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REVIEW ARTICLE

VEGF and Neurotrophins Interaction in the Retinal Neurovascular Unit Homeostasis: A Target for Ocular Disease Treatment and Management

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Abstract

Emerging evidence underscores the central role of the retinal neurovascular unit (RNVU) in the pathogenesis of major retinal disorders, including diabetic retinopathy, age-related macular degeneration, and glaucoma. Traditionally considered as primarily vascular diseases, these conditions are now increasingly recognized to involve early neurodegenerative processes that may precede vascular dysfunction. Although anti-VEGF therapies have revolutionized the treatment of neovascular retinal diseases, long-term VEGF inhibition has been associated with adverse effects, including retinal atrophy and diminished neuroprotection, underscoring the need for more targeted strategies. Recent studies have highlighted the differential roles of VEGF-A splice isoforms, particularly the pro-angiogenic VEGF-Axxxa and the anti-angiogenic VEGF-Axxxb, in maintaining RNVU homeostasis and contributing to disease progression. In parallel, neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) have demonstrated the ability to exert neuroprotective, anti-inflammatory, and vasomodulatory effects, partly through modulation of VEGF-A signaling. Notably, we have recently demonstrated that NGF modulates VEGF-A isoform expression and VEGFR-2 levels in diabetic retinas, further supporting the hypothesis of a functional cross-talk between neurotrophins and angiogenic pathways. Based on this evidence, a new model is proposed, in which NGF and BDNF interact bidirectionally with VEGF-A to preserve RNVU integrity. This integrated therapeutic perspective, combining neurotrophic support with selective modulation of VEGF-A isoforms, may enhance treatment efficacy, reduce long-term side effects, and minimize the burden of care in chronic retinal neurodegenerative diseases.

Keywords BDNF · neurotrophins · NGF · ocular diseases · retinal neurovascular unit · VEGF

Introduction

The retinal neurovascular unit (RNVU) is a complex structure consisting of retinal cellular components and blood vessels, which is crucial for maintaining retinal health and vision. Damage or alteration of the RNVU can lead to various retinal diseases, including diabetic retinopathy (DR), which is characterised by altered vascularisation, inflammation, and neurodegeneration [1], and glaucoma, as a consequence of optic nerve damage [2]. The physiological functionality of the retina is therefore assured by factors which control cell-to-cell communication in RNVU, regulating the balance of pro- and anti-apoptotic pathways and, in turn, determining cell fate. Among trophic factors, the vascular endothelial growth factor A (VEGF-A), has been demonstrated to play a central role in the maintenance of the structural and functional retinal integrity [3]. Intravitreal injection (IVT) of anti-VEGF agents is the current gold standard treatment of vascular retinal diseases to counteract pathological neo-angiogenesis, but it might also induce potential local adverse effects. Experimental observations have reported increased apoptosis of retinal cells following the administration of anti-VEGF agents [4] which is accompanied by a consistent decrease in retinal nerve growth factor (NGF) expression [5]. More recently,

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we found that anti-VEGF agents deeply impact neurotrophins (NTs) homeostasis, inducing an imbalance in pro-NTs expression and a reduction in TrkA and TrkB phosphorylation, which profile the activation of retinal cell death pathways [6]. Moreover, it has been recently demonstrated that NGF-mediated anti-apoptotic and neuroprotective pathways, which prevent the loss of retinal ganglion cells (RGCs) and the accumulation of microvascular defects in DR, are associated with the regulation of VEGF-A isoforms and the vascular endothelial growth factor receptor 2 (VEGFR-2) expression in adult retina [7]. In addition, NGF is able to stimulate its family related molecule brain-derived neurotrophic factor (BDNF) in both retina and retinal central pathway areas [8], supporting the involvement of these NTs in the maintenance of retina structure and functions. Avoiding neuro-retinal alterations or degeneration is one of the main open questions in the use of anti-angiogenic factors in ophthalmology, and it is therefore crucial to identify new disease-modifying agents which might preserve the RNVU. Further, less invasive methods of drug administration, such as intranasal administration might be also taken into account in order to reduce the possible side effects of the intraocular drug accumulation, inflammation and/or hemorrhage which are associated with IVT injection. This review recapitulates the current understanding of the implication of VEGF-A and its isoforms in the pathophysiology of the RNVU, as well as the VEGF-A interaction with other NTs such as NGF or BDNF. All these recent discoveries could lead to implementing NGF or BDNF-based therapeutics for treating retinal degenerative diseases at their onset, to avoid the adverse outcomes of anti-VEGF therapies.

The RNVU

RNVU & Eye Homeostasis

The retina, as an intrinsic part of the central nervous system, is organized into a complex neurovascular unit [9] composed of neurons, glial cells (including astrocytes, Müller cells, and microglia), and vascular components such as endothelial cells and pericytes [10]. As illustrated in Fig. 1, the RNVU mirrors the layered organization of the retina, enabling tight spatial and functional coupling between neural activity, metabolic support, and blood supply. This integrated architecture is essential for maintaining retinal homeostasis through the regulation of synaptic transmission, metabolic exchange, and preservation of the inner blood–retinal barrier (BRB) [11]. Retinal neurons are spatially organized to enable signal integration and propagation, with synaptic processing occurring primarily within the outer and inner plexiform layers, while RGC axons form the nerve fiber layer conveying visual information to the brain [12, 13]. Glial cells within the RNVU are central to retinal function. Müller cells, which span the entire retinal thickness and interact with virtually all retinal cell types, regulate extracellular ion homeostasis, neurotransmitter recycling, metabolic support, and BRB integrity [14]. Through these functions, Müller cells act as a key regulatory hub within the RNVU and represent a critical element in maintaining neurovascular balance. Astrocytes, located mainly in the nerve fiber and ganglion cell layers, provide mechanical support and regulate vascular tone, while participating in the transfer of nutrients and metabolic waste. Microglia, the resident immune cells of the retina, are highly dynamic and perform continuous surveillance of the retinal microenvironment. Under physiological conditions, they contribute to synaptic remodelling and neuroprotection, but upon activation in response to injury or chronic stress, they secrete proinflammatory cytokines and may exacerbate tissue damage [15]. The retinal vasculature is organized into three primary plexuses: superficial (SVP), intermediate (IVP) and deep (DVP), each closely aligned with corresponding neuronal layers. Endothelial cells, pericytes, and associated glial processes work in concert to maintain the BRB and respond to fluctuating metabolic demands [16].

RNVU Alteration and Ocular Diseases

Disruption of RNVU integrity is increasingly recognized as a central feature in the pathophysiology of retinal degenerative diseases, including DR and age-related macular degeneration (AMD) [17, 18]. Alteration affecting any component of the RNVU (neuronal, glial, or vascular) can therefore compromise retinal homeostasis resulting in local inflammation or apoptosis, impaired synaptic communication, BRB breakdown, and progressive neurodegeneration [19]. This provides a conceptual framework for therapeutic strategies aimed at restoring neurovascular balance rather than targeting individual pathways in isolation. DR, AMD, and glaucoma represent major causes of vision loss in adults, characterized by progressive neurovascular compromise, BRB disruption, and, in some cases, neovascularization or edema [20–27]. Early pathological changes involve neuronal dysfunction and RGC apoptosis that precede microvascular damage and are mediated by oxidative stress, mitochondrial dysfunction, and NF-κB–mediated inflammatory signalling [19]. Microvascular changes, such as basement membrane thickening, pericyte loss, endothelial cell dropout, microaneurysm formation, and vascular leakage, further compromise the RNVU and accelerate disease progression [28]. Other RNVU-related conditions, including retinal vascular occlusions (RVO) and hypertensive retinopathy, may similarly result in irreversible vision impairment.

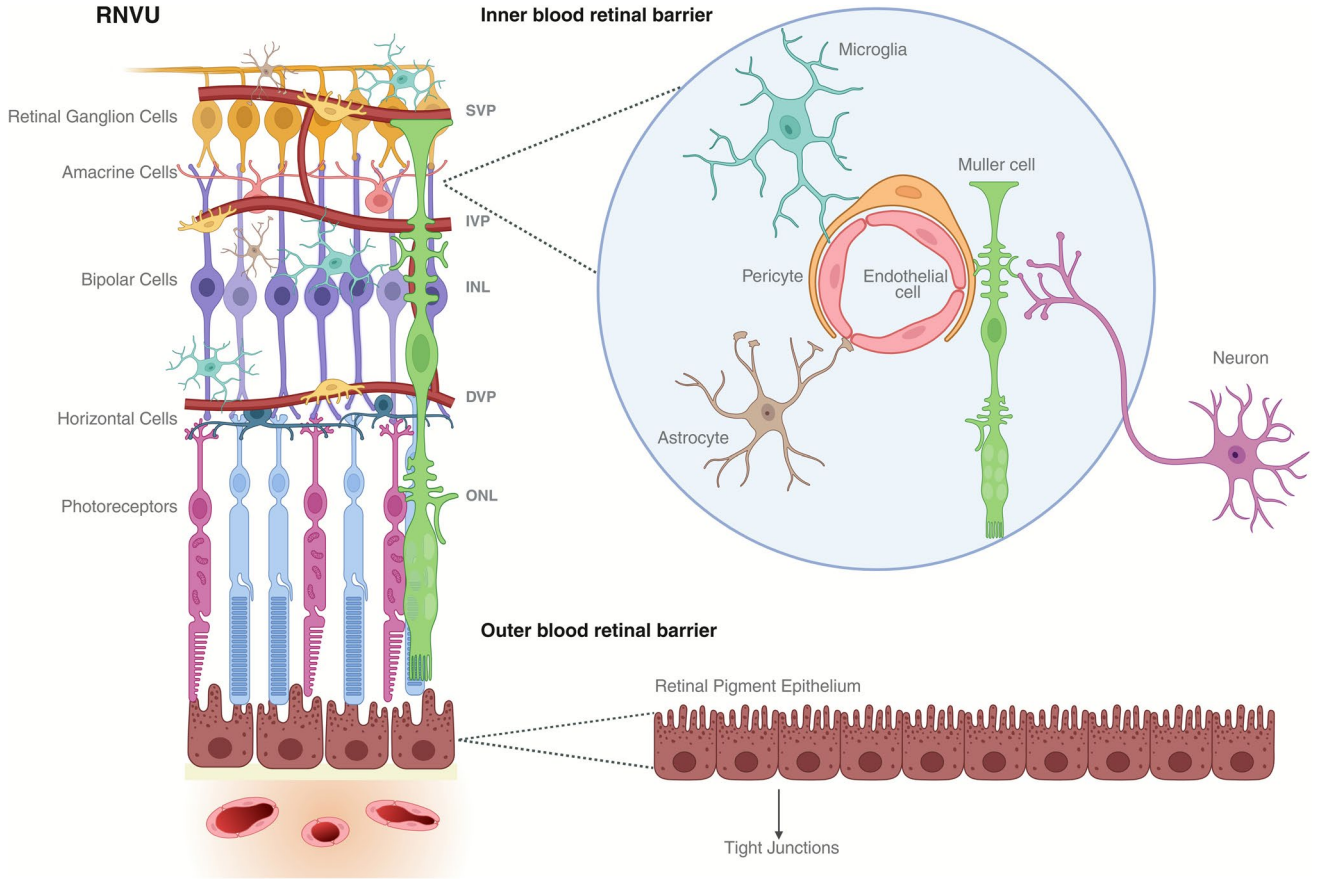

Fig. 1 This image, created with BioRender.com, illustrates the structure of the retinal neurovascular unit (RNVU) and its relationship with the inner and outer blood-retinal barriers. On the left, the vertical organization of the retinal layers is depicted, including photoreceptors, horizontal cells, bipolar cells, amacrine cells, and retinal ganglion cells. These neuronal components are supported by Müller cells, which span the entire thickness of the retina. Three vascular plexuses are shown: the superficial vascular plexus (SVP), intermediate vascular plexus (IVP), and deep vascular plexus (DVP), each associated with specific retinal layers. The inset on the right provides a magnified view of the inner blood-retinal barrier, highlighting the key cellular components: endothelial cells forming tight junctions, pericytes, astrocytes, microglia, and Müller cells. This multicellular interaction maintains vascular integrity and neuronal homeostasis. At the bottom, the outer blood-retinal barrier is represented by the retinal pigment epithelium, which forms tight junctions that regulate molecular exchange between the neural retina and the underlying choroid.

VEGF

VEGF and its Isoforms

VEGF is a central molecule involved in blood vessels formation of under both healthy and disease conditions [29]. The human VEGF family is composed of several proteins with distinct biological properties, including VEGF-A, -B, -C, -D, and placental growth factor (PlGF). Other less common isoforms have also been described, such as VEGF-E of viral origin, VEGF-F derived from snake venom, and EG-VEGF, which is secreted by endocrine tissues [30]. Among these family members, VEGF-A represents the most extensively studied and biologically relevant angiogenic isoform. VEGF-A is expressed as multiple splice isoforms, generated through the use of alternative splice sites within exons 6, 7, and 8 in both normal and diseased tissues [31, 32]. Splicing of the VEGF-A gene produces five protein isoforms in humans: VEGF-A121 and VEGF-A165, which are secreted, and VEGF-A145, VEGF-A189, and VEGF-A206, which are tightly bound to the cell surface [7]. Additionally, alternative splicing of the terminal exon (exon 8) gives rise to two distinct isoform families: VEGF-Axxxa, resulting from proximal splicing, and VEGF-Axxxb, from distal splicing (Fig. 2). These isoforms contain the same number of amino acids but differ in their C-terminal sequences [32–34]. This small variation, consisting of just six amino acids at the C-terminus, leads to concrete functional differences: while VEGF-Axxxa isoforms are strongly pro-angiogenic, VEGF-Axxxb isoforms exhibit anti-angiogenic, anti-migratory, and anti-permeability properties [35, 36].

Under physiological conditions, VEGF-A activity is regulated by extracellular matrix binding and inhibitory factors, which help maintain vascular stability and quiescence. In

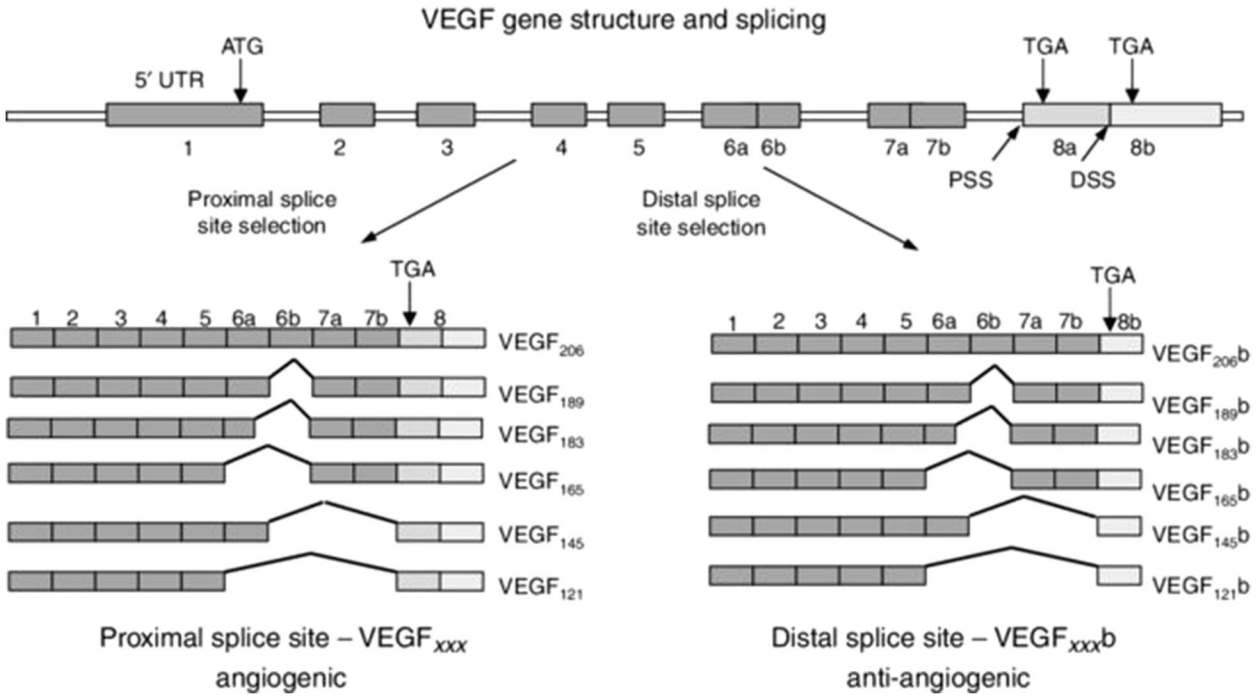

Fig. 2 This figure provides an overview of the alternative splicing of the vascular endothelial growth factor A (VEGF-A) gene and the structural and functional domains of its isoforms. The genomic structure of the VEGF-A gene is shown, including exon–intron organization and alternative splice sites, notably within exons 6, 7, and 8. The various VEGF-A isoforms resulting from alternative splicing are illustrated. The left side shows pro-angiogenic isoforms (e.g., VEGF-A206, VEGF-A189, VEGF-A165, VEGF-A121), while the right panel shows anti-angiogenic isoforms (e.g., VEGF-A165b), which differ at the C-terminal region due to the use of alternative 3′ splice sites in exon 8. Source: Pritchard-Jones R. *et al.*, "Expression of VEGF(xxx)b, the inhibitory isoforms of VEGF, in malignant melanoma," British Journal of Cancer, 2007, 97(2), pp. 223–230. https://doi.org/10.1038/sj.bjc.6603839. Licensed under Creative Commons Attribution 4.0 International (CC BY 4.0).

pathological states, VEGF-A can be released or activated, for example through protease-mediated cleavage, promoting endothelial cell survival, migration, and increased vascular permeability [37–41].

VEGF Mechanism of Action

Functionally, as shown in Fig. 3, all VEGF proteins act similarly by forming biologically active dimers that interact with specific tyrosine kinase receptors [42], although the most substantial pro-angiogenic effects are mediated by the activation of VEGFR-1 and VEGFR-2 [43], predominantly expressed on endothelial cells [44]. Upon ligand binding, these receptors undergo dimerization, which activates their intracellular tyrosine kinase domains by autophosphorylation of key tyrosine residues. This activation triggers a series of downstream signaling cascades involving pathways such as mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), Src kinase, and phospholipase C gamma (PLCγ) [45]. Among the VEGF receptors, VEGFR-2 is considered the principal mediator of VEGF's pro-angiogenic effects, promoting endothelial cell proliferation and migration. Activation of VEGFR-2 stimulates the Ras-Raf-MEK-ERK cascade as well as the PI3K-Akt pathway, both of which promote endothelial cell proliferation and new vessel formation [46]. VEGF signaling also regulates vascular permeability. The PI3K/Akt axis activates PLCγ, which modulates intracellular calcium levels and stimulates endothelial nitric oxide synthase (eNOS) production via nuclear factor of activated T cells, contributing to increased vascular permeability [47]. Furthermore, VEGFR-2 phosphorylation leads to the VE-cadherin internalization and disruption of inter-endothelial junctions, thus increasing endothelial permeability [48]. The differential affinity of VEGF isoforms for VEGFR-1 and VEGFR-2 is modulated by co-receptors such as neuropilin-1 (NRP1) and heparan sulfate proteoglycans (HSPGs), which influence ligand-receptor binding and downstream signaling [49, 50]. Consequently, within the VEGF-A family, different isoforms exhibit distinct biochemical properties and effects on vascular growth. In particular, the anti-angiogenic VEGF-Axxxb variants act as weak VEGFR-2 agonists due to alternative splicing of exon 8, which encodes the binding sites for HSPGs and NRP1 [51]. Understanding these structural and functional differences is crucial for the development of therapies that selectively target angiogenic VEGF-A isoforms, minimizing interference with anti-angiogenic forms.

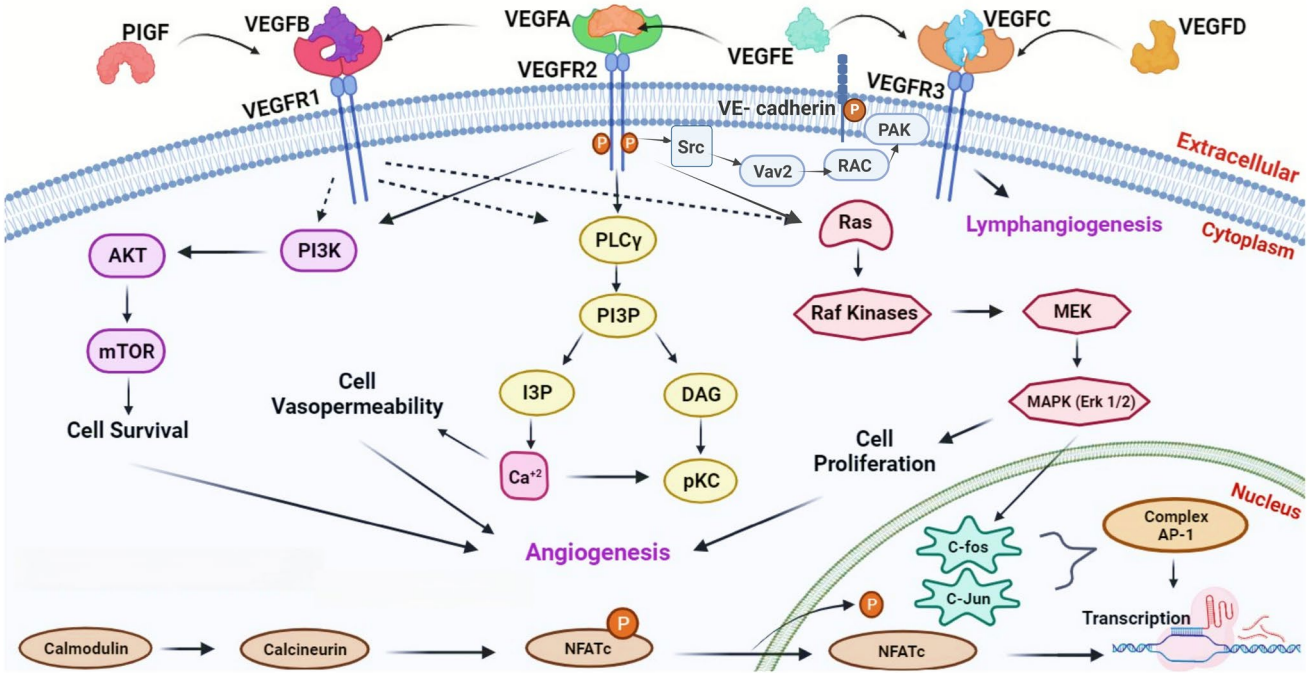

Fig. 3 This figure illustrates the *vascular endothelial growth factor* (VEGF) signaling pathways involved in angiogenesis, lymphangiogenesis, and cell proliferation. VEGF ligands (PlGF, VEGF-B, VEGF-A, VEGF-C, VEGF-D, and VEGF-E) bind to their respective receptors VEGFR-1, VEGFR-2, and VEGFR-3, triggering distinct downstream signaling cascades. VEGFR-1 primarily activates the PI3K–AKT–mTOR pathway, promoting cell survival and modulating vascular permeability. VEGFR-2, the main mediator of angiogenesis, activates PLCγ, leading to IP3 and DAG production, calcium mobilization, and PKC activation, which contribute to endothelial cell migration, proliferation, and neovascular formation. Activation of the Ras–Raf–MEK–MAPK pathway further promotes cell proliferation. Cross-talk with VE-cadherin, Src, and RAC is also shown, highlighting additional regulation of endothelial junctions and vascular dynamics. VEGFR-3 is primarily activated by VEGF-C and VEGF-D, driving lymphangiogenesis through similar downstream pathways. This figure is adapted and modified from the publication of Nayarisseri, A., *et al.* "Potential inhibitors of VEGFR1, VEGFR2, and VEGFR3 developed through Deep Learning for the treatment of Cervical Cancer". Sci Rep 14, 13,251 (2024). https://doi.org/10.1038/s41598-024–63762-w. Licensed under Creative Commons Attribution 4.0 International (CC BY 4.0).

VEGF-A in the Eye

Among the VEGF family, VEGF-A plays a central role in angiogenesis and is critically involved in several conditions, including ocular neovascularization, other diabetic complications, and ocular cancers such as retinoblastoma [52, 53]. Both VEGF-Axxxa and VEGF-Axxxb isoforms are present in various human ocular tissues, including the iris and vitreous, with particularly high relevance in the RNVU [54]. Importantly, their biological activity strongly depends on their balance [7]. Diseases characterized by neovascularization in the RNVU, including AMD and DR, are strongly influenced by dysregulated VEGF-A expression [55]. In addition, VEGF-A is a key mediator in retinopathy of prematurity (ROP), a neonatal eye disorder that remains a major cause of irreversible childhood blindness [54, 56, 57]. VEGF-A is considerably upregulated in DR, particularly in RPE cells, glial cells, and vitreal fibroblasts [58], representing one of the earliest signs of vascular dysfunction in this disease [7]. Early signs of DR were traditionally thought to be exclusively vascular. They begin with the loss of pericytes, followed by apoptosis of capillary cells. Hypoxia is a key regulator of VEGF-A upregulation: as capillary dropout and ischemia occur, retinal cells accumulate HIF-1α, which induces VEGF-A expression and promotes pathological neovascularization and macular edema [59, 60]. However, recent evidence suggests that cellular dysfunction and death may occur early in diabetes, affecting not only vascular components but also retinal neurons and glial cells [61]. Moreover, early activation of Müller glial cells, which play a key role in regulating VEGF-A levels within the retina, may initiate molecular inflammatory processes that are critical in the progression of DR [44]. Similarly, VEGF-A plays a central role in choroidal neovascularization and its consequences (vascular leakage, hemorrhage, and scarring) in AMD [44], where its levels are substantially increased [62]. In contrast, VEGF-A165b appears to be downregulated in angiogenic disorders of RNVU [56], highlighting the importance of the VEGF-Axxxa/VEGF-Axxxb balance in retinal disease. Beyond its role in angiogenesis, VEGF-A is increasingly recognized as a trophic factor for non-endothelial cells in the neuroretina, including RGCs [63], photoreceptors, and Müller cells [43]. For instance, VEGFR-2 is highly expressed in retinal neurons. Compared with other

VEGF-Axxxa isoforms, VEGF-A165b, in physiological contexts, plays a protective role in the retina by promoting cell survival without inducing pathological angiogenesis. It has been recently demonstrated that VEGF-A165b preserves retinal neuronal and endothelial cell viability, highlighting its potential as a therapeutic agent to mitigate the harmful effects of pro-angiogenic VEGF-A165a in retinal diseases [64].

Anti-VEGF Treatments in Ophthalmology

Overview of Intravitreal Anti-VEGF Agents

Intravitreal anti-VEGF agents are biotechnologically engineered molecules designed to selectively bind VEGF with high affinity [52] (Table I). Their most widespread use in ophthalmology is for the treatment of neovascular AMD (nAMD) [55]. Currently, the three most frequently utilized anti-VEGF therapies in clinical practice, particularly for nAMD, diabetic macular edema (DME) and RVO, are Aflibercept, Bevacizumab, and Ranibizumab.

Mechanism of Action and Pharmacokinetic Considerations

Aflibercept is a recombinant fusion protein with a molecular weight of approximately 115 kDa. It consists of the second immunoglobulin (Ig) domain of VEGFR-1 and the third Ig domain of VEGFR-2, fused to the Fc portion of human IgG1. This structure enables it to bind various isoforms of VEGF-A and VEGF-B, as well as placental growth factor (PlGF). In comparison, both Ranibizumab and Bevacizumab selectively target all isoforms of VEGF-A [65]. Bevacizumab is a full-length monoclonal antibody with a molecular weight of approximately 149 kDa, initially developed as an anti-cancer agent [66]. Despite its original indication, it is now widely used off-label for nAMD and other retinal conditions characterized by macular edema and pathological angiogenesis [67]. Ranibizumab, by contrast, is a smaller antibody fragment (~48 kDa), specifically engineered for intraocular application. It has undergone affinity maturation to enhance its binding to VEGF-A, making it highly effective in targeting ocular neovascularization. Thanks to its high affinity for VEGF-A, Ranibizumab acts by inhibiting VEGF-A action and blocking its stimulation of VEGFR-1 and VEGFR-2 receptors [68]. Compared to Bevacizumab and Aflibercept, Ranibizumab is smaller in molecular size and lacks the Fc region, which leads to a faster systemic clearance, lower systemic exposure and a reduced capacity to inhibit circulating plasma-free VEGF following intravitreal administration [65]. In contrast, although only limited amounts of Bevacizumab and Aflibercept enter the systemic circulation, their exposure levels are sufficient to suppress systemic VEGF *in vivo*. These pharmacokinetic and pharmacodynamic differences are clinically relevant, as systemic VEGF plays a critical role in maintaining vascular homeostasis. Prolonged circulating VEGF suppression may contribute to an increased risk of adverse events. In particular, patients with pre-existing renal, cardiovascular, or neurological conditions, may be more susceptible to systemic complications, including kidney injury, stroke, or cognitive decline [69]. Moreover, in the context of ROP, particular caution is warranted, as systemic VEGF suppression may theoretically interfere with physiological vascular and organ development [69]. Taken together, these findings suggest that the pharmacokinetic and pharmacodynamic profiles of intraocular anti-VEGF agents should be carefully considered in relation to potential systemic adverse effects [70].

Emerging Anti-VEGF Therapies

In addition to established agents, several novel anti-VEGF therapies have been developed to improve efficacy and reduce injection burden. A novel anti-VEGF agent developed for the management of nAMD has shown promising results, offering extended durability of effect alongside improvements in visual acuity when administered at 12-week intervals [71]. Brolucizumab, a humanized single-chain variable fragment (scFv) antibody targeting VEGF-A, differs structurally from conventional full-length IgG antibodies. Due to its smaller size, it penetrates retinal tissues more efficiently, resulting in enhanced local activity, prolonged therapeutic action, and a potentially lower incidence of systemic side effects. Laboratory studies have demonstrated that Brolucizumab possesses a markedly higher binding affinity for VEGF-A isoforms compared to Bevacizumab, and is capable of effectively blocking VEGF-A interactions with VEGFR-1 and VEGFR-2 at substantially lower concentrations than those required for Ranibizumab [72]. In 2022, Faricimab received approval as a new therapeutic option. It is a humanized, bispecific monoclonal IgG antibody designed to simultaneously inhibit VEGF-A and angiopoietin-2 (Ang-2), two key mediators involved in retinal vascular pathology [73]. Faricimab acts on dual pathways, interfering with mechanisms linked to neovascularization, inflammation, and vascular instability. Elevated levels of Ang-2, in particular, have been associated with endothelial dysfunction and pericyte loss under inflammatory conditions [74]. Phase 3 clinical trials have shown that Faricimab is non-inferior to Aflibercept in maintaining best corrected visual acuity and controlling neovascular activity in patients with nAMD [73]. What distinguishes Faricimab is not only its dual-target mechanism but also its favorable pharmacokinetic profile, which supports longer dosing intervals. Moreover, unlike some earlier agents, Faricimab has not been linked to major safety issues, reinforcing its potential as a durable and well-tolerated treatment option [75]. Continuous clinical monitoring

Table I Overview of Anti-VEGF Agents Currently Used in the Treatment of Neovascular Retinal Diseases

Drug	Structure	Molecular Targets	Molecular Weight	Main Indications	Key Pharmacological Features	Clinical Considerations
Aflibercept	Recombinant fusion protein (VEGFR-1[f] domain 2 + VEGFR-2 domain 3 + Fc of IgG1)	VEGF-A[e], VEGF-B, PlGF	~115 kDa	nAMD[b], DME[a], RVO[d]	High binding affinity; Fc-mediated systemic persistence; blocks multiple VEGF isoforms and PlGF[c]	Allows extended dosing (up to 12 weeks); detectable systemic exposure; caution in high-risk patients
Bevacizumab	Full-length humanized monoclonal IgG1 antibody	VEGF-A	~149 kDa	Off-label: nAMD, DME, RVO	Long systemic half-life; Fc-dependent recycling; prolonged circulating VEGF inhibition	Off-label in ophthalmology; higher systemic exposure; potential concern in patients with vascular comorbidities
Ranibizumab	Humanized monoclonal Fab fragment	VEGF-A	~48 kDa	nAMD, DME, RVO	Designed for intraocular use; high affinity; minimal circulating exposure; limited VEGF suppression; rapid systemic clearance	Minimal systemic absorption; lower risk of systemic adverse events; suitable for patients at higher risk
Brolucizumab	Humanized single-chain variable fragment (scFv)	VEGF-A	~26 kDa	nAMD	Smallest anti-VEGF agent; deep retinal penetration; prolonged intraocular activity	Effective at low concentrations; associated with intraocular inflammation and vasculitis
Faricimab	Humanized bispecific monoclonal IgG antibody	VEGF-A, Angiopoietin-2	~150 kDa	nAMD, DME	Dual-target mechanism; reduces neovascularization and inflammation; extended durability	Approved for extended dosing (up to 16 weeks); long-term systemic safety

[a]DME = diabetic macular edema

[b]nAMD = neovascular age-related macular degeneration

[c]PIGF = placental growth factor

[d]RVO = retinal vein occlusion

[e]VEGF = vascular endothelial growth factor

[f]VEGFR = vascular endothelial growth factor receptor

remains crucial to promptly detect and address potential adverse effects that may arise over time. In parallel with the anti-VEGF agents currently in use, several new therapeutic strategies are progressing through late-stage clinical trials. These include extended-release formulations and innovative drug delivery technologies designed to lessen the burden of frequent IVTs [76]. Additionally, gene therapy approaches, such as RGX-314 and Ixo-vec, designed to provide sustained VEGF suppression from a single administration, are showing promising results in early-phase trials, potentially representing a paradigm shift in the long-term management of retinal vascular diseases [77, 78].

Adverse Effects and Safety Considerations

Anti-VEGF therapies have importantly transformed the management of neovascular retinal diseases. However, their repeated use has been associated with potential adverse effects, including retinal atrophy and impaired neuroprotective mechanisms [79].

Ocular side effects are typically mild and may include subconjunctival hemorrhage [80], transient intraocular pressure elevation [81], vitreous opacities [82], intraocular inflammation such as uveitis and vitritis, and, less frequently, retinal detachment [76]. Nonetheless, rare but serious complications have been reported, including infectious endophthalmitis and sterile intraocular inflammation [83]. Although anti-VEGF drugs are administered locally via IVT, small quantities may enter systemic circulation, potentially impacting distant organs. These findings underscore the importance of strategies aimed at minimizing the adverse effects associated with anti-VEGF therapies.

NTs

The NT family is a group of structurally related proteins that play critical roles in neuronal survival, differentiation and development. NGF was the first NT identified by Rita Levi-Montalcini in the 1950s, when she observed that mouse sarcoma tissues were able to induce excessive nerve growth in chick embryos [84]. Besides NGF, the most extensively studied NTs include BDNF, Neurotrophin-3 (NT-3), and Neurotrophin-4 (NT-4). At the molecular level, NTs exert their effects through high-affinity binding to specific receptor tyrosine kinases: NGF primarily binds TrkA, BDNF and NT-4 bind TrkB, and NT-3 preferentially binds TrkC. In addition to these receptors, p75NTR, a member of the tumor necrosis factor (TNF) receptor superfamily, can bind all NTs with comparable affinity [85]. Only aspects of NT biology relevant to their therapeutic application in ocular diseases are discussed below.

Pro-forms and Mature Forms of NTs

As shown in Fig. 4, all NTs are initially synthesized as pre-pro-neurotrophin precursors. Within the endoplasmic reticulum (ER), the signal peptide is cleaved, resulting in the formation of pro-neurotrophins (pro-NTs). These pro-NTs can spontaneously form homodimers, which are then transported to the Golgi apparatus and subsequently to the trans-Golgi network (TGN), where they undergo proteolytic cleavage by resident protein convertases to produce their biologically active mature forms [86]. Mature NTs are then sorted into vesicles destined for constitutive secretion. Notably, the pro-NT forms can also be secreted into the extracellular space [87]. These precursor forms are now recognized as biologically active molecules capable of signaling through specific receptors [88]. NGF itself is initially synthesized as pre-pro-NGF and then as pro-NGF, which can be processed intracellularly or extracellularly to yield mature NGF [89–93]. Alternative splicing and post-translational modifications further contribute to the molecular heterogeneity of pro-NGF, influencing its stability and biological activity [94–96]. Increasing evidence indicates that pro-NGF and mature NGF exert distinct, and sometimes opposing, effects, highlighting the importance of their relative balance in physiological and pathological conditions [97, 98]. BDNF follows a similar maturation pathway, being synthesized as pro-BDNF and subsequently cleaved to mature BDNF by intracellular or extracellular proteases [99–106]. Both forms can be secreted and display different biological functions depending on receptor engagement and cellular context.

NTs Molecular Mechanism of Action

NGF and BDNF are key members of the NT family, exerting potent neurotrophic effects essential for the development, maintenance, and plasticity of the nervous system. Both factors support neuronal survival, differentiation, and synaptic function, and are also involved in modulating inflammatory responses and pain signaling pathways. NGF and BDNF exert their biological effects primarily through activation of TrkA and TrkB receptors, respectively (Fig. 4). Ligand binding induces receptor dimerization and autophosphorylation, leading to activation of downstream signaling pathways such as MAPK/ERK, PI3K/Akt, and PLCγ, which regulate multiple neuroprotective and plasticity-related processes [91, 107–112]. In parallel, NTs can also activate p75NTR, a receptor associated with signaling pathways that may promote apoptosis, synaptic pruning, or inflammatory responses, depending on ligand form and co-receptor availability [113, 114]. Notably, pro-NGF displays higher affinity for p75NTR and preferentially signals through a complex involving the co-receptor sortilin, which has been implicated in neurodegeneration and synaptic dysfunction

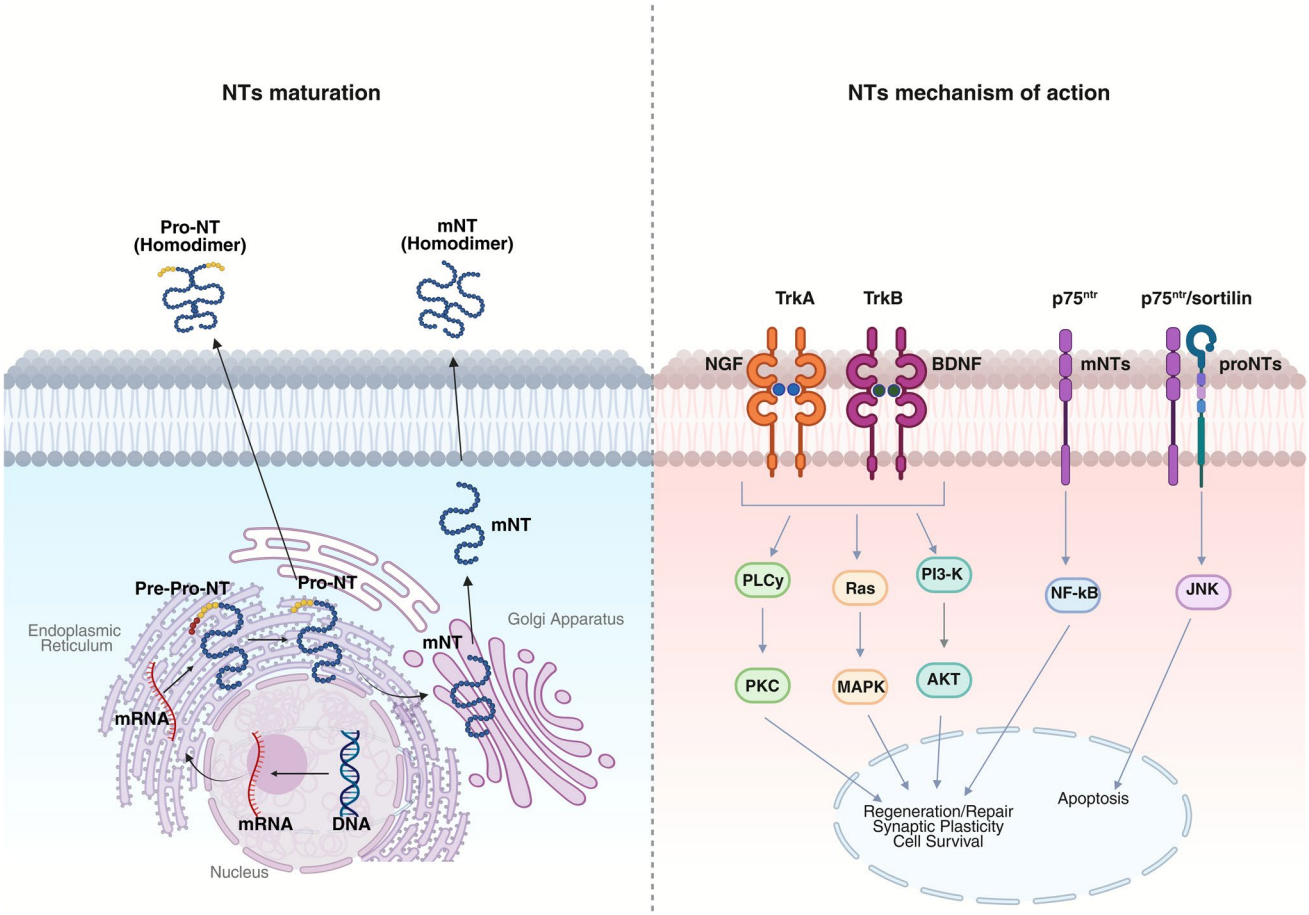

Fig. 4 This image, created with BioRender.com, illustrates the maturation process and mechanisms of action of neurotrophins (NTs). On the left, the NT biosynthesis pathway is depicted, beginning in the nucleus with DNA transcription into mRNA, followed by translation of the pre-pro-NT in the endoplasmic reticulum. The precursor then undergoes proteolytic cleavage to form the pro-NT, and subsequently the mature NT (mNT), which is processed in the Golgi apparatus before being secreted as a homodimer. On the right, the mechanisms of action of NTs are shown. Mature NTs (such as NGF and BDNF) bind to specific tropomyosin receptor kinases (TrkA, TrkB), activating intracellular signaling cascades including PLCγ/PKC, Ras/MAPK, and PI3K/AKT pathways, leading to cell survival, regeneration, synaptic plasticity, and repair. In contrast, pro-NTs bind with high affinity to the p75NTR receptor, often in complex with sortilin, activating the JNK pathway and promoting apoptosis. Mature NTs can also bind to p75NTR, but with lower affinity, leading in some contexts to NF-κB pathway activation and alternative cellular responses.

[98, 115–120]. Similar dual signaling properties characterize BDNF biology. While mature BDNF promotes trophic and plasticity-enhancing effects through TrkB, proBDNF preferentially binds p75NTR and has been associated with pro-apoptotic signaling and synapse elimination [121–124].

NTs and RNVU

NGF in RNVU

Neurotrophic factors are necessary for the maintenance of RNVU homeostasis and are locally synthesized by both retinal neurons and glial cells [125, 126]. Immunohistochemical analyses in rat models have demonstrated widespread expression of NGF throughout the retinal layers, with the highest levels detected in RPE cells, RGCs, and Müller glia [127]. NGF receptors are also differentially expressed across retinal cell types: the high-affinity receptor TrkA is primarily localized to NGF-responsive neurons, whereas the low-affinity receptor p75NTR is predominantly found in glial cells [128]. Similarly, pro-NGF has been observed throughout the retina in animal models, including the RPE, photoreceptor outer segments, all nuclear and plexiform layers, RGC layer, microglia, and Müller cells [129]. In pathological contexts such as retinal degenerative diseases, a marked upregulation of both pro-NGF and p75NTR has been reported, along with a reduction in mature NGF levels. In DR, for example, reduced NGF availability has been associated with photoreceptor degeneration. Moreover, pathological conditions such as ischemia and hyperglycemia increase peroxynitrite formation, inhibiting matrix metalloproteinase-7 and impairing pro-NGF cleavage, which leads to its accumulation in

the RNVU [130]. Beyond its neurotrophic role in supporting neuronal and glial survival, NGF also contributes to the development, maintenance, and regeneration of retinal microvascular cells [19]. In experimental DR models, NGF protects pericytes and limits the formation of non-perfused capillaries, primarily through TrkA-mediated PI3K/Akt signaling [131, 132]. Conversely, activation of the pro-NGF/p75NTR axis in DR models promotes pericyte apoptosis, increases the release of inflammatory cytokines, and contributes to the breakdown of the BRB [133]. These findings highlight the critical importance of maintaining a proper NGF/pro-NGF balance to preserve retinal homeostasis and vascular integrity.

BDNF in RNVU

BDNF is also essential for retinal integrity, particularly through its support of RGC survival and its regulation of neurovascular dynamics [134]. Dysregulation of BDNF expression has been implicated in the progression of several retinal pathologies, where its deficiency may contribute to neuronal loss and vascular impairment. For instance, in patients with AMD, it has been demonstrated that the concentration of BDNF in the aqueous humor decreases, which may be responsible for the thinning of outer nuclear layer due to the inefficient protective effect on photoreceptors [135]. As observed for pro-NGF, elevated levels of pro-BDNF have been reported in degenerative retinal conditions, indicating a detrimental shift in the NT signaling balance [136]. Moreover, emerging evidence shows that Müller glia contributes markedly to BDNF production, particularly under hypoxic or hyperglycemic stress, in which it supports glial survival via PI3K/Akt and MAPK/ERK signaling [137]. BDNF exhibits notable anti-inflammatory properties, reducing pro-inflammatory cytokines production and inhibiting microglial overactivation, thereby protecting retinal tissue from inflammation-driven neurodegeneration and vascular damage [138, 139]. Beyond its neuroprotective effects, BDNF helps maintain the BRB by stabilizing endothelial cells and regulating tight junction proteins, such as zonula occludens-1 and occludin, which control vascular permeability and limit fluid accumulation, particularly in DME [140].

Therapeutic Perspectives

NGF and BDNF influence structural and functional changes in the RNVU, particularly by protecting retinal neurons and glial cells from early dysfunction that often precedes vascular defects. These observations provide a rationale for developing novel NT-based therapies. Notably, Cenegermin, a recombinant human NGF, is currently the only NGF-based drug approved for clinical use, specifically for the treatment of neurotrophic keratitis [141]. Although its application is limited to the cornea, its approval highlights the therapeutic potential of NGF in ocular tissues and encourages further investigation into its possible use in retinal neuroprotection, potentially preventing downstream vascular complications.

VEGF-A and NTs in RNVU

VEGF-A and NGF

Building on the neuroprotective roles of NTs, recent studies have highlighted their complex interplay with VEGF-A in the retina. NGF has been shown to induce VEGF-A expression in multiple retinal cell populations, including Müller cells [142, 143]. Specifically, NGF promotes VEGF-A expression and secretion in Müller cells through the activation of PI3K/AKT and ERK1/2 signaling pathways [144] and stimulates Müller cell proliferation in a time-dependent manner via activation of the TrkA receptor. Inhibition of TrkA abolishes NGF-driven VEGF-A upregulation, confirming a receptor-dependent mechanism. Together, these findings indicate that NGF promotes retinal angiogenesis by both enhancing VEGF-A expression and activating Müller cell proliferation [144]. Dysregulation in the synthesis of VEGF-A and NGF, along with alterations in the expression or activation of their respective receptors, has been implicated in retinal degenerative processes. These changes impact both vascular and neuronal components of the retina, mirroring the pathological mechanisms observed in DR [145]. In diabetic rat models, VEGF-A isoforms are differentially regulated: VEGF-A121 is markedly upregulated under diabetic conditions but nearly absent in control and NGF-treated retinas, whereas exogenous NGF selectively increases VEGF-A165 expression, suggesting that NGF modulates not only the overall VEGF-A levels, but also isoform-specific expression patterns [7]. Moreover, recent studies on mouse models of DR have demonstrated that topical NGF is able to reduce RGC loss, which characterizes the early stages of the disease, and to prevent the onset of vascular damage [146].

VEGF-A and BDNF

The interplay between VEGF-A and BDNF has been extensively studied in the context of retinal diseases. BDNF levels are dysregulated in several ocular pathologies and are therefore considered potential biomarkers for early disease detection. For example, patients with AMD exhibit altered serum concentrations of BDNF compared to healthy individuals [147]. Similarly, clinical studies have reported significantly reduced serum BDNF levels in patients with both non-proliferative and proliferative DR [148]. In the context

of DR, reduced BDNF levels are commonly associated with elevated VEGF-A expression and pathological neovascularization. Under hyperglycemic conditions, VEGF-A has been shown to suppress BDNF expression, leading to increased NF-κB activation and cytokines production in Müller cells. Conversely, anti-VEGF treatment restores BDNF levels and attenuates inflammatory signaling [149]. This mechanism highlights not only the anti-inflammatory potential of BDNF [150], but also offers a possible explanation for the clinical efficacy of anti-VEGF therapies in DME, even in the absence of neovascularization. Therapeutic administration of exogenous BDNF in the early stages of DR has shown promising effects in downregulating VEGF-A, protecting the BRB, and preserving neuronal integrity. However, these effects are dose-dependent, as moderate BDNF supplementation exerts neuroprotective and anti-angiogenic effects, whereas higher concentrations may paradoxically promote inflammation and angiogenesis [149]. Consequently, optimizing BDNF therapy requires careful dose calibration to maximize neuroprotective benefits while minimizing potential adverse inflammatory responses. Adding to this complexity, more recent studies have highlighted the pivotal role of VEGFR-2 signaling in Müller glial cells as a key modulator of BDNF expression under diabetic conditions [151]. Furthermore, VEGF-A itself has been shown to upregulate BDNF via the activation of AKT/ERK pathways in hyperglycemic Müller cells [134]. These observations underscore the need to investigate the interaction between VEGF-A and BDNF with consideration for cellular context and tissue specificity. Notably, while anti-VEGF therapy normalizes BDNF signaling in diabetic models, VEGF-A blockade in non-diabetic retinas has been shown to impair NT pathways, with reduced TrkB activation and increased pro-BDNF accumulation [7]. This apparent discrepancy may reflect the dual role of VEGF-A, which is deleterious when overexpressed in DR but physiologically neuroprotective under normal conditions.

NGF/BDNF & VEGF-A: A Hypothesized Neuroprotective and Anti-Angiogenic Synergy within the RNVU

Emerging evidence indicates that disruption of the RNVU plays a central role in the pathogenesis of several sight-threatening diseases, including DR, AMD, ROP, and glaucoma [17, 18]. Historically, these conditions were attributed primarily to vascular abnormalities; however, accumulating data reveal that neurodegeneration often precedes vascular compromise [61]. Although anti-VEGF therapies have revolutionized the management of neovascular retinal diseases, their prolonged use has been associated with adverse outcomes such as retinal atrophy and diminished neuroprotection [17, 152]. The mechanisms underpinning VEGF's dual roles are still not fully understood, particularly regarding its splice isoforms, such as the angiogenic VEGF-Axxxa and the anti-angiogenic VEGF-Axxxb. Recent studies suggest that the balance between these isoforms could influence both physiological and pathological states of the RNVU, warranting deeper investigation into their differential expression in ocular tissues. As reported in paragraphs 5.1 and 5.2, several studies have demonstrated the efficacy of NGF and BDNF ocular treatments to counteract the progression of retinal neurodegeneration, also by modulating vascular endothelium and inflammation through their interaction with VEGF-A. Moreover, as mentioned, our recent study demonstrated that ocular administration of NGF affects the VEGF-A isoforms expression, as well as the VEGFR-2, in the retina of diabetic rats, further supporting the concept that this NT might contribute, directly or indirectly, to rebalancing diabetes-induced RNVU alterations [7]. However, these interactions remain incompletely characterized, especially within the highly specialized microenvironment of the RNVU. Our preliminary investigations also suggest a correlation between the expression of NTs and their receptors with the distribution of VEGF-A165a and VEGF-A165b isoforms in both healthy and retinal degeneration conditions (unpublished observations), thus contributing to the concept that a bidirectional interaction between NTs and VEGF-A might favor neuroprotective mechanisms and help maintain the structural and functional integrity of the RNVU. Given the multiple cell type targets of NTs in the eye, and the interplay between NGF and BDNF in the regulation of the visual system, a perspective model of NTs and VEGF-A roles and interactions in RNVU is illustrated in Fig. 5.

Based on this model, combined NGF/BDNF and anti-VEGF therapeutic strategies may offer superior efficacy in the treatment of retinal degeneration, as previously suggested [146]. Such an approach could also mitigate the long-term adverse effects associated with chronic VEGF-A suppression by contrasting the pro-NGF/pro-BDNF activation of pro-inflammatory and pro-apoptotic pathways. In particular, the possibility of selectively targeting specific VEGF-A isoforms with minimal impact on neuroprotective pathways could pave the way for refined treatment strategies. Such targeted modulation would allow for preservation of RNVU homeostasis while avoiding the neurotoxic effects observed with broad-spectrum anti-VEGF agents. Incorporating neurotrophic support into therapeutic regimens could also reduce treatment burden and dependency on repeated anti-VEGF IVT, thus highly contributing to the success of the treatment by decreasing patient discomfort.

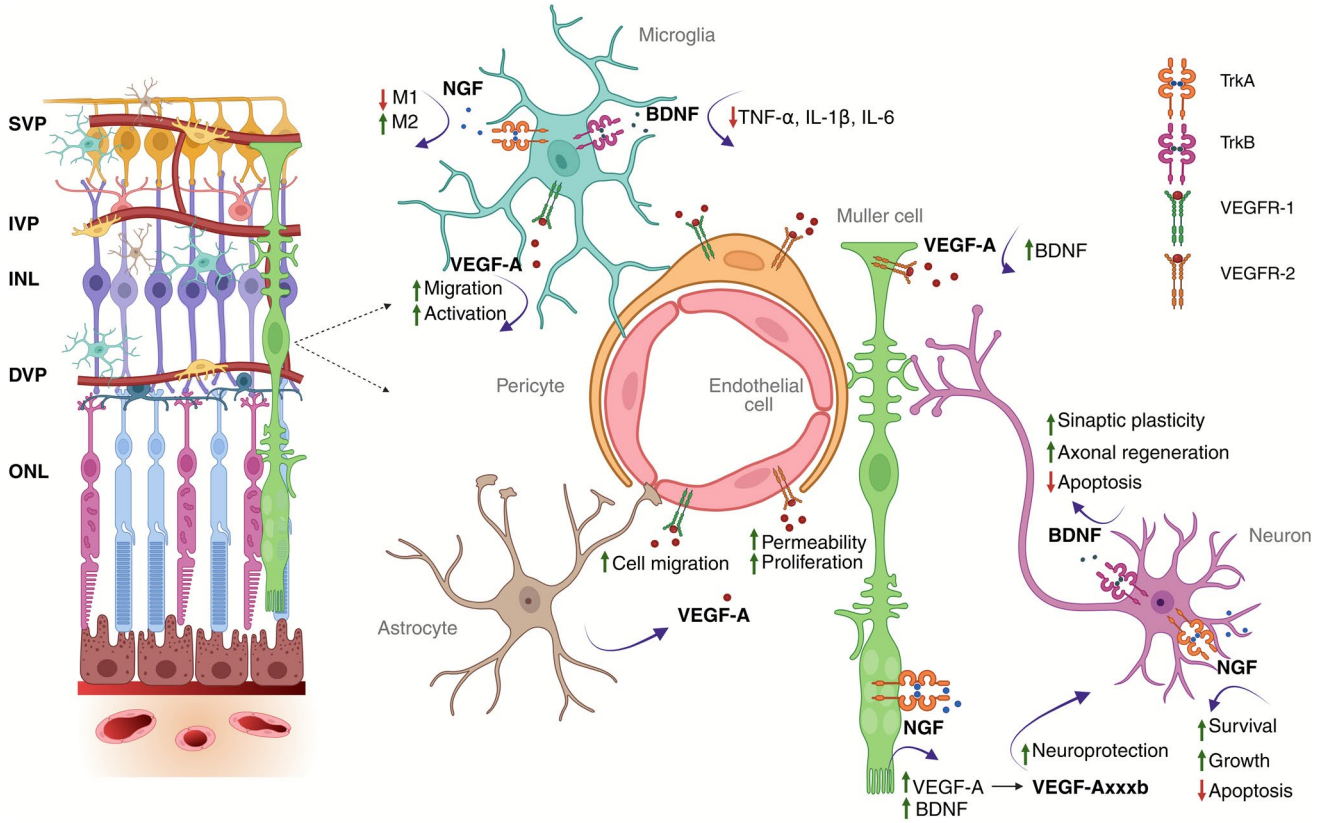

Fig. 5 This image, created with BioRender.com, provides an overview of the cellular composition of the retinal neurovascular unit (RNVU) and highlights the complex interactions among vascular endothelial growth factor A (VEGF-A), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF). The molecular crosstalk between these three factors is illustrated across the main cellular components of the RNVU, including neurons, Müller cells, astrocytes, microglia, pericytes, and endothelial cells. VEGF-A promotes endothelial cell proliferation and permeability [44], stimulates microglial activation and migration, and also regulates the release of BDNF from Müller cells [134]. NGF supports neuronal survival and growth, modulates apoptosis, and influences Müller cell activity by promoting the release of both BDNF and VEGF-A [8, 142], with particular effects on specific VEGF-A isoforms [7]. BDNF, in turn, enhances synaptic plasticity, axonal regeneration, and neuroprotection and contributes to the regulation of microglial cytokine production [150]. The figure underscores how the fine-tuned balance between VEGF-A, NGF, and BDNF is essential for maintaining RNVU homeostasis.

Conclusion

An integrated, neurovascular-centered approach represents a promising frontier in the treatment of retinal diseases. Rather than focusing exclusively on angiogenesis inhibition, future therapies may benefit from a dual-modality strategy that combines controlled modulation of VEGF-A isoforms with the administration of neurotrophic factors like NGF and BDNF. Despite encouraging preclinical findings, clinical translation remains in its infancy. Additional studies are necessary to define the temporal dynamics of neurovascular alterations in retinal pathologies and to evaluate the safety, efficacy, and feasibility of such combinatory interventions in human subjects. A deeper understanding of the VEGF-A/NTs interplay, particularly in relation to specific isoforms and their receptor signaling cascades, could ultimately redefine therapeutic paradigms and offer more balanced, long-term neurovascular protection in retinal disease management.

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Declarations

Conflict of interest The authors declare no competing interests.

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