic and functional data indicate that NT-3 and NT-4 may both exhibit high affinity binding to p75^{NTR} on some types of neurons (Curtis *et al*, 1995; Dechant *et al*, 1997; Ryden *et al*, 1995). Some binding cooperativity has been noted for p75^{NTR} (Rodriguez-Tebar *et al*, 1992) and it is possible this may enhance formation of high-affinity sites in a cell-specific manner through interactions of p75^{NTR} with unidentified cytoplasmic or transmembrane components.

p75^{NTR} is widely expressed in the nervous system during development. High levels of p75^{NTR} are observed in many central neuronal populations during development, including spinal motor neurons and brain stem motor nuclei, lateral geniculate nucleus, thalamic nuclei, amygdala, cortical subplate neurons, olivary pretectal nucleus, cuneate nucleus, as well as Purkinje cells, the external granule layer and deep nuclei of the cerebellum (Buck *et al*, 1988; Ernfors *et al*, 1988; Heuer *et al*, 1990a,b; Schatteman *et al*, 1988). In the adult, high levels of p75^{NTR} are maintained in magnocellular neurons of the basal forebrain (Hefti *et al*, 1986; Schatteman *et al*, 1988; Springer *et al*, 1987; Yan and Johnson, 1988) and lower levels are found within the caudate/putamen, on cerebellar Purkinje cells and ventricular subependymal cells and within several central nuclei, including the ventral premaxillary, mesencephalic trigeminal, hypoglossal, raphe and suprachiasmatic groupings (Henry et al, 1994; Koh et al, 1989; Pioro and Cuello, 1988; Schatteman et al, 1988; Sofroniew et al, 1989).

In the periphery, p75^{NTR} is found within dorsal root ganglia sensory neurons, within sympathetic neurons and in some enteric and parasympathetic neurons (Carroll *et al*, 1992; Schatteman et al, 1993; Yan and Johnson, 1988). There is variable p75^{NTR} expression within neurons of the DRG (Schatteman *et al*, 1993; Verge *et al*, 1992); although sensory neurons within the DRG can be grouped into subpopulations by virtue of their trk expression and their peripheral target innervation, no correlation between p75^{NTR} expression and sensory neuron physiology or phenotype has yet been established.

The highest expression of p75^{NTR} occurs outside the nervous system. During development, mesenchymal cells, presumably fibroblasts, located in the axilla and pelvis and within developing limb buds express very high levels of p75^{NTR} (Heuer *et al*, 1990a; Heuer *et al*, 1990b; Wheeler and Bothwell, 1992). Mesenchymal expression of p75^{NTR} is also observed within several developing organs, including kidney, lung and testes, the developing inner ear and hair follicles (Byers *et al*, 1990; von-Bartheld *et al*, 1991; Wheeler and Bothwell, 1992). Within the kidney, p75^{NTR} expression has been observed in uninduced mesenchyme at early developmental stages and in glomerular podocytes at later developmental times (Alpers *et al*, 1993; Durbeej 1993). Somitic expression of p75^{NTR} is observed within dermatome and sclerotome and although early muscle precursor cells present in the myotome do not express the receptor, the later stage myoblasts show high p75^{NTR} expression (Wheeler and Bothwell, 1992). In mature animals, nonneuronal p75^{NTR} expression is more restricted and is limited to endothelial cells, perivascular fibroblasts and dental pulp cells (Byers *et al*, 1990; Wheeler and Bothwell, 1992; Yan and Johnson, 1988).

Functional aspects of p75^{NTR}

The actions of p75^{NTR} fall into two categories. First, p75^{NTR} functionally collaborates with trk receptors to either enhance (Barker and Shooter, 1994; Hantzopoulos *et al*, 1994; Verdi *et al*, 1994) or reduce neurotrophin-mediated trk receptor

activation (Benedetti *et al*, 1994; Ip *et al*, 1993; MacPhee and Barker, 1997). Second, $p75^{NTR}$ acts autonomously to activate signaling cascades that may be involved in apoptosis (Casaccia-Bonnefil *et al*, 1996; Frade *et al*, 1996). There is some question regarding the specific mechanisms employed by $p75^{NTR}$ to achieve these effects but they may be closely interrelated. Before considering a comprehensive view of the physiological actions of $p75^{NTR}$, these separate functions will first be discussed individually.

Functional collaborations of $p75^{NTR}$ with trkA

Substantial evidence indicates that one of the main physiological roles of the $p75^{NTR}$ is to collaborate with trk receptors to modulate neurotrophic responses. When $p75^{NTR}$ or trkA are individually expressed in transformed cells, most NGF binding sites show low nanomolar affinity for NGF, distinct from the high affinity binding site present on PC12 cells or sensory neurons (Rodriguez-Tebar *et al,* 1992). However, when the two receptors are coexpressed, levels of high affinity sites rise dramatically (Hempstead *et al*, 1991; Mahadeo *et al*, 1994) and NGF-mediated trkA activation is increased (Verdi *et al*, 1994). Consistent with this, the NGF responsiveness of embryonic sensory and postnatal sympathetic neurons derived from $p75^{-/-}$ animals is considerably reduced compared to neurons derived from their wild-type counterparts (Davies *et al*, 1993; Lee 1994). $p75^{NTR}$ mediates this increased responsiveness by increasing the association rate with which NGF binds trkA and thereby increasing the amount of NGF which ultimately becomes bound to trkA (Barker and Shooter, 1994; Mahadeo *et al*, 1994). Blocking NGF binding to $p75^{NTR}$ using MC192 or BDNF reduces binding of NGF to trkA (Barker and Shooter, 1994; Lachance *et al*, 1997) and mutant forms of NGF which bind trkA but not $p75^{NTR}$ are less effective than wild type NGF in activating trkA on cells where $p75^{NTR}$ and trkA are co-expressed (Ryden *et al*, 1997). This indicates that the simple presence of the $p75^{NTR}$ is insufficient for the increased trkA responsiveness and that NGF binding to $p75^{NTR}$ is required for this effect. Together, the data show that a normal physiological function of $p75^{NTR}$ is to increase the ability of trkA to bind and respond to low NGF levels. This is likely of considerable importance *in vivo*; reduction in the ability of trkA to bind limiting quantities of NGF in $p75^{NTR-/-}$ mice may account for the progressive loss of sensory and sympathetic nerve endings observed as these animals approach adulthood (Lee *et al*, 1992, 1994).

In fibroblasts, $p75^{NTR}$ slightly increases the transforming capacity of trk receptors through establishment of an autocrine loop. Intriguingly, mutant forms of $p75^{NTR}$ which

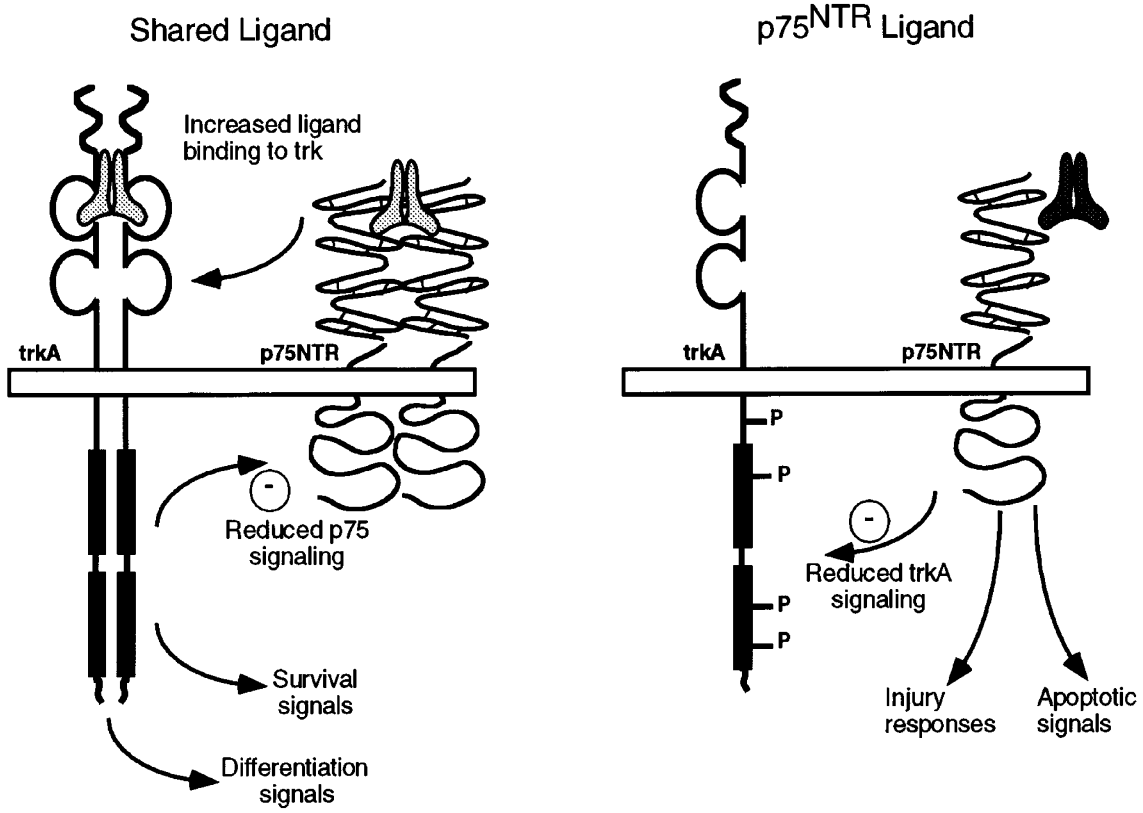

Figure 2 $p75^{NTR}$ facilitates apoptosis in cells expressing trk by reducing latent trkA activity. Left panel: when a preferred ligand for trk is available, $p75^{NTR}$ increases the ability of trk to bind and thereby respond to low ligand concentrations. Activated trk reduces $p75^{NTR}$ signaling and limits the ability of $p75^{NTR}$ intracellular signals to reduce trk signaling. Right panel: when a non-preferred ligand or trk non-ligand is presented, binding to $p75^{NTR}$ predominates. This activates a signaling cascade that results in serine phosphorylation of trkA, thereby reducing its basal activation, resulting in reduced trk-derived survival signals

lack most of the intracellular domain increase trkA-, trkB- and trkC-mediated transformation much more effectively than the wild-type $p75^{NTR}$ (Hantzopoulos *et al*, 1994). The most likely explanation for this is that while the $p75^{NTR}$ extracellular domain is capable of delivering neurotrophin for use by the trk receptor, the $p75^{NTR}$ intracellular domain somehow acts to reduce the ability of trk to either recognize or respond to the preferred ligand. Receptor acylation may be involved in this process since the juxtamembrane domain which mediates most of the inhibitory effect contains a cysteine residue (Cys 279) which is a target for receptor palmitoylation (Barker *et al*, 1994).

Several experiments suggest that the $p75^{NTR}$ can *reduce* trkA tyrosine phosphorylation. The relatively high level of ligand-independent constitutive tyrosine phosphorylation present on trk receptors expressed in Sf9 or 293 cells is strongly attenuated in the presence of $p75^{NTR}$, indicating that $p75^{NTR}$ may play a physiological role reducing basal levels of trk phosphorylation (Kaplan, personal communication and Barker, unpublished results). Furthermore, whereas $p75^{NTR}$ *increases* responses of trks to preferred ligands, it also reduces trk responses to nonpreferred ligands. NT-3 and NT-4/5 activate trkA in fibroblasts (Barker *et al*, 1993; Berkemeier *et al*, 1991; Ip *et al*, 1993) and in mutant PC12 cells which lack $p75^{NTR}$ expression (Benedetti *et al*, 1994) yet neither ligand effectively activates trkA in PC12 cells in which both trkA and $p75^{NTR}$ are coexpressed (Ip *et al*, 1993). Similarly, NT3-mediated activation of trkB is muted in cells co-expressing $p75^{NTR}$ compared to cells expressing trkB alone (Ip *et al*, 1993). These results suggested that *in vivo*, $p75^{NTR}$ may act as a form of high-gain filter which reduces responses to non-preferred ligands and enhances responses of preferred ligands; consistent with this, postnatal sympathetic neurons derived from $p75^{NTR-/-}$ mice show greater responses to NT-3 than their wild-type counterparts (Lee *et al*, 1994).

The deficits of the trk-$C^{-/-}$ mice are considerably milder than in NT-$3^{-/-}$ lines, suggesting strongly that non-preferred ligands such as NT-3 do indeed mediate effects *in vivo* through trkA or trkB (Tessarollo *et al*, 1997) and the role of $p75^{NTR}$ in regulating this activation may therefore have considerable physiological importance.

The physical arrangement of $p75^{NTR}$ and trkA receptors required for their positive or negative collaboration has not been established. However, fluorescence recovery after photobleaching and co-patching studies have suggested that the two receptors are co-localized within plasmalemmal patches through a mechanism involving an extracellular interaction (Ross *et al*, 1996; Wolf *et al*, 1995). The identity of these plasmalemmal patches is uncertain but $p75^{NTR}$ expressed in fibroblasts has been detected in caveoli (Bilderback et al, 1997). It has been difficult to determine whether p75NTR and trk receptors independently co-localize to some subplasmalemmal domain or whether they interact directly but conditions in which $p75^{NTR}$ can be co-immunoprecipitated with trkA, trkB or trkC have now been identified (Barker, Zeindler, unpublished results) and the structure-function relationship of this direct interaction is under investigation.

Table 1 Ligand binding specificities of trk receptors

	Preferred	Non-preffered	Non-ligand
trkA	NGF	NT-3. NT-4	BDNF
trkB	BDNF, NT-4	NT-3	NGF
trkC	NT-3	none	NGF, BDNF, NT-4

Preferred ligand show high affinity binding to trk receptors. Non-preferred ligands show low but detectable binding affinity for listed trk receptors. Non-ligands do not bind or activate the corresponding trk receptor

$p75^{NTR}$ may reduce the responses of trk receptors to non-preferred ligands through a process termed receptor transmodulation. This mechanism has been best described with regard to the effect of TNF on insulin signaling, where a TNF-mediated reduction in insulin signaling occurs via TNF-dependent serine and threonine phosphorylation of the insulin receptor and its downstream tyrosine kinase signaling partner, IRS (Feinstein *et al*, 1993; Hotamisligil *et al*, 1994; Kanety *et al*, 1995; Mothe and Van Obberghen, 1996). TNF receptor-mediated activation of sphingomyelinase activity and the subsequent accumulation of ceramide appear to be key components of this signaling cascade (Hotamisligil *et al*, 1996; Kanety *et al*, 1996; Peraldi *et al*, 1996). $p75^{NTR}$ also mediates sphingomyelinase activation and we have asked if $p75^{NTR}$ activation results in selective phosphorylation of serine or threonine residues within trkA which correlate with a reduction in subsequent ligand-mediated trkA activity. Both BDNF and C2-ceramide, a cell-permeable ceramide analogue, increase trkA phosphoserine content and concomitantly reduce trkA activation (MacPhee and Barker, 1997), suggesting that receptor transmodulatory mechanisms operating through a ceramide-dependent pathway contributes to the regulation of trkA by $p75^{NTR}$. BDNF can therefore reduce trk activity both by reducing NGF binding to trkA as well as by an intracellular path involving ceramide generation.

$p75^{NTR}$ signaling in the absence of trk receptors

Signaling events which are mediated through TNF receptor superfamily members are becoming increasingly clear (reviewed in Baker and Reddy, 1996; Darnay and Aggarwal, 1997; Tewari and Dixit, 1996). Ligand-dependent activation of sphingomyelinase and accumulation of ceramide has been observed with some family members and a candidate protein which directly interacts with the p55 TNF receptor intracellular domain and which may play a role in this pathway has been identified (Adam-Klages et al, 1996). Downstream events, such as the activation of NF-κB and jun kinase have been well studied and the pathways leading to their activation remain somewhat controversial, particularly with regard to the role of ceramide. Nontheless, proximal signaling elements that contribute to this signaling have been identified. TRAF proteins, which directly interact with several TNF receptor superfamily member intracellular domains appear to play a crucial role in activation of both the NF-κB and the jun kinase (JNK) pathways (Hsu et al, 1996; Natoli et al, 1997; Rothe et al, 1995). Downstream interactors that connect TRAF proteins to IkB kinase activation or to the

MEKK/JNK pathway remain uncertain but several candidates have been identified. The ability of TNF receptor superfamily members to activate apoptosis has come under intense scrutiny and a surprisingly short and direct pathway has emerged, at least for death-domain containing proteins such as fas. Interactions of the receptor's death domain with the cytoplasmic death domain-containing proteins TRADD and FADD result in activation of the apoptotic cascade via the death-domain containing caspase known as FLICE or caspase 8 (reviewed in Chinnaiyan and Dixit, 1997). Details of the activation cascade now emerging suggest that bcl-2 family members and the mammalian ced4 homologue may directly regulate caspase 8 activation (Chinnaiyan *et al*, 1997).

How do the signaling events mediated by $p75^{NTR}$ relate to those activated by other TNF receptor superfamily members? One of the first clues that $p75^{NTR}$ had a direct signaling role came from studies of Dobrowsky and colleagues who found that neurotrophin binding to $p75^{NTR}$ resulted in activation of sphingomyelinase and production of ceramide (Dobrowsky *et al*, 1994, 1995). Since then, $p75^{NTR}$-dependent activation of sphingomyelinase has been observed not only in transformed cells but also in primary oligodendrocytes (Casaccia-Bonnefil *et al*, 1996) and in primary mesencepalic neurons, where a $p75^{NTR}$-mediated increase in ceramide levels correlates with increased dopamine release (Blochl and Sirrenberg, 1996). Other signaling events mediated by $p75^{NTR}$ include the activation of NF-κB in fibroblasts and Schwann cells (Carter *et al*, 1996) and the activation of JNK in oligodendrocytes (Cascaccia-Bonnefil *et al*, 1996), PC12 cells and transfected 293 cells (Lachance, Zeindler, MacPhee, Barker unpublished observations). These signaling events show interesting ligand and cell-type specificities. For example, even though sphingomyelinase is activated by all the neutrophins in 3T3 fibroblasts (Dobrowsky *et al*, 1995), $p75^{NTR}$-mediated JNK activation does not occur in this cell type (Casaccia-Bonnefil *et al*, 1996). Furthermore, in $p75^{NTR}$-expressing fibroblasts, NT-3 is the most potent and NGF the least effective ligand for sphingomyelinase activation (Dobrowsky *et al*, 1995) whereas in rat oligodendrocytes, NGF effectively activates sphingomyelinase while NT-3 has no effect (Casaccia-Bonnefil *et al*, 1996). In contrast to the pan-neurotrophin mediated activation of sphingomyelinase, only NGF appears capable of direct $p75^{NTR}$-mediated activation of JNK and NF-κB pathways in cells where the receptor is not co-expressed with trk (Carter *et al*, 1996; Casaccia-Bonnefil et al, 1996). With regard to JNK and NK-κB activation, it is important to note that the effects of $p75^{NTR}$ are very modest when compared to activities of other membrs of the TNF receptor superfamily and can sometimes be observed only under relatively non-physiological conditions (Carter *et al*, 1996; Casaccia-Bonnefil *et al*, 1996) (Lachance, Bhaker, Barker unpublished observations). This may indicate either that the actions of the receptor are limited to conditions of cellular stress, that cells studied to date do not contain an optimal complement of signal transduction elements or that more physiologically relevant pathways remain to be elucidated.

$p75^{NTR}$ and cell death

Before considering studies which suggest an involvement of $p75^{NTR}$ in apoptosis, it is important to draw distinctions between the models systems that have been employed to study this problem. Receptor-mediated apoptosis, such as that mediated by the fas or the TNF-R1 receptors, occurs in response to ligand binding and does not require ongoing transcription or translation. Indeed, inhibition of transcription or translation often increases the amount of apoptosis induced by these receptors, in part by reducing the anti-apoptotic effect mediated by NF-κB-driven transcription (Van Antwerp *et al*, 1996; Wang *et al*, 1996). Ligand binding to these receptors activates the JNK pathway and some evidence has suggested a causal link between this event and the induction of apoptosis (Verheij *et al*, 1996). However, receptor mediated activation of the JNK pathway is not obligatory for apoptosis and the TRADD-caspase 8 pathway described above accounts for most of the receptor-mediated apoptosis mediated by Fas ligand or TNF (Hsu *et al*, 1996; Liu *et al*, 1996; Natoli *et al*, 1997). By contrast, the neurotrophin-withdrawal paradigms which have been developed as models for developmental neuronal apoptosis differ in several critical respects. Withdrawing NGF from sympathetic neurons or from differentiated PC12 cells results in loss or trk survival signals and produces apoptosis which is dependent upon ongoing transcription and translation (Rukenstein *et al*, 1991). The specific transcriptional events that are required to mediate neurotrophin-withdrawal induced apoptosis remain unclear but, unlike the receptor-mediated apoptosis described above, activation of the JNK pathway and increases in c-*jun* dependent transcription which occur following neurotrophin withdrawal play a critical role (Estus *et al*, 1994; Ham *et al*, 1995).

Several studies suggest that $p75^{NTR}$ plays a role in neuronal apoptosis resulting from neurotrophin withdrawal. PC12 cells (Barrett and Georgiou, 1996) or dorsal root sensory neurons (Barrett and Bartlett, 1994) which have reduced $p75^{NTR}$ levels show attenuated NGF withdrawal-induced apoptosis and treatment of transected dorsal root sensory neurons *in vivo* with p75 antisense oligonucleotides reduces subsequent sensory neuron loss (Cheema *et al*, 1996). Consistent with this, both sympathetic and dorsal root sensory neurons derived from $p75^{NTR-/-}$ mice show delayed apoptosis compared to their wild-type counterparts following NGF withdrawal (Lee, personal communication). Furthermore, numbers of forebrain cholinergic neurons are significantly increased in mice in which the $p75^{-/-}$ gene is disrupted (Vanderzee *et al*, 1996; Yeo *et al*, 1997). Using neurotrophin-withdrawal paradigms, we have recently shown that BDNF, which acts as a $p75^{NTR}$-specific ligand on PC12 cells, increases activation of the JNK pathway as well as the frequency of apoptosis of differentiated PC12 cells subjected to neurotrophin withdrawal (unpublished observations) and Dr. Freda Miller and colleagues (McGill University) have recently found that BDNF treatment of sympathetic neurons increases apoptosis and JNK activation (Bamji *et al*, 1997). The possibility that BDNF may increase developmental apoptosis *in vivo* through a $p75^{NTR}$-dependent mechanism is underscored by the finding that numbers of sympathetic

neurons are increased in BDNF$^{-/-}$ mice (Bamji *et al*, 1997). The effect of BDNF on these neurons *in vivo* could be due to p75^{NTR} signaling or, since BDNF competes with NGF for p75^{NTR} binding sites, may involve a reduction in NGF binding to trkA. Since BDNF is expressed in both PC12 cells and sympathetic neurons, it is possible that a BDNF-dependent autocrine loop may play some role in mediating the apoptotic effect of p75^{NTR} in these cell types.

Other studies have suggested that p75^{NTR} is capable of directly activating apoptosis *in vivo*. Early studies which raised the possibility that p75^{NTR} might mediate apoptosis showed that *in vivo* administration of MC192, a monoclonal antibody directed against rat p75^{NTR}, results in loss of sympathetic neurons (Taniuchi and Johnson, 1985) and that NGF treatment of transected facial mononeurons, which express high levels of p75^{NTR} as a result of injury, resulted in a reduction in cell number (Sendtner *et al*, 1992). More recent studies have shown that NGF administration to the developing chick isthmo-optic nucleus, which express p75^{NTR} and trkB but not trkA, produced profound neuronal loss (von Bartheld et al, 1994) and that the normal developmental apoptosis of chick retinal cells is reduced with antibodies directed against NGF or p75^{NTR} (Frade *et al*, 1996). Considerable difficulty has been encountered in developing *in vitro* systems for the study of ligand-dependent apoptotic effects of p75^{NTR} but recent studies have shown that NGF increases apoptosis of serum-starved rat oligodendrocytes differentiated *in vivo* (Casaccia-Bonnefil *et al*, 1996) and that overexpression of p75^{NTR} in MG87 fibroblasts results in cell death (unpublished observations), perhaps due to activation of an autocrine loop. Using fibroblasts in which p75^{NTR} expression was regulated through a tetracycline responsive element, NGF, but not BDNF, was shown to facilitate apoptosis (unpublished results). Together, the available data suggests BDNF facilitates cell death in cells where p75^{NTR} is co-expressed with trkA yet only NGF is capable of mediating a p75^{NTR}-dependent apoptotic response in cells lacking trkA.

An accessory to the act: a model for p75^{NTR}-facilitated apoptosis

The apoptotic effects of p75^{NTR} can be placed into three separate categories. In the first, p75^{NTR} increases apoptosis of cells following neurotrophin withdrawal; this effect is not strictly dependent upon added ligand but in cases where p75^{NTR} and trkA are coexpressed, relatively low levels of added BDNF can facilitate this effect (Bamji *et al*, 1997; Barrett and Georgiou, 1996). Several observations suggest that the most likely effect of p75^{NTR} in these circumstances is to reduce trk-derived survival signals. Compared to other receptor tyrosine kinases, trk receptors show an unusually strong tendency for ligand-independent transphosphorylation (Ferrari *et al*, 1995; Ferrari and Greene, 1996; Hempstead *et al*, 1992; Kaplan *et al*, 1991; Rabin and Mocchetti, 1995) and co-expression of p75^{NTR} sharply reduces this ligand-independent activation of trk receptors. By extension, it is likely therefore that under physiological circumstances, one role of p75^{NTR} is to help dampen trk activity which persists after ligand withdrawal. In this model, increased jnk activity and apoptosis resulting from BDNF treatment of cells co-expressing p75^{NTR} and trkA would be due to a p75^{NTR}-mediated reduction in trk signaling rather than from direct activation of apoptotic pathways. The mechanism by which p75^{NTR} reduces trk signaling under physiological circumstances remains unclear but for now, the best possibility is a receptor transmodulatory mechanism in which BDNF binding to p75^{NTR} activates a ceramide-dependent cascade resulting in serine phosphorylation of the trk receptor and a reduction in ligand-regulated activity (MacPhee and Barker, 1997). This transmodulatory effect of p75^{NTR} should reduce not only latent trkA signaling but, since NT-3 and NT-4 bind more efficiently to p75^{NTR} than trkA, also probably reduces the response of trkA (and possibly trkB) to non-preferred ligands. trk signals do of course signal very efficiently in response to preferred ligand and it is likely that ligand-activated trk supersedes any p75^{NTR}-mediated transmodulatory effect, possibly by reducing p75^{NTR}-mediated ceramide production (Dobrowsky *et al*, 1995).

The most relevant physiological setting for this 'dampening' action of p75^{NTR} is under circumstances in which neurons fail to compete effectively for limiting amounts of neurotrophins and must be cleared from the nervous system. Thus, increased basal forebrain cholinergic (Vanderzee *et al*, 1996) and sympathetic neuron survival observed in the p75$^{NTR-/-}$ animals (Bamji *et al*, 1997) may be due to increased levels of basal trkA activity as well as to increased activation of trk receptors in response to non-preferred ligands rather than to loss of a specific apoptotic effect of p75^{NTR}. It is interesting to consider recent results of Brennan *et al* (1996) in light of this model. p75$^{NTR+/-}$ and NGF$^{+/-}$ mice were interbred and examined for *in vivo* sympathetic neuron survival. Intriguingly, higher sympathetic neuron survival was observed in NGF$^{+/-}$, p75$^{-/-}$ mice than in NGF$^{+/-}$, p75$^{+/+}$ mice – one interpretation of this result is that the lack of p75^{NTR} in the NGF$^{+/-}$, p75$^{-/-}$ animals allows trkA on the sympathetic neurons to respond much more effectively to non-preferred ligands such as NT-3 or NT-4.

The second category of p75^{NTR}-mediated apoptosis involves NGF-dependent, trkA-independent signaling. The mechanisms responsible for this form of neurotrophin-mediated death remain unclear; while it is possible that p75^{NTR} mediates apoptosis in selected cell populations which lack trkA expression through direct signaling mechanisms akin to those described for TNF-R1 and fas, there is still little data supporting this notion. p75^{NTR} overexpression studies have clearly shown that p75^{NTR} (Majdan *et al*, 1997) or its intracellular domain can activate cell death machinery in neurons and some mesenchymal cell types. However, several non-neuronal cell types that readily support TNF-R1 or fas-mediated apoptotis do not support p75^{NTR}-mediated cell death (PAB, unpublished results), indicating that elements which are required for p75^{NTR} to manifest its apoptotic effect are likely expressed in a cell-specific manner. Indeed, it is uncertain if direct p75^{NTR}-mediated apoptosis requires recruitment of TRADD or FADD-like proteins or even if caspase activ-ation plays a role in p75^{NTR}-mediated death. Differences between

p75^{NTR} and fas death domain structure and oligomerization suggests that these two types of receptors are likely to employ different signaling strategies. It is notable that intensive efforts from several labs have so far failed to identify death domain-containing proteins which physically interact with p75^{NTR}.

In some cells which express p75^{NTR}, the receptor appears to be involved in apoptosis under specific *in vitro* conditions but these apoptotic effects of p75^{NTR} are relatively subtle (Casaccia-Bonnefil *et al*, 1996), suggesting that p75^{NTR} may normally be a relatively weak apoptotic activator. p75^{NTR}-mediated death is only observed under relatively high ligand concentrations and under conditions of cell stress, the effect of p75^{NTR} seem to be to push cells that already have 'one foot in the grave' to an apoptotic path. Perhaps the most likely explanation for these NGF-dependent effects of p75^{NTR} is a weak, relatively inefficient interaction with apoptotic signal transduction elements. These interactions would presumably be stabilized by signaling intermediates that are expressed in a cell-specific manner in specific cell types. As noted above, the structure of the p75^{NTR} death domain differs very significantly from apoptotic death domain within the fas receptor (Huang *et al*, 1996; Liepinsh *et al*. 1997); it is possible that when overexpressed at high levels, p75^{NTR} or p75^{NTR} intracellular domains may overcome the requirement for signaling intermediates and stimulate apoptotic paths by weakly activating apoptotic paths in a non-physiological manner.

The third category of p75^{NTR}-mediated apoptosis involves situations where p75^{NTR} overexpression causes increased cell death in the absence of ligand and where NGF addition reduces this apoptotic effect (Bunone *et al*, 1997; Rabizadeh *et al*, 1993). These results have led to the notion that in some cells, p75^{NTR} is a constitutive activator of apoptotic pathways in the absence of ligand and that NGF binding ablates this signaling. While it is not possible to rule this out, it is hard to reconcile this hypothesis with the fact that p75^{NTR} activates NF-κB, sphingomyelinase and apoptosis in a ligand dependent manner in a number of cell systems. It is striking how closely the results from the studies of Rabizadeh *et al* (1993) and Bunone *et al* (1997) resemble the apoptotic effects seen in cells expressing trkA. Indeed, if the cells used in these analyses have even very low levels of trkA receptors or if they express trkB or trkC receptors, the effects of p75^{NTR} and the subsequent NGF-mediated rescue could be explained by the receptor modulatory mechanisms discussed above. Although the model described explains only trkA-p75^{NTR} interactions, a similar model could account for p75^{NTR}-trkB or -trkC effects. For example, if survival of these cells normally involves an NT3-trkC autocrine loop, the effect of overexpressing p75^{NTR} might be to sequester endogenous NT-3 from the trkC receptor, thereby reducing cell survival. The survival promoting activity of NGF would not be direct but would instead result from the ability of NGF to compete NT-3 from p75^{NTR}, thereby allowing NT-3 to bind trkC and activate survival pathways. Determining whether the effects of p75^{NTR} in these circumstances are direct or indirect will no doubt eventually be solved by structure-function analyses using a panel of p75N^{NTR} mutants.

Closing remarks

The neurotrophins are unique in their ability to bind and activate different classes of receptor with distinct bioactivities and this results in complex receptor-receptor interactions in which the biological effects of p75^{NTR} varies dramatically depending on whether it is coexpressed with trk receptors and on ligand supply. When coexpressed with trk receptors, p75^{NTR} acts to enhance neurotrophin binding and trk receptor activation, to limit responses of trk receptors to non-preferred ligands, to reduce basal levels of trk signaling and to enhance apoptosis following neurotrophin withdrawal. When expressed in the absence of trkA, p75^{NTR} activates signaling paths in an NGF-dependent fashion. Compared to other members of the TNF receptor superfamily, p75^{NTR} is a relatively poor activator of these signaling events but this may reflect the failure to identify appropriate cellular contexts or even the appropriate p75^{NTR} ligand. Future efforts focusing on the identity of cytosolic proteins which interact with p75^{NTR} and mediate its signaling events will no doubt shed interesting new light on the actions of this enigmatic receptor.

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