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Implication of the neurotrophin receptor p75^{NTR} in vascular diseases: beyond the eye

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Abstract

Introduction—The p75 neurotrophin receptor (p75^{NTR}) is a member of TNF-α receptor superfamily that bind all neurotrophins, mainly regulating their pro-apoptotic actions. Ischemia is a common pathology in different cardiovascular diseases affecting multiple organs, however the contribution of p75^{NTR} remains not fully addressed. The aim of this work is to review the current evidence through published literature studying the impact of p75^{NTR} receptor in ischemic vascular diseases.

Areas covered—In the eye, several ischemic ocular diseases are associated with enhanced p75^{NTR} expression. Ischemic retinopathy including diabetic retinopathy, retinopathy of prematurity and retinal vein occlusion are characterized initially by ischemia followed by excessive neovascularization. Beyond the eye, cerebral ischemia, myocardial infarction and critical limb ischemia are ischemic cardiovascular diseases that are characterized by altered expression of neurotrophins and p75^{NTR} expression. We surveyed both clinical and experimental studies that examined the impact of p75^{NTR} receptor in ischemic diseases of eye, heart, brain and peripheral limbs.

Expert commentary—p75^{NTR} receptor is a major player in multiple ischemic vascular diseases affecting the eye, brain, heart and peripheral limbs with significant increases in its expression accompanying neuro-vascular injury. This has been addressed in the current review along with the beneficial vascular outcomes of p75^{NTR} inhibition.

Keywords

Ischemic vascular diseases; p75^{NTR}; diabetic retinopathy; retinopathy of prematurity; critical limb ischemia; inflammation; vascular dysfunction

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Declaration of interest

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1. Role of p75^{NTR} in ischemic vascular diseases

Ischemia is defined as depriving a tissue of its blood supply and the functional consequences have been appreciated for many years. The cardiovascular diseases that are initiated by local or systemic tissue ischemia remain the chief cause of death in the United States [1]. It has become apparent that the restoration of blood flow after a period of ischemia can place ischemic organs at risk of further cellular necrosis and thereby limit the recovery of function. It is widely recognized that the microvasculature is very vulnerable to the deleterious consequences of ischemia and reperfusion [2]. Nevertheless, brief episodes of occlusion and reflow at the end of ischemic insult were shown to reduce infarct size in the coronaries, a strategy called ischemic post-conditioning [3]. Ischemic preconditioning first defined by Murry et al. in 1986 [4] was also shown to reduce coronary infarct size in dogs.

The p75 neurotrophin (p75^{NTR}) receptor is normally expressed during development and its level was shown to markedly increase under certain pathological conditions including; mechanical damage, axotomy, stroke, epileptic seizures as well as focal ischemia [5–7]. In the current review, we attempted to assess the published literature to define the contribution of p75^{NTR} receptor to ischemic vascular diseases in the eye including retinopathy of prematurity (ROP), diabetic retinopathy (DR) as well as other organs including brain, heart, and peripheral limbs.

2. Discovery and structure of p75^{NTR}

Although p75^{NTR} receptor was discovered as early as 1968, it was not cloned till 1986 by Chao et al. [8] and the nucleotide sequence of the human receptor was determined in the same year by Johnson et al. [9]. P75^{NTR} was known as nerve growth factor (NGF) receptor, which is present on the cell surface of sympathetic neurons and neural crest-derived sensory neurons [10,11]. P75^{NTR} is the first identified member of the tumor necrosis factor (TNF) receptor superfamily that can bind all neurotrophins including NGF, brain-derived nerve factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin4/5 with approximately equal affinity in most cells [12]. It was reported to be ‘the low-affinity’ receptor for target-derived neurotrophins, with Trk tyrosine kinases being the main receptor. Thus, p75^{NTR} may either act as a common subunit in a neurotrophin receptor complex with members of Trk family or act independently to mediate biological actions of each neu-rotrophin [13].

P75^{NTR} is a single transmembrane protein with an N-terminal extracellular domain (ECD); containing four repeated modules of six cysteines [9,14] and a C-terminal intracellular domain (ICD). Because p75^{NTR} lacks intrinsic catalytic activity, it signals by undergoing conformational rearrangements through ligand binding and co-receptor interactions. In addition, a series of proteolytic cleavage and recruitment of diverse intracellular proteins directs its signaling function [15]. Regulated intramembrane proteo-lysis of p75^{NTR} consists of ectodomain shedding of p75^{NTR} by α-secretase that results in formation of a membrane-bound C-terminal fragment (CTF). CTF is subsequently cleaved by γ-secretase complex, liberating the ICD [16]. The ICD of p75^{NTR} can be palmitoylated at cysteine 279 [17] or phosphorylated on serine and threonine residues [18]. These posttranslational modifications

confer roles in protein–protein interaction, proper intracellular folding of the receptor or in directing its cellular localization [19].

3. Regulation of p75^{NTR} expression

The structure of the p75^{NTR} proximal promoter resembles a house-keeping gene, with a high GC content, and multiple Sp1 binding sites [20]. GC element binding proteins have an important role in regulation of p75^{NTR} promoter function and its expression [21]. On the other hand, specificity protein 1 (Sp1) is a ubiquitous transcription factor implicated in the expression of numerous genes and typically regarded as a constitutive transcription factor that perform housekeeping functions [22]. Hyposmolarity was shown to induce p75^{NTR} expression in primary neurons, targeting the Sp1-rich conserved element in the upstream promoter sequences of rat, mouse, and human p75^{NTR} gene. Sp1 turnover is strongly inhibited by hyposmolarity, resulting in its accumulation and subsequent injury-induced p75^{NTR} gene expression [22]. The expression of p75^{NTR} receptor was shown in tissue injury accompanied by edema *in vivo* [23] and *in vitro* [22]. In primary neuronal cells, excitotoxicity and Sp1 were shown to be involved in induction of p75^{NTR} expression [24].

The expression of p75^{NTR} receptor can be induced by many other factors. Peterson and Bogenmann showed that osmotic swelling, altered by brain injuries such as physical trauma, epileptic seizures, or microbial infection induced p75^{NTR} expression in a nitric-oxide-dependent manner [23]. Inflammatory cytokines IL-1β and TNF-α were shown to regulate p75^{NTR} expression in CNS neurons and astrocytes through distinct cell-type specific signaling mechanism as reported [25]. Hempstead group in 2014 reported p75^{NTR} induction after focal cerebral ischemia, which was independent of transcription but required active translation. Basal level of neuronal p75^{NTR} was shown to be maintained, in part, through miR-592 with an inverse correlation between miR-592 and p75^{NTR} levels in adult brain [26]. Individual tyrosine autophosphorylation sites of TrkA were shown to play a role in regulating p75^{NTR} expression; particularly Y490 and 785 as reported by Mearow group in 2005 [27]. Furthermore, his group reported the importance of Trk-dependent phospholipase C-gamma and protein kinase C-delta in regulation of p75^{NTR} expression, in response to neurotrophin stimulation [28].

4. Signaling and biological functions of p75^{NTR}

Since p75^{NTR} receptor lacks intrinsic catalytic activity, it signals by interaction with several intracellular proteins. The most prominent intracellular feature of p75^{NTR} ICD is the death domain (DD), an ~80 amino acid association module, initially identified in related proapoptotic tumor necrosis factor receptor (TNFR) superfamily members though not showing their self-aggregation property [29]. P75^{NTR} is an unusual member of the TNFR family owing to its tendency to dimerize rather than trimerize and its ability to act as a co-receptor with tropomyosin receptor kinases (Trks) [19]. When p75^{NTR} co-receptors with one of the Trks, it refines their affinity and specificity for neurotrophins. For instance, p75^{NTR} increases the affinity of TrkA to NGF [30], while restricting its binding of NT3, and it also relaxes the specificity of TrkC [31].

Survival can be promoted by $p75^{NTR}$ receptor in response to NGF in an NF-κB-dependent manner [32]. $P75^{NTR}$ can also co-receptor with Nogo receptor [33] to regulate axonal growth through interaction with the small GTPase; RhoA. In absence of neurotrophins, a constitutive interaction between RhoA and $p75^{NTR}$ receptor maintains RhoA activation and inhibition of axonal growth, whereas, neurotrophin binding to $p75^{NTR}$ dissociates RhoA, blocking its activity and promoting axonal growth [34].

The main action of $p75^{NTR}$ receptor is to mediate apoptosis via forming a co-receptor with sortilin; a member of Vps10p-domain receptor family [35]. Several intracellular proteins were shown to be involved in $p75^{NTR}$-mediated apoptotic action. Interaction of TNF receptor-associated factor-6 with $p75^{NTR}$ was shown to be required for Jun N-terminal Kinase (JNK) activation and $p75^{NTR}$-mediated apoptosis [36,37]. Neurotrophin receptor-interacting melanoma-associated antigen (MAGE) homolog (NRAGE) was identified to interact with $p75^{NTR}$ cytosolic region and mediate cell death in JNK-dependent mitochondrial pathway. NRAGE was shown to induce cytosolic accumulation of cytochrome *c*, activation of caspases-3, -9, and -7, and caspase-dependent cell death [38]. The neurotrophin receptor interacting factor (NRIF) was also reported to be essential for $p75^{NTR}$-dependent JNK activation and apoptosis through a mechanism that requires p53 and NRIF nuclear translocation [39,40]. NRIF can directly bind the ICD of $p75^{NTR}$ forming a complex, which translocates to the nucleus. The NRIF can then act as a transcription factor by binding to DNA and activate transcription of apoptotic genes [41]. Finally, $p75^{NTR}$-associated cell death executor was also shown to be involved in $p75^{NTR}$-induced cell death upon NGF binding [42].

The apoptotic effect of $p75^{NTR}$ receptor is extensively demonstrated in the literature. The first report for apoptotic effect of $p75^{NTR}$ receptor came from Bredesen's group where over-expression of $p75^{NTR}$ receptor increased the rate of cell death [43]. In a subsequent study by Barrett and Bartlett in 1994, downregulation of $p75^{NTR}$ by antisense oligonucleotides increased the survival of sensory neurons [44]. Several *in-vivo* reports confirmed the apoptotic action as well. Cheema et al. reported that $p75^{NTR}$ receptor was responsible of death of axotomized sensory neurons in the dorsal root ganglia of newborn rats [45]. Overexpression of $p75^{NTR}$ ICD resulted in marked increase in neuronal death during development in sensory and sympathetic ganglia [46]. In $p75^{NTR}$ knockout mice, apoptosis was reduced where the number of sympathetic neurons at 2 weeks of age was much higher than normal [47]. Genetic deletion of $p75^{NTR}$ also reduced apoptosis of spinal cord neurons at E11.5 and of retinal neurons at E15.5 [48]. Apoptosis and cell cycle arrest mediated by $p75^{NTR}$ in neuronal cells was reported in many other studies [49–51]. Given its well-documented role in neurodegeneration, $p75^{NTR}$ was studied in retinal neurodegenerative diseases. However, whether $p75^{NTR}$ can contribute to ischemic vascular diseases remains poorly understood. In the next section, we will survey the literature to assess the role of $p75^{NTR}$ in ischemic vascular diseases in the eye and other organs.

5. Role of $p75^{NTR}$ in ischemic diseases of the eye

Different diseases affect the eye in the context of ischemia that can cause visual impairment and eventually blindness. Examples include DR, ROP, and retinal vein occlusion. The retina

is a typical neurovascular system with a delicate organization of neurons, glia, and microvasculature. The retina is particularly vulnerable to microvascular damage due to its high metabolic and oxygen demands and its dependence on an intact blood–retinal barrier [52]. Damage can be caused by either microvascular leakage following breakdown of the inner blood retinal barrier or microvascular occlusion both of which can be distinguished from each other by fluorescein angiography [53]. $P75^{NTR}$ receptor was genetically proven to be involved in cell death in the developing mouse retina [48] that was facilitated through NRAGE (neurotrophin receptor interacting MAGE homolog) [54]. In the adult retina, localization of $p75^{NTR}$ was first shown to be in both RGCs [55] and Müller cells [56,57] at the level of light microscope. Later in 1998, in SD rat retinas, it was clear that $p75^{NTR}$ is localized in the processes of Müller cell that wrap around RGCs and not in RGCs themselves [58]. In the next section, we will review the role of $p75^{NTR}$ in ischemic retinopathy diseases.

6. $P75^{NTR}$ and DR

DR is the second leading cause of blindness in working-age, affecting both genders equally [59]. Patients with type 1 diabetes may show evidence of retinopathy as early as 5 years after the onset of diabetes, and almost all patients show varying degrees of retinopathy 20 years later. Background retinopathy may even be present at the time of diagnosis of type 2 diabetic patients, consistent with the long duration of subclinical hyperglycemia in such patients and more than 60% of type 2 diabetic patients will experience retinopathy after 20 years of diabetes onset [53]. Although DR was previously perceived as a sole microvascular complication, it is now widely accepted that diabetes affects multiple cell types in the retina resulting in neurodegeneration, inflammation and alteration of microvasculature [60]. DR begins with microa-neurysms and progress into exudative changes such as leakage of lipoproteins and blood that lead to macular edema. Then ischemic changes collateralization and dilatation of venules, followed by proliferative changes, abnormal vessels on the optic disk and retina, proliferation of fibroblasts, and vitreous hemorrhage (reviewed in [61]). As discussed before, $p75^{NTR}$ is expressed in the retina, suggesting its involvement in pathophysiology of DR [62].

One of the early and landmark studies that established the link between diabetes and $p75^{NTR}$ receptor, was reported by Hammes et al. in 1995. They investigated whether NGF plays a role in diabetes-induced degeneration of neurons and the development of occluded (acellular) retinal capillaries, a surrogate marker for ischemia. They reported that diabetes induced upregulation of $p75^{NTR}$ receptor mainly within Müller cells that was associated with programmed cell death in RGCs and Müller cells. Diabetes-induced programmed cell death was also found to affect retinal vasculature resulting in peri-cyte loss and formation of acellular occluded capillaries [63]. These effects were ameliorated by exogenous NGF treatment for 3 months, suggesting that diabetes downregulates NGF levels or function in the retina [63].

Later, in 2008, our group has reported significant $p75^{NTR}$ expression in diabetic retinas of human and rat samples. Paradoxically, diabetes stimulated retinal NGF at the mRNA level and triggered significant neurodegeneration in diabetic rat retinas [64]. In the same study, we

have seen that diabetes-induced peroxynitrite formation impaired NGF survival signal by selective nitration and inhibition of TrkA receptor at tyro-sine 490 [64]. In a subsequent study conducted in 2011, treatment of diabetic animals with epicatechin, a selective nitration inhibitor resulted in restoration of TrkA phosphorylation at Y490 and reduction of $p75^{NTR}$ expression [65]. Blocking nitration or silencing $p75^{NTR}$ resulted in protecting retinal neurons from cell death *in vitro* [65]. These studies established a possible link and cross talk between the activation of the survival receptor: TrkA and the expression of $p75^{NTR}$ in diabetic retina.

In 2011, we made the discovery that diabetes impairs the processing of the NGF precursor (proNGF) resulting in accumulation of proNGF at the expense of NGF [66]. Murine NGF is translated from two major alternatively spliced transcripts to produce 34- and 27-kDa species. Removal of the signal sequence reduces these translation products to proNGF species of 32 and 25 kDa [67–69]. Higher molecular-weight-glycosylated NGF precursors have been also identified [69,70]. proNGF undergoes further posttranslational processing to generate the mature product; NGF, of ~13 kDa. It can be extracellularly processed to NGF by the enzyme matrix metalloproteinase 7 [71] or cleaved intracellularly by furin and other proconvertases [72]. While NGF binds the survival receptor TrkA, proNGF binds with high affinity to $p75^{NTR}$ to mediate cell death [73].

Imbalance of proNGF to NGF was associated with retinal neurodegeneration and breakdown of the blood–retina barrier [66]. The contribution of $p75^{NTR}$ to retinal inflammation and vascular dysfunction was demonstrated under diabetic condition. The genetic deletion of $p75^{NTR}$-blunted diabetes-induced proNGF/NGF imbalance, increase in NF-κB and TNF-α, ganglion cell loss, and vascular permeability *in vivo* and *in vitro* [74]. The apoptotic effect of $p75^{NTR}$ was not limited only to neurodegen-eration observed in early diabetes. Apoptotic effect of proNGF/$p75^{NTR}$ signaling pathway was also demonstrated in brain endothelial cells (ECs) [75] and endothelial lineage cells [76]. Our recent work showed that stable overexpression of the cleavage-resistant form of proNGF in the rodent retina triggered $p75^{NTR}$ expression [77,78] that was associated with development of occluded (acellular) capillaries. Overexpression of the cleavage-resistant proNGF-induced EC apoptosis that was inhibited by silencing $p75^{NTR}$ receptor in retinal ECs *in vivo* and *in vitro* [78]. All of these findings underscore the importance of $p75^{NTR}$ receptor as a potential therapeutic target in DR.

Clinically, Humpert et al. studied the alteration of the three distinct isoforms of $p75^{NTR}$ receptor; full length, ECD, and ICD in the serum of type 2 diabetic patients. Levels of the ECD of $p75^{NTR}$ (~24 kDa) were reduced and levels of the ICD (~51 kDa) were increased, whereas the immune-reactivity of full length $p75^{NTR}$ was not altered. Nevertheless, none of the three forms seemed to be a marker of peripheral or autonomic neuronal function in patients with type 2 diabetes [79]. Our group has reported that the alteration of proNGF and NGF levels observed in retina and vitreous is mirrored in serum of diabetic patients. In addition, CTF(27 kDa) and ICD (22 kDa) fragments of $p75^{NTR}$ receptor were significantly increased in vitreous and serum samples of diabetic patients and thus, both imbalance in the proNGF to NGF ratio and $p75^{NTR}$ shedding pattern could serve as biomarkers for DR [80].

So far, the contribution of $p75^{NTR}$ is well-characterized in neuro- and microvascular degeneration in DR, however its role in the angiogenic phase (proliferative DR; PDR) remain unclear. Our group reported positive correlation between proNGF and progression of DR, with proNGF level getting higher in the proliferative stage of the disease [66]. Diabetes triggers early $p75^{NTR}$ expression [64] and the level remains steady in PDR. Previous literature identified clear angiogenic effects of NGF via activation of TrkA in models of angiogenesis [81]. Our group was the first to show that proNGF can be a potential player in angiogenic behavior in PDR [82]. Interestingly, proNGF was shown to mediate angiogenic signal at least in part through activation of TrkA receptor. Furthermore, inhibition of $p75^{NTR}$ did not significantly alter angiogenic response of retinal ECs to exogenous proNGF. Yet, its inhibition was associated with enhanced TrkA activation [82]. These findings highlight the cross talk between the two main receptors for neurotrophins: Trk and $p75^{NTR}$.

7. P75NTR and ROP

ROP, an ischemic ocular disorder, is the dominant cause of severe visual impairment in childhood in North America and Europe [83]. ROP proceeds following an initial phase of degeneration of the retinal microvasculature (vaso-obliteration) that is associated with cessation of progression of vascular growth toward the retinal periphery resulting in ischemic retina [84]. In the subsequent phase of the disease, the ensuing retinal ischemia predisposes to abnormal compensatory neovascular-ization [85]. Various risk factors that have been linked to the development of ROP include low birth weight, low gestational age, supplemental and oxygen therapy [86]. ROP is associated with significant sequelae, the most serious being retinal detachment, which results in blindness. However, even milder forms of ROP increase the incidence of pathologies that negatively impact visual acuity [87].

Although neurotrophins are heavily involved in the growth, survival, proliferation, and migration of neurons in the developing brain and retina, there are limited data whether premature birth and development of ROP is associated with alteration in neurotrophins. Clinically, serum levels of BDNF were found to be lower in preterm infants compared to full-term [88,89]. In humans, levels of NGF, BDNF, and NT-3 were significantly decreased in amniotic fluids in mothers that went through severe infections and later were associated with cerebral abnormalities [90]. The role of BDNF in ROP was further supported by a recent study that examined single nucleotide polymorphism (SNP) in a large cohort of premature infants with levels of ROP severity. The results showed that two intronic SNPs in the gene BDNF (rs7934165 and rs2049046) were associated with severe ROP in a large candidate gene study of infants with threshold ROP [91]. Nevertheless, no data exist on the levels or role of $p75^{NTR}$ in ROP from clinical studies.

Experimentally, the role of neurotrophins and $p75^{NTR}$ is beginning to unfold. The study by Liu et al. examined the contribution of NGF and its receptor to retinal pathological neovascularization using oxygen-induced retinopathy (OIR) mouse model. The results showed increased expression of NGF mRNA that was associated with pathological retinal neovascularization by postnatal day (p17). Inhibiting TrkA receptor using compound K252a prevented retinal neovascularization [92]. Yet, the role of $p75^{NTR}$ was not examined in this study. More recent work identified a critical role of $p75^{NTR}$ in retinal angiogenesis. Genetic

deletion of $p75^{NTR}$ receptor protected against vaso-obliteration and retinal neovas-cularization in OIR model [93]. Deletion of $p75^{NTR}$ was linked to decreased stabilization of HIF-1α and subsequent decreasing induction of HIF-1α target genes including VEGF in hypoxia [93]. These results lend further support to ongoing studies showing that pharmacological inhibition of $p75^{NTR}$ receptor-prevented glial activation, inflammation, and protected against retinal neovascu-larization [94]. Moreover, we have observed that genetic deletion of $p75^{NTR}$-prevented vascular cell death, enhanced reparative central capillary growth, and prevented pathological retinal neovas-cularization. The mechanisms involve restoring levels of NGF and BDNF and improving TrkA-mediated survival and angiogenic signal [95,96]. Thus, inhibition of $p75^{NTR}$ can provide potential therapeutic target for ischemic retinopathy.

8. Role of $p75^{NTR}$ in optic neuropathy and glaucoma

Although glaucoma is perceived as neurodegenerative disease of the retinal ganglion cells or their axons that make the optic nerve tract, models that involve elevated intraocular pressure cause retinal ischemia. Increased expression of $p75^{NTR}$ receptor (60-kDa fragment [mature non-glycosylated form] and 50-kDa fragment [ectodomain fragment], as well as sortilin [90 kDa, mature form] were reported at 3, 5, and 7 days after retinal ischemia [97]. On the other hand, another study by Guo et al. reported no change in mRNA levels of $p75^{NTR}$ receptor in ischemic rat retina using permanent bilateral common carotid artery occlusion model. In the same model, mRNA or protein levels of neurotrophic factors (NGF, BDNF, NT-3, and GDNF) and their receptors (TrkA, TrkB, and TrkC) showed marked and persistent downregulation [98]. These results suggest that deprivation of neurotrophins can drive neurodegeneration.

Using retinal degeneration models induced by glaucoma or optic nerve transection, Bai et al. differentially validated each neurotrophin receptor as a pharmacological target for retinal neuroprotection. The authors have reported that activation of TrkA alone is neuroprotective whereas, activation of $p75^{NTR}$ is neurotoxic through paracrine production of TNF-α and α(2)-macroglobulin [99]. Activation of $p75^{NTR}$ pathway induced apoptosis in RGCs through robust expression of TNF-α via a non-cell autonomous signaling pathway in adult rodents [100]. Earlier in 2009, Lebrun-Julien et al. examined the non-cell-autonomous mechanism by which glial cells exacerbate neuronal death following excitotoxic injury. *N*-methyl-D-aspartate (NMDA) induces NF-κB activation in Müller glia resulting in production of TNF-α, which induces neurotoxicity in susceptible neurons through increasing Ca^{2+}-permeable AMPA receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepro-pionic acid receptor); a non-NMDA-type ionotropic transmem-brane receptor for glutamate that mediate fast synaptic transmission in the CNS [101].

9. Role of $p75^{NTR}$ in other ocular diseases

Apart from diabetic milieu, genetic ischemic diseases of the retina are also associated with upregulation of $p75^{NTR}$ receptor as demonstrated in the retinas of 14 weeks old Royal College of Surgeons (RCS) rats. The RCS rats developed progressive capillary dropout and subretinal neovascularization which were accompanied by retinal gliosis. These effects were

associated with increases in proNT3 and TNFα expression and were ameliorated by intraperitoneal administration of erythropoietin [102].

The $p75^{NTR}$ receptor is expressed in RPE as well and was reported to dramatically increase in dystrophic rat retinas [103]. Zhang et al. suggested the potential therapeutic activity of $p75^{NTR}$ receptor against diseases of RPE associated with hypoxia or oxidative stress. They showed that $p75^{NTR}$ was highly expressed in human choroidal neovascularization membranes and its knockdown in hypoxic RPE cells rescued RPE proliferation activity; probably by suppressing pro-angiogenic factors and inhibition of apoptosis [104]. In a rat model of choroidal angio-genesis, the antiangiogenic effect of human T-lymphocyte-derived microparticles was attributed to proapoptotic activity of pigment epithelium-derived factor (PEDF)/$p75^{NTR}$ in the RPE-intact but not the RPE-removed choroid [105].

10. Role of $p75^{NTR}$ receptor in vascular diseases: beyond the eye

In the next sections, we will assess the role of $p75^{NTR}$ receptor in ischemic vascular diseases affecting the brain, heart, and peripheral limbs and how alteration of $p75^{NTR}$ expression correlates with neurovascular injury.

11. Role of $p75^{NTR}$ receptor in stroke

Stroke is defined as being an ‘acute neurologic dysfunction of vascular origin with sudden occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain’ [106]. The two main types of stroke are ischemic and hemorrhagic, out of which ischemic subtype accounts for approximately 85% of stroke incidence. When an ischemic stroke occurs, the blood supply to the brain is interrupted, and brain cells are deprived of glucose and oxygen they need to function [107]. Several reports showed that $p75^{NTR}$ receptor regulates cerebral ischemia-induced neuronal injury after unilateral middle cerebral artery occlusion [5,108]. Attenuation of inhibitory signal of neuronal growth induced by $p75^{NTR}$/Nogo-A (Neurite outgrowth inhibitor) has been proven neuroprotective through increasing the release of BDNF and increased phosphorylation of its receptor: TrkB [109]. Decreasing the expression of Nogo-A, NgR (NOGO receptor), and $p75^{NTR}$ receptor was shown to be neurotective in cerebral ischemia in response to treatment with herbal medicine extraction *Panax notoginseng* saponins [110] or tonifying liver and kidney-essence herbs [111].

Hempstead and co-workers demonstrated that, the NGF precursor; proNGF binds $p75^{NTR}$ with high affinity and induces $p75^{NTR}$-dependent apoptosis of sympathetic neurons in culture [71]. Her group further studied the role of proNGF/$p75^{NTR}$ in neuronal ischemic injury and reported the rapid upregulation of both, the ligand and the receptor after focal cerebral ischemia. The rapid upregulation of $p75^{NTR}$ receptor after ischemic injury was independent of transcription and correlated inversely with the levels of miR-592 [26].

12. Role of $p75^{NTR}$ in Alzheimer disease

Alzheimer disease (AD) is the most common and subtle form of neurodegenertive disease that affects the cognitive functions of the elderly. The $p75^{NTR}$ was reported to be expressed

in the cerebral cortex of AD patients [112,113]. Amyloid-beta (Aβ) plays a pivotal role in the pathogenesis of AD and has become the major therapeutic target [114]. The correlation between $p75^{NTR}$ receptor and Aβ is complex. Some studies reported that Aβ peptide induces neurotoxi-city by binding to $p75^{NTR}$ receptor and activating JNK [115,116], whereas Zhang et al. reported that $p75^{NTR}$ expression protected neurons against Aβ-induced toxicity [117]. In 2009, Longo's group reported a significant role of $p75^{NTR}$ receptor in enabling Aβ induced neurodegeneration [118]. Recently, his group confirmed the protective effect of LM11A-31, a non-peptide $p75^{NTR}$ ligand, which blocks the action of proNGF, *in vivo* in a mouse model of AD. LM11A-31 prevented deficits in novel object recognition and deficits in water maze performance. In addition, LM11A-31 was able to reduce neuritic dystrophy apparent in basal fore-brain, hippocampus, and cortex [119] and in late-stage AD mouse model [120]. Another study showed the efficacy of $p75^{NTR}$ ligands, LM11A-31 and LM11A-24, in preventing fundamental tau-related pathologic mechanisms in AD [121]. Recently, it was reported that nullifying $p75^{NTR}$ level in transgenic AD mice (Tg2576) reduced accumulation of Aβ and ameliorated cognitive deficits [122]. These findings lend further support to that targeting $p75^{NTR}$ as a new class for treatment of AD.

13. Role of $p75^{NTR}$ receptor in peripheral limb ischemia

Critical limb ischemia (CLI) occurs at the end of peripheral arterial disease, which is associated with excessively high risk for cardiovascular events, including myocardial infarction and death [123]. Mortality rates as high as 20% within 6 months from diagnosis and exceeding 50% at 5 years have been reported for CLI [124]. The impact of $p75^{NTR}$ receptor on hind limb ischemia under diabetic conditions was extensively studied by Emanueli group. They first reported increased $p75^{NTR}$ expression in capillary ECs belonging to ischemic limb muscles under diabetic conditions in 2004 [81]. NGF supplementation protected ECs from apoptosis induced by type-1 diabetes and facilitates reparative neovascularization. Later, the upregulation of $p75^{NTR}$ receptor and its contribution to ECs apoptosis and diabetes-induced microvascular liabilities was reported [76]. In that study, they showed that gene transfer-induced $p75^{NTR}$ expression impaired angiogenic response of cultured ECs and endothelial progenitor cells *in vitro*. Moreover, intramuscular $p75^{NTR}$ gene delivery impaired blood flow recovery in a mouse model of limb ischemia. These disturbed functions were associated with suppression of VEGF-A-mediated Akt survival pathway [76]. Later, the link between the interleukin-33 receptor; ST2 and $p75^{NTR}$ was investigated. Expression of ST2 was upregulated by $p75^{NTR}$ receptor and circulating ST2 level could be used to predict mortality in CLI patients [125]. In 2015, a novel paracrine mechanism of how increased $p75^{NTR}$ expression in diabetic ischemic limbs impairs microvascular complications. The $p75^{NTR}$ upregulated level of miR-503 in ECs and induced shedding of endothelial microparticles carrying miR-503 to vascular pericytes. The integrin-mediated uptake of miR-503 in the recipient pericytes reduces expression of VEGF-A, resulting in impaired pericyte coverage of capillaries and subsequent impaired neovascularization [126].

14. Role of p75^{NTR} in ischemic heart diseases

Sympathetic neurons from p75$^{NTR-/-}$ mice were also shown to grow more robustly in response to NGF than do their wild-type counterparts [127]. Regulation of cardiac sympathetic innervation and function by p75^{NTR} receptor was reported by the group of Habecker. In 2008, they showed that adult p75$^{NTR-/-}$ mice had decreased sympathetic density and altered distribution resulting in depressed heart rate [128]. Later in 2010, they reported that the subendocardium of the left ventricle in p75$^{NTR-/-}$ adult mice was essentially devoid of sympathetic nerve fibers, whereas the innervation density of the subepicardium was normal. This implicates the importance of neurotrophin signaling in controlling sympathetic innervation to the heart. In accordance to that, Yuan et al. have shown p75^{NTR} to be involved in sudden cardiac death after myocardial infarction where deletion of p75^{NTR} had increased sympathetic heterogeneity and resulted in more spontaneous ventricular arrhythmias [129]. Activation of p75^{NTR}, mediated by proNGF and BDNF, was responsible for peri-infarct sympathetic denervation after cardiac ischemia–reperfusion injury, whereas its activation attenuated NGF-induced sympathetic hyperinnervation in the distal peri-infarct ventricle [130]. Hempstead group reported in 2012 that, p75^{NTR} receptor is required for proNGF-induced cardiomyopathy where proNGF-expressing mouse exhibited cardiac microvascular endothelial activation, decrease in pericyte process length, and increased vascular permeability, a phenotype that was rescued by deletion of p75^{NTR} receptor [131].

15. Expert commentary and 5-year view

P75^{NTR} receptor is involved in multiple processes including physiological development as well as responses in injury; yet, still much to explore and unravel about the complicated role of p75^{NTR} in neurovascular system. The major role of p75^{NTR} receptor in mediating neuro- and vascular degeneration has been shown in multiple ischemic vascular diseases affecting the eye, brain, heart, and peripheral limbs. Yet, limited studies have been conducted to study angiogenic vascular repair upon modulating p75^{NTR} receptor. Thus, further preclinical studies are warranted using various models of angiogenesis including pathological and reparative angiogenesis to expand our understanding of the contribution of p75^{NTR} to the angiogenic mechanisms. In addition, current literature provided evidence for the beneficial vascular outcomes of p75^{NTR} inhibition. In particular, recently developed ligands that modulate p75^{NTR} activity show promising results in ameliorating neurovascular injury. Over the next few years, it is anticipated to see published work from both preclini-cal and clinical studies to validate the therapeutic effects of the newly developed non-peptide ligands that can modulate p75^{NTR} activity in ischemic diseases.

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Key issues

- Discovery, structure and regulation of $p75^{NTR}$
- Signaling and multiple biological functions of $p75^{NTR}$.
- Role of $p75^{NTR}$ in ischemic vascular diseases: Examine the contribution of $p75^{NTR}$ in neuro- and microvascular degeneration.
- Role of $p75^{NTR}$ in ischemic diseases of the eye: diabetic retinopathy, retinopathy of prematurity, optic neuropathy and glaucoma and other ocular diseases.
- Role of $p75^{NTR}$ receptor in vascular diseases beyond the eye: Role of $p75^{NTR}$ receptor in stroke, Alzheimer disease, peripheral limb ischemia and ischemic heart diseases.
- Potential of $p75^{NTR}$ inhibitors as therapeutics to comate ischemic vascular diseases.