# The NK-1 Receptor Signaling in the Eye

Subjects: Neurosciences

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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.

inflammation corneal nerves neurokinin-1 receptor

## 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][2][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].

## 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][9][10].

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 [11][12]. 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 [11][13][14].

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 [15].

## 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 [16][17][18], and has the highest affinity for NK1R. Dissociation of SP from NK1R is mediated by metalloproteases [19][20][21][22]. 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][23][24]. 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 [25][26]. Different active Gα subunits transmit the signals from the NK1R ($G_{q/11}$, $G_s$, $G_{12/13}$, and $G_i$) [27].

The $G_{q/11}$ subunit is involved in the regulation of the MAPK-ERK pathway, leading to proliferation in neural progenitor cells [28]. 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) [29]. 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) [30][31]. Besides, the increased $Ca^{2+}$ and DAG concentrations stimulate the phosphorylation of Ras/Raf proteins, which also promote cell proliferation and differentiation [32][33]. 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**) [34][35].

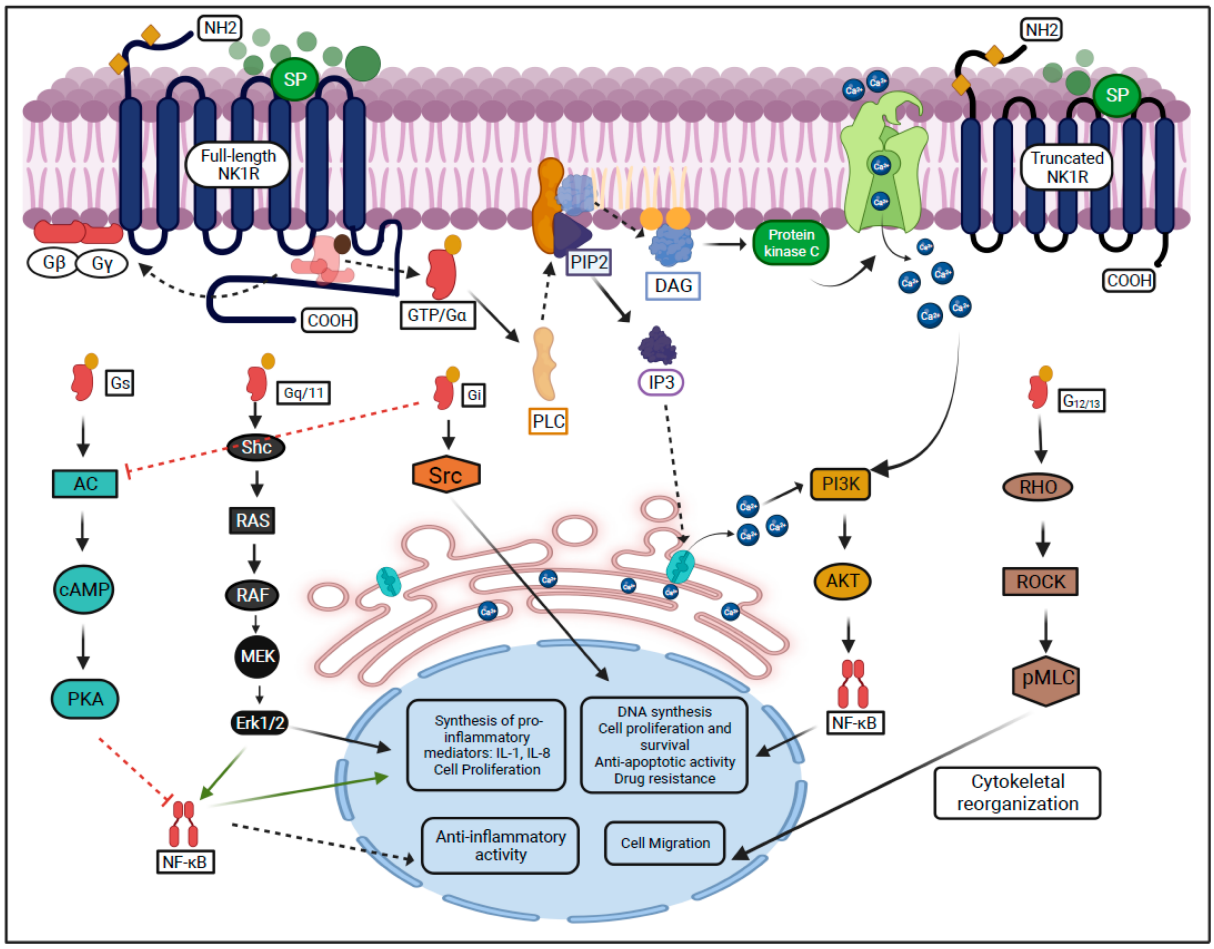


**Figure 1.** SP-mediated activation of NK1R and its downstream signaling pathways.

The GTP/$G_{12/13}$ complex induces cytoskeletal remodeling through the Rock/Rho signaling pathway and leads to cell migration [32][36]. 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 [37][38].

The GTP/Gi complex activates the Src, which leads to the transactivation of the tropomyosin receptor kinases and promotes cell proliferation [39][40]. Previously, the Gi subunit has been reported to suppress cyclic AMP in vitro and activate directly SRC in murine fibroblast cells [41][42].

The Gs subunit is encoded by GNAS (guanine nucleotide binding protein) abundantly found in neuron precursors [30][43][44]. It has been reported that the Gs suppresses tumor progression in the medulloblastoma cell line and inhibits T lymphocyte proliferation in S49 lymphoma cells [45][46].

## 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][47][48][49].

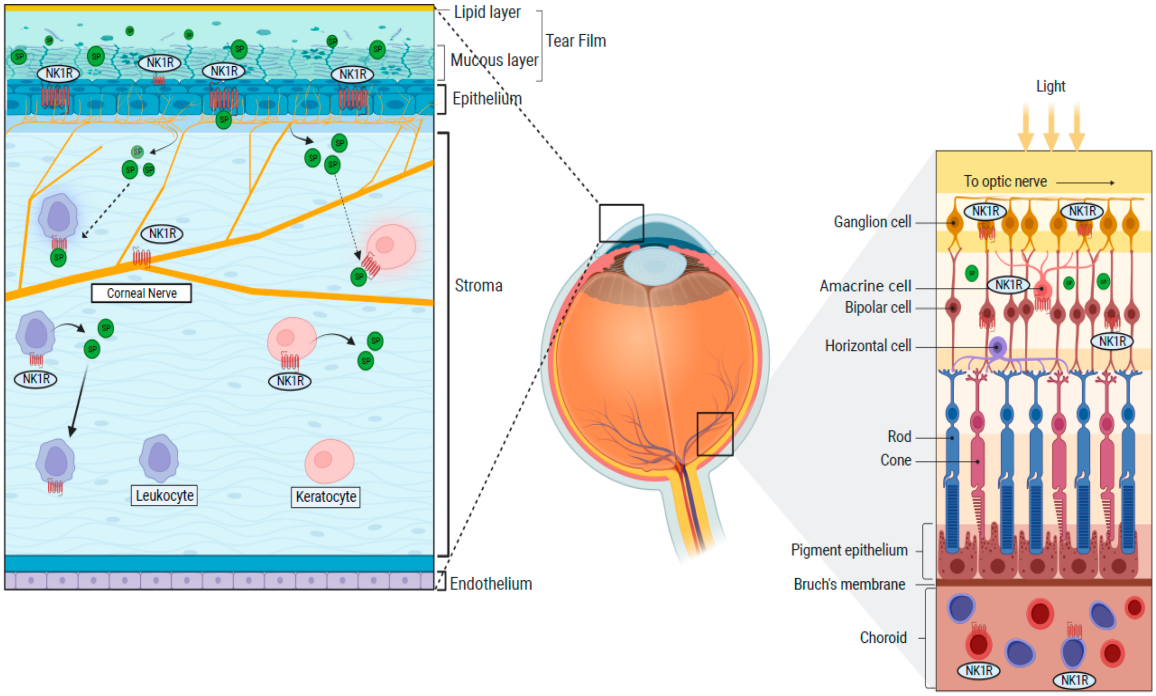


**Figure 2.** Distributions of the NK1R in the cornea and the retina.

In the cornea, the epithelium, keratocytes, and corneal nerves express the NK1R [17][18][47]. Moreover, NK1R is expressed on limbal vasculature (on endothelial cells), where it promotes vascular permeability and lymphangiogenesis [3][50][51]. NK1R is also expressed on the iris sphincter smooth muscle fibers and vascular endothelial cells in the choroid [18][48]. The lacrimal gland also expresses NK1R, while the tear fluid contains large amounts of SP, both in mice and humans [52][53][54][55]. Finally, non-neural cells populating the eye, such as immune cells (T-cells, dendritic cells, lymphocytes, and monocytes), also show NK1R expression [3][56][57]. SP-mediated activation of the NK1 receptor induces different effects in different tissues. For instance, it modulates contraction in the iris sphincter muscle [58].

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.

# 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 [17][55][59][60][61].

## 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][62][63]. 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][64][65].

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 [66][67][68].

## 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][62][69][70][71]. 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 [51][72][73][74].

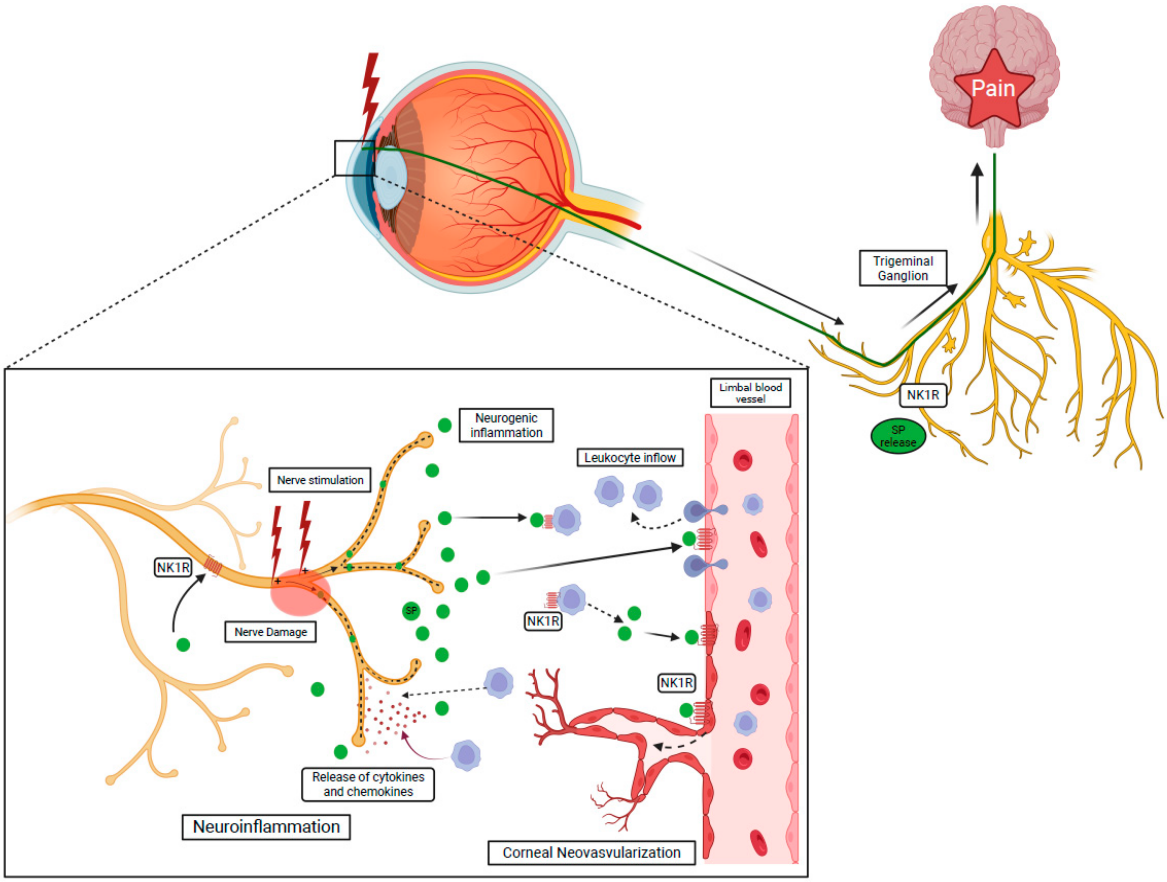


**Figure 3.** NK1R activation via SP induces the recruitment of the leukocyte through the breakdown of the blood–tissue barrier and initiates neurogenic inflammation. Activated leukocytes release cytokines and chemokines leading to nerve damage, called neuroinflammation.

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 [75][76]. 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 [77][78]. In conclusion, existing evidence suggest that the exact roles of SP and its receptor NK1 in PVR needs further elucidation.

Herpes Simplex Keratitis (HSK) is associated with increased levels of SP in severe cases [79]. 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 [17][80][81].

### 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 [82][83].

Ocular surface pain is a consequence of most ocular surface diseases, injuries, and surgery [84]. 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 [82][85]. SP can bind to the NK1R expressed on corneal nerves, therefore inducing nerve depolarization and pain [3][86]. 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 [87].

## 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 [17][18][87].

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 [60][62][88]. 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 [71][89]. Spantide I inhibited the synthesis of IL-8 in corneal epithelial cells, reduced infiltration of inflammatory cells, and decreased hemangiogenesis [90][91]. Spantide II was able to reinstate the previously

abolished immune privilege in the cornea and allowed long-term survival of corneal grafts [92]. CP-96,345 reduced the SP-mRNA expression and inhibited IL-8 gene expression [93].

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