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Nerve growth factor in diabetic retinopathy: beyond neurons

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Abstract

Diabetic retinopathy (DR), a major ocular complication of diabetes, is a leading cause of blindness in US working age adults with limited treatments. Neurotrophins (NTs), a family of proteins essential for growth, differentiation and survival of retinal neurons, have emerged as potential players in the pathogenesis of DR. NTs can signal through their corresponding tropomyosin kinase related receptor to mediate cell survival or through the p75 neurotrophin receptor with the co-receptor, sortilin, to mediate cell death. This review focuses on the role of NGF, the first discovered NT, in the development of DR. Impaired processing of proNGF has been found in ocular fluids from diabetic patients as well as experimental models. Evidence from literature and our studies support the notion that NTs appear to play multiple potential roles in DR, hence, understanding their contribution to DR may lead to promising therapeutic approaches for this devastating disease.

Keywords

acellular capillary; angiogenesis; diabetic macular edema; diabetic retinopathy; inflammation; neurodegeneration; neurotrophins; p75^{NTR}

Diabetic retinopathy (DR), a major complication of diabetes, is the leading cause of blindness in the US working-age adults [1]. Although the mechanisms behind this disease are not fully understood, chronic hyperglycemia due to lack of functioning insulin is thought to be the underlying cause of damage in diabetic retina [2–4] (reviewed by [5]). Early changes in the diabetic retina include neuronal death of retinal ganglion cells (RGC), glial cell activation and elevated levels of inflammatory mediators [6–10]. The relationship between neurodegeneration, an early event in the diabetic retina, and damage to the microvasculature, which occurs as the duration of diabetes increases, is emerging as an increasingly important area of study (reviewed by [11,12]). Diabetes-induced damage to the microvasculature includes impaired blood flow through capillaries caused by pericyte and endothelial cell loss, microaneurysms and leukostasis [13–18]. Damage to the blood retinal

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barrier is evidenced by increased microvascular permeability, macular edema and decreased visual acuity [19,20]. Endothelial cell death and acellular capillary formation further decrease the blood supply to the inner retina creating an ischemic environment, which stimulates growth of abnormal, fragile and leaky blood vessels [21–23]. In the proliferative stage of DR, vascular leakage causes severe vision loss and even blindness. Current treatments such as laser photocoagulation, vitreoectomy and anti-VEGF injections are invasive with considerable side effects [24,25]. Understanding the molecular mechanisms behind DR is critical for the development of new treatments that prevent damage to microvasculature and preserve retinal neuronal function. Recent findings indicate that diabetes-induced alterations in neurotrophin (NT) expression play multiple roles in the diabetic retina. Originally identified as trophic factors for neurons, NTs are a family of structurally and functionally related proteins that are essential for growth, differentiation and survival of several cell types including retinal neurons, glia and endothelial cells. Similar to the brain, the retina is a typical neurovascular unit where retinal capillaries (endothelial and pericyte cells) interact and communicate with the other cell components of the neurovascular unit: Müller glia, astrocytes and neurons (as depicted in Figure 1). The present review examines the potential role of NTs and their receptors in the pathogenesis of DR.

NTs & their receptors

All four mammalian NTs and their receptors are expressed in the retina. The first member of the family is NGF. Others include brain-derived neurotrophic factor (BDNF), NT-3, NT-4/5 [26–28]. Our understanding of the role of NTs in DR is limited with the exception of NGF, the first NT to be discovered and the most studied. NGF plays an important role in neurodegeneration, inflammation, vascular permeability and injury, all important processes in the pathogenesis of DR [29–36]. NTs are traditionally released by glia as proforms that are cleaved, either intracellularly or extracellularly, to form the mature proteins [37]. Generally, mature NTs bind to their cognate tyrosine kinase (Trk) receptors causing autophosphorylation of the Trk receptor, which initiates signaling events that typically activate prosurvival pathways. Affinity of Trk receptors for mature NTs is enhanced by the association of Trk with the NT receptor (p75^{NTR}) (reviewed in [38]). Unlike mature NTs, the proneurotrophins bind preferentially to p75^{NTR}, which in combination with its co-receptor sortilin, a member of VPS 10p-domain receptor family [39], generally activate inflammatory and apoptotic pathways. Although the activation of p75^{NTR} is not unique to proNGF, the differential outcome of specific proNT/p75^{NTR} interactions is an area of ongoing study (reviewed by [40]). The p75^{NTR} receptor, which lacks a catalytic domain, signals through association of effector molecules with the p75^{NTR} cytoplasmic tail (p75^{ICD}) (reviewed by [38,41]). The activated p75^{NTR} receptor undergoes intramembrane proteolysis, a process by which the sequential α -secretase- and γ -secretase-catalyzed cleavage of the extracellular and intracellular domains (ICD), respectively, releases the p75^{ICD}. The p75^{ICD} can then interact with proteins in the cytoplasm or be translocated to the nucleus, where it may directly regulate transcription [42–47]. For example, the p75^{ICD} may play a role in activating NF- κ B via its association with TNF receptor-associated factor 6 (TRAF6), leading to the release and activation of NF- κ B [48] and reviewed in [49]. Given the wide

variety of signaling pathways available to the p75^{NTR} receptor, much work remains to delineate the specific mechanisms by which p75^{NTR} modulates retinal cell function under diabetic conditions.

ProNGF/NGF imbalance in the diabetic retina

The widespread involvement of NGF in retinal dysfunction is rooted in the diabetes-induced proNGF/NGF imbalance and alterations in TrkA and p75^{NTR} receptor function and expression. Although early studies on NGF expression in the diabetic retina reported significant increases in NGF in serum and tears of diabetic patients and rat retinal lysates [30,50,51], these studies depend on techniques such as ELISA and mRNA expression, which could not distinguish between the precursor and mature forms of NGF. More recently, proNGF-specific antibodies have become available that specifically recognize proNGF, enabling researchers to effectively study both NGF and proNGF in the diabetic retina. Impaired maturation of proNGF caused by the oxidative milieu of the diabetic retina results in increased expression of proNGF, with a corresponding decrease in NGF. Diabetes-induced proNGF/NGF imbalance is associated with a reduction in both activity and expression of matrix metalloproteinase (MMP)-7, one of the enzymes that cleaves proNGF to form mature NGF [37,52]. Decreased MMP-7 expression and function have been observed in the vitreous and aqueous humor of humans with DR and proliferative DR, as well as in the retinal lysates of diabetic rats, and Müller glial cell cultures [31,32]. Restoration of MMP-7 activity is associated with the return of NGF and proNGF to control levels in these tissues [31].

The proNGF/NGF imbalance is exacerbated by diabetes-induced alterations in function and expression of the TrkA and p75^{NTR} receptors. The oxidative milieu of the diabetic retina causes increased formation of nitrotyrosine moieties including increased tyrosine nitration of the TrkA receptor. In conjunction with TrkA nitration, phosphorylation of the TrkA-Y490 site is impaired reducing the activation of downstream survival pathways [30,32,53]. In both streptozotocin-induced diabetic rat retinas, reducing nitrate stress restored TrkA-Y490 phosphorylation and RGC survival to control levels [30–32]. In addition to alterations in TrkA function, expression of the p75^{NTR} receptor is increased in diabetic retinas, which combined with increased proNGF expression, favors activation of proapoptotic and proinflammatory pathways [30,32,33]. In the diabetic retina, this shift toward proNGF/p75^{NTR} signaling is accompanied by neurodegeneration, evidenced by death of RGC, vascular dysfunction and activation of RhoA/p38MAPK, a common pathway implicated in both neuronal death and vascular permeability [29,31,54–59]. The action of proNGF/p75^{NTR} does not depend on additional factors present in the diabetic milieu, as evidenced by studies in which overexpression of cleavage-resistant proNGF, in otherwise healthy rodent retinas, causes increased neuronal cell death and vascular permeability [33,54,60].

Role of proNGF in retinal inflammation

The proNGF/p75^{NTR}-mediated release of inflammatory mediators by Müller cells is emerging as an important pathway in the pathogenesis of DR. Glial activation and increased inflammation (reviewed by [61,62]) are hallmarks of the diabetic retina. In both rat retinas

overexpressing proNGF and in diabetic rodent retinas, levels of proNGF and p75^{NTR} are elevated within Müller cells, which also exhibit increased expression of glial fibrillary acidic protein, a sign of glial activation [29–33,63]. In these two models, p75^{NTR} plays a key role in the regulation of inflammatory mediators and their downstream actions. In the rat proNGF overexpression model, which is independent of the diabetic milieu, Müller cell changes are accompanied by increased expression of NF-κB, p-NF-κB, TNF-α and IL-1β, which, along with glial activation, are blunted by knockdown of p75^{NTR} [33]. In p75^{NTR} knockout mice (p75^{NTR} KO), deletion of exon III encoding the p75^{NTR} ligand binding region renders these mice insensitive to diabetes-induced decreases in NGF and increases in proNGF, NF-κB, p-NF-κB and TNF-α as well as deleterious effects of diabetes-induced inflammation such as RGC death, glial activation and vascular leakage [33,64]. Interestingly, although p75^{NTR} KO mice appear impervious to the effects of diabetes-induced inflammation, non-diabetic p75^{NTR} KO mice exhibit constitutively lower levels of NGF and higher levels of proNGF, NF-κB, p-NF-κB and TNF-α (26 kD membrane-bound form) than their wild-type counterparts. A comparison of mRNA levels between p75^{NTR} knockout and wild-type mice suggest that these protein alterations are due to post-translational protein processing rather than changes in gene expression. In fact, deleting or antagonizing the p75^{NTR} receptor in primary Müller cell cultures increased membrane-bound TNF-α, while decreasing the soluble form (17 kD). Additionally, increased secretion of TNF-α (17 kD) by wild-type primary Müller cells exposed to peroxynitrite or to proNGF is absent in Müller cells lacking the p75^{NTR} receptor [33]. Together, these results suggest a complex role of the p75^{NTR} receptor in retinal inflammation that affects both the expression and action of inflammatory mediators.

Although the molecular mechanisms by which proNGF/p75^{NTR} stimulates Müller cell secretion of inflammatory mediators are not yet known, a variety of *in vitro* studies provide valuable insights. The p75^{NTR} receptor has been shown to activate NF-κB, particularly when cells are under stress [65,66]. In accord with this observation, high glucose-proNGF-stimulated cells of the Müller cell line, rMC-1, have increased expression of inflammatory mediators TNF-α, NF-κB and p-NF-κB that is reduced by inhibition of p75^{NTR} or its intracellular cleavage [33]. Because p75^{NTR} signal transduction depends on intramembrane proteolysis to liberate the p75^{ICD}, the p75^{ICD} is a likely candidate to play a critical role in p75^{NTR} inflammatory pathways. The p75^{ICD} can recruit intracellular effector proteins that determine specific signaling pathways [42,43] allowing for several possible signaling scenarios. For example, the p75^{ICD} in combination with a complex of effector proteins including TRAF6 can recruit IκB-kinase-β. This will allow the possibility that p75^{NTR} intramembrane proteolysis and activation of NF-κB [48] and reviewed in [49]. Another possibility is that the p75^{ICD} translocates to the nucleus where it can act as a transcription enhancer [47]. Given the wide variety of signaling pathways available to the p75^{NTR} receptor, studies are warranted to delineate the additional mechanisms by which p75^{NTR} mediates the release of inflammatory mediators in the diabetic retina.

Role of proNGF/NGF in retinal neurodegeneration

Although NGF and proNGF play important roles in survival and death during retinal neurogenesis, the mechanisms by which this occurs in the diabetic retina are not fully

understood. One contributor to diabetes-induced RGC death is the reduction in trophic support due to decreased NGF expression. The importance of NGF in RGC survival is illustrated by recent studies, in which NGF supplementation reduced diabetes-induced RGC death [29,35]. In contrast, reductions of available NGF via injection of anti-NGF antibody worsened RGC loss in diabetic rat retinas [36]. Another factor in diabetes-induced RGC death is the direct activation of proapoptotic pathways in RGCs by proNGF interaction with the p75^{NTR} receptor. Our work demonstrated that proNGF-induced apoptosis in primary RGC cultures is accompanied by increased p75^{NTR} expression, and Rho kinase-dependent activation of RhoA, p38MAPK and JNK [54], all participants in apoptotic pathways downstream of the p75^{NTR} receptor [52,55,56,67,68]. Additionally, in both diabetic rats and in a rat model overexpressing proNGF, the p75^{NTR} receptor and apoptotic markers, cleaved poly (ADP-ribose) polymerase and caspase-3, are also increased in a Rho kinase-dependent manner [54]. Collectively, these results suggest a mechanism of retinal neurodegeneration triggered by proNGF/p75^{NTR} activation of RhoA and p38MAPK/JNK apoptotic pathways in RGC. However, this mechanism is not without controversy. Although the p75^{NTR} receptor directly mediates neuronal death in the developing retina, there is disagreement whether the p75^{NTR} receptor is expressed by RGCs in the mature retina [54,69–72]. Another pathway by which proNGF can cause ganglion cell death involves paracrine effect of proNGF/p75^{NTR}-mediated secretion of TNF- α by Müller cells [33,72,73]. The proNGF-stimulated secretion of TNF- α and subsequent loss of ganglion cells are p75^{NTR}-dependent, as evidenced by the findings that p75^{NTR} knockout mice [64] are insensitive to both proNGF and diabetes-induced loss of RGCs [33,72].

Role of proNGF/NGF in vascular permeability & injury

The disturbed balance of elevated proNGF and impaired NGF levels in the diabetic retina is believed to affect the homeostasis of retinal cells including endothelial cells. Supplementation of NGF has been shown to promote endothelial cell survival by preventing pericyte loss and the formation of occluded capillaries in the diabetic retina [29]. In other systems, proNGF/p75^{NTR} has been shown to mediate apoptosis in endothelial cells [74] and to decrease heart microvascular pericyte process length [75]. The paracrine effect of proNGF/p75^{NTR} in Müller cells resulting in secretion of inflammatory mediators including TNF- α [31–33,72,73] is expected to adversely affect retina capillaries. TNF- α is a potent cytokine known for inducing vascular injury as evidenced by increased permeability and endothelial cell death both *in vivo* and *in vitro* [18,59,76–80]. The proNGF/p75^{NTR}-mediated increase in TNF- α is accompanied by increased vascular permeability that is blocked by inhibition of the p75^{NTR} receptor or its cleavage [33,60]. The importance of the p75^{NTR} receptor in mediating vascular permeability is further demonstrated in transgenic p75^{NTR} KO mice [64], where deletion of the p75^{NTR} receptor exon III renders p75^{NTR} KO mice insensitive to diabetes-induced vascular permeability and glial activation [33]. Current studies by our group focus on delineating the direct action of proNGF/p75^{NTR} on endothelial cells. One possibility is that proNGF/p75^{NTR}-mediated activation of RhoA leads to degradation of tight junction proteins and increased permeability. RhoA is a molecular switch known to be activated in the diabetic retina, and activation of RhoA/p38MAPK is a common pathway implicated in both neuronal death and vascular permeability [29,31,54–

59]. One question yet to be answered is what relationship does proNGF/p75^{NTR}-mediated permeability have with VEGF? VEGF is a family of proteins that are important in the regulation of vascular permeability and angiogenesis in eye diseases including DR (reviewed by [81]). Although proNGF has not been reported to alter VEGF expression, NGF has been shown to stimulate increased VEGF expression in brown adipose tissue as well as diabetic models of hind limb ischemia and wound repair [82–84]. In rabbit retina, intravitreal injection of bevacizumab, an anti-VEGF antibody, has been shown to reduce NGF levels [85]. In contrast, another study in mouse retina showed that application of anti-NGF antibody could enhance VEGF expression [86]. The mutual regulation of proNGF and VEGF expression and whether proNGF modulates retinal vasculature independent of VEGF remains to be fully elucidated.

Role of proNGF/NGF in ischemic neovascularization

Given the role of NTs as regulators of growth, differentiation and survival, their emerging role in diabetes-induced retinal neovascularization is not surprising. Endothelial cell death and acellular capillary formation decrease the blood supply to the inner retina creating an ischemic environment, which stimulates growth of abnormal, fragile and leaky blood vessels [21–23]. In addition to VEGF, the well-studied angiogenic factor in proliferative diabetic retinopathy (PDR) [87], NTs have recently been detected in ocular fluids from patients with proliferative DR [28,31]. NGF contributes to retinal neovascularization in the oxygen-induced retinopathy mouse model by TrkA activation, which is attenuated by inhibition of Trk receptors [88]. NGF has also been shown to activate TrkA receptor on CD34⁺ endothelial progenitor cells, stimulating their angiogenic behavior [89]. NTs can induce angiogenesis by acting directly on Trk-expressing endothelial cells and on subsets of Trk-expressing bone marrow-derived hematopoietic cells or indirectly via induction of pro-angiogenic factors, such as VEGF [90,91]. The mechanism by which TrkA activates NT-mediated angiogenesis may also be via NGF/TrkA-mediated elevations in VEGF levels through the PI3-K/Akt pathway [92]. The cross-talk between NGF and VEGF in retinal angiogenesis is illustrated by the finding that VEGF inhibition by intravitreal bevacizumab injection down regulates NGF and increased retinal apoptosis in rabbits [85]. Since proNGF levels have been shown to be elevated in ocular fluids from PDR patients [31], there is great possibility that proNGF can contribute to development of proliferative stage of the disease. Interestingly, proNGF induces a potent angiogenic response in retinal endothelial cells. This response is blocked by inhibition of TrkA suggesting that, proNGF can contribute to PDR, at least in part, via activation of TrkA [93]. Taken together, these studies point to the potential contribution of proNGF and NGF and their receptors in the development of DR. A diagram that depicts possible interactions and receptor combinations of NGF, proNGF with TrkA and p75^{NTR} is shown in Figure 1.

Role of BDNF & other NTs in the diabetic retina

Although our current knowledge of NTs in the diabetic retina centers about the proNGF/NGF axis, diabetes-induced alterations of other NTs are emerging as possible players in the pathogenesis of DR. BDNF, the second NT to be discovered, is a trophic factor important for the development and survival of retinal neurons [94]. Recent studies

indicate that BDNF levels are decreased in serum of patients with PDR and in the retina and serum of diabetic rats [28,95,96]. This downregulation of BDNF may be induced by the cytokine and transcription enhancer, high-mobility group box-1 [28]. On the other hand, conflicting reports have been published as to the effect of diabetes on BDNF receptor, TrkB, with some investigators reporting decreases in TrkB expression and others reporting increases [96,97]. Without question, however, BDNF is an important source of trophic support to both neurons and endothelial cells. The diabetes-induced decrease in BDNF expression is accompanied by degeneration of amacrine cells that is rescued by intraocular injection of BDNF [95]. *In vitro*, BDNF supplementation rescues cultured retinal neurons from hyperglycemia-induced apoptosis and increases both the expression and phosphorylation of TrkB [98,99]. In endothelial cells, BDNF also plays a role in stimulating cell survival. Sequestration of endogenous BDNF causes apoptosis in brain-derived endothelial cells, while exogenous BDNF stimulates angiogenesis via TrkB phosphorylation and activation of the PI3-kinase/Akt pathway [74]. BDNF is gaining recognition as a mediator of angiogenesis (reviewed by [100]), however, whether it plays this role in the ischemic environment of the diabetic retina remains to be seen.

Although studies on the remaining NTs, NT-3 and NT-4 in the diabetic retina are limited, their role in supporting retinal cells during development suggests that they may also play a role in the diabetic retina [101–104]. In contrast to BDNF, increased levels of NT-3 and NT-4 have been detected in diabetic rat retinas and in the vitreous of patients with PDR [28]. NT-3 is thought to maintain the retinal environment and to act as a mitogen [104]. Although in rat retinal explants, NT-3 had minimal effect on RGC survival and neurite outgrowth [105,106], NT-3 does show promise as a mediator of angiogenesis. NT-3 stimulated human umbilical vein endothelial cell proliferation, survival, migration and network formation [90]. Levels of both NT-3 and phosphorylated TrkC increase in response to ischemia and NT-3 is able to promote angiogenesis in ischemic limbs [90]. NT-4, on the other hand, plays a role in neuronal survival and outgrowth. In rat retina *in vitro*, NT-4 protects RGC from apoptosis and increases the outgrowth of neurites in isolated rat retinas through a TrkB signaling pathway and reduction in endoplasmic reticulum stress-related factors [99,105–108]. NT-4 has also been shown to promote neovascularization that is as potent as that induced by VEGF [109]. Together, these findings support a potential role of the NT-3 and NT-4/Trk axis in the pathogenesis of DR.

Expert commentary & five-year view

The role of NTs in the pathogenesis of DR is emerging as a promising new area of study that may lead to the identification of new therapeutic targets to combat this blinding disease. NTs are known to be essential for growth, differentiation and survival in the developing and mature retina. Not surprisingly, NTs also play important roles in the diabetic retina, in which hyperglycemia and oxidative stress lead to inflammation and a disruption of retinal homeostasis. The imbalance between proNGF/NGF levels that is accompanied by upregulation of p75^{NTR} over TrkA receptor activation plays a critical role in steering events such as neurodegeneration, inflammation and vascular dysfunction in the diabetic retina. However, we are just beginning to understand the complex mechanisms by which these processes occur. Compared with proNGF and NGF, the roles of BDNF, NT-3 and NT-4 in

the diabetic retina are less defined. Current studies indicate that all three of these NTs play roles in neuronal and endothelial survival that are altered by hyperglycemic and ischemic environments. These findings support the potential role of BDNF, NT-3 and NT-4 in mediating apoptosis and angiogenesis in the diabetic retina. Despite what we have learned so far about NTs in the diabetic retina, much remains to be learned. Future studies on the role of NTs/Trk/p75^{NTR} axis in the diabetic retina will help us to more fully understand its role in the neurodegeneration and vascular dysfunction that contribute to the pathogenesis of DR.

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Key issues

- Diabetic retinopathy (DR): current treatments and challenges to identify new treatments.
- Importance of neurotrophins: types of neurotrophins and their receptors.
- ProNGF/NGF imbalance in the diabetic retina.
- Role of proNGF in retinal inflammation.
- ProNGF/NGF contribution to neurodegeneration associated with DR.
- Role of proNGF in vascular permeability and injury.
- ProNGF/NGF contribution to ischemic neovascularization.
- Role of other neurotrophins in DR.

Figure 1. A diagram showing typical neurovascular unit of the retina: neurons, capillaries, Müller and astrocytes

Enlarged box (A) shows the proinflammatory role of proNGF in glia cells via activation of the neurotrophin receptor p75^{NTR} resulting in autocrine effect of sustaining proNGF expression and paracrine effect of secreting TNF-α and IL-1β. Enlarged box (B) shows the cleavage of proNGF to its mature form NGF and the possible downstream signaling pathways. NGF can activate the receptor TrkA in conjunction with p75^{NTR} resulting in neuronal cell survival. NGF and proNGF can activate TrkA resulting in EC survival and/or angiogenic response. ProNGF can activate p75^{NTR} in conjunction with sortilin resulting in neuronal death or endothelial cell death that eventually will result in development of acellular capillary formation, a hallmark of diabetic retinopathy. EC: Endothelial cell; NTR: Neurotrophin receptor.