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Review

The NK-1 Receptor Signaling: Distribution and Functional Relevance in the Eye

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Abstract: Neurokinin-1 receptor (NK1R) signaling pathways play a crucial role in a number of biological processes in the eye. Specifically, in the ocular surface, their activity modulates epithelial integrity, inflammation, and generation of pain, while they have a role in visual processing in the retina. The NK1R is broadly expressed in the eye, in both ocular and non-ocular cells, such as leukocytes and neurons. In this review, we will discuss the roles of neurokinin-1 receptors and substance P (SP) in the physiopathology of eye disorders. Finally, we will review and highlight the therapeutic benefits of NK1R antagonists in the treatment of ocular diseases.

Keywords: inflammation; corneal nerves; neurokinin-1 receptor; substance P; wound healing; neurokinin-1 receptor antagonist; corneal epithelium

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1. Introduction

1.1. The Tachykinin Peptide Family and Its Receptors

The tachykinin peptide family is one of the largest peptide families in mammals, which regulates key biological processes, such as wound healing and inflammation. The tachykinin family consists of three genes and multiple neuropeptides. Neurokinin A (NKA), neuropeptide K (NPK), neuropeptide gamma (NPγ), and SP are expressed by the tachykinin precursor 1 (TAC1) gene through alternative splicing. Neurokinin B (NKB) is encoded by TAC3 gene. TAC4 gene expresses both hemokinin-1 (HK-1) and endokinins [1–3].

Tachykinin receptors genes (TACR1, TACR2, and TACR3) encode tachykinin 1 (NK1R), 2 (NK2R), and 3 (NK3R), respectively [4]. SP and HK-1 bind with high affinity to NK1R, NKA to NK2R, and NKB to NK3R. NKA and NKB bind to NK1R with low affinity (almost 100 times lower than SP). NKB and SP have a low affinity for NK2R, while NKA and SP exhibit low affinity for NK3R [5,6].

The NK1R is widely expressed in the eye, including ocular (corneal and retinal cells) and non-ocular cells (endothelial cells, leukocytes, and neurons) [3,7].

1.2. NK1R Structure

NK1R is a G-protein coupled receptor with extracellular glycosylation sites. It is located on the cell membrane and it contains 1221 nucleotides and 5 exons. It exists in two isoforms: one which is full length, and the other which is truncated and generated through alternative splicing [8–10].

Both the truncated and the full-length NK1R are embedded seven-transmembrane receptors containing extracellular amino-terminal domain with glycosylation sites and an intracellular carboxy-terminal domain. Both receptors share three extracellular (E1, E2, and E3), and three intracellular loops (C1, C2, and C3), whereas the C4 intracellular loop is different. The truncated form lacks the intracellular Ser/Thr residues in the C4 loop. That leads to the absence of interaction with β-arrestin and an impaired interaction with G-proteins [1,9,11,12].

The full-length form contains 407 amino acids, whereas the truncated form contains only 311. Specifically, the truncated form lacks 96 amino acids in its C-terminal site, due to the presence of a premature stop codon before exon-5. The two types of NK1R are also different in term of SP affinity, the full-length form being ten times more affine to SP, despite the fact that the SP binding domain is similar in both isoforms [7,11,13]. In fact, nanomolar concentrations of SP are sufficient to activate the full length NK1R, whereas micromolar concentrations of SP are required to activate truncated-NK1R [13].

The short carboxyl tail of the truncated form leads to partially active and less efficient SP-mediated NK1R signaling. This is mediated by the interaction with G-proteins and downstream pathways [13,14]. Specifically, the full-length isoform via SP rapidly activates the downstream RAS-RAF-MEK-ERK pathway and NF-κB. That increases IL-8 mRNA expression and intracellular Ca^{2+} concentrations. However, the NK1R truncated form is less effective in increasing IL-8 and intracellular calcium levels than the full form. Moreover, the activation of the truncated form has no effect on NF-κB expression. Finally, the truncated NK1R induces protein kinase C (PKC) downregulation and delays the activation of the RAS-RAF-MEK-ERK signaling pathway [12,13,15].

In addition to the effects of the carboxyl tail, the presence of glycosylation also impacts NK1R function. Indeed, the glycosylated NK1R is more stable probably because it favors NK1R anchoring to the cell membrane [16].

1.3. NK1R Signaling Activity

NK1R, a member of the G protein-coupled receptors superfamily regulates multiple signaling pathways in the eye. Substance P (SP) is a neuropeptide abundantly expressed on the ocular surface, including cornea and the retina [17–19], and has the highest affinity for NK1R. Dissociation of SP from NK1R is mediated by metalloproteases [20–23]. SP-NK1R interaction leads to increased cell proliferation and/or migration of corneal epithelial, endothelial cells, keratocytes, and leukocytes. Moreover, it stimulates corneal and retinal neurogenesis [3,24,25]. The binding of SP to the NK1R activates G proteins subunits (G-alpha, G-beta, and G-gamma), and leads to dissociation of the GDP/Gα subunit complex. The dissociated G-beta and G-gamma subunits remain bound to the cell membrane, whereas the GTP/Gα complex further leads to the activation of phospholipase C (PLC) and the production of second messengers [26,27]. Different active Gα subunits transmit the signals from the NK1R ($G_{q/11}$, G_s, $G_{12/13}$, and G_i) [28].

The $G_{q/11}$ subunit is involved in the regulation of the MAPK-ERK pathway, leading to proliferation in neural progenitor cells [29]. The GTP/$G_{q/11}$ complex activates PLC, which stimulates the hydrolysis of phospholipids and the production of second messengers, such as DAG (diacylglycerol) and IP3 (inositol 1,4,5-triphosphate) [30]. DAG activates protein kinase C leading to an increase in intracellular Ca^{2+} concentrations, which is followed by the activation of phosphoinositol 3-kinase (PI3K), Akt serine/threonine kinase, and NF-κB. This leads to the synthesis of cytokines interleukin-1 and -8 (IL-1 and IL-8) [31,32]. Besides, the increased Ca^{2+} and DAG concentrations stimulate the phosphorylation of Ras/Raf proteins, which also promote cell proliferation and differentiation [33,34]. On the other hand, IP3 binds to inositol 1,4,5-trisphosphate receptors (IP3R) on the endoplasmic reticulum leading to increased Ca^{2+} concentrations in the cytosol (Figure 1) [35,36].

The GTP/$G_{12/13}$ complex induces cytoskeletal remodeling through the Rock/Rho signaling pathway and leads to cell migration [33,37]. The $G_{12/13}$ subunit leads to cell invasion and metastasis and has been described in breast and prostate cancer cell lines through the activation of the RhoA family [38,39].

The GTP/Gi complex activates the Src, which leads to the transactivation of the tropomyosin receptor kinases and promotes cell proliferation [40,41]. Previously, the Gi subunit has been reported to suppress cyclic AMP in vitro and activate directly SRC in murine fibroblast cells [42,43].

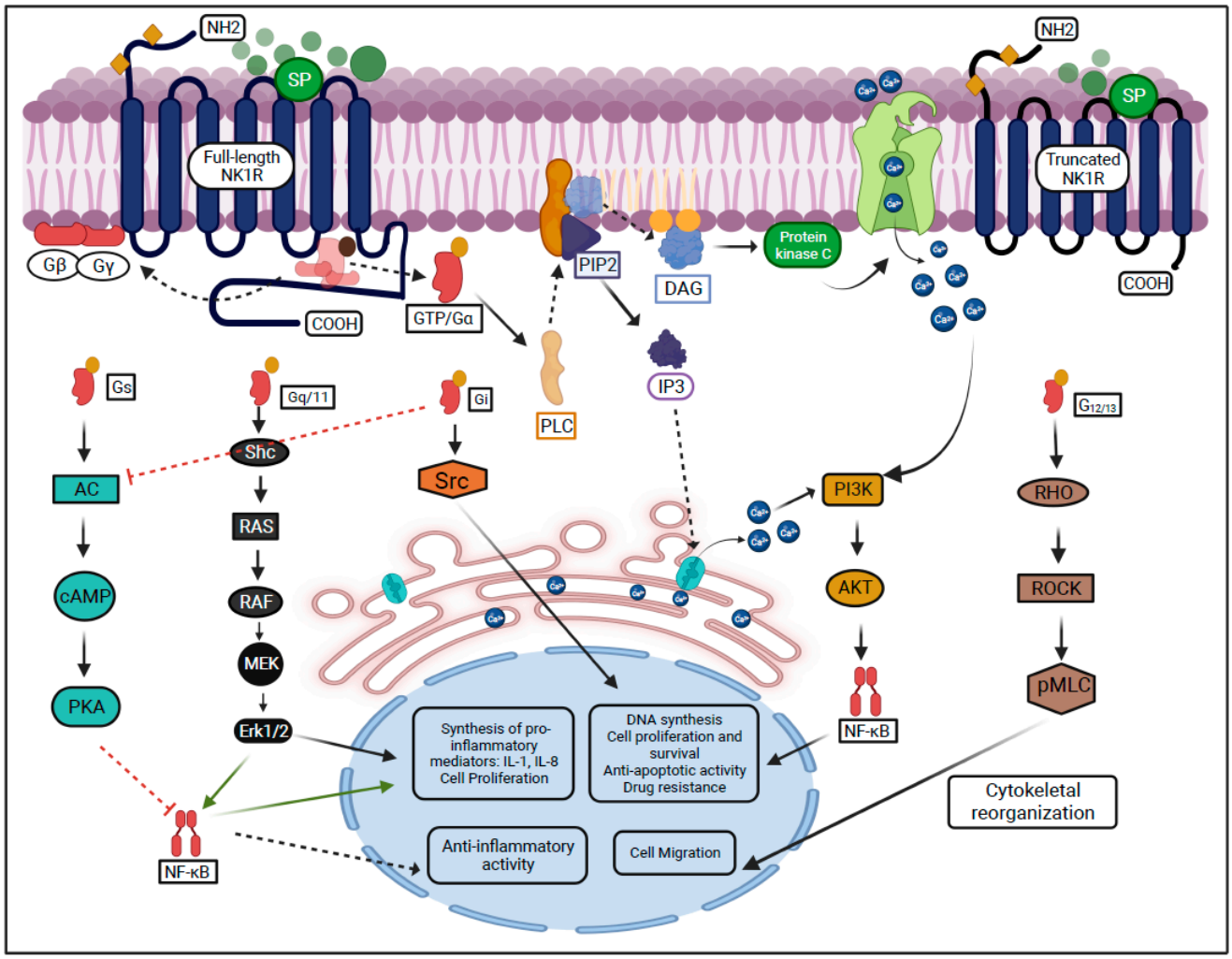

Figure 1. SP-mediated activation of NK1R and its downstream signaling pathways.

The Gs subunit is encoded by GNAS (guanine nucleotide binding protein) abundantly found in neuron precursors [31,44,45]. It has been reported that the Gs suppresses tumor progression in the medulloblastoma cell line and inhibits T lymphocyte proliferation in S49 lymphoma cells [46,47].

The activation of NK1R by SP is followed by the initiation of a molecular mechanisms ultimately leading to the onset of inflammation. Specifically, the GTP/Gs complex stimulates adenylyl cyclase to promote the synthesis of other second messengers, cAMP, which further induce activation of protein kinases, modulate the function of sodium and calcium channels and inhibit NF-κB [9,27,48,49]. The activation of protein kinase C is mediated by arachidonic acids, and favors the onset of neurogenic inflammation. Arachidonic acids are generated through hydrolysis of phospholipids promoted by phospholipase A_2 [50–52]. Finally, the increased intracellular Ca^{2+} concentrations lead to the activation of mitogen-activated-protein kinases (MEK/ERK), which promote cell proliferation, migration, leukocyte activation, and the synthesis of IL-1 and IL-8 [27,40].

1.4. Distribution of NK1R in the Eye

NK1R is broadly expressed in the cornea, iris, retina and choroid, conjunctiva, optic nerve, and lacrimal gland (Figure 2) [3,53–55].

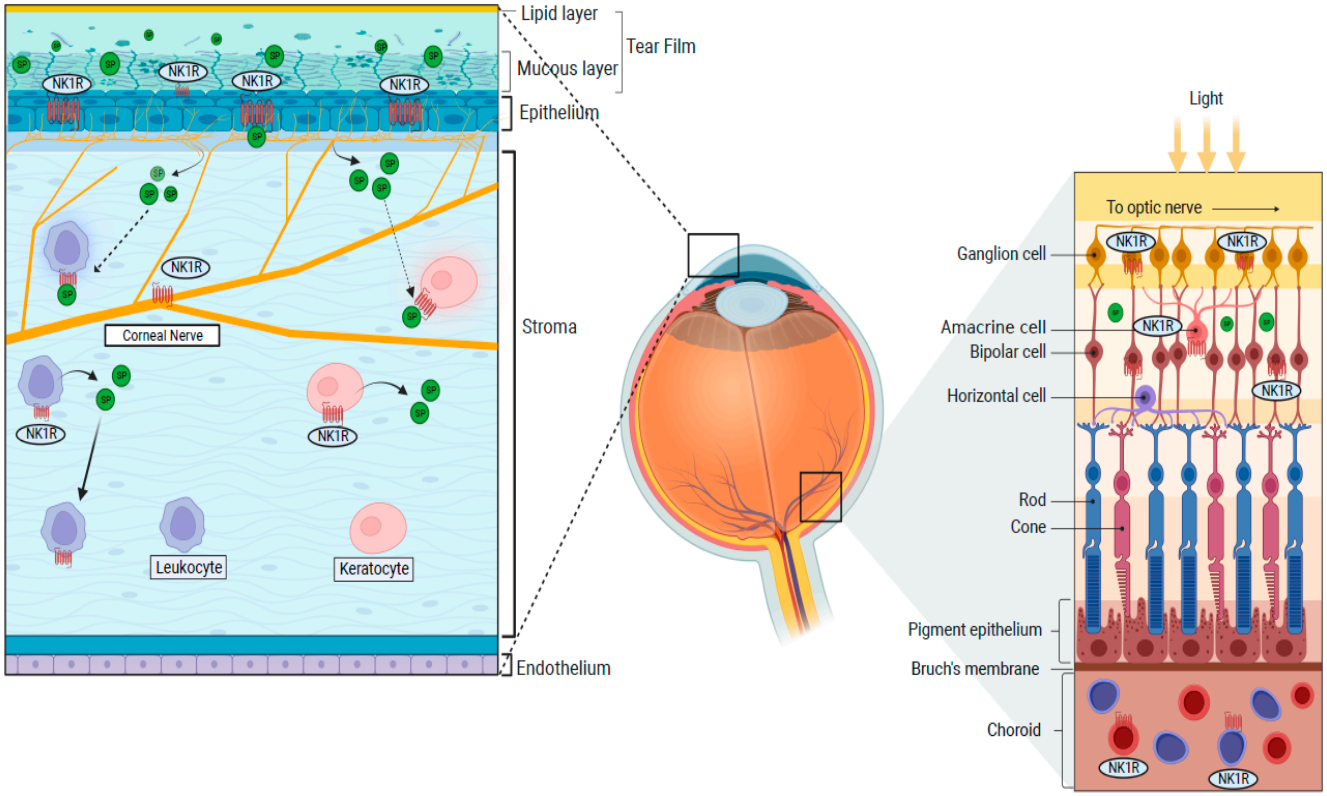

Figure 2. Distributions of the NK1R in the cornea and the retina.

In the cornea, the epithelium, keratocytes, and corneal nerves express the NK1R [18,19,53]. Moreover, NK1R is expressed on limbal vasculature (on endothelial cells), where it promotes vascular permeability and lymphangiogenesis [3,56,57]. NK1R is also expressed on the iris sphincter smooth muscle fibers and vascular endothelial cells in the choroid [19,54]. The lacrimal gland also expresses NK1R, while the tear fluid contains large amounts of SP, both in mice and humans [58–61]. Finally, non-neural cells populating the eye, such as immune cells (T-cells, dendritic cells, lymphocytes, and monocytes), also show NK1R expression [3,62,63]. SP-mediated activation of the NK1 receptor induces different effects in different tissues. For instance, it modulates contraction in the iris sphincter muscle [64].

Multiple types of retinal cells express the NK1R: specifically, bipolar, amacrine, ganglion cells, and neurons located in the interplexifom layer. Interestingly, the expression profiles and distribution of NK-1 receptors in the retinal subpopulations (cone bipolar, dopaminergic amacrine, and cholinergic cells) display significant differences among mammals [65,66]. In addition, SP-mediated NK1R activation appears to be specific of certain development stages. For instance, activation of the NK1R in amacrine cholinergic cells lead to increased intracellular Ca^{2+} in the young rabbit retina, where it also contributes to the development of retinal neurons. In the adult rabbit retina, instead, NK1R activation leads to the modulation of visual signaling in the cone bipolar and dopaminergic amacrine cells. However, it needs further elucidation developmentally in human retinal subpopulations [65,67].

It should be noted, however, that the expression profiles and distribution of the full-length versus truncated form of NK1R remains unknown in the eye.

1.5. NK1R in Wound Healing, Inflammation, and Pain

Activation of the NK1R has been specifically studied in the pathophysiology of corneal epithelial wound healing, ocular surface inflammation, and pain [18,61,68–70].

1.5.1. NK1R and Corneal Epithelial Wound Healing

The corneal epithelium is frequently exposed to injuries because it is located on the outer surface of the eye, which can result in severe visual impairment [3,71,72]. Moreover, damage and/or activation of corneal nerves—which are distributed on the epithelial surface—result in the release of large amounts of SP. Substance P can then bind to the NK1R abundantly expressed on the corneal epithelium and nerves [3,73,74].

Indeed, it has long been known that NK1R activation is instrumental to the maintenance of an intact corneal epithelium [71,73,74]. For instance, it has been reported that knocking down NK1R in murine models is associated with excessive desquamation and increased epithelial cell proliferation, reduced tear secretion, and corneal nerve and dendritic cell density. Moreover, absence of NK1R appears to be associated with earlier development herpes stromal keratitis (HSV) in experimental models [55,61]. On the other hand, *TAC1KO* (i.e., SP-KO) young mice did not show any obvious alteration of the corneal epithelium or nerve density, while it seems that accelerated neuropathy may develop during aging [75]. Interestingly, administration of a SP-derived peptide was effective in the treatment of neurotrophic keratopathy, a condition where impaired epithelial cell proliferation and migration is well acknowledged [76–79]. Mechanistically, it has been reported that the activation of G-protein subunits and tyrosine kinase pathways are responsible for the increased epithelial cell proliferation/migration following NK1R activation [80–82]. On a different note, blocking the NK1R pharmacologically improved epithelial wound healing in an alkali burn model. It should be noted that the apparent discrepancy between these studies could be explained by the different models used, the alkali burn being associated with intense inflammation [3,71]. It is well possible that while SP is beneficial up to a certain amount, its favorable effects are overcome by massive inflammation associated with its excessive release. Excessively increased SP levels can lead to stem cell exhaustion and acceleration in the senescence of the corneal epithelium. However, it was demonstrated that treatment with NK1R antagonist fosaprepitant significantly ameliorated clinical signs of LSCD [83].

The activation of NK1R not only impacts the corneal epithelium, but also the stroma. In fact, it induces migration of keratocytes through activation of the phosphatidylinositol (PI3Ks) and Rac1/RhoA, resulting in improved wound healing [3,25,84].

The role of NK1R and its ligand SP in the maintenance of an intact corneal epithelium is epitomized by diabetic keratopathy, a form of neurotrophic keratopathy associated to sensory neuropathy and epithelial instability and/or disruption. SP levels are reduced in patients with type 1 diabetes, although it is not clear if this is simply a reflection of reduced corneal nerve density, which is commonly observed in these subjects [85–87].

1.5.2. NK1R and Ocular Inflammation

Activation of NK1R has a cardinal role in the modulation on multiple layers of the inflammatory response. In the cornea, the inflammatory response can be initiated by the release of the principal NK1R ligand, SP, following damage and/or stimulation of corneal nerves (neurogenic inflammation) (Figure 3) [3,71,88–90]. The NK1R is expressed by virtually all the key players of the inflammatory response: vascular endothelial cells, leukocytes, and nerves. Specifically, proliferation and migration of lymphatic endothelial cells are achieved through regulation of the VEGFR3 expression following SP-mediated NK1R activation and facilitated by the recruitment of neutrophils with angiogenic activity [57,91–93].

Besides promoting leukocyte influx into the cornea, SP also shifts the leukocyte phenotypes towards an "activated" mode. In fact, macrophages, dendritic cells, neutrophils, and lymphocytes all express the NK1R. Activation of this receptor promotes the production of pro-inflammatory cytokines, such as MIP-1B (macrophage inflammatory protein-1 beta), IL-6, TNF-α (tumor necrosis factor-α), and IL-8 from macrophages, dendritic cells, and lymphocytes [19,61,94]. Those cytokines have been described in ocular inflammation, including uveitis, glaucoma, retinal (macular) edema, and neovascularization. Most of activities of cytokines are mediated by NF-κB [95–97].

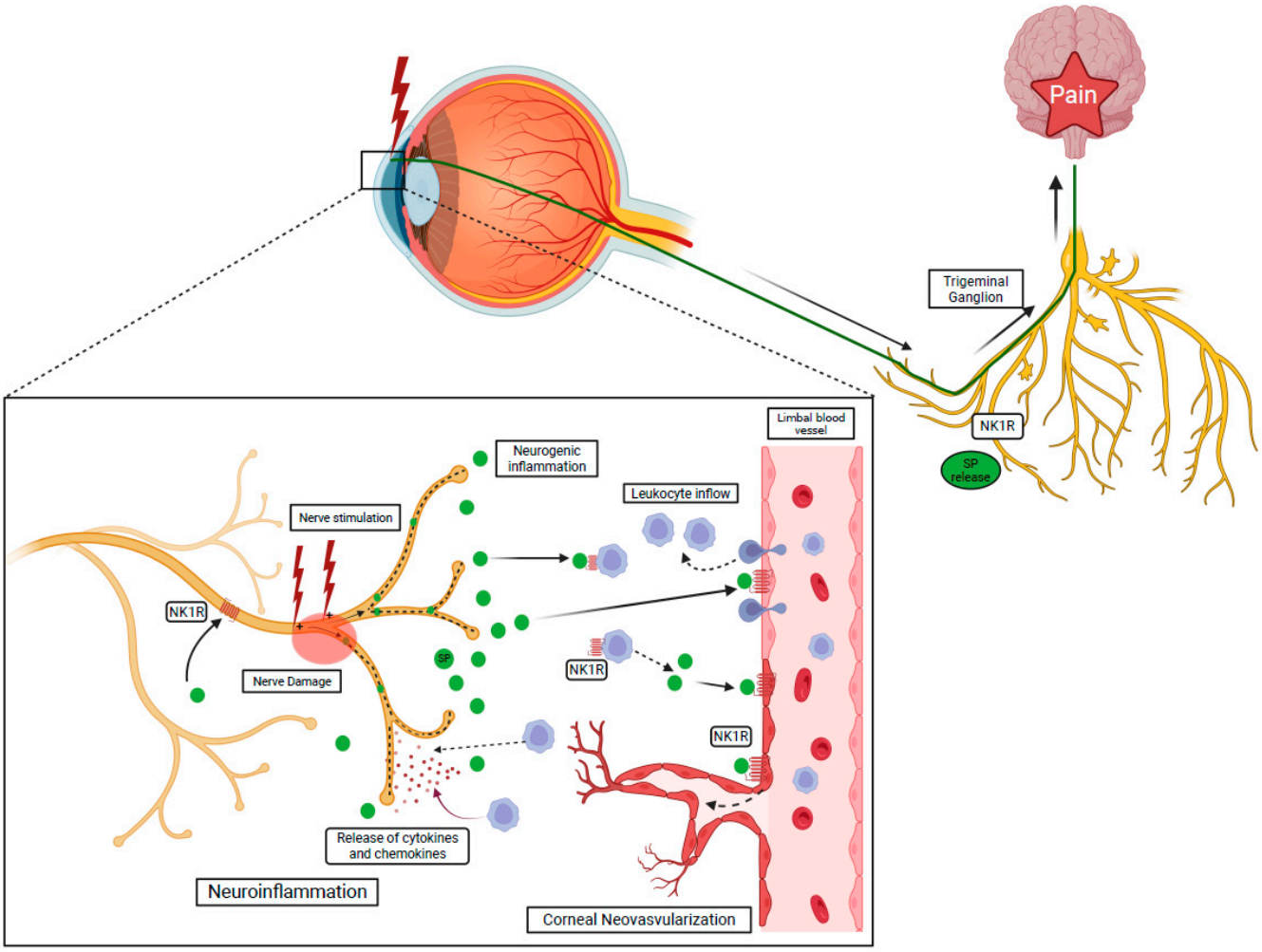

Figure 3. NK1R activation via SP induces the recruitment of the leukocyte through the breakdown of the blood–tissue barrier and initiates neurogenic inflammation. Activated leukocytes release cytokines and chemokines leading to nerve damage, called neuroinflammation.

Recognition of pathogens and their clearance is accomplished by ocular and non-ocular cells including surface epithelia, keratocytes, and antigen-presenting cells (APCs) [9,98,99]. Corneal epithelial cells and keratocytes activate immune cells through the secretion of cytokines, including IL-1α and TNF-α [100]. Besides, corneal nerves are involved in the protection of the ocular surface through the secretion of SP, which induces neutrophil influx [101]. On the other hand, APCs residing in the peripheral cornea recognize pathogens through toll-like receptors (TLRs) [99,102]. For instance, dendritic cells (DC) express the NK1R on their membrane and its activation is associated with prolonged DC survival and type 1 immune response [102,103].

While the neuroinflammatory response is originally designed to achieve rapid pathogen clearance and wound healing, its derangement/prolonged activation can have a role in highly prevalent ocular disorders, such as dry eye disease [104–106] and chronic pain [107,108].

Corneal neovascularization is a leading cause of blindness worldwide [109–111]. It was shown that patients affected with corneal neovascularization express higher levels of SP in the tear fluid [90] and that NK1R blockade impairs corneal hem- and lymphangiogenesis in pre-clinical models [57,71].

Moreover, experimental evidence shows that SP, acting through the NK1R, abolishes the ocular immune privilege through modulation of pro-inflammatory mediators after

retinal laser burn (RLB) [112], and that pharmacological blockade of NK1R results in reduced corneal graft rejection [113–115].

Finally, SP has a role in the progression of pterygium, a form of conjunctival degeneration [61,116]. Specifically, the NK1R promotes the mobilization of fibroblast and vascular endothelial cells from the bulbar conjunctiva towards the cornea and favors pterygium progression [61,117].

Age-related macular degeneration (AMD) is a degenerative disorder of the macula that affects elderly people, leading to severe visual impairment. There are two different forms of AMD: dry and neovascular AMD. The role of NK1R in the neovascular form of AMD has been studied in pre-clinical models. Indeed, pharmacological blockade of the NK1R resulted in the reduction of AMD-associated choroidal neovascularization (CNV) [118,119]. By contrast, it was demonstrated that SP has beneficial effects on retinal pigment epithelium (RPE) through induced migration and proliferation of retinal pigment cells following laser-induced damage in RPE both in vitro and in vivo. Therefore, the effect of NK1R on the pathophysiology of AMD could be different depending on the nature and/or stage of AMD [120,121].

The role of NK1R has also been studied in other retinal diseases. Proliferative vitreoretinopathy (PVR) is a serious complication of retinal detachment and is characterized by the growth and contraction of subretinal membranes within the vitreous cavity, ultimately leading to visual loss [122,123]. While the exact pathophysiology of PVR is still incompletely understood, it seems clear that an altered inflammatory response is involved. Interestingly, SP levels are increased in the ocular fluids of PVR patients. On the other hand, a study on mice showed that SP can inhibit the progression of PVR through modulation of cytokines including TNF-α [124,125]. In conclusion, existing evidence suggest that the exact roles of SP and its receptor NK1 in PVR needs further elucidation.

Retinoblastoma is a rare malignant tumor of childhood that occurs in the retinal subpopulations [126,127]. It is caused by the inactivation of the *RB gene* during development. Retinoblastoma cells express the NK1R. Interestingly, it has been shown that nanomolar concentrations of SP induce retinoblastoma cell proliferation [128]. By contrast, micromolar concentrations of NK1R antagonist (L-733060) and aprepitant prevent retinoblastoma cell proliferation which suggests that the SP/NK1R axis can be therapeutically employed to treat retinoblastoma [129,130].

The potential role of NK1R antagonists has also been investigated in different inflammatory ocular conditions such as allergic conjunctivitis [131]. Research on an animal model of allergic conjunctivitis revealed that an NK1R antagonist, L-703606, significantly reduced the ocular redness along with the SP levels in tear fluids. Moreover, a reduction in the number of infiltrating neutrophils and eosinophils was observed. Finally, the expression of pro-inflammatory cytokines was decreased by topical administration of L-703606 in the conjunctiva. However, the effect of the NK1R antagonist on corneal epithelium remains elusive in the study [132].

Ultraviolet radiation type B (UVR-B) poses a significant risk for the progression of cataract and promotes ocular inflammation. It was shown that fosaprepitant treatment of UVR-B-irradiated animals is associated with reduced NK1R expression in different ocular tissues [133,134].

Graft versus host disease (GVHD) is an inflammatory condition that occurs following the introduction of donated bone marrow or stem cells with a host. Preclinical models of ocular GVHD (oGVHD) show increased expression of NK1R endothelium and epithelium. This was likely a consequence of CD8+ T lymphocytes activation and the release of pro-inflammatory cytokines [53].

Herpes Simplex Keratitis (HSK) is associated with increased levels of SP in severe cases [135]. It was reported that CD8 T cell proliferation was significantly reduced in mice treated with an NK1R antagonist, L-760735, compared to controls, suggesting a key role for SP in herpes-induced corneal inflammation. In conclusion, blocking of SP suppresses the inflammation and infiltrating of immune cells [18,136,137].

1.5.3. NK1R and Ocular Pain

The activation of the NK1R is known to simultaneously promote inflammation and pain [3]. Corneal pain is normally generated by the activation of transient receptor potential. Trigeminal neurons are responsible for collection of sensory stimuli reaching the cornea and transmit them to the pons via their central branch. From there, the sensory information is further transmitted to the thalamus and cortex, through central neurons [138,139].

In the human cornea, three subgroups of trigeminal nociceptors have been identified. Mechano-nociceptors (20%) respond to mechanical stimuli, and are involved in acute pain. Polymodal nociceptors (70%) are activated by chemical and mechanical stimuli. Thermoreceptors (10%), instead, respond to temperature fluctuations [138,140,141]. The relevance of the SP-NK1R pathway in humans has been demonstrated before. In fact, the NK1R is expressed in the trigeminal subnucleus caudalis, where activation by SP initiates acute and/or chronic pain responses [142,143]. It should be noted that while acute pain has beneficial effects on the cornea by inducing eye blinking and tear production, over time, substantial alterations of ion channel expression on corneal nerves and extensive rewiring of the trigeminal neural circuitry occur, which result in chronic neuropathic pain [3,144]. Chronic pain has a key role in highly prevalent diseases (e.g., dry eye) and can in some cases become a disease by itself [145,146].

Ocular surface pain is a consequence of most ocular surface diseases, injuries, and surgery [147]. SP, acting through the NK1R, is involved in conveying corneal pain to the trigeminal ganglion. Specifically, it was shown that large amounts of SP are released in the tear fluid following nerve injury/stimulation [138,148]. SP can bind to the NK1R expressed on corneal nerves, therefore inducing nerve depolarization and pain [3,149]. Recently, it was demonstrated that topical application of an NK1R antagonist, fosaprepitant, resulted in a substantial decrease of corneal pain and leukocyte infiltration as a consequence of nerve-released SP blockade [75].

1.6. NK1R Antagonists and Their Potential in Eye Diseases

NK1R and/or SP are promising targets to treat a number of ocular diseases and pain [18,19,75].

Different NK1R antagonists, including Fosaprepitant, Lanepitant, Spantide I/II, L-732138 and SR140333, L-733060, and aprepitant have been shown to be effective in ocular graft versus host diseases and pre-clinical models of eye diseases [69,71,114]. One of these medications, Fosaprepitant, has been in clinical use for years, with an excellent safety profile, for the treatment of nausea associated with chemotherapy. Fosaprepitant, applied topically to the ocular surface, effectively reduced ocular surface pain, hem- and lymphangiogenesis, and decreased the level of SP in the tear fluid [90,150]. Spantide I inhibited the synthesis of IL-8 in corneal epithelial cells, reduced infiltration of inflammatory cells, and decreased hemangiogenesis [101,151]. Spantide II was able to reinstate the previously abolished immune privilege in the cornea and allowed long-term survival of corneal grafts [113]. CP-96,345 reduced the SP-mRNA expression and inhibited IL-8 gene expression [152].

Finally, L-732138 prevented SP-dependent cell migration in pterygium fibroblast and inhibited migration of pterygium microvascular endothelial cells [116]. L-732138, L-733060, and aprepitant were effective to inhibit the proliferation of retinoblastoma and induce apoptosis [126,129,130].

Some of these medications have been tested in human clinical trials, although not for eye diseases, but mainly as analgesics, antidepressants, or for the treatment of nausea and cancer [11,71,153–156].

2. Conclusions

NK-1 receptors activate an intricate molecular machinery that controls key biological responses in the eye. These include modulation of the inflammatory response, wound healing and pain [157,158]. Emerging evidence suggests that activities mediated by the

NK1R could be beneficial or detrimental to wound healing, depending on the amount and timing of activation.

In any case, the expression of the NK1R on multiple populations of ocular and non-ocular cells, and the secretion of its ligand SP in tears, further add complexity to the picture. At the same time, the involvement of NK1R and its principal ligand SP in such basic biological mechanisms makes the manipulation of its activity extremely attractive in terms of treatment.

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