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p75 neurotrophin receptor signaling in nervous system injury and degeneration: paradox and opportunity

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Injury or insult to the adult nervous system often results in reactivation of signaling pathways that are normally only active during development. The p75 neurotrophin receptor ($p75^{NTR}$) is one such signaling molecule whose expression increases markedly following neural injury in many of the same cell types that express $p75^{NTR}$ during development. A series of studies during the past decade has demonstrated that $p75^{NTR}$ signaling contributes to neuronal and glial cell damage, axonal degeneration and dysfunction during injury and cellular stress. Why the nervous system reacts to injury by inducing a molecule that aids the demise of cells and axons is a biological paradox that remains to be explained satisfactorily. On the other hand, it may offer unique therapeutic opportunities for limiting the severity of nervous system injury and disease.

Introduction

Neurotrophic factors are secreted proteins that play key roles in most aspects of the life of neurons, including their generation, survival, migration, maturation, axonal growth, synaptic connectivity and injury responses [1]. Most importantly, neurotrophic factors are required for the sustained function of the adult nervous system and show potent neuroprotective and regenerative functions in animal models of neurodegenerative diseases and neurotrauma [2]. These properties have made neurotrophic factors prime candidates for therapeutic intervention against diseases of the nervous system, and have attracted tremendous interest from academia, biotech and pharmaceutical industries.

$p75^{NTR}$ is a transmembrane receptor for neurotrophic factors of the neurotrophin family (Figure 1a,b) which includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) [1,3–6]. In addition to $p75^{NTR}$, neurotrophins signal via TrkA, B and C members of the receptor tyrosine kinase family [1,7]. The two receptor systems can function synergistically, antagonistically or independently of each other in different cell types [8,9] (Figure 1c). Neurotrophins are initially synthesized as precursors (pro-neurotrophins) which are then cleaved to produce mature proteins. It has more recently been appreciated that pro-neurotrophins can also be released and have biological actions on cells [10]. The pro-domain interferes with Trk receptor binding and activation, and thus renders pro-neurotrophins selective $p75^{NTR}$ ligands. On the other hand, the pro-domain interacts with the sorting receptor sortilin, which then associates and cooperates with $p75^{NTR}$ to bind pro-neurotrophins with high affinity [11] (Figure 1c). Pro-neurotrophins can induce cell death [12] and decrease synaptic function [13,14], and thereby in many ways oppose the functions of mature neurotrophins [9].

Similar to other members of the tumor necrosis factor receptor (TNFR) superfamily, $p75^{NTR}$ contains a so-called death domain in its intracellular region [15] (Figure 1a). The death domain mediates interactions with other cellular components, allowing the receptor to regulate intracellular signaling events [3,4]. Some of the pathways regulated by $p75^{NTR}$ in response to neurotrophins include NF-κB [16], c-Jun kinase (JNK) [17,18] and caspases [19]. $p75^{NTR}$ can also activate the small GTPase RhoA [20], but this requires a different set of ligands derived from myelin, such as myelin-associated glycoprotein (MAG) and Nogo [21–23], and two different coreceptors: a lipid-anchored ligand-binding subunit known as the Nogo receptor (NgR), and Lingo-1 [24,25] (Figure 1c). When activated in cultured neurons, this pathway leads to growth-cone collapse and inhibition of axonal growth [26]. Intriguingly, whereas myelin-derived ligands induce RhoA activity through $p75^{NTR}$, neurotrophin binding to $p75^{NTR}$ has been shown to downregulate RhoA activity in neurons [20,27].

$p75^{NTR}$ is widely expressed in the developing nervous system. Sensory and sympathetic neurons, spinal cord and brainstem motoneurons, and neurons in the cerebral cortex, cerebellum, hippocampus, basal forebrain and caudate putamen all express $p75^{NTR}$ at some stage of their development [28–31]. Subpopulations of peripheral and central glial cells, including radial glial and neural stem cells, also express $p75^{NTR}$ at various stages of development [32]. In most cells, $p75^{NTR}$ expression is switched off at adult stages. A few areas, however, retain $p75^{NTR}$ expression at lower levels, including basal forebrain cholinergic neurons, sensory neurons and spinal cord motoneurons [28,30,33,34].

After reviewing some of the effects of neural injury on $p75^{NTR}$ expression, this article summarizes some of the functions of this receptor in various injury and cell-death paradigms, as well as axonal pruning and degeneration. In closing, we highlight the therapeutic opportunities lying ahead through manipulation of $p75^{NTR}$ signaling, and

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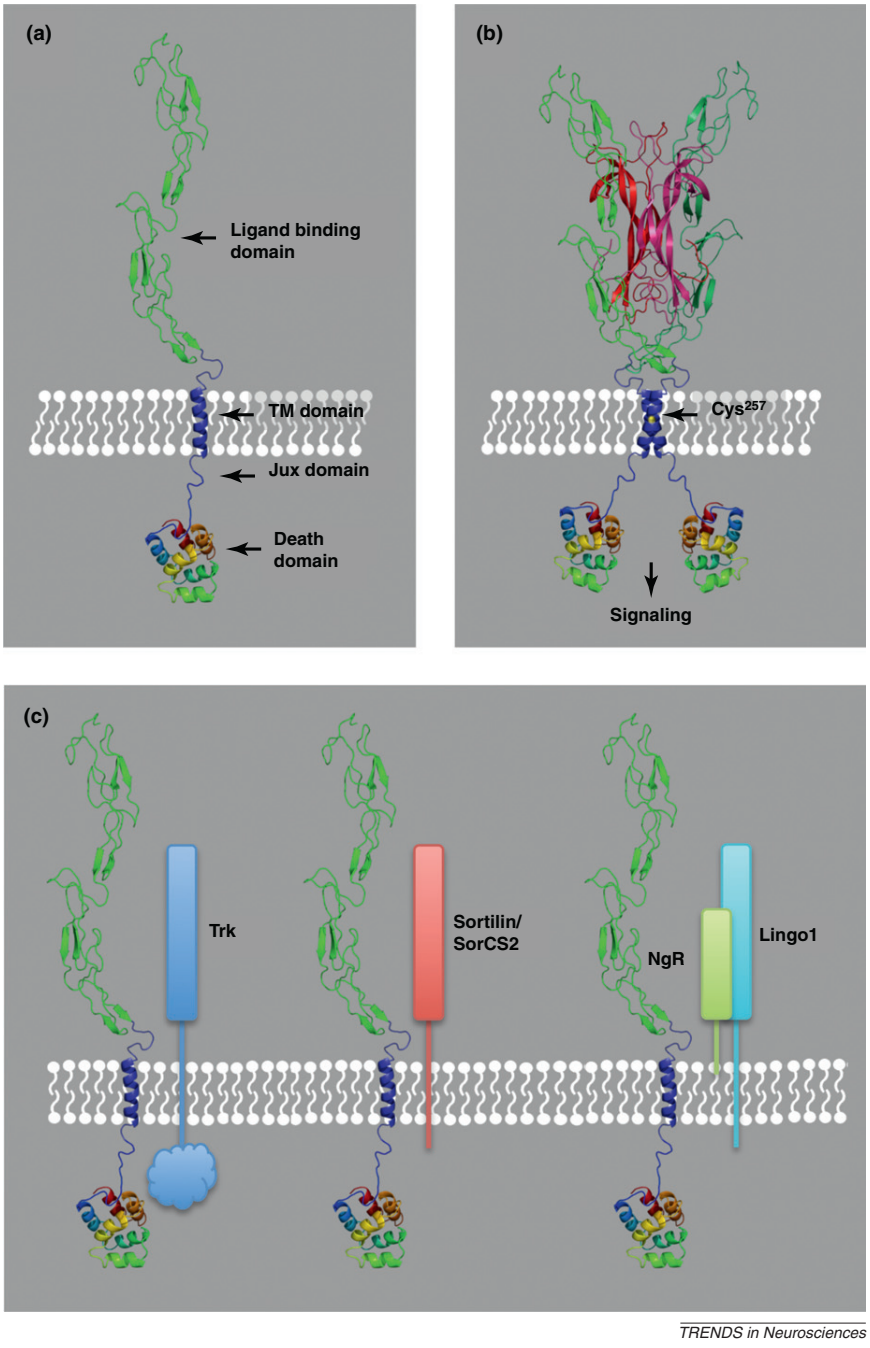

Figure 1. p75^{NTR} structure, activation, signaling and coreceptors. **(a)** Structural view of a p75^{NTR} subunit in the plasma membrane, with structural models of the extracellular (ligand-binding) domain [112,113] and the death domain [15] approximately drawn at scale. TM, transmembrane. Jux, juxtamembrane (a flexible domain, unstructured in solution [15], linking the TM and death domains). **(b)** Model of p75^{NTR} activation in response to neurotrophin-binding (adapted from [105]). Cys^{257} in the TM domain is essential for transmitting conformational changes from the extracellular to the intracellular domains upon ligand-binding. Neurotrophin-binding results in the separation of the dimerized death domains, resulting in the activation of downstream signaling pathways. **(c)** p75^{NTR} coreceptors. p75^{NTR} cooperates with receptor tyrosine kinases from the Trk family (TrkA, B and C) for high-affinity binding of neurotrophins [118]. Sortilin-family receptors (including SorCS2) cooperate with p75^{NTR} for high-affinity binding of pro-neurotrophins [11]. Nogo receptor (NgR) and Lingo-1 bind myelin-derived ligands and signal to RhoA through p75^{NTR} [24,25]. It has not yet been demonstrated whether these coreceptors engage p75^{NTR} as a dimer.

ponder the possible physiological significance of the existence of endogenous pathways that mediate cell death and axonal degeneration in response to injury.

Adult re-expression of p75^{NTR} following injury and cellular stress

Many different types of injury and cellular stressors are potent inducers of p75^{NTR} expression in neuronal and glial cells (Table 1). Peripheral nerve crush or transection induce strong upregulation of p75^{NTR} expression in spinal cord and facial motoneurons that persists for 2–3 weeks after the lesion [30,35,36]. p75^{NTR} is also strongly upregulated in motoneurons of superoxide dismutase 1 (SOD1)-G93A transgenic mice, an animal model of amyotrophic lateral sclerosis (ALS), and in spinal cords from patients with ALS [37]. Peripheral nerve ligation or transection also

Table 1. Induced expression and functional consequence of $p75^{NTR}$ signaling after neural injury and cellular stress

Tissue/cell type	Injury/lesion/model	Species	$p75^{NTR}$ expression and functional consequence
DRG neurons and glia	Nerve ligation or transection	Rat	↑ $p75^{NTR}$ [38–40]
Schwann cells	Axotomy or demyelinating lesions	Rat, mouse	↑ $p75^{NTR}$ [41–43] Schwann cell death [41]
Spinal cord	SOD1-G39A transgenic mouse model and ALS patients	Mouse, human	↑ $p75^{NTR}$ [37]
Oligodendrocytes	Spinal cord injury, multiple sclerosis	Rat, human	↑ $p75^{NTR}$ [44,45] Cell death [44]
Motoneuron	Nerve crush, transection, oxidative stress	Rat	↑ $p75^{NTR}$ [30,35,36] Neuronal death [68,69,76]
Retina	Optic nerve axotomy, ocular hypertension, ischemic injury, glaucoma	Rat	↑ $p75^{NTR}$ [46–48] Retinal ganglion cell death [82,83,116]
Corticospinal neurons	Axotomy	Mouse	↑ $p75^{NTR}$ [49] Neuronal death [49,67]
Cerebellar Purkinje cells	Axotomy	Rat	↑ $p75^{NTR}$ [50]
Hippocampal neurons	Seizures	Rat, mouse	↑ $p75^{NTR}$ [19,51] Neuronal death [19,75]
Basal forebrain neurons	Excitotoxic insults, seizures	Rat	↑ $p75^{NTR}$ [52] Neuronal death [77]
Striatal interneurons	Ischemic stroke	Rat	↑ $p75^{NTR}$ [53]
Cortical neurons	Hypo-osmolar stress	Mouse	↑ $p75^{NTR}$ [55]
Cortical and basal forebrain neurons	Alzheimer's disease	Human	↑ $p75^{NTR}$ [56,57]

lead to increased $p75^{NTR}$ expression in glial cells and sensory neurons [38–40]. Schwann cells in distal sciatic nerve segments upregulate $p75^{NTR}$ expression after axotomy [41,42] and demyelinating lesions [43]. Thoracic contusion of the spinal cord leads to induction of $p75^{NTR}$ expression in oligodendrocytes [44]. $p75^{NTR}$ is also strongly upregulated in oligodendrocytes of plaques extracted from brains of patients with multiple sclerosis [45]. In the retina, optic nerve axotomy [46], ocular hypertension [47] and ischemic injury [48] all result in elevated $p75^{NTR}$ expression. In the brain, axotomy results in increased $p75^{NTR}$ expression in corticospinal neurons [49] and in cerebellar Purkinje cells [50]. $p75^{NTR}$ is strongly upregulated by neuronal activation following seizures in the hippocampus [19,51] and excitotoxic insults to basal forebrain cholinergic neurons [52]. Ischemic stroke increases $p75^{NTR}$ expression in striatal interneurons [53]. Hypo-osmolar stress induces $p75^{NTR}$ in cortical neurons by *O*-GlcNAcylation of the Specificity Protein 1 (Sp1) transcription factor [54,55]. Finally, cortical and basal forebrain cholinergic neurons from patients with Alzheimer's disease (AD) also show elevated levels of $p75^{NTR}$ [56,57].

Intriguingly, neural injury and stress induce $p75^{NTR}$ in cells that expressed the receptor at some earlier point in development. $p75^{NTR}$ re-expression may thus be part of a program of lesion-induced plasticity that to some extent recapitulates developmental mechanisms. Most of the earlier work reporting elevated $p75^{NTR}$ expression after nervous system lesions and neuronal stress did not address its functional consequences. Two decades ago it was widely expected that, as a neurotrophin receptor, $p75^{NTR}$ would play some kind of a protective role during injury. However, the subsequent finding that $p75^{NTR}$ plays a role in neuronal death turned the intellectual tide, leading to the discovery of pathogenic activities of this receptor in neural injury and disease.

Effects of $p75^{NTR}$ signaling in neuronal and glial cell death after injury

A role for $p75^{NTR}$ in apoptotic cell death emerged during the early 1990s following observations of $p75^{NTR}$-mediated cell death, first in transfected cells [58], but later through endogenous receptors in sensory neurons [59], cells of the isthmo-optic nucleus [60], retinal neurons [61], oligodendrocytes [62], and sympathetic [63] and hippocampal neurons [17]. Two possible physiological scenarios were envisaged for the role of $p75^{NTR}$ in cell death, namely development and injury. Several examples of a role for $p75^{NTR}$ in promoting cell death during development have been uncovered [64,65].

With regards to injury, it was first shown by Bartlett and colleagues in 1996 that reduction of $p75^{NTR}$ levels using antisense oligonucleotides could prevent the loss of axotomized neurons in dorsal root ganglia, thus implicating $p75^{NTR}$ in injury-mediated cell death [66]. Numerous subsequent studies have highlighted a role for $p75^{NTR}$ in neuronal or glial cell death after injury (Table 1). For instance, blocking $p75^{NTR}$ signaling with neutralizing antibodies prevented the death of corticospinal neurons after axotomy [49]. A comparable result has also been obtained in sortilin knockout mice [67], thus implicating pro-neurotrophins in this effect. Survival and regeneration of axotomized motoneurons were found to be improved in $p75^{NTR}$ knockout mice compared to control animals [68,69]. Death of Schwann cells after sciatic nerve axotomy was also diminished in $p75^{NTR}$ knockout mice [41]. Intriguingly, *in vitro* studies have suggested that $p75^{NTR}$ is able to induce either death or survival in Schwann cells, depending upon expression of receptor-interacting serine/threonine-protein kinase 2 (RIP2), an adaptor protein for the receptor [70]. As pointed out earlier [71], the effects of $p75^{NTR}$ on Schwann cells after injury may be complex given the role of $p75^{NTR}$ in myelination [72]. Indeed, in a model of remyelination after peripheral nerve injury, transplanted

wild-type Schwann cells were better at remyelinating lesioned nerves than were cells lacking $p75^{NTR}$ [73], and spontaneous remyelination after sciatic nerve crush was impaired in the absence of $p75^{NTR}$ [74].

In the hippocampus, pilocarpine-induced seizures induce $p75^{NTR}$ expression, caspase-3 activity and neuronal death. Pilocarpine-induced neuronal death was attenuated in mice lacking $p75^{NTR}$ or neurotrophin receptor-interacting factor (NRIF), a $p75^{NTR}$ effector protein [19,75]. These studies established for the first time the role of caspase-6 as an upstream activator of caspase-3 in the apoptotic pathway activated by $p75^{NTR}$ in hippocampal neurons [19]. Apoptotic death of oligodendrocytes after spinal cord injury was also diminished in $p75^{NTR}$ knockout mice [44]. In this case, the lesion resulted in the production of the pro-NGF precursor at the site of injury, which was capable of inducing potent oligodendrocyte death in a $p75^{NTR}$-dependent manner [44]. In another study, pro-NGF produced by reactive astrocytes in response to oxidative stress promoted motoneuron cell death in a $p75^{NTR}$-dependent manner [76]. Pro-neurotrophins were also found to be produced by basal forebrain astrocytes after kainic acid-induced seizures [77]. The seizures elevated $p75^{NTR}$ and sortilin expression and induced caspase-3 activation in basal forebrain neurons, but fewer dying neurons were found in brains of mice lacking $p75^{NTR}$ [77]. Interestingly, this study found that the effects of pro-neurotrophins on cell death were dominant over the survival activity of mature neurotrophins in cultures of basal forebrain neurons [77]. Neural injury therefore alters the ratio of pro- to mature neurotrophins, thus shifting the balance from survival to death. This finding is significant in light of several reports indicating elevated levels of pro-neurotrophins in the brains of AD patients [78–80].

$p75^{NTR}$ has also been shown to contribute to neuronal cell degeneration in a non-cell-autonomous fashion. A recent study has shown that pro-NGF promotes the death of adult retinal ganglion cells via $p75^{NTR}$ signaling from Müller glia [81], a specialized type of glia present in the vertebrate eye and the only cell type in the retina that expresses $p75^{NTR}$ [46]. Pro-NGF induced robust expression of tumor necrosis factor alpha (TNFα) in Müller cells which was required for pro-NGF-induced death of retinal neurons. Moreover, retinas from mice lacking $p75^{NTR}$ or sortilin were resistant to the effects of pro-NGF on TNFα expression and cell death. Similar observations were also made in retinal degeneration as a consequence of glaucoma [82]. These results provided an explanation for the apparent lack of neuroprotective effects of NGF in retinal injury, despite expression of prosurvival TrkA receptors in retinal ganglion cells [82,83] (Figure 2).

Effects of $p75^{NTR}$ signaling in axonal degeneration and synaptic plasticity in the adult nervous system

The discovery of a role for $p75^{NTR}$ in neuronal death prompted researchers to test whether $p75^{NTR}$ signaling might also antagonize other functions, such as axonal growth, target innervation and synaptic plasticity. In 1999, Miller and colleagues demonstrated that BDNF inhibited axonal growth of developing sympathetic neurons through $p75^{NTR}$ *in vitro* and restricted sympathetic innervation of the pineal gland *in vivo* [84]. These and subsequent observations led to the development of a model of sympathetic axon competition in which activity-dependent production of BDNF by the axons that ultimately survived led to axonal degeneration via the activation of $p75^{NTR}$ in other axons [85,86]. A role for $p75^{NTR}$ in axonal degeneration has also been uncovered upon ectopic expression of $p75^{NTR}$ in embryonic stem cell (ESC)-derived neurons [87]. A recent study has shown that binding of pro-NGF, the precursor of NGF, to a complex between $p75^{NTR}$ and sortilin-related VPS10 domain containing receptor 2 (SorCS2) can induce growth-cone collapse in cultured hippocampal neurons by downregulating the activity of Rac, a member of the Rho family of small GTPases [88]. Although the possible relationship between this process and $p75^{NTR}$-mediated axonal degeneration has not yet been explored, it is tempting to speculate that the latter might in some cases be initiated by growth-cone retraction following engagement of pro-neurotrophins with $p75^{NTR}$.

A role for $p75^{NTR}$ in axonal degeneration in the adult nervous system has also recently been uncovered [89]. Focusing on the basal forebrain – one of the few areas where expression of $p75^{NTR}$ is maintained in the adult brain – $p75^{NTR}$ was shown to help to prevent cholinergic fibers from aberrantly spreading collaterals while projecting to the corpus callosum through a highly myelinated tract termed the supracallosal pathway [89]. Indeed, significantly more off-track collaterals were observed in the supracallosal pathway of $p75^{NTR}$ null mutants compared to wild-type mice. Moreover, myelin was shown to induce degeneration of cholinergic axons in cultures of wild-type septal neurons, but had no effect on $p75^{NTR}$ knockout neurons. Intriguingly, neutralizing antibodies for BDNF also prevented the effects of myelin on axonal degeneration, suggesting that both myelin and neurotrophin binding to $p75^{NTR}$ are required for degeneration of septal axons (Figure 3a). Because neutralizing antibodies directed towards BDNF would be expected to affect both mature as well as pro-BDNF forms, these experiments do not address the type of neurotrophin involved in the effects of $p75^{NTR}$ on axonal degeneration. Neither is it clear whether the effects of myelin on axonal degeneration are also mediated by $p75^{NTR}$ or by other myelin receptors, such a Troy [90,91]. The requirement of $p75^{NTR}$ could simply reflect the requirement of BDNF. Myelin can activate the RhoA pathway via $p75^{NTR}$ [92], and this pathway was indeed shown to be required for myelin-mediated degeneration of sympathetic axons [89]. However, the role of RhoA in axon degeneration of central nervous system (CNS) neurons, including those from septal cholinergic neurons, has not been established. This could be important because, in contrast to myelin, neurotrophin binding to $p75^{NTR}$ is known to decrease RhoA activity [20,92].

In addition to RhoA, activation of caspase 6 was also shown to be required for myelin-mediated degeneration of both sympathetic and septal cholinergic axons *in vitro* [89]. A role for caspase 6 in axon pruning had previously been uncovered downstream of death receptor 6 (DR6), a member of the TNFR superfamily related to $p75^{NTR}$ [93]. BDNF neutralizing antibodies prevented activation of caspase 6 in sympathetic axons, but the role of myelin here is less clear. Interestingly, caspase 6 had already been implicated

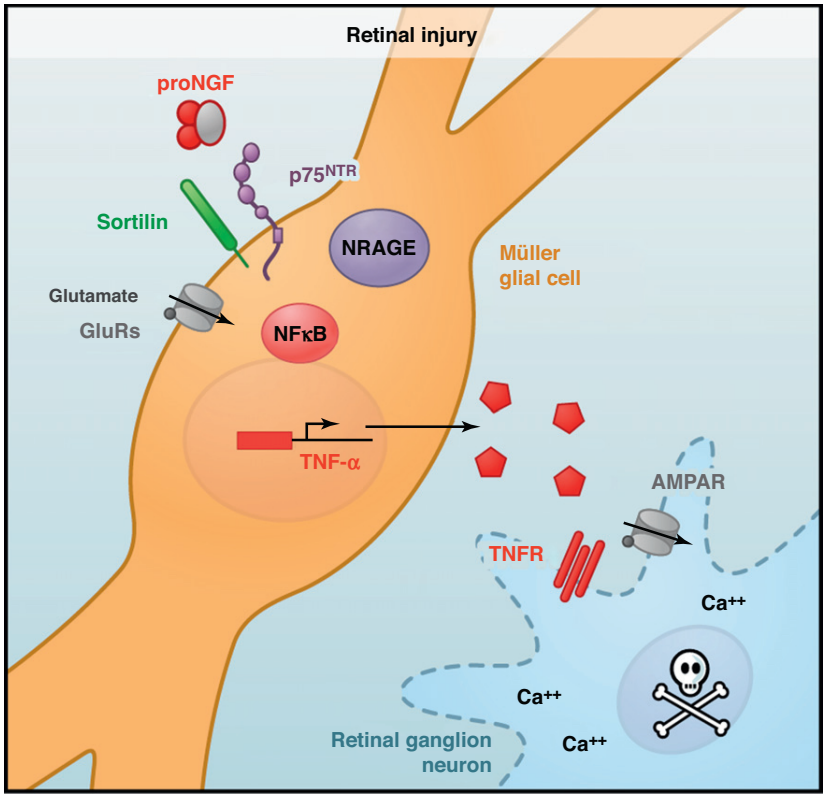

Figure 2. Indirect effects of $p75^{NTR}$ in neuronal injury mediated by glia. In retinal disease models, degeneration of retinal ganglion neurons (RGNs) is induced by various means such as optic nerve axotomy or excitotoxic injury (acute), as well as chronic disease states such as glaucoma. Invariably, retinal injury results in the upregulation of the expression of $p75^{NTR}$, which is, however, confined to the Müller glial cells and is not found in the dying neurons [81]. Despite this, $p75^{NTR}$ is believed to contribute to the death of RGNs via the upregulation of TNFα (another death receptor ligand) in Müller glial cells [81]. Increased expression of TNFα by a variety of stimuli, including excitotoxic injury by NMDA or glutamate, largely depends on NF-κB, a pathway also known to be activated by $p75^{NTR}$. Release of TNFα by Müller glia after activation of NMDA receptors or direct activation of $p75^{NTR}$ by pro-NGF leads to the subsequent death of RGNs [81,119]. Specific blockade or gene deletion of $p75^{NTR}$, NF-κB inhibition or NRAGE (neurotrophin receptor interacting mage homolog) gene knockout, all decrease TNFα levels and protect RGNs from death in various models of retinal injury [81,82,119]. On the other hand, none of the above manipulations afford RGN protection when TNFα is directly administered (i.e. bypassing Müller glia) [81]. The mechanism by which TNFα in turn kills RGNs appears also indirect and does not involve the direct activation of caspases by TNFR. Instead, TNFR-mediated gene expression is suggested to increase cell surface expression of AMPA receptors (AMPAR), thus rendering RGNs susceptible to Ca^{++} overload and excitotoxic cell death [119]. In summary, death receptors such as $p75^{NTR}$ or TNFR may not function by inducing a simplistic death cascade in cells that express them, but rather integrate a variety of signals from multiple cell types and the environment before committing a neuron that is injured beyond repair to death.

in $p75^{NTR}$-mediated death of hippocampal neurons by NGF or BDNF [19], suggesting that this may be a neurotrophin-specific effect. Whether myelin and neurotrophins operate via parallel or overlapping pathways, as well as the relationship between RhoA and caspase 6 in the induction of axonal degeneration, are questions that remain to be addressed.

Although it is not yet clear how myelin and neurotrophins cooperate to mediate axonal degeneration, it is tempting to speculate that a similar process contributes to the failure of myelinated fibers to regenerate after neural injury, leading to the release of myelin fragments and upregulation of $p75^{NTR}$ and pro-neurotrophins (Figure 3b). Additional mechanisms might operate in concert, as suggested by a recent study reporting that Schwann cell-derived $p75^{NTR}$ prevented spontaneous reinnervation of the adult spinal cord after dorsal root injury [94].

Axonal degeneration mediated by $p75^{NTR}$ may also contribute to the significant loss of synaptic connectivity associated with AD (Figure 3b). The neurotoxic amyloid-β (Aβ) peptide, which accumulates in AD, has been shown to interact with the extracellular domain of $p75^{NTR}$ and induce neuronal death [95,96] as well as neuritic dystrophy in a mouse model of AD [97]. In particular, this latter study showed that neurons from $p75^{NTR}$ knockout mice not only showed reduced sensitivity to Aβ-induced cell death but were also protected from Aβ-induced neuritic dystrophy. Intriguingly, degeneration of basal forebrain cholinergic neurites in the Thy1-$hAPP^{Lond/Swe}$ mouse model of AD was significantly reduced when these mice were crossed with $p75^{NTR}$ knockout mice, despite the presence of the same Aβ load [97]. Although basal forebrain neuron death was not addressed *in vivo* in these mice, *in vitro* data suggested that the effects of $p75^{NTR}$ in Aβ-induced cell death may occur at higher Aβ concentrations [95]. This is significant because degenerative changes resulting from cytoskeletal derangements and neuritic dystrophy precede neuronal death and manifest early in AD, contributing to the early symptoms of dementia. Together, these data suggest that $p75^{NTR}$ plays a significant role in enabling Aβ-induced neurodegeneration.

The functional antagonism of $p75^{NTR}$ to many of the trophic actions of mature neurotrophins through Trk

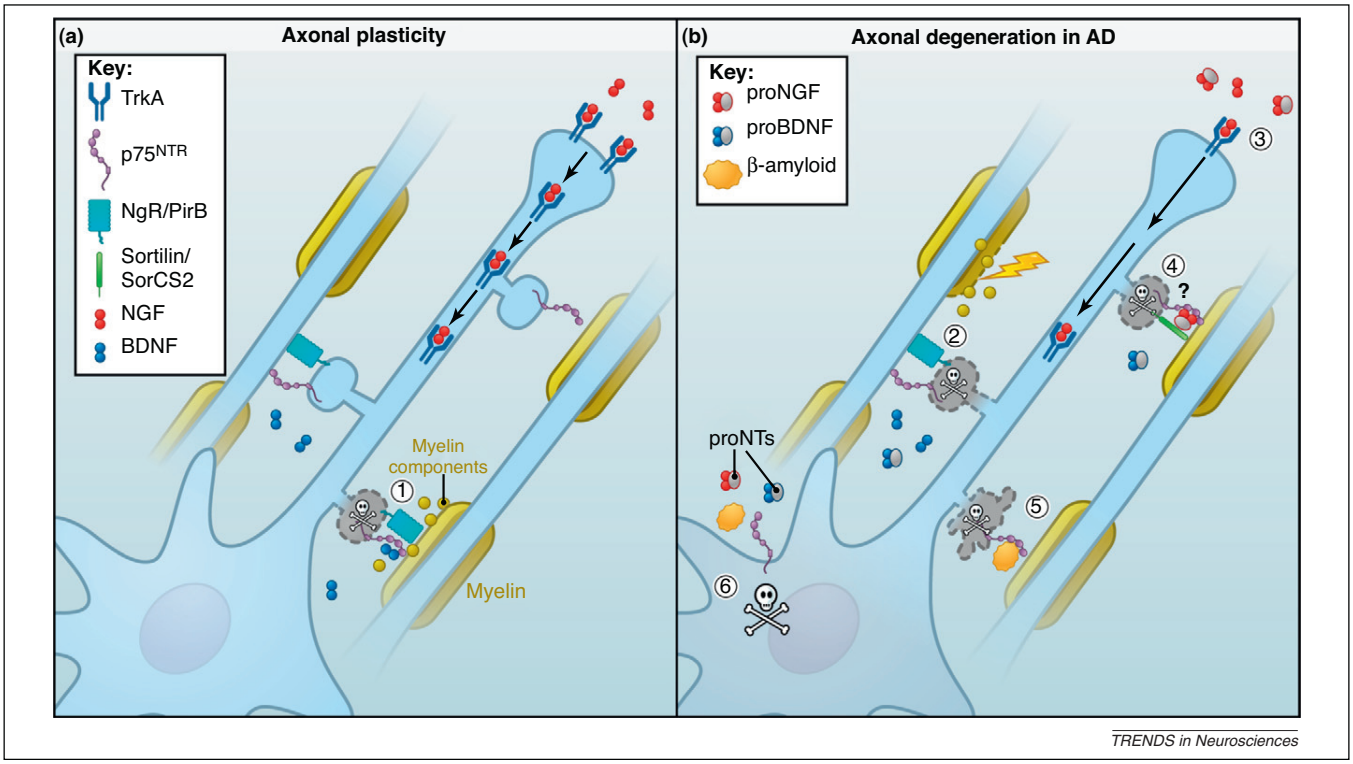

Figure 3. Potential mechanisms of $p75^{NTR}$ involvement in axonal degeneration. **(a)** Axonal degeneration is essential for the precision and plasticity of cholinergic connections in the adult healthy brain, where elimination of aberrant collaterals that could disrupt normal circuitry occurs in physiological conditions. **(1)** This degeneration has been shown to occur locally through $p75^{NTR}$ signaling and requires both BDNF and the axon being in close contact to myelin [89]. The degradation of axons in contact with myelin is highly dependent on the levels of NGF in these axons, as basal forebrain cholinergic neurons specifically require NGF for trophic support. In this paradigm, high NGF would override myelin-induced regression of axons, whereas low NGF would cause all axons exposed to myelin to degrade. Thus, a homeostatic balance between TrkA and $p75^{NTR}$ signaling underlies functionality. **(b)** Aberrant axonal degeneration seen in neurodegenerative diseases such as Alzheimer's disease (AD) may represent a homeostatic mechanism [as in **(a)**] gone awry. This may occur, for example, by exposure to higher concentrations of $p75^{NTR}$ ligands including BDNF [120] or by increased sensitization to myelin components during disease conditions [121] **(2)**. Notably, aging-related and pathological (as in AD) demise of the cholinergic basal forebrain system correlates with loss of functional responses to NGF and a striking reduction in the retrograde transport of NGF in cholinergic neurons [122]; this may result from either decreased levels of TrkA (reported in aging [123]) or defective processing of pro-NGF (seen in injury conditions [77]) or both **(3)**. As suggested in **(a)**, when the critical concentration of NGF drops, axons in close contact with myelin begin to degrade, as if their demise were a default mechanism kept at bay by NGF–TrkA signaling. Region-specific alterations in BDNF levels have also been reported in AD-affected brains [120], and ineffective processing of pro-BDNF may also occur in these conditions. Whether sufficient levels of BDNF are maintained locally or whether pro-neurotrophins bound to a $p75^{NTR}$–sortilin/SorCS2 complex [88] could induce axonal degeneration **(4)** are issues remaining to be resolved. In addition to neurotrophins and their pro-peptides, $p75^{NTR}$ mediates cell death by the Aβ peptide both *in vitro* and *in vivo* [96]. Furthermore, absence of $p75^{NTR}$ protects neurites from dystrophy and cytoskeletal derangements seen in a transgenic mouse model of AD [97] **(5)**. In all, it is increasingly apparent that in pathological aging, and other neurodegenerative conditions with progressive cognitive decline, significant loss of cholinergic function occurs via dendritic, synaptic and axonal degeneration rather than via cell death. $p75^{NTR}$ appears to be a key modulator in the establishment and maintenance (by elimination) of functional connections, and hence is an attractive candidate for mediating the loss of connectivity in disease. A composite hypothesis may yet implicate $p75^{NTR}$ in neuronal cell death at later stages of neurodegenerative disease, possibly through the accumulation of death ligands such as Aβ in addition to pro-NGF and/or pro-BDNF [6].

receptors has prompted an examination of the role of $p75^{NTR}$ in functional and structural plasticity at synapses. In 2004, Lu and colleagues found that pro-BDNF facilitated long-term depression (LTD) in the hippocampus [98], an effect that directly opposed the potentiating effects of mature BDNF through TrkB receptors [9]. Subsequent work demonstrated that $p75^{NTR}$ was required for normal expression of glutamate receptors and efficient hippocampal LTD [13,99]. Paralleling the effects on synaptic function, it has also been found that hippocampal neurons of mice lacking $p75^{NTR}$ have a higher spine density and greater dendritic complexity than those from wild-type mice [100]. Conversely, overexpression of $p75^{NTR}$ in slices of wild-type hippocampus significantly reduced dendritic complexity and spine density. In another study, application of pro-BDNF to neuromuscular synapses *in vitro* decreased synaptic efficacy and caused a retraction of presynaptic terminals by activation of presynaptic $p75^{NTR}$ [14]. Together, these studies suggest that elevated levels of $p75^{NTR}$ and pro-neurotrophins following neural injury or disease may contribute to ensuing pathological processes by multiple mechanisms, including attenuation of synaptic efficacy, reduction of dendritic complexity and spine density, and induction of axonal degeneration.

Biological paradox: homeostasis getting out of hand

Why does the nervous system react to injury by inducing a molecule that aids the demise of cells, axons and synapses? On the face of it, the nervous system would seem to be much better off without $p75^{NTR}$ when challenged by injury or disease. We do not yet have a satisfactory explanation to this paradox. Admittedly, $p75^{NTR}$ signaling has also been shown to mediate some positive effects after injury, as observed in some cases of nerve remyelination [73,74] and experimental allergic encephalomyelitis [101]. It could therefore be argued that, following the discovery of the role of $p75^{NTR}$ in cell death, subsequent research has emphasized the detrimental activities of this receptor at the expense of its positive effects, an argument that echoes

a recent debate in the study of the related Fas receptor [also known as cluster of differentiation 95 (CD95)] [102]. Aside from this, it could be useful to consider for a moment the methodologies used to reveal the proapoptotic and prodegenerative effects of $p75^{NTR}$. Nearly all injury paradigms utilized in this research involve quite severe lesions to the nervous system, the majority of which would probably be life-threatening to an organism in the wild. It is difficult to see how a mere reduction in $p75^{NTR}$ expression or activity could make much of a difference to an organism severely compromised by a massive seizure, stroke or nerve damage. In such circumstances, mechanisms limiting $p75^{NTR}$ expression would simply fail to evolve. However, seizures, stroke and axotomy may also occur at much smaller scales, involving perhaps a few cells or axons, too few to be useful as an experimental paradigm. Under those conditions, elimination of a few malfunctioning neurons, glial cells, or their connections may be beneficial for the nervous system and the longer-term survival of the organism. Here $p75^{NTR}$ finds itself in a situation akin to that of mediators of inflammatory responses. An inflammatory response involves cells infiltrating a wound and cleaning up damage. Nevertheless, there can be 'too much of a good thing', and with a severe injury, more damage can be done than good. Evolutionarily speaking, an animal with a torn knee would probably not survive very long in the wild, so having an aggressive inflammation process is not much of an added problem in that case. Seen in this light, rather than an evolutionary glitch, the deleterious effects of $p75^{NTR}$ signaling in neural injury and disease could be part of an homeostatic mechanism that becomes out of control. Finding experimental support for this concept may require the analysis of more limited lesion paradigms, as well as novel genetic and imaging tools. The study by Park et al. [89] showing astray basal forebrain axons in white matter of $p75^{NTR}$ knockout mice represents one of the first examples of the homeostatic function of $p75^{NTR}$ in the adult brain.

Outstanding questions

The role of $p75^{NTR}$ signaling in neural injury and disease brings both challenges and opportunities (Box 1). Clearly, the signaling pathways underlying the effects of $p75^{NTR}$ in neural injury need to be better understood. How $p75^{NTR}$ couples to different signaling pathways and how these contribute to $p75^{NTR}$ function remain key challenges in the field. With regard to cell death pathways, it is still unclear how $p75^{NTR}$ signals to JNK and caspases in different cell types, and also how this pathway is balanced against the effects mediated by increased NF-κB activity. As the NF-κB pathway can mediate pro-survival as well as pro-inflammatory responses (which can lead to cell death, see e.g. Figure 2), it will also be important to elucidate the contribution of NF-κB signaling to $p75^{NTR}$-mediated cell damage in different injury paradigms. Answers to these questions will require the development of an accurate structure–function map linking motifs within the $p75^{NTR}$ intracellular domain to specific interactors and signaling events. This would in turn allow the generation of genetic tools for probing the physiological importance of the different signaling pathways engaged by $p75^{NTR}$. It should also be noted that, in many of the disease paradigms studied so far, it is still unclear whether $p75^{NTR}$ kills cells by cell-autonomous or non-cell-autonomous mechanisms. Resolving this question will require studies in animal models with conditional ablation of $p75^{NTR}$ signaling in specific classes of neurons and glial cells.

Box 1. Outstanding questions

- How does $p75^{NTR}$ couple to different downstream signaling pathways? How do these distinct pathways contribute to $p75^{NTR}$ function?
- Does $p75^{NTR}$ kill neurons after injury by cell-autonomous or non-cell-autonomous mechanisms?
- What are the similarities and differences between $p75^{NTR}$ functions during development and after injury/insult in the adult CNS?
- How do the different $p75^{NTR}$ ligands elicit distinct responses through the same receptor?
- Is there complete overlap between the $p75^{NTR}$ signaling pathways mediating axon growth inhibition and axonal degeneration or are there important distinctions?
- What are the specific molecular mechanisms that induce adult $p75^{NTR}$ expression during neural injury and neurodegeneration?

$p75^{NTR}$ is not always bad news for neurons: although it exacerbates the death of axotomized sensory and motoneurons, $p75^{NTR}$ contributes to their survival during development [68,69,103,104]. This duality is not unique to $p75^{NTR}$ and can be found in other members of the TNFR superfamily [64,102]. It may result from intrinsic differences in the complement of intracellular mediators and coreceptors between developing and adult cells. In line with this, NGF was found to increase survival of young cultures of Schwann cells through $p75^{NTR}$ signaling via RIP2, but to induce cell death in older cultures – in which RIP2 is downregulated [70]. On the other hand, different extracellular environments, such as the balance between neurotrophins and pro-neurotrophins, may also contribute to different, or even opposed, $p75^{NTR}$ activities. Understanding how different $p75^{NTR}$ ligands can elicit different responses through the same receptor is another key challenge in the field.

In the case of the effects of $p75^{NTR}$ on axons, it is unclear whether inhibition of axonal growth (as observed in response to myelin components) and axonal degeneration proceed through different or similar pathways. Because the latter requires both myelin and neurotrophins, it may conceivably engage a different combination of intracellular mediators. It is also possible that different mechanisms of receptor activation are at play. This possibility is supported by recent results demonstrating the importance of transmembrane residue Cys^{257} in the formation of disulphide-linked $p75^{NTR}$ dimers, and in receptor activation by neurotrophins – but not by myelin-derived molecules such as Nogo or myelin-associated glycoprotein (MAG) (Figure 1b) [105]. These and other results [106] suggest that different $p75^{NTR}$ activation mechanisms, perhaps related to different receptor complexes, may operate in response to different $p75^{NTR}$ ligands.

The mechanisms that induce $p75^{NTR}$ expression during injury and neurodegeneration remain ill-defined. One study found that hypo-osmotic stress can regulate $p75^{NTR}$ by increasing cellular levels of Sp1 in primary cortical neurons [55]. More recently, the pro-inflammatory

cytokines IL-1β and TNF-α, which are highly expressed in the injured brain [107], were shown to contribute to $p75^{NTR}$ upregulation in both astrocytes and neurons [108]. IL-1β induced $p75^{NTR}$ via p38 mitogen-activated protein kinase (MAPK) in neurons, and via both p38 MAPK and NF-κB in astrocytes. TNF-α, on the other hand, induced $p75^{NTR}$ via NF-κB both in neurons and astrocytes, showing that the mechanisms governing this regulation are both cytokine- and cell-type specific. It would be interesting to determine whether these mechanisms also contribute to $p75^{NTR}$ induction during development or are exclusive to inflammation-mediated changes in the adult.

Therapeutic opportunities

$p75^{NTR}$ signaling can induce neuronal death, reduce axonal growth and decrease synaptic function; hence, there is a strong rationale for inhibiting $p75^{NTR}$ in neural injury and neurodegeneration. As for any transmembrane receptor, the most obvious process to target is ligand binding. Functional neurotrophin epitopes important for $p75^{NTR}$ binding have been mapped by site-directed mutagenesis [109–111], and later confirmed by X-ray crystallography [112,113]. This information has been used to design small $p75^{NTR}$-binding peptides [114] and organic compounds [115]. However, there is no clear consensus at present as to whether these have agonistic or antagonistic functions on $p75^{NTR}$ signaling and bioactivity [82,115–117]. One set of $p75^{NTR}$ antagonists has been reported to show neuroprotective activity in retinal degeneration following glaucoma or optic nerve transection [82]. Glaucoma and axotomy represent both chronic and acute models of neurodegeneration, and $p75^{NTR}$ expression is upregulated in both cases. The fact that $p75^{NTR}$ antagonism can protect retinal ganglion cells after both acute and chronic lesions, suggests these injury paradigms may be promising models for developing $p75^{NTR}$-based therapies.

Approaches to block ligand-binding are limited by the relatively high affinity of neurotrophins for $p75^{NTR}$ and cannot distinguish between prosurvival and proapoptotic effects of the receptor. Other processes that would be amenable for targeting by inhibitors are receptor activation and downstream signal propagation. Compared to ligand binding, however, the development of strategies to block these processes will require greater mechanistic understanding. The mechanism of $p75^{NTR}$ activation by neurotrophin ligands has recently begun to be clarified [105], opening the door to strategies directed at specifically inhibiting this process. On the other hand, targeting downstream signal propagation will require development of a structure–function map of the intracellular region of $p75^{NTR}$ and the identification of specific structural motifs responsible for the activation of different pathways.

Concluding remarks

In summary, work over recent years has indicated that the adult induction of $p75^{NTR}$ may be part of a homeostatic program that removes defective neurons, axons and synapses upon limited injury and degeneration. A downside of this function is the exacerbated damage that $p75^{NTR}$ signaling produces following severe lesions and in pronounced neurodegeneration. Many such circumstances are encountered in neural injury, stroke and neurodegenerative diseases in humans, and thus there is a strong rationale for inhibiting $p75^{NTR}$ signaling as a therapeutic approach for these conditions. Efficient ways of inhibiting this receptor will require a greater mechanistic understanding of its activation by different classes of ligands and its communication with downstream signaling pathways.

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