

## Review Article

## Neurokinin receptors and their implications in various autoimmune diseases

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## ABSTRACT

Neurokinin receptors belong to the GPCRs family and are ubiquitously expressed throughout the nervous and immune systems. Neurokinin receptors in coordination with neurokinins playing an important role in many physiological processes, including smooth muscle contraction, secretion, proliferation, and nociception. They also contribute to various disease conditions such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, psoriasis, and cancer. Neurokinin receptors antagonist are potent and highly selective and showing success in treating chemotherapy-induced nausea and vomiting. In this review, discuss the various neurokinin receptor expression on immune cells and their importance in various inflammatory and autoimmune diseases and their therapeutic importance.

## 1. Introduction

Tissue homeostasis is the coordinated action of different cells and molecules in the tissue and external microenvironment. The nervous and immune system is known to communicate through common molecular signaling cues and respond to multiple environmental conditions. Crosstalk between both systems plays an important role in health and disease (Karmakar and Lal, 2021). During infection, inflammatory cytokines secretion increases in the body, resulting in fever, lethargy, anorexia, and social isolation. These physiological and behavioral changes allow us to fight infections (Medzhitov et al., 2012). Apart from behavioral modifications, several cytokines show immunomodulatory effects on different neurological systems.

The interplay between the immune and nervous systems relies on the physical contact between the cells as well as the soluble factors such as neurotransmitters, neuropeptides, and cytokines. Neural reflexes represent a very crucial role in regulating both innate and adaptive immune systems. In this process, pathogenic molecules, cytokines, and other factors are sensed by sensory neurons that generate an action potential and transport signal to the brain stem. Signals generated from the central nervous system (CNS) travel through the motor neurons to the secondary lymphoid organs and result in the release of neurotransmitters that also interact with specific receptors present on immune cells and modulate immune response (Andersson and Tracey, 2012). The detailed molecular mechanism of how neurotropic receptors alters the differentiation and function of various immune cells in the secondary lymphoid organs or the inflamed tissue is not well studied. It is well known that immune cells

secrete different cytokines, which influence the expression of neurotransmitters. Further immune cells also express receptors for various neurotransmitters such as acetylcholine, dopamine, neuropeptides, and serotonin suggesting strong evidence of neuro-immune communication (Halder and Lal, 2021; Karmakar and Lal, 2021; Kerage et al., 2019).

Neuropeptides are a diverse class of signaling molecules present in the central nervous system and the peripheral nervous system and regulate neural activity (van den Pol, 2012). Neuropeptides play a role in maintaining normal physiological conditions such as gut motility, digestion, and enzyme secretion. These neuropeptides can also modulate the immune response and help maintain homeostasis in the body (Mashaghi et al., 2016). Substance-P (SP), a neuropeptide first discovered by Euler and Gaddum in 1931 from the horse brain and intestine. SP belongs to the most prominent member of structurally related tachykinin family neuropeptides (Steinhoff et al., 2014). The tachykinin members are identified by the presence of the signature sequence X-Phe-X-Gly-Leu-Met-NH<sub>2</sub> (Steinhoff et al., 2014). The major tachykinin family members are SP, neurokinin A (NKA), neurokinin B (NKB), neuropeptide K (NPK), and neuropeptide  $\gamma$  (NP- $\gamma$ ), and are encoded by *Tac* genes. SP, NKA, NPK and NP- $\gamma$  are encoded by *Tac1* gene; NKB are incoded by *Tac3*, and hemokinin 1 (HK-1) and endokinins encoded by *Tac4* gene (Steinhoff et al., 2014). *Tac2* was assigned to encode for the NKA precursor but later was found to be identical to *Tac1*. SP and its receptor are known as neurokinin-1 receptor (NK1R), have a wide distribution in the body. This review discussed how different neurokinin receptors and how it alters the immune response in various immune cells in different autoimmunity.

Neurokinin receptors are ubiquitously expressed on the nervous and immune systems and control various physiological functions and are

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**Abbreviations**

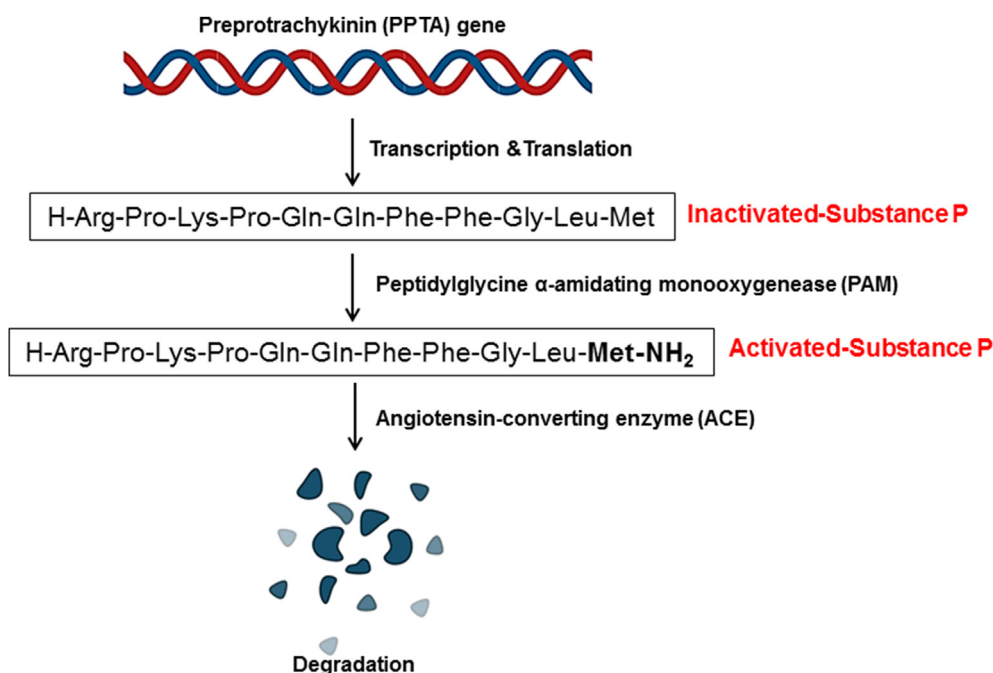
ACE	Angiotensin-converting enzyme	NKA	Neurokinin A
CNS	Central nervous system	NKB	Neurokinin B
cAMP	cyclic adenosine monophosphate	NKC	Neuropeptide C
DAG	Diacylglycerol	NK cells	Natural killer cells
GPCR	G protein-coupled receptor	NCR	Natural cytotoxicity receptors
GM-SCF	Granulocyte-macrophage colony-stimulating factor	PAM	Peptidyl $\alpha$ -amidating monooxygenase
HK-1	Hemokinin-1	PP2A	Protein phosphate 2A
IBD	Inflammatory bowel disease	PPTA	Preprotrachykinin
IBS	Irritable bowel syndrome	RA	Rheumatoid arthritis
IP3	Inositol triphosphate	SP	Substance P
MS	Multiple sclerosis	TCR	T cell receptor
		TLR	Toll-like receptor
		TNF- $\alpha$	Tumor necrosis factor-alpha

associated with multiple immunopathological conditions. Several immune cells including B cells, T cells, DCs, and macrophages express NK1Rs and modulate immune response (Mathers et al., 2007; Morelli et al., 2020). There are three main classes of neurokinin receptors, NK1R, NK2R, and NK3R. Neurokinin receptors are encoded by the *Tacr* gene, which consists of 5 exons. These receptors are G protein-coupled receptors (GPCR), having seven transmembrane loops, with extracellular NH<sub>2</sub> and intracellular COOH terminal (Steinhoff et al., 2014). Neurokinin receptors show variable binding affinity towards each tachykinin protein family member (Douglas and Leeman, 2011).

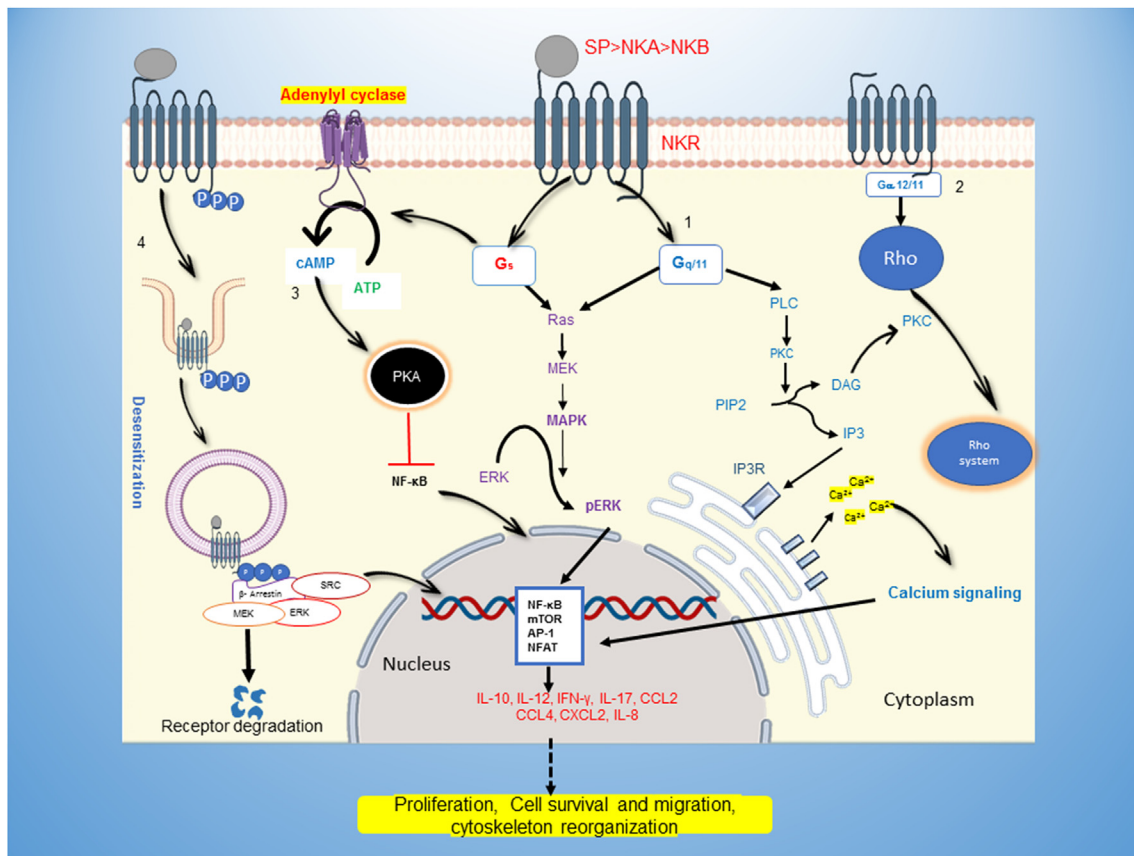
## 2. Distribution and isoform of neurokinin receptors

Neurokinin receptors are widely expressed in the various systems including the nervous, cardiovascular, genitourinary, immune, digestive system. They are also expressed in different tissues and glands including the salivary gland, skin, and muscles (Costa et al., 2006; Eglezos et al., 1991; Evangelista, 2001; Green et al., 2006; Renzi et al., 2000; Satheshkumar and Mohan, 2014). Distributions of neurokinin receptors are very uneven among the various organs. NK1R and NK3R receptors are present in the central nervous system and peripheral tissues. The

expression of NK1R is described in the lungs (Grubor et al., 2004), Substance P and NK1R in the placenta (Munoz et al., 2010), and kidney epithelial cells (Vigna, 1999). NK1Rs are also expressed in T and B cells in Peyer's patches and spleen (Stanisz et al., 1987). The expression of neurokinin receptors in different immune cells has been studied and shown to have a crucial role in modulating immune response (Eglezos et al., 1991). These receptors are structurally conserved and show a high degree of sequence similarity between different species. It is observed that there is almost 94.5% sequence identity of these receptors among rats and humans (Fong et al., 1992). Two isoforms of NK1R have been described, the (full-length NK1R (f-NK1R; 407aa) and the C-terminus truncated (t-NK1R) variants. These two isoforms differ in the length at C-terminus (Lai et al., 2006a; Mantyh et al., 1996). f-NK1R is a functional variant of this receptor and upon signaling it promotes the binding of f-NK1R to G<sub>αq/11</sub> and results in an increased cytosolic Ca<sup>+2</sup> whereas t-NK1R lacks this function (Spitsin et al., 2018; Tuluc et al., 2009). The distribution of NK1R isoforms in both CNS and peripheral tissues, and long isoform is present in abundance in the CNS except in cerebellum and thalamus (Caberlotta et al., 2003). NK2R is the first neurokinin to be cloned through the oocyte expression system (Masu et al., 1987). The expression of different isoforms in various immune cells is not well studied.



**Fig. 1. Metabolism of substance P.** PPTA (located on 6A1; 6.331 cM in *Mus musculus* and 7Q 21.3 in *Homo sapiens*) gene encodes for SP. Inactivated SP is activated by peptidylglycine amidating monooxygenase (PAM) through the process of amidation. SP is degraded by the angiotensin-converting enzyme (ACE).



**Fig. 2. NKRs signaling.** (1) Tachykinin binding to its receptor induces a GTP to GDP exchange on G subunits, dissociating Gq from G and activating downstream effectors, including PLC. This enzyme catalyzes the conversion of PIP<sub>2</sub> into the second messengers IP<sub>3</sub> and DAG, resulting in calcium mobilization and PKC activation. (2) The activation of Rho/Rock, which controls cytoskeletal reorganization and cell migration, is regulated by the G12/13 subunit. (3) G<sub>s</sub> activation of AC catalyzes the conversion of ATP to cyclic AMP (cAMP), which then binds to the cAMP-dependent PKA regulatory subunits. (4) Another MAPK-regulating mechanism can emerge during NK-1R internalization and protein recruitment β-arrestin, allowing endocytosed NK1R to continue signaling and trafficking to early endosomes, where degradation occurs.

NK1R receptor having two sites for glycosylation (Asn-14 and Asn-18) both in mice and humans. It has been shown that glycosylation contributes to receptor internalization and further downstream signaling (Tansky et al., 2007). The human NK2R has two sites for glycosylation (Asn-11 and Asn-19), whereas, in mice, it has only one glycosylation site (Asn-19). Human NK3R having glycosylation at three sites (Asn-23, Asn-50, and Asn-73) while in mice at Asn-9, Asn-23, Asn-40, and Asn-60 (Steinhoff et al., 2014). Tachykinins exhibit preferential binding towards different neurokinin receptors. The order of affinity for the NK1R is SP > NKA > NKB. However, NKA > NKB > SP for the NK2R and NKB > NKA > SP for the NK3R (Maggi, 2000; Regoli et al., 1994). Among various tachykinins, SP is the most studied neuropeptide. SP is an undecapeptide with the amino acid sequence Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH<sub>2</sub> (Chang et al., 1971).

### 3. Neurokinin and their synthesis

SP, NKA, NPK, and NP-γ peptides are encoded by preprotrachykinin A (PPTA) or *Tac 1* gene (Nawa et al., 1984). The human and rat PPTA gene consists of seven exons, whereas the mouse has six exons (Severini et al., 2002). The exon 3 and 6 encode for SP and NKA, respectively (Krause et al., 1987). Exons 3, 5, and 6 encode for NP-γ and exons 3, 4, 5, and 6 encode for NPK (Kawaguchi et al., 1986). NKB is encoded by the preprotrachykinin B (PPTB) or *Tac 3* gene (Folkers et al., 1984). The mouse and rat PPTB gene consist of seven exons, in which exon 5 encodes for NKB (Folkers et al., 1984; Kotani et al., 1986; Page et al., 2000). HK-1 is encoded by the preprotrachykinin C (PPTC) or *Tac 4* gene. The PPTC gene

consists of four exons in mice and rats, whereas five exons in humans in which exon 2 encodes for HK-1 (Kurtz et al., 2002; Zhang et al., 2000).

Transcription of PPTA genes gives rise to pre-mRNA by alternate splicing mechanism and generates different isoforms. Translation and post-translational modification give rise to the final active peptide sequence. Active peptides are packed into secretory vesicles in the Golgi apparatus and transported to axons of nerve terminals (Holmgren and Jensen, 2001; Krause et al., 1987). SP metabolism involves two different enzymes, peptidoglycine α-amidating monooxygenase (PAM), which converts inactivated form of SP into activated SP, and angiotensin-converting enzyme (ACE) responsible for SP degradation (Fig. 1).

### 4. NK1R signaling

Neurokinin receptors coupled to the G-protein (Gq/11 and G<sub>αs</sub>) which in turn activates phosphoinositide metabolism and generate various secondary messengers (Palanche et al., 2001; Rashid et al., 2004; Steinhoff et al., 2014). However, phospholipase C is a crucial intracellular effector molecule in neurokinin signaling, but it also leads to the activation of adenylyl cyclase via G<sub>αs</sub> activation in neuroblastoma cells. It also shows inhibition of adenylyl cyclase via G<sub>αi</sub> activation in the rat salivary gland (Mantyh et al., 1996; Seabrook et al., 1996). NK1R is structurally conserved receptors showing the highest affinity for SP.

SP binds to NK1R and activates various signaling pathways. These pathways imply different secondary messengers such as diacyl-glycerol (DAG), inositol trisphosphate (IP<sub>3</sub>), and cyclic adenosine

monophosphate (cAMP) (Morelli et al., 2020; Vigna, 1999). The binding of SP on NK1R activates phospholipase C, which leads to the degradation of phospholipid molecules and results in the generation of DAG, IP<sub>3</sub>, and cAMP, which in turn activates various downstream signaling molecules such as protein kinase A, protein kinase C, and phospholipase A2 (Douglas and Leeman, 2011; Rosso et al., 2012). All these molecules activate different transcription factors in a cell-specific manner and promote inflammation, proliferation, survival, neural activation, and migration (Fig. 2).

The activation of mitogen-activated protein kinases (MAPKK or MEK) is responsible for the activation of secondary messengers. MEKs activate extracellular signal-related kinases 1/2 (ERK1/2), which is translocated to the nucleus and modulates cytokine expression through serine/threonine-protein kinase, mammalian target of rapamycin (mTOR), and transcription factors such as AP-1 and NF-κB (Fig. 2). These transcription factors regulate the expression of several cytokines, including anti-inflammatory IL-10 and proinflammatory IL-12. Notably, NK1R is known to regulate chemokines like CCL2, CCL4, CXCL2, and IL-8 (CXCL8) via NF-κB, thereby recruiting immune cells at the sites of inflammation (Fiebich et al., 2000; Guo et al., 2002; Koon et al., 2005; ZHAO et al., 2002). It has been shown that SP-NK1R signaling also induces growth regulatory arachidonic acid metabolites, including prostaglandin E2 and prostacyclin in human fibroblast cells (Kähler et al., 1993). NK1R signaling induces apoptosis independent cellular blebbing, which involves the Rho-associated ROCK system in HEK293 cells (Meshki et al., 2009). TGF-β delays NK1R internalization and increases the SP-mediated production of proinflammatory cytokines such as IFN-γ and IL-17 from intestinal T cells (Beinborn et al., 2010). The endosome system in the cells is known for degradation and recycling of receptors, but it also represents an active site for signal transduction (DeWire et al., 2007). Arrestins play a critical role in NK1R-mediated endocytosis. β-arrestin was found to recruit the NK1R, Src, MEKK, and ERK1/2 to endosomes and thereby assemble a signalosome that mediates ERK1/2 phosphorylation activation, which results in proliferation and anti-apoptotic effect (DeFea et al., 2000).

Cell surface metalloendopeptidase neprilysin (NEP) mediates degradation of extracellular SP, thereby restricts NK1R activation (Lu et al., 1997). After activation with SP, G protein-coupled kinases (GRK) and β-arrestin are responsible for signaling. In a particular process, GRK2, 3,

and 5 phosphorylate serine and threonine residues present at the C-terminal tail, which further enhance the affinity of NK1R for β-arrestin. β-arrestin mediates G protein uncoupling and receptor desensitization and endocytosis (Barak et al., 1999). Endothelin-converting enzyme 1 is a membrane metalloendopeptidase that resides in endosomes, disassembling the SP/NK1R/β-arrestin/Src signalosome, further ubiquitination of NK1R and translocate to lysosomes, where it is degraded, thereby attenuates signaling (Pelayo et al., 2011). Truncated NK1R that lacks phosphorylation sites at the C-terminal tail show resistance to desensitization (Li et al., 1997). The resensitization mechanism of the NK1R involves protein phosphatase 2A enzyme (PP2A), where PP2A interacts with non-internalized NK1R and mediated resensitization process (Murphy et al., 2011).

## 5. Neurokinin receptors and their role in immune cell modulations

Hematopoiesis is a complex process mediated by several soluble factors, intercellular and intracellular interactions. Hematopoiesis involves bi-directional crosstalk between the nervous system and bone marrow. Receptors for various neurotransmitters are present on bone marrow resident cells and regulate hematopoiesis (Kang et al., 2004; C. C. Zhang, 2012). SP and NK1R interact with its neurokinin receptor present on bone marrow stromal cells and modulate hematopoiesis in the bone marrow. SP and various tachykinin have been implicated in B cell maturation and T cell development in the thymus (Corcoran et al., 2007). Several studies have shown the expression of neurokinin receptors in different immune cells. Moreover, B cells, T cells, DCs, and macrophages express NK1Rs and modulate immune response (Mathers et al., 2007; Morelli et al., 2020). The existences of neurokinin receptors in various immune cells represent a significant role in immunological response and maintaining homeostasis (Table 1). The role of neurokinin receptors in different immune cells are discussed below-

### 5.1. T cells

Activated T cells express the *PPTA* gene and produce SP, whereas resting T cells in humans do not express SP and NK1Rs (Lai et al., 1998). In rodents, activated T cells also synthesize SP and modulate T cell

**Table 1**  
Neurokinin receptors and their effect on various immune cells.

S. No.	Immune cells	Neurokinin receptor	Function	Reference
1	T cells	NK1R	T cell proliferation, IFN-γ production, IL-12 expression. Enhances the migration through MIP-1a chemokine. Enhances Ca <sup>2+</sup> -dependent TCR signaling and promote survival of activated T cells, mainly Th1 and Th17	(Calvo et al., 1992; Blum et al., 2003a; Blum et al., 2001) (Guo et al., 2002; Morelli et al., 2020)
2	B cells	NK1R	Augments secretion of IgA. SP induces IgG and IgM production from B-cell lymphoma	Pascual et al. (1991)
3	NK cells	NK1R	SP-NK1R interaction shows the dual effect on the cytotoxicity of NK cells. SP-NK1R interaction promotes the antiviral and anti-tumor activity of NK cells.	(Lang et al., 2003; Monaco-Shawver et al., 2011), (Douglas et al., 2001), (Evans et al., 2008)
4	Eosinophils	NK1R and NK2R	Promotes migration and recruitment of alveolar eosinophils. SP-NK1R mediates degranulation of eosinophils.	(Alessandri et al., 2003; Kroegel et al., 1990)
5	Neutrophils	NK1R	SP-NK1R signaling results in superoxide formation and enhancement of phagocytosis. SP-NK1R interaction upregulates MIP-1a, MIP-2, CCR1, and CXCR2 in neutrophils.	(Bar-Shavit et al., 1980; Serra et al., 1988; Tanabe et al., 1996), Sun et al. (2007)
6	Dendritic cells	NK1R and NK2R	NK1R promotes DCs-mediated T cell proliferation. NK1R promotes bone marrow-derived DCs survival via PI3K-Akt signaling. NK2R signaling promotes Th2 response via DCs.	(Lambrecht et al., 1999; Janelsins et al., 2009) Kitamura et al. (2012)
7	Mast cells	NK1R	Neurokinin receptors mediate cytokine and chemokine such as GM-CSF, IL-3, MCP-1, IP-10, TNF-α, and IL-8 production from mast cells.	(Ansel et al., 1993), (Kulka et al., 2008)
8	Monocyte and macrophages	NK1R	Induces IL-12 production from macrophages. SP enhance phagocytosis in macrophages.	(Bar-Shavit et al., 1980; Kincy-Cain and Bost, 1997; Arsenescu et al., 2005)

response through an autocrine manner (Lambrecht et al., 1999). It has been shown that NK1R<sup>-/-</sup> mice show reduced T cell proliferation (Lambrecht et al., 1999). The presence of NK1R is crucial for IFN- $\gamma$  production from T cells in Schistosoma infection (Blum et al., 2003). Cytokines are also known to modulate SP/NK1R expression in murine T cells. It is reported that IL-12 induces the expression of NK1R and SP in T cells, and IL-10 blocks SP production and NK1R expression in murine T cells (Fig. 3) (Blum et al., 2008a,b; Blum et al., 2001; Calvo et al., 1992; Payan et al., 1983b). SP/NK1R modulates T lymphocytes' migration by up-regulating the expression of MIP-1 $\beta$  and a  $\beta$ -chemokine. The NK1R mediates the migration as it is abolished using the NK1R antagonist, CP96345 (Guo et al., 2002). In the IL-10<sup>-/-</sup> mice, intestinal inflammation is mediated by NK1R expression on lamina propria T cells. Antagonizing of NK1R is known to reverse intestinal inflammation, highlighting the importance of NK1R and SP in mucosal inflammation (Weinstock et al., 2003). TGF- $\beta$  delays NK1R internalization, thereby, increased SP-mediated production of proinflammatory cytokines such as IFN- $\gamma$  and IL-17 from intestinal T cells (Beinborn et al., 2010). A very recent study suggested that simultaneous NK1R and TCR activation is necessary for Ca<sup>2+</sup>-dependent TCR signaling and survival of activated T cells, mainly in Th1 and Th17 cells (Fig. 3) (Morelli et al., 2020). But how does neurokinin signaling affects development, differentiation, and function during inflammation and autoimmune diseases is not very well studied.

## 5.2. B cells

It was reported that SP and NKA were involved in the hematopoiesis process. Hemokinin-1 plays an important role in the differentiation and survival of mouse B cells (Grassin-Delyle et al., 2011; Tran et al., 2011). SP augments the secretion of immunoglobulins, especially IgA, in the Peyer's patches, spleen, and mesenteric lymph nodes. Some B cell lymphoma is known to produce IgG and IgM upon treatment with SP (Pascual et al., 1991). SP was shown to enhance immunoglobulin secretion, especially IgM and IgG, upon lipopolysaccharide treatment in murine splenic B cell culture and show crosstalk between NK1R and TLR4 (Pascual et al., 1991). The molecular mechanism of NK1R signaling on B cell maturation and differentiation is not well defined and needs to be investigated.

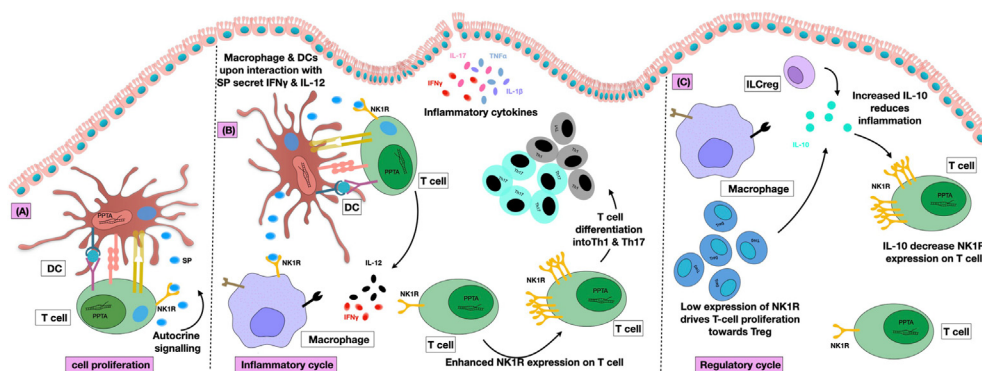
## 5.3. Natural killer (NK) cells

Among different neurokinin receptors, NK1R is present on NK cells and modulates their effector function. It has been shown that

preincubation of NK cells with SP results in partial inhibition of cytotoxicity and degranulation of the YTS human colon NK cell line against EBV-transformed B cells. The inhibitory effect was also evident in NK cells isolated from human PBMCs (Monaco-Shawver et al., 2011). SP-NK1R interaction does not alter the NF-KB pathway, instead, it substantially reduces receptor-induced pERK activation (Monaco-Shawver et al., 2011). In the absence of preincubation with SP, increased cytotoxicity has been observed against the K562 cell line (Lang et al., 2003). SP promotes cytotoxicity by enhancing the production of perforin, granzymes, and natural cytotoxicity receptors (NCR) (Fu et al., 2011). Natural killer cells are primarily known for their anti-viral and anti-tumor immunity (Paul and Lal, 2017). Compelling studies suggested the role of SP/NK1R in its anti-viral activity and anti-tumor activity (Manske and Hanson, 2005). Moreover, Manske et al. has shown that SP-treated splenocytes delay tumor growth into SCID mice, suggesting that SP treatment before tumor challenge primes the immune system and regulates the tumor development (Manske and Hanson, 2005). However, Akazawa et al. also suggested the involvement of SP and NK1R in cancer progression (Akazawa et al., 2009). SP enhances the proliferation and migration of tumor cells, NK1R antagonist inhibits migration and neo-angiogenesis (Brener et al., 2009). Some studies suggested the direct effects of SP on the activity of NK cells in HIV patients. Further, using SP antagonists results in enhancing natural killer cell activity, delaying the progression of HIV disease, providing survival benefits (Douglas et al., 2001; Evans et al., 2008).

## 5.4. Eosinophils

Investigations reveal that SP is present in human eosinophils and liver granulomas of Schistosoma infected mice (Aliakbari et al., 1987; Weinstock et al., 1988). In inflammatory diseases, eosinophils are reported near the SP-producing neurons (Smyth et al., 2013). Neurokinin receptors are responsible for the migration of alveolar eosinophils in distal airways. Pretreatment with the antagonist of neurokinin receptors, specifically NK1R and NK2R, results in reduced hypersensitivity pneumonitis. In the allergic pleurisy model, treatment with NK1R antagonist suppressed eosinophils recruitment (Alessandri et al., 2003; Tibério et al., 2003). NK2R is crucial for the development of IL-5 induced hyper airway responsiveness in guinea pigs, indicating its involvement in eosinophils functions (Kraneveld et al., 1997). SP mediates eosinophils activation and degranulation, followed by oxidative burst (Kroegel et al., 1990). A recent study showed the effect of SP and its receptor on eosinophils from atopic and non-atopic individuals, and NK2R was more



**Fig. 3. Different immune cells and NK1R interaction in the intestine.** (A) T cell proliferation- (i) Bone marrow-derived DCs was shown to have PPTA gene and synthesized SP, contributing to T cell proliferation induced by DCs. (ii) In the absence of DCs, activated T cells also synthesized SP, and it acts in an autocrine manner to modulate T cell response. (B) Inflammatory Cycle (i) Macrophages, DCs, and activated T cells upon activation secrete IFN- $\gamma$  and IL-12 and enhance NK1R expression on T cells, and derive the proliferation of Th1 and Th17. (ii) Th1, Th17, and other inflammatory immune cells secrete inflammatory cytokines such as IFN- $\gamma$ , IL-17, TNF- $\alpha$ , and IL-1 $\beta$ , which in turn modulates intestinal inflammation. (C) Regulatory cycle. Regulatory macrophages and ILCs secrete IL-10, decreasing NK1R expression on T cells. Reduced NK1R expression derives T cell proliferation towards Treg, which in turn reduces inflammation.

responsive to SP in atopic patients by promoting chemotaxis and  $\text{Ca}^{+2}$  influx (Friedman and Levi-Schaffer, 2015). These findings suggest the important role of NK2R in eosinophils and allergic immune responses.

### 5.5. Neutrophils

NK1R expression in neutrophils has been documented in several studies, including granulomas, inflamed periregular tissues, and inflamed bronchoalveolar lavage (Hoshino et al., 1999; Tuncer et al., 2004). Upon binding to its receptor, SP activates different signaling pathways in neutrophils, and most importantly, it increases intracellular  $\text{Ca}^{+2}$  levels associated with inositol 1, 3, 5 triphosphate (Serra et al., 1988). These signaling pathways result in superoxide formation and enhancement of phagocytosis (Bar-Shavit et al., 1980; Serra et al., 1988; Tanabe et al., 1996). NK1R mediates the influx of neutrophils, and the use of antagonists of NK1R ameliorates inflammation (Christian M. Kähler, 2001; Perretti et al., 1993). IL-1 $\beta$  drives NK1R-mediated neutrophils accumulation in the murine air-pouch model (Ahluwalia et al., 1998). SP-NK1R interaction results in the upregulation of chemokines MIP-1 $\alpha$ /CCL3 and MIP-2/CXCL2 and chemokine receptors CCR1 and CXCR2 in neutrophils (Sun et al., 2007).

### 5.6. Dendritic cells (DCs)

Dendritic cells (DCs) are professional antigen-presenting cells and are potent in stimulating innate and adaptive immune responses. SP and its receptors, NK1R has been reported in murine and human DCs (Marriott and Bost, 2001). Bone marrow-derived murine DCs expressed *PPTC* mRNA, which encodes hemokinin-1 (Marriott and Bost, 2001; Nelson et al., 2004). Likewise, bone marrow-derived DCs are shown to have *PPTA* gene transcription and synthesis of SP, which contributes to T cell proliferation induced by DCs (Fig. 3). In the absence of DCs, TCR ligation and soluble CD28 is responsible for signaling through the NK1R (Lambrech et al., 1999). NK1R signaling activates DCs to elicit type-1 immunity by IL-10 synthesis without affecting the low level of IL-12 production (Janelsins et al., 2013). NK1R through skin resident Langerhans cells promotes the generation of Th1 and Tc1-biased immune responses in mice (Janelsins et al., 2009). NK1R promotes bone marrow-derived DCs survival via PI3K-Akt signaling and also rescues them from apoptosis induced by the deprivation of GM-CSF and IL-4 (Janelsins et al., 2009). NKA-NK2R signaling in DCs stimulates Th1 response and enhances IFN- $\gamma$  production both *in-vivo* and *in-vitro* (Kitamura et al., 2012). NK1R antagonist ameliorates ocular disease by inhibiting DCs-mediated Th17 activation (Yu et al., 2020). Together, these studies suggested the dual role of neurokinin receptors in tissue-resident DCs.

### 5.7. Mast cells

Several studies have shown that mast cells are present close to SP-positive nerves in various tissues, including lungs, intestine, brain, diaphragm, and skin (Bischoff et al., 2004; Columbo et al., 1996; Dimitriadou et al., 1997; Skofitsch et al., 1985). Similarly, studies have shown the expression of neurokinin receptors in human mast cells, mucosal mast cell lines, and peritoneal mast cells (Cooke et al., 1998; Okada et al., 1999). Functional expression of the NK1R in bone marrow-derived mast cells is induced by IL-4 and stem cell factors (van der Kleij et al., 2003). Neurokinin receptors in human mast cells modulate different functions such as degranulation, histamine release, cytokines, and chemokines (Ansel et al., 1993; Kulka et al., 2008). SP-NK1R interaction is essential to increase the number of mature mast cells in a hypertensive heart, which results in cardiac fibrosis (Widiapradja et al., 2019). Similarly, SP/NK1R, along with IL-33, is crucial for mast cell-mediated inflammatory response, including psoriasis (Theoharides et al., 2010). It was reported that SP and IL-33 collectively induce mast cells to secrete IL-1 $\beta$  and TNF- $\alpha$  involved in psoriasis (Taracanova and Theoharides, 2015). SP plays a

vital role in neurogenic inflammation. Mast cells secrete the tryptase enzyme, which triggers protease activator receptor-2 expression on neurons, results in SP release, which in turn mediates neurogenic inflammation (Vergnolle et al., 2001). Moreover, SP induces the expression of corticotrophin-releasing hormone receptor-1, which further stimulates NK1R expression, thereby exerts proinflammatory effects (Asadi et al., 2012). SP is also known to enhance vasodilation and granulocyte infiltration in the skin in a mast cell-dependent manner (Yano et al., 1989). Together, these studies suggest an important role of neurokinin-based regulation of immune response by mast cells.

### 5.8. Monocyte and macrophages

SP and its receptor are expressed on human and murine macrophages and monocytes (Bost et al., 1992; Germonpre et al., 1999; Ho et al., 1997). It is also reported that SP and NK1R are expressed in macrophages in the placenta (Hofbauer cells) (Munoz et al., 2013). Similarly, NK1R expression has been reported in human peripheral lymphoid cells, including monocytes and macrophages (Goode et al., 2000). Monocytes and macrophages, including THP-1 cell lines, express the truncated form of NK1R (Chernova et al., 2009; Lai et al., 2006b). Neurokinin receptors mediate several functions, including elevates IL-10 and TNF- $\alpha$  from monocytes and monocytes-derived macrophages (Ho et al., 1996). SP/NK1R interaction results in IL-12 production from murine macrophages. Most evidently, IL-12 and STAT4 are responsible for PPTA mRNA expression at the inflammation site (Arsenescu et al., 2005; Kincy-Cain and Bost, 1997). SP/NK1R signaling results in an increased  $\text{Ca}^{+2}$  level independent of NF- $\kappa$ B transcriptional factor, whereas NF- $\kappa$ B regulates expression of NK1R in human macrophages (Marriott et al., 2000; Simeonidis et al., 2003). In murine schistosomiasis, IL-12 and IL-33 induce the expression of SP from macrophages (Blum et al., 2008a,b). However, IL-10 blocks SP production from T cells, whereas TGF- $\beta$  blocks SP production from macrophages (Blum et al., 2008a,b). Additionally, SP enhances inflammatory cytokine production via ERK/p38 MAPK is mediated via NF- $\kappa$ B activation (Sun et al., 2008). It was also reported that macrophages in culture secrete  $\text{O}_2$ ,  $\text{H}_2\text{O}_2$ , thromboxane, and nitric oxide upon treatment with SP in culture (Hartung and Toyka, 1983; Jeon et al., 1999). Moreover, SP was shown to induce phagocytosis in mouse peritoneal macrophages (Bar-Shavit et al., 1980). SP/NK1R interaction also induces monocyte tissue factor synthesis in a time and concentration-dependent manner (Khan et al., 2012). HIV infection of macrophages augmented by increased expression of CD163, which is induced by SP. Furthermore, NK1R antagonist CP96345 ameliorates HIV infection in macrophages (Lai et al., 2001; Tuluc et al., 2014; Wang et al., 2007). NK1R antagonist aprepitant drug suppresses HIV-1 infection of microglia/macrophages (Wang et al., 2008).

Among different neurokinin receptors, NK1R has been studied thoroughly in various immune cells, while very little is known about NK2R and NK3R. Here, we can conclude that NK1R signaling has implications in different immune responses, thereby suggesting its role in several pathophysiological conditions, including various autoimmune disorders.

## 6. Role of NKRs in various autoimmune disorders

Neural reflexes play an important role in autoimmune diseases such as multiple sclerosis (MS), inflammatory bowel disease, rheumatoid arthritis, systemic lupus, and type 1 diabetes (Steinhoff et al., 2014). Inflammatory reflex maintains immunological homeostasis in a coordinated manner. In brief, inflammatory cytokines sensed by afferent vagus nerves and particular information from specific organs traveled to the brain stem. Afterward, the response generated to specific signal travel through the efferent vagus nerve and acetylcholine secreted from nerve endings. Acetylcholine binds to its receptors present in different immune cells and activates anti-inflammatory pathways (Andersson and Tracey, 2012; Halder and Lal, 2021). Gateway reflex provides a necessary explanation of how pathogenic immune cells breach the blood-brain

barrier and responsible for neuroinflammatory diseases. The hallmarks of neurogenic inflammation are increased vascular permeability, plasma extravasation, edema formation, and leukocyte infiltration (Harrison and Geppetti, 2001). In addition to neurogenic inflammation, other stimuli such as pain and stress activate inflammation amplifier genes in immune and non-immune cells like endothelial cells, resulting in higher production of inflammatory cytokines (Kamimura et al., 2019). Inflammatory cytokines increase the permeability of blood vessels and promote infiltration of immune cells at the effector sites. Thus, the gateway reflex is critical for maintaining homeostasis in specific immune-privileged organs (Kamimura et al., 2019). Neural reflex in coordination with the immune system has been studied thoroughly in various pathophysiological conditions. Here we have listed a few neurokinin-mediated autoimmune diseases.

### 6.1. Inflammatory bowel disease (IBD)

IBD is a multifactorial, chronic inflammation of the gastrointestinal tract and includes two major phenotypes, Crohn's disease (CD) and ulcerative colitis (UC). These phenotypes have different clinical characteristics and immune responses. IBD is characterized by inflammation, ulceration, and hemorrhage along the gastrointestinal tract. The role of various immune cells such as innate lymphoid cells, dendritic cells, macrophages, monocytes, B cells, and T cells in IBD pathogenesis is mostly known. Dysregulation of delicate equilibrium between neural and immune systems is quite evident in IBD, and these neural mediators may act as a potential tool to treat IBD (Norton et al., 2021). Among various neuronal receptors, neurokinin receptors are widely distributed in the brain and periphery, including the gastrointestinal tract localized in the mesenteric and submucosal plexus and extending out to all tissue layers gut (Goode et al., 2000a,b). Various studies suggested the role of the NK1R in maintaining signs and symptoms of IBD and irritable bowel syndrome (IBS) (Koon et al., 2005; Reed et al., 2005). However, few studies have suggested the role of NK1R in tissue recovery via epidermal growth factors (Castagliuolo et al., 2000, 2002). A paradigm of crosstalk during the inflammatory and regulatory cycle has been described in Fig. 3.

Among different neurokinin receptors, various studies suggested the role of NK1R, and elevated levels of SP were observed in the colonic mucosa of IBD patients (Norton et al., 2021; Patel et al., 2020). On the cellular level, it has been revealed that SP-NK1R interaction stimulates lamina propria T cells and macrophages to secrete IFN- $\gamma$  and IL-12, which drives CD4 T cells differentiation towards Th1, a vital component of intestinal immune response (Blum et al., 2003; Kincy-Cain and Bost, 1997). IL-12, IL-18, and TNF- $\alpha$  induce T cells to express NK1R, whereas IL-10 prevents its expression (Blum et al., 2008). One study revealed that TGF- $\beta$  delays internalization of SP/NK1R complex, thereby stimulate SP-mediated IFN- $\gamma$  and IL-17 production from intestinal T cells. The enhanced production of these cytokines contributes to the pathogenesis of IBD (Beinborn et al., 2010). Hwang et al. showed that SP could ameliorate the dextran sodium sulfate (DSS)-induced intestinal damage in mice (Hwang et al., 2018).

### 6.2. Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disorder specified by the breakdown of the blood-brain barrier, multifocal inflammation, degeneration of myelin sheath (Sonar and Lal, 2017, 2018; Trapp and Nave, 2008). The different neurotransmitters are known to play a very crucial role in the pathogenesis of MS. Notably, it is reported that SP and NK1R interaction in human astrocytes activates NF- $\kappa$ B pathways, which results in the production of proinflammatory cytokines such as IL-6, IL-8, TNF- $\alpha$ , GM-SCF, and reactive oxygen species, and drive CNS-related diseases (Lieb et al., 1996; Palma and Manzini, 1998). SP is known to induce vasodilation, which promotes the accumulation of immune cells, exacerbates inflammatory responses, and enhances CNS disorders' severity (Corrigan et al., 2016; Maggi, 1997b). SP-NK1R interaction plays

a role in cytokine storms and seizures related to neurocysticercosis granulomas (Garza et al., 2010; A. Garza et al., 2008). NK1R antagonists were shown to have promising results in the treatment of neurodegenerative (Bergström et al., 2004; Quartara et al., 2009).

### 6.3. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease that manifests as the inflammation of synovial joints, promotes destruction and deformity. Several studies show the role of various immune cells, including B cells, T cells, macrophages, and DCs, in the pathogenesis of RA (Cope, 2008; Gaffen, 2009; Kinne et al., 2000; Samuels et al., 2005; Yu and Langridge, 2017). Besides, neural pathways are known to play a significant play role in the pathogenesis of RA. The experimental arthritis model shows the involvement of SP, and exogenous SP increases the severity of the disease. NK1R antagonist was shown to reduce inflammation and pain (Ahmed et al., 1995; Hong et al., 2002; Levine et al., 1984). In humans, SP's altered expression has been observed in the synovial fluid of RA patients, and SP stimulates synoviocytes to produce IL-6, IL-8, and prostaglandin in RA patients (Alstergren et al., 1995; Grimsholm et al., 2005; Keeble and Brain, 2004; Raap et al., 2000). Serum level of SP was also reported to act as disease activity and sub-clinical inflammation indicator in RA (Barbosa-Cobos et al., 2018).

### 6.4. Insulin-dependent diabetes mellitus (type 1 diabetes)

Type 1 diabetes is a T cell-mediated autoimmune disease that leads to the destruction of insulin-secreting cells, causing insulin deficiency and hyperglycemia (Hassan et al., 2012). Neural connection in diabetes is not much explored. Very few studies support the presence of neurokinin receptors on islet cells in mice, which mediate the extravasation of granulocytes, inflammation, and tissue degeneration (Persson-Sjögren et al., 2005). However, the study suggested the regulatory role of SP in diabetic foot ulceration, and SP promotes wound healing by modulating macrophages towards the M2 phenotype (Leal et al., 2015). SP is also known to preserve the pancreatic  $\beta$ -cells in type 1 and type 2 diabetes by immune modulation and apoptosis (Um et al., 2018).

### 6.5. Psoriasis

Psoriasis is a chronic inflammatory disease characterized by skin barrier disruption and immune dysfunction. The role of different immune cells, including T cells, DCs, and macrophages, is quite evident in psoriasis' pathogenesis (Lowe et al., 2014). In psoriasis, inflammatory myeloid-derived DCs secrete IL-12 and IL-23 that drive CD4 T cell differentiation towards pathogenic Th1 and Th17 cells (Hänsel et al., 2011). Neural connection, primarily neurokinin receptors, was shown to have disease-enhancing effects in psoriasis (Pincelli et al., 1994; Sandoval-Talamantes et al., 2020). It has been demonstrated that increased innervations of SP positive nerve fibers in the plaque of psoriasis (Jiang et al., 1998). SP mediates an array of psoriasis events, including initiation of the inflammatory cascade that stimulates T cell subset and metabolite secretion from mast and macrophages, which augments severity in psoriasis (Maggi, 1997a; Payan et al., 1983a).

## 7. The antagonist of neurokinin receptors

Neurokinin receptors and their ligands contribute to the pathogenesis of several diseases, including acute and chronic inflammation, nociception, psychotic disorder, IBS, IBD, and cancer. The antagonist for these receptors may be a useful approach to treat many diseases. There are several clinical trials have been performed targeting different neurokinin receptors in several diseases (Table 2). Among them, remarkable success has been obtained in treating nausea and vomiting after chemotherapy. Here, we have listed several antagonists and their role in different diseases.

**Table 2**  
List of neurokinin antagonist in clinical trials.

S.No	Antagonists	NCT No.	Stage of clinical trials	Diseases	Receptor	Functions	References
1	GR205171	NCT003886 NCT006097 NCT013819	Phase 2 Phase 2 Phase 1	Psychiatric disorders	NK1R	Blockage of NK1R	(Kramer et al., 1998), (Mathew et al., 2011; Rupniak et al., 2000)
2	SB-223412 Talnetant	NCT001027 NCT003063 NCT000446	Phase 2 Phase 2 Phase 2	Psychotic drug (Schizophrenia)	NK3R	Modulate monoaminergic neurotransmission	(Dawson et al., 2008; de la Flor and Dawson, 2009; Sanger, 2004)
3	SB-223412 Talnetant	NCT001085	Phase 2	IBS	NK3R	Modulate monoaminergic neurotransmission	Sanger (2004)
4	SR-142-801 Osanetant			Drug addiction, schizophrenia,	NK3R	Inhibit NKB binding to its receptor; modulate dopaminergic activity in the core of the nucleus accumbens.	(De Souza Silva et al., 2006; Emonds-Alt et al., 1995; Jocham et al., 2006; Quartara and Altamura, 2006)
5	T-2328			Chemotherapy-induced emesis	NK1R	Inhibit the specific binding of SP to its receptor NK1R in the vomiting center	Watanabe et al. (2008)
6	L-773,060 L-760,735			Psychiatric disorders	NK1R	Blockage of NK1R	Kramer et al. (1998)
7	Fosaprepitat (also known as MK-0517 and L758,298 (FDA approved))	NCT017317 NCT009421  NCT016979 NCT015949 NCT008159 NCT011151 NCT009921	Phase 2 Phase 1  Phase 2 Phase 3 Phase 1 Phase 1 Phase 1	Chemotherapy Induced nausea and vomiting	NK1R	Inhibit the specific binding of SP to its receptor NK1R in the vomiting center	(Navari, 2008) (Adra et al., 2016; Van Laere et al., 2012; Weinstein et al., 2016, 2018)
8	MK-0869	NCT009541  NCT009921 NCT000309 NCT000983	Phase 3  Phase 1 Phase 3 Phase 4	Cisplatin chemotherapy	NK1R	Inhibit the specific binding of SP to its receptor NK1R in the vomiting center, an inhibitor of CYP3A4	(de Wit et al., 2003; Tattersall et al., 2000) Hu et al. (2014)
9	MK-0869	NCT000407 NCT000309 NCT000383 NCT000494 NCT000348 NCT000429 NCT000382 NCT000344 NCT000395	Phase 3 Phase 3 Phase 3 Phase 3 Phase 3 Phase 3 Phase 3 Phase 4 Phase 3	Major depressive disorder	NK1R	Inhibit the specific binding of SP to its receptor NK1R	(Keller et al.; Snyder et al., 2018)
10	Nepadutant			Asthma, Post-operative ileus	NK2R	Inhibits NKA binding to its receptor; NK2R	(Carini et al., 2001; Quartara et al., 2009) Schelfhout et al. (2009)
11	Nepadutant	NCT006583 NCT015318 NCT012553	Phase 1 Phase 2  Phase 2	IBS (Gastrointestinal disorders)	NK2R	Inhibits NKA binding to its receptor; NK2R	(Carini et al., 2001; Quartara et al., 2009)
12	Ibodutant	NCT021096 NCT013024	Phase 3 Phase 2	IBS	NK2R	Inhibits NKA binding to its receptor; NK2R	(Quartara et al., 2009; Szymaszkievicz et al., 2019; Tack et al., 2016)
13	DNK-333  DNK-333  DNK-333	NCT006966 NCT003973  NCT010397	Phase 2 Phase 2  Phase 2	IBS  Asthma  Atopic Dermatitis	NK1R/ NK2R  NK1R/ NK2R NK1R	It binds with similar and high affinities to human NK1R and NK2R receptors. Protect against NKA induced bronchoconstriction.  It binds with similar and high affinities to human NK1R and NK2R.	(Joos et al., 2004; Quartara et al., 2009; Zakko et al., 2011) Joos et al. (2004) –
14	Rolapitant	NCT022847 NCT014949 NCT015026 NCT015013 NCT023866 NCT024361 NCT005321 NCT003966	Phase 1 Phase 3 Phase 3 Phase 1 Phase 1 Phase 2 Phase 2	Chemotherapy-induced nausea	NK1R	Inhibit the specific binding of SP to its receptor NK1R in the area of postrema, nucleus tractus solitaries, and visceral afferent nerves.	Rapoport et al. (2015)

(continued on next page)



Table 2 (continued)

S.No	Antagonists	NCT No.	Stage of clinical trials	Diseases	Receptor	Functions	References
15	Rolapitant	NCT005321	Phase 2	cough	NK1R	Inhibit the specific binding of SP to its receptor NK1R	–
16	Saregutant	NCT003933 NCT003313 NCT004260 NCT003950 NCT002514 NCT002501 NCT002553 NCT004118	Phase 3 Phase 3 Phase 3 Phase 3 Phase 3 Phase 3 Phase 3 Phase 3	Depressive disorder	NK2R	Potentially block the binding of NKA to its receptor.	Micale et al. (2008)

## 8. Conclusion and future perspectives

Neurokinin receptors are widely expressed in various systems, including the nervous, cardiovascular, genitourinary, immune, digestive system. They are also quite prevalent in several tissues and glands including the salivary gland, skin, and muscle. These receptors belong to the GPCRs family and mediate various functions such as smooth muscle contraction, secretion, proliferation, nociception. Intriguingly, they also perform a significant role in modulating immune cell proliferation and cytokine production. These receptors and their ligands are evident in the pathogenesis of several diseases, including acute and chronic inflammation, nociception, psychotic disorder, IBS, IBD, and cancer. The antagonist for these receptors may be a helpful approach to treat many diseases.

NK1R has been studied thoroughly among different neurokinin receptors, whereas significantly less is studied regarding other receptors in the nervous and immune system. There is a lack of information about different neurokinin in various immune cells and their role in modulating the immune response in homeostasis and diseased condition. NKRs antagonist is safe and potent, but many are failed in clinical trials. Complete information about three-dimensional structures of neurokinin receptors, agonist, antagonist, and signaling molecules will help solve the mystery behind the failure of different clinical trials. The detailed molecular mechanism of SP-NK1R signaling in the different immune cells and its effect on the development, differentiation, migration, and function in the secondary lymphoid tissues and site of inflammation is not well defined and needs to be investigated.

### CRedit authorship contribution statement

**Amrita Mishra:** Conceptualization, Writing – review & editing.  
**Girdhari Lal:** Conceptualization, Writing – review & editing.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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