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Neuropeptide Substance P and the Immune Response

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Abstract

Substance P is a peptide mainly secreted by neurons and is involved in many biological processes, including nociception and inflammation. Animal models have provided insights into the biology of this peptide and offered compelling evidence for the importance of substance P in cell-to-cell communication by either paracrine or endocrine signaling. Substance P mediates interactions between neurons and immune cells, with nerve-derived substance P modulating immune cell proliferation rates and cytokine production. Intriguingly, some immune cells have also been found to secrete substance P, which hints at an integral role of substance P in the immune response. These communications play important functional roles in immunity including mobilization, proliferation and modulation of activity of immune cells. This Review summarizes current knowledge of substance P and its receptors, as well as its physiological and pathological roles. We focus on recent developments in the immuno-biology of substance P and we discuss the clinical implications of its ability to modulate the immune response.

Keywords

Immune regulation; neuropeptides; cell-to-cell communication; signaling; cellular dynamics

1. Introduction

Substance P (SP) is a highly conserved peptide that was originally discovered in 1931 by Von Euler and Gaddum in the equine brain and gut extracts -- distinct from acetylcholine -- capable of inducing hypotension and muscle contraction (US & Gaddum, 1931). This substance was purified and dried in powder form (hence the name substance P) (Chang & Leeman, 1970); highly conserved homologues were later identified in mice, rabbits and humans (Figure 1a). SP is encoded by the *TAC1* gene (located on chromosome 7 in humans)

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and is a member of the tachykinin peptide hormone family (Severini et al, 2002) (Figure 1b); the family also contains three other neuropeptides, also encoded by *TAC1*, namely neurokinin A, neuropeptide K, and neuropeptide γ (Krause et al, 1987; Nawa et al, 1983). SP is expressed by many cell types including neurons (Ansel et al, 1996; Hokfelt et al, 1980; Holzer, 1988; Pickel et al, 1977), astrocytes (Barker & Larner, 1992; Michel et al, 1986), microglia (Lai et al, 2000), epithelial cells (Watanabe et al, 2002), and endothelial cells (Milner et al, 2004). Immune cells, such as T cells (Lai et al, 1998), macrophages (Ho et al, 1997; Marriott & Bost, 2000), dendritic cells (Lambrecht et al, 1999), or eosinophils (Weinstock et al, 1988) also display significant levels of SP expression (Ho et al, 1997; Lai et al, 1998; Metwali et al, 1994). SP is also expressed by some stem cells and progenitor cells (Li et al, 2000), including immunomodulatory mesenchymal stem cells (MSC) (Cho et al, 2005). Such widespread expression of SP in diverse cell types may suggest its participation in a wide variety of physiological and pathophysiological functions, by activating a multitude of signaling pathways.

1.1. Structure

Physico-chemical properties of substance P underlie its function. The SP peptide is comprised of 11-amino acids (RPKPQQFFGLM-NH2) (Chang et al, 1971) with a net positive charge at physiologic pH. Positively charged residues are located on the N-terminus while the C-terminus contains hydrophobic residues; this separation renders SP as an amphiphilic peptide (Figure 1b). The amphiphilic nature of substance P governs its direct interaction with lipid bilayer membranes, but the functional importance of this interaction is not clear. Importantly, SP mediates its functions by interacting specifically with surface receptors, i.e. members of the neurokinin (NK) family of G protein–coupled receptors (Figure 1c).

Substance P is stable in plasma but has a short half-life in tissues. The half-life of SP is defined by the kinetics of chemical or enzymatic degradation in the extra cellular environment, by binding to cells, and by the dynamics of cellular internalization. Reported values for SP half-life are in the range of seconds to tens of minutes in tissues and blood, while in extracted blood plasma, SP is stable on the timescale of hours (McGregor & Bloom, 1983; Rameshwar et al, 2001a; Skidgel et al, 1984).

1.2. Neurokinin receptors

NK receptors are of three canonical types, namely NK1R, NK2R and NK3R, often co-expressed by the same cell. Among these, NK1R, which typically localizes to lipid rafts (Monastyrskaya et al, 2005), is a G-protein coupled receptor and displays the highest affinity for substance P. This receptor has two isoforms with differing affinities: a high affinity receptor, NK1R-F (407 residue-long full length version) and the low affinity NK1R-T (311 residue-long truncated version) (Fong et al, 1992; Lai et al, 2006; Lai et al, 2008). The full-length NK-1R (NK1R-F) is the predominant form expressed at certain sites in the human brain, whereas the truncated NK-1R (NK1R-T) is widespread throughout the central nervous system and in peripheral tissues (Caberlotto et al, 2003). The activation of NK1R by SP depends on the microarchitecture and the composition the plasma membrane. For example when cholesterol is depleted, the NK1R-mediated signaling is abolished (Monastyrskaya et

al, 2005). The NK1R receptor isoforms are expressed by neurons (Marshall et al, 1996; Todd et al, 2000), epithelial (Bockmann, 2002), endothelial (Greeno et al, 1993), smooth muscle cells (Maghni et al, 2003), as well as fibroblasts (Liu et al, 2006). Intriguingly, some immune cells including T and B lymphocytes (Lai et al, 1998), natural killer cells (Feistritzer et al, 2003), dendritic cells (Marriott & Bost, 2001), monocytes/macrophages (Germonpre et al, 1999; Ho et al, 1997), microglia and astrocytes (Chauhan et al, 2008), eosinophils and mast cells, express NK1R (van der Kleij et al, 2003). It remains unclear why cells express three different classes of NK receptor family with varying affinities, and what benefit this complexity confers to cells.

1.3. Regulatory mechanisms

Interaction of substance P with its receptors leads to internalization and recycling of the receptor, a process that regulates the sensitivity of the cell to SP. Desensitization is mediated by two proteins, a kinase and β-arrestin and is followed by rapid internalization (McConalogue et al, 1998). Resensitization involves pH-induced dephosphorylation and recycling of NK1R (Figure 2, right panel) (Grady et al, 1995). Activation of NK1R stimulates translocation of G-protein-coupled-receptor kinases (GRKs) from the cytosol to the plasma membrane where they specifically phosphorylate SP-occupied NK1R molecules (Figure 2, right panel) (Nishimura et al, 1998). β-arrestins also translocate to the plasma membrane, where they interact with the phosphorylated NK1R (McConalogue et al, 1999). The SP/NK1R- β-arrestin complex is rapidly internalized and subsequently exposed to an acidic environment, which hydrolyzes phosphate groups from NK1R. Substance P is then detached from NK1R and degraded by proteolytic enzymes; in turn, NK1R recycles to the cell surface, leading to resensitization (Grady et al, 1995). The process of de/re-sensitization typically (but not always) involves internalization and recycling and is tightly regulated. The phosphorylation of NK1R by GRKs depends on the concentration of available SP. NK1R undergoes extensive phosphorylation and prolonged association with β-arrestins for hours following exposure to high concentrations of SP (>10 nM). In contrast, minimal phosphorylation is seen after exposure to low concentrations of SP(<1 nM) (Roosterman et al, 2004; Vigna, 1999). Transforming growth factor β (TGF-β) delays SP-induced NK1R internalization and thus enhances the activity of NK1R in T cells (Beinborn et al, 2010), whereas inflammatory cytokines typically promote upregulation of NK1R (Blum et al, 2001; Weinstock et al, 2003a). Resensitization is regulated at a number of levels. An intracellular enzyme, endothelin-converting enzyme-1, controls the translocation of the receptors back to the surface; the enzyme is in turn subject to post-translational regulation (Pelayo et al, 2011; Whyteside et al, 2014). Recycling of NK1R depends on its ubiquitination state, which determines whether the internalized receptor is degraded or returns to the cellular membrane. Further, re-sensitization critically depends on Ras-related proteins (RABs), including RAB4a, RAB5a and RAB11a (Roosterman et al, 2004). RABs are themselves subject to a number of regulatory mechanisms (Lo et al, 2012; Mukherjee et al, 2011). Above, we mentioned that NK1R-F shows higher affinity to SP than NK1R-T, potentially due to the role of the C-terminal domain in NK1R folding (Tuluc et al, 2009). Interestingly, the relatively lower affinity of the NK1R-T to SP might impair its desensitization and internalization leading to more persistent responses after receptor-ligand interactions (Reviewed in Tuluc et al, 2009). Finally, while in the majority of cases NK1 receptors are

recycled via the mechanisms explained above, for a subpopulation of NK1 receptors, desensitization and resensitization may take place without receptor internalization and surface return, respectively (Murphy et al, 2011).

1.4. Signaling pathways

Interaction of substance P with NK1 receptors signals to several intracellular pathways (Figure 2a). These pathways involve second messengers, such as diacyl-glycerol (DAG), inositol trisphosphate (IP_3), and cyclic adenosine monophosphate (cAMP), which control expression of cytokines, and modulate ion channel activities. SP-NK1R coupling activates phospholipase C and adenylate cyclase to generate DAG/IP_3 and cAMP respectively, and eventually signals to mitogen-activated protein kinases (known as MAPKK or MEKs). MEKs activate extracellular signal-related kinases 1/2 (ERK1/2), which translocates into the nucleus and mediates the expression of cytokines through the serine/threonine protein kinase, mammalian target of rapamycin (mTOR), as well as the transcription factors, such as AP-1, and NF-κB. Figure 2a highlights pathways that regulate expression of several cytokines, including the balance of anti-inflammatory interleukin (IL)-10 and pro-inflammatory IL-12. Importantly, NK1R regulates chemokines like CCL2, CCL4, CXCL2, and IL-8 via NF-κB, thereby recruiting immune cells to sites of inflammation (Christian et al, 1994; Derocq et al, 1996; Fiebich et al, 2000; Foldenauer et al, 2013; Guo et al, 2002; Koizumi et al, 1994; Koon et al, 2005; Lieb et al, 1997; Quinlan et al, 1999; Sun et al, 2008b; Zhao et al, 2002).

1.5. Pathophysiology

SP exerts a wide range of physiological as well as pathological effects. The most widely known roles of SP are in nociception and neurogenic inflammation (Cao et al, 1998; De Felipe et al, 1998; Lembeck & Holzer, 1979; Xanthos & Sandkuhler, 2014), both primarily mediated by the NK1R receptor. However, the diverse expression of NK1R on various non-neuronal cell types (Ho et al, 1997; Lai et al, 1998) suggests other functions in addition to its role in pain, including growth-promoting effects on smooth muscle cells (Nilsson et al, 1985; Payan, 1985), skin fibroblasts (Nilsson et al, 1985), and synoviocytes (Lotz et al, 1987); regulating the integrity of extracellular matrix by controlling the expression of matrix metalloproteinases and tissue inhibitors of metalloproteinase in fibroblasts (Cury et al, 2008); regulating angiogenesis and vasodilation by controlling the release of nitric oxide (Bull et al, 1996; Ziche et al, 1994) (Ziche et al, 1990); and regulating bone metabolism (Liu et al, 2007). SP is known to be involved in bone marrow fibrosis (Rameshwar et al, 2001a), tumor cell proliferation (Castagliuolo et al, 2000; Luo et al, 1996), and inflammatory processes (O'Connor et al, 2004). Neurogenic inflammation plays a major role in rheumatoid arthritis (RA). SP is significantly increased in synovial fluid in RA patients (Pavlova et al, 1976). Elevated levels of SP and upregulated NK-1R expression are seen in the rectum and colon of patients with inflammatory bowel disease (IBD), and well correlate with disease activity (O'Connor et al, 2004). SP is a part of a immune regulatory mechanism that amplifies inflammation at intestinal mucosal surfaces in the acute phase of IBD (Weinstock, 2015). In particular, the ability of human mesenteric preadipocytes from IBD patients to release IL-17A increases in response to SP. In psoriasis, a disease that is characterized by hyper-proliferation of keratinocyte, elevated amounts of SP is seen in the

skin. Importantly, SP stimulates mast cells to generate IL-1 family cytokines, which in turn stimulate keratinocyte proliferation (Taracanova & Theoharides, 2015). Finally, current models suggest that SP generated by immune cells stimulates Th1 and Th17 autoreactive cells that migrate to the CNS where they target nerves (Vilisaar et al, 2015). These and other evidences together indicate that SP is a significant player in autoimmunity.

Finally, expression of SP receptors is markedly increased during infection, especially on lymphocytes and macrophages. In human immunodeficiency virus (HIV) infection, activation of NK1R by SP contributes to increased HIV-1 infection in macrophages (Tuluc et al, 2014). In the following sections we elaborate on the immunobiology of SP and provide insights into the immunomodulatory roles of SP in disease processes.

2. Immunobiology of Substance P

The immune system provides protection from a wide range of pathogens. One component of immunity, the phylogenetically ancient innate immune response, fights infections from the moment of first contact and is the fundamental and generic defensive weapon of both uni- and multi-cellular organisms (Kimbrell & Beutler, 2001). An essential element of an immune response is the communication between cells. For example, after injury or infection tissue resident cells such as nerves, vascular cells and immune cells actively interact in a paracrine or contact dependent manner. These communications precede recruitment of non-resident immune cells and may lead to development of adaptive immune responses (Gasteiger & Rudensky, 2014; Iwasaki & Medzhitov, 2015). Adaptive immunity provides specific defense tools in vertebrates that are critical for elimination of alloantigens. Cells of both the innate and adaptive immune system contribute to the generation of substance P and are also targets to this neuropeptide (Ho et al, 1997; Lai et al, 1998). In the following sections we discuss how substance P controls the immune responses at multiple levels ranging from recruitment and proliferation to modulation of immune cell activation (Table 1).

2.1. Immune cell migration

Substance P is a key player in cellular migration and exerts this function either directly or via induction of a number of chemokines, their receptors, and adhesion molecules. Substance P participates in migration of several innate immune cells, such as neutrophils. For example, neutrophils show an attenuated chemotactic response to exogenous IL-1β in NK1R deficient mice (Ahluwalia et al, 1998). SP can also augment leukocyte recruitment indirectly via inducing expression of chemokines, such as macrophage inflammatory proteins (MIP-1β or CCL4 (Guo et al, 2002); MIP-2 or CXCL2 [49]), monocyte chemoattractant protein-1 (MCP-1 or CCL2) (Castellani et al, 2009; Sun et al, 2008b), CCL5 (Chernova et al, 2009), and IL-8 (Tran et al, 2000). SP stimulates human corneal (Tran et al, 2000) and epithelial cells (Koon et al, 2005; Zhao et al, 2002) as well as neutrophils (Serra et al, 1994), mast cells (Okayama et al, 1998), and fibroblasts to produce IL-8 (Figure 2a) (Huang et al, 2008), a powerful neutrophil chemotactic protein. In activated human T lymphocytes, SP significantly upregulates the expression of MIP-1β, a β-chemokine that mediates the migration of lymphocytes and monocytes to the site of

inflammation. This process is mediated by NF-kB and is abrogated by the specific NK1R antagonist CP-96,345 (Guo et al, 2002). SP can also regulate the movement of dendritic cells toward lymph nodes via modulating the expression of chemokine receptors and adhesion molecules. For example, SP upregulates the expression of chemokine receptor CCR7 (Forster et al, 2008; Takashima, 2013) as well as the adhesion molecule, Macrophage-1 antigen (Mac-1, CD11b/CD18), and its ligand, ICAM-1 (CD54) on $NK1R^{+}$ dendritic cells, all facilitating the direction of these cells toward lymph nodes (Janelsins et al, 2013; Mathers et al, 2007; Takashima, 2013). Substance P acts as a potential determinant of endothelial-leukocyte interactions by inducing the expression of an endothelial-leukocyte adhesion molecule (ELAM-1) by the microvascular endothelium (Matis et al, 1990). Immune cell recruitment by SP is fundamental to neurogenic inflammation, which is a critical component of a number of pathologies. For example, substance P recruits leukocytes to the peripheral terminals of nociceptors, where they release neuroactive mediators that contribute to neuropathic pain (Ren & Dubner, 2010). In summary, SP appears to play a key role in regulating immune cell migration typically via regulating the expression of chemokines and adhesion molecules.

2.2. Immune cell proliferation

Cells proliferate by division into daughter cells, a process that lies at the heart of immunology (Kan & Hodgkin, 2014; Mashaghi & Dekker, 2014). Substance P regulates the proliferation of lymphocytes, bone marrow cells, and vascular endothelial cells. Studies show that substance P stimulates human T cell proliferation in vitro, probably through upregulation of IL-2 expression (Calvo et al, 1992; Nio et al, 1993; Payan et al, 1983; Rameshwar et al, 1993; Scicchitano et al, 1988). $NK1R^{-/-}$ mice have reduced proliferative response of T cells, suggesting that SP modulates proliferation of T cells (Lambrecht et al, 1999). Human bone marrow mononuclear cells and fibroblasts also proliferate in response to substance P (Rameshwar et al, 2001b). Furthermore, it has been shown that SP could enhance proliferation of bone marrow stem cells (Mei et al, 2013).

The role of nerve-derived SP in hematopoiesis has been supported through its local and systemic effects on NK1R expressing bone marrow stem cells (BMSCs). Substance P exerts the hematopoietic effect through induction of IL-1 and stem cell factor (SCF) in bone marrow stroma (Rameshwar & Gascon, 1995). This effect arises from direct contact of SP generating-nerve endings with the bone marrow stroma. Systemically delivered SP may also affect hematopoietic stem cells (HSCs), such as promoting the generation of colony-forming units in the peripheral blood (Hong et al, 2009).

Substance P targets immune cells to promote angiogenesis (Ziche et al, 1990). Substance P may regulate angiogenesis directly by inducing endothelial cells to produce nitric oxide (Ziche et al, 1994), or indirectly via its interactions with mast cells and granulocytes. Substance P enhances the expression of vascular endothelial growth factor (VEGF) in mast cells, an action augmented by IL-33 (Shaik-Dasthagirisaheb et al, 2013), but VEGF blockade does not abolish the proangiogenic property of SP (Katsanos et al, 2008). SP may also modulate angiogenesis by enhancing migration, adhesion, and expression of angiogenic genes by granulocytes. This property of substance P has been exploited to induce

angiogenesis at the site of implants (Kohara et al, 2010). Finally, we note that angiogenesis induced by factors like SP can in turn promote immune response by facilitating trafficking of immune cells to tissues. For instance, in healthy cornea angiogenesis is actively suppressed which leads to corneal immune privilege. Breakdown of angiogeneic privilege is a major risk factor for corneal transplant rejection. Interestingly, inhibition of NK1R by Lanepitant (an NK1R antagonist) significantly reduces corneal angiogenesis (Bignami et al, 2014).

2.3. Immune cell activation

Substance P modulates the activity of innate and adaptive immune cells via a number of intracellular pathways (examples are shown in Figure 2a). A critical role of substance P lies in its ability to modulate the production of various cytokines by a wide range of immune cells (Table 1). These include cytokines with pro-inflammatory (e.g. IL-1), immunomodulatory (e.g. IL-10), and chemotactic properties (e.g. IL-8). Cytokines in turn may modulate the effect of substance P; IL-12, IL-18, and TNFα induce NK1R expression in T cells (Blum et al, 2001; Weinstock et al, 2003a), whereas IL-10 and TGF-β prevent NK1R expression (Beinborn et al, 2010; Weinstock et al, 2003b). Moreover, IL-1, IL-4, and IFN-γ induce NK1R expression in macrophages (Marriott & Bost, 2000; Simeonidis et al, 2003).

Substance P modulates the activation of various innate immune cells (e.g. phagocytosis and secretion of cytokines), and promotes the survival of innate immune cells such as natural killer cells, macrophages, dendritic cells, neutrophils, mast cells, and eosinophils. Substance P enhances the cytotoxicity of human natural killer cells by up-regulating their production of cytotoxic-associated molecules (perforin, granzyme) and natural cytotoxicity receptors (NCR) (Fu et al, 2011). SP enhances phagocytosis in both neutrophils and macrophages. In human neutrophils, SP potentiates phagocytosis via stimulating respiratory burst, and production of reactive oxygen intermediates (ROIs) (Serra et al, 1988; Wozniak et al, 1989). These processes are fundamental to many pathologies, such as migraine where substance P degranulates dural mast cells (Ottosson & Edvinsson, 1997). Substance P also enhances phagocytosis in murine peritoneal macrophages via its N-terminus (Bar-Shavit et al, 1980), induces oxidative burst, and stimulates synthesis and release of arachidonic acid metabolites (e.g. PGE2,TXB2) and toxic oxygen radicals (Hartung & Toyka, 1983; Murris-Espin et al, 1995). In addition, substance P enhances the survival of dendritic cells by promoting Bcl-2 expression and subsequent decrease in caspase 3 (Janelsins et al, 2009). In human and murine mast cells, SP induces degranulation and subsequent release of histamine and serotonin (Ansel et al, 1996) and up-regulates Toll-like receptor (TLR)-2, thereby promotes its activation (Tancowny et al, 2010). Moreover, SP increases the expression of corticotropin-releasing hormone receptor-1 (CRHR-1) by human mast cells, the activation of this receptor leads to secretion of IL-8, TNF-a, and VEGF, while CRH itself induces the expression of the truncated NK1R (NK1R-T) (Asadi et al, 2012). Finally SP stimulates activation, degranulation and release of O2- and TXB2 from eosinophils (Kroegel et al, 1990).

Substance P also plays a critical role in activation of adaptive immune cells. SP enhances immunoglobulin secretion in murine Peyer’s patches, splenic lymphocytes and mesenteric

lymph nodes in an isotype-specific manner (particularly IgA). In certain B cell lymphoma clones, substance P directly stimulates secretion of IgA, but not of IgM. However, in the presence of lipopolysaccharide (LPS), substance P stimulates a three-fold increase in IgM secretion (Pascual et al, 1991), indicating a cross-talk between NK1R and TLR4. Depletion of substance P in rodents by capsaicin administration or treatment with a substance P antagonist, decreases the number of antibody-secreting cells (Eglezos et al, 1990).

The role of Substance P in T cell activation and differentiation of helper T cell subsets has been investigated in several studies, although few of them achieved remarkable results. For example, during the inflammatory response caused by murine schistosomiasis, SP binds to NK1R on T cells and induces the production of IFN-γ, a Th1 signature cytokine, while it has no effect on the secretion of Th2 cytokines, such as IL-4 and IL-5 [36]. In a murine colitis model, it was shown that expression of NK1R in mucosal T cells in IL-10 deficient mice was associated with Th1-mediated intestinal inflammation (Weinstock et al, 2003b). In addition, via binding to NK1R on DCs, SP can induce a Th1 and T cytotoxic (CTL)-1 bias of effector T cells in mice [79]. In another murine study, NK1R signaling in DCs caused an inhibition of IL-10 synthesis and secretion without affecting on IL-12 production. However, after cutaneous administration of these NK1R-signaled DCs, IL-12 was upregulated in host DCs resulting in a remarkable Th1 immune response [78]. Regarding Th17 immunity, one study showed that SP promoted the generation of human memory Th17 cells from non–Th17-committed $CD4^+$ memory T cells, but not from naïve $CD4^+$ T cells. They also showed that the other members of the tachykinin family, neurokinins A and B, had no effect on the differentiation of naive and memory T cells (Cunin et al, 2011). Finally, administration of substance P during the primary immune response amplifies the secondary immune response by activating CD8+ T lymphocytes (Ikeda et al, 2007).

Substance P affects immunomodulatory capacity of mesenchymal stem cells (MSC). Evidence suggests that SP treatment may recover the immunosuppressive function of late passage MSCs by potentiating their ability to secrete TGF-β1, which can enhance the therapeutic activity of ex vivo expanded MSCs in long-term culture. Using an NK1R anagonist, the restoration of the weakened activity of MSCs could be abolished (Jin et al, 2015).

It is important to note that the two NK1 receptor isoforms mediate different immunological effects when activated by SP (Tuluc et al, 2009). For example, SP upregulates NF-κB and IL-8, and stimulates PKCδ, via NK1R-F but not NK1R-T in certain human cells. There are also differences in the timing of SP-induced ERK activation in cells expressing the two different forms of the receptor. ERK activation via NK-1R-F is more rapid than via NK1R-T. These data suggest the role of the carboxyl terminus of NK1R in activation of downstream signaling pathways (Lai et al, 2008). On the other hand, Chernova et al. reported that human peripheral blood monocytes express NK1R-T but not NK1R-F; however, SP interactions with NK1R-T do not lead to calcium (Ca2+) mobilization. When NK1R-F is transfected into monocytes, SP can mobilize Ca2+. Furthermore, via NK1R-T, SP can enhance the CCR5 ligand CCL5-elicited Ca2+ mobilization leading to chemotaxis, indicating that even the NK1R-T can be functional in monocytes. From these results, we can conclude that in human monocytes, NK1R-T activates selected signaling pathways and mediates chemotaxis

(Chernova et al, 2009). Concurrently, Lai et al. showed that a human monocyte/macrophage cell line expresses only NK-1R-T, which can not trigger a Ca^{2+} response upon addition of SP, although SP increases the CCR5-preferring ligand RANTES (CCL5)-mediated Ca^{2+} increase in these cells. When these cells differentiate to a macrophage-like phenotype, they express NK-1R-F, which led to an SP (10^{-6} M)-induced Ca^{2+} response (Lai et al, 2006). Taken together, both truncated and full length NK-1R are functionally active in innate immune cells and their functional roles seemingly depend on the cell type and may differ between primary cells and cell lines.

2.4. Immunopharmacology of Substance P

The list of NK1R antagonists (NKAs) is growing. NKAs are of two types, peptide antagonists and non-peptide antagonists. An example of the former group is spantide, a therapeutic peptide which can treat corneal infection (Hazlett et al, 2007). The most well known non-peptide antagonist is aprepitant, a morpholine derivative used as an anti-emetic, anti-depressant, anxiolytic, and anti-tumor drug (Kramer et al, 1998; Kramer et al, 2004; Munoz & Rosso, 2010; Rupniak & Kramer, 1999). Several studies have reported the effect of NKAs on innate and adaptive immune responses, including the modulation of cytokine production, immune cell proliferation, and immune cell migration. Spantide I, for example, enhances proinflammatory (e.g. IL-1β and TNF-α) and anti-inflammatory cytokines (e.g. IL-10), and suppresses Th1-associated cytokines (e.g. IL-18, IL-12 and INFγ) (Hazlett et al, 2007). Spantide suppresses IL-2 production by human and murine T cells, and thus may suppress T cell proliferation (Rameshwar et al, 1993). Spantide antagonizes the role of SP in immune cell recruitment; for example, it decreases the influx of neutrophils and CD4+ T cells in the corneal lesions. When treated with spantide I, corneal IL-6 and CCL3 production was reduced in animal models (Twardy et al, 2011). Similar functions have been reported for other NK1R antagonists as well. Lanepitant suppresses leukocyte infiltration, and lymph- and hemangiogenesis in the cornea (Bignami et al, 2014). Spantide also suppresses secretion of immunoglobulins from B cells in rats (Eglezos et al, 1990). Finally, NKAs can suppress hemangiogenesis by decreasing stem cell factor (SCF), IL-1, IL-3, and GM-CSF (Rameshwar et al, 1994; Rameshwar & Gascon, 1995). Taken together, these results indicate that major advances in our understanding of the mechanism of action of SP have emerged in the past decade via pharmacologic blockade of SP in animal models.

There are few clinical trials using the SP antagonist, aperpitant, in HIV-infected patients. In a clinical trial conducted by Pablo Tebas, Steven D. Douglas and colleagues in HIV-infected patients, aprepitant did not show significant antiviral activity, although aprepitant-treated patients showed decreased numbers of CD4+PD1+ T-cells, so-called exhausted T-cells, and decreased plasma levels of substance P and soluble CD163, suggesting that blockade of the NK1R pathway plays a role in regulating monocyte activation in HIV infection (Tebas et al, 2015).

3. Immunomodulatory role of the substance P in disease

In this section we briefly discuss the clinical implications of SP immunobiology for neurology, and ophthalmology, with particular focus on SP and ocular surface diseases, where neuropeptide research is on the rise (see Table 2).

3.1. Neurologic diseases

The immunomodulatory role of SP in neurologic conditions has been widely recognized. Substance P exerts its immunomodulatory role within the central nervous system (CNS) through its ability to bias the inflammatory response towards Th17 immunity, as well as through its ability to regulate Th1/Th2 balance towards either Th1 or Th2 response depending on the nature of antigens (Cunin et al, 2011; Levite, 1998). In addition to regulating Th1 and Th2 cells, SP can bias the inflammatory response towards Th17 immunity (Cunin et al, 2011), which is implicated with the pathogenesis of multiple sclerosis/experimental autoimmune encephalomyelitis (EAE). In this way, SP may contribute to the maintenance of CNS inflammation during the chronic phase of EAE (Reinke et al, 2006). NK1R antagonists, such as CP-96,345 stabilize the blood-brain-barrier and down-regulate Th1 type cytokines (Nessler et al, 2006).

SP has a well-recognized role in nociceptive neurotransmission (De Felipe et al, 1998). SP may recruit CNS glial cells under pathological pain conditions (Grace et al, 2014). For example, bone fracture pain is associated with increased expression of glial activation markers, which can be attenuated with an NK1R antagonist (Li et al, 2015). It is not yet clear whether these effects are direct, as inhibition of nitric oxide can attenuate the pro-inflammatory effects of SP (Guo et al, 2007). Given the ability of microglia and astrocytes to oppose opioid analgesia (Grace et al, 2015), it is notable that co-administration of an NKR1 antagonist with morphine for six days attenuates hyperalgesia and expression of glial activation markers (Tumati et al, 2012).

In Parkinson’s disease, CNS immune cells such as microglia and astrocytes are activated and release pro-inflammatory cytokines (Depino et al, 2003; McGeer & McGeer, 2008; Mosley et al, 2006; Thornton & Vink, 2012). Substance P has been found to mediate this inflammatory response, which can be suppressed using NK1R antagonists. These observations suggest possible use of NK1R antagonists for neuroprotection in Parkinson’s disease (Thornton & Vink, 2012). Finally, SP can enhance blood-brain barrier permeability by disrupting tight junction proteins (Lu et al, 2008), which facilitates edema (leading to increased pressure in the cranium or spinal canal) following traumatic brain injury, spinal cord injury and stroke (Lewis et al, 2013). Accordingly, NK1Rs are therapeutic targets for these conditions (Vink & van den Heuvel, 2010).

3.2. Ocular diseases

Neuropeptides are generated by a number of cells in the eye. For example, sensory nerves of the eye generate substance P, while vasoactive intestinal polypeptide and neuropeptide Y are secreted by parasympathetic and sympathetic innervations of the eye, respectively (Jones & Marfurt, 1998; Miller et al, 1981). In the retina, the principal SP localizations are amacrine

cells in the proximal inner nuclear layer and displaced amacrine cells in the ganglion cell layer (Brecha et al, 1989; Fukuda et al, 1981; Zhang & Yeh, 1992). Involvement of SP has been described in a few inflammatory and pathological conditions of the retina. Amacrine-derived SP has been reported to be involved in the loss of immune privilege post retinal laser burn through its potential to promote an inflammatory environment that in turn activates resident macrophages and microglia. NK1R antagonists could prevent or curb inflammation post ocular trauma (Lucas et al, 2012). On the other hand, there are reports on anti-inflammatory effects of SP in the retina. SP can reportedly prevent laser-induced retinal degeneration in vivo, by suppressing inflammation and reducing neovascularization. Its anti-inflammatory effects are exerted via reduction of TNF-α and increase of IL-10; the anti-angiogenic effects are achieved via downregulation of CD31+ retinal vessels (Hong et al, 2015).

Substance P plays significant roles in corneal biology and diseases. A number of sources have been identified for corneal SP, namely trigeminal sensory neurons, corneal epithelial cells, stromal keratocytes, and immune cells (Lai et al, 1998; Watanabe et al, 2002). Several reports have explored the role of SP in maintaining corneal epithelial integrity and regulating regeneration of the corneal epithelium. The corneal epithelium is the first barrier against bacteria and other foreign antigens, and actively interacts with other corneal cells, such as resident immune cells and corneal nerves (Kubilus & Linsenmayer, 2010; Lai et al, 1998). Substance P targets corneal epithelial cells via binding to NK1R receptor. Substance P contributes to the maintenance of tight junctions in human corneal epithelial cells by upregulating the tight junction proteins, E-cadherin (Araki-Sasaki et al, 2000) and ZO-1 (zonula occludens) (Ko et al, 2009). Corneal epithelial cells also respond to SP by increased synthesis of IL-8 and MIP-2, which in turn lead to the recruitment of neutrophils (Tran et al, 2000). Substance P functions as an important modulator of corneal (epithelial) wound healing by affecting the process of corneal epithelial migration via enhancing the effect of migrating-promoting agents and modulating epithelial cell attachment to the extracellular matrix. The synergistic effect of SP and insulin-like growth factor (IGF)-1 has recently been reported, yet studies are needed to elucidate the exact underlying mechanism. Substance P likely promotes corneal epithelial cell migration by IGF-1, fibronectin, and IL-6. This sensitization is likely mediated by a signaling pathway triggered by the NK1R, one that leads to the activation of phospholipase C, the IP3-mediated release of Ca^{2+} from the endoplasmic reticulum (ER) and the activation of calmodulin-dependent protein kinase II (CaM-PK II). In turn, the target proteins of CaM-PK II may stimulate signaling pathways activated by IGF-1 (or its C domain), fibronectin, or IL-6 (Yamada et al, 2005). Additionally, SP and IGF-1 stimulate the attachment of corneal epithelial cells to various extracellular matrix proteins by upregulating α5β1 integrin (fibronectin receptor/integrins function as cell-surface receptors for fibronectin, an adhesion glycoprotein which provides a temporary matrix for epithelial migration) and inducing tyrosine phosphorylation of focal adhesion kinase and paxillin in corneal epithelial cells (Nakamura et al, 1998a; Nakamura et al, 1998b). This synergistic effect of SP and IGF-1 improves healing of corneal epithelial wounds and defects in individuals with neurotrophic and anhidrotic keratopathy, Riley-Day syndrome, herpetic keratitis, and in rats with diabetic keratopathy (Brown et al, 1997; Chikama et al, 1998; Nakamura et al, 2003; Nishida et al, 1997). Even though the

importance of SP in corneal wound healing has been suggested, it was mainly explored in the context of the local effect of SP on accelerated wound healing. SP may also act systemically, recruiting CD29+stromal-like cells from the periphery to the site of injury, resulting in accelerated wound healing (Hong et al, 2009).

By modulating the balance between pro- and anti-inflammatory cytokines, SP may affect susceptibility to corneal infections. Substance P has been shown to downregulate the mTOR pathway, leading to decreased expression of the anti-inflammatory cytokine IL-10 and up-regulation of the pro-inflammatory cytokines IL-12p40 and IL-23 (Figure 2). In animal models, this change results in increased susceptibility to corneal infection (Foldenauer et al, 2013; Xu et al, 2011). In contrast, SP regulates the IFN-γ production of natural killer cells, and thus protects against bacterial infection. Treatment with SP antagonist spantide I significantly decreases corneal IFN-γ and IL-18 protein levels, which leads to corneal infection and perforation. IL-18 up-regulates IFN-γ production by natural killer cells through IL-12 independent mechanisms and exerts a protective role in the cornea of infected mice, such as after Pseudomonas aeruginosa infection (Lighvani et al, 2005).

Substance P directly stimulates corneal neovascularization, an effect which can be blocked by NK1R antagonists(Bignami et al, 2014). Normal cornea is known to have angiogenic and immune privilege. Breaking angiogenic privilege can lead to disruption of immune privilege as well (Cursiefen, 2007). An increased SP level, which is seen in inflammation (Michaels et al, 1998; O'Connor et al, 2004), could challenge the privilege by stimulating endothelial cell proliferation. Loss of angiogenic privilege has clinical significance in corneal graft rejection (Qazi & Hamrah, 2013).

The cornea constitutes one of the most densely innervated tissues in the human body (Muller et al, 2003; Rozsa & Beuerman, 1982) and corneal nerve density and function is affected in a number of corneal pathologies such as dry eye disease (Benitez del Castillo et al, 2004; Benitez-Del-Castillo et al, 2007; Erdelyi et al, 2007; Labbe et al, 2013; Villani et al, 2007; Villani et al, 2013; Zhang et al, 2011). In healthy cornea, SP is generated by corneal nerves and epithelium and serves to protect epithelial integrity (Miller et al, 1981; Shimizu, 1982; Tervo et al, 1981; Yamada et al, 2005). In dry eye disease, desiccating stress disrupts the epithelial integrity and induces nerve loss(Stevenson et al, 2012). One expects that substance P production increases initially by the stressed epithelium and nerve fibers as a defensive mechanism to protect the epithelial integrity. SP then recruits immune cells via enhancing the production of chemokines, like IL-8. As the disease progresses, nerve and epithelial loss expectedly lead to reduced production of SP, while inflammation results in higher production of SP by the residents and recruited immune cells. In other words, a reduction in nerve density, such as in the chronic phase of dry eye disease, would expectedly lead to a reduction in SP level. In contrast, inflamed nerve cells, like those seen in early dry eye disease, would expectedly generate higher levels of SP. Corneal transplantation could be another interesting condition: Here, we expect a sudden release of copious amount of SP in the graft bed along with an immediate reduction in the production of nerve-derived SP in the grafted cornea. Other sources, such as macrophages, might produce more SP at the later stages. In high-risk setting (HR), where inflammation exists prior to transplantation(Inomata et al, 2015), SP level is likely higher than normal even before transplantation. SP generation

likely increases with the progression of alloimmune response and leads to increased angiogenesis and graft rejection. These hypotheses, however, remain to be tested in specific disease contexts.

4. Concluding remarks

Substance P represents an important component of the immune response. Despite the insight that has been gained from *in vitro* and *in vivo* studies, the several unresolved questions related to the role of SP in immunobiology remain to be elucidated. For example, the relationship between SP receptor levels of expression in different cell types and diseases is still unknown. This presents a challenge when interpreting clinical studies, where NK1R antagonists may need to be stratified to appropriate patient subsets. We need model systems that are simple enough to allow elucidation of the roles and responses of different cell types and their environment, that will help elucidate the role of SP in interactions between nerve, immune, vascular cells, as well as connective tissue cells. The cornea is potentially an excellent model system for such studies, as it carries the highest density of nerve cells and has proven to be an invaluable model system for immunology and angiogenesis. The clinical implications of such studies are potentially significant. Cornea transplants, for instance, are the most common human tissue transplants in the United States. It is likely that several studies related to substance P immunobiology using ocular surface disease models will emerge in the years to come.

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References

Ahluwalia A, De Felipe C, O'Brien J, Hunt SP, Perretti M. Impaired IL-1beta-induced neutrophil accumulation in tachykinin NK1 receptor knockout mice. Br J Pharmacol. 1998; 124:1013–1015. [PubMed: 9720767]

Ansel JC, Kaynard AH, Armstrong CA, Olerud J, Bunnett N, Payan D. Skin-nervous system interactions. J Invest Dermatol. 1996; 106:198–204. [PubMed: 8592075]

Araki-Sasaki K, Aizawa S, Hiramoto M, Nakamura M, Iwase O, Nakata K, Sasaki Y, Mano T, Handa H, Tano Y. Substance P-induced cadherin expression and its signal transduction in a cloned human corneal epithelial cell line. J Cell Physiol. 2000; 182:189–195. [PubMed: 10623882]

Asadi S, Alysandratos KD, Angelidou A, Miniati A, Sismanopoulos N, Vasiadi M, Zhang B, Kalogeromitros D, Theoharides TC. Substance P (SP) induces expression of functional corticotropin-releasing hormone receptor-1 (CRHR-1) in human mast cells. J Invest Dermatol. 2012; 132:324–329. [PubMed: 22089831]

Asahina A, Hosoi J, Beissert S, Stratigos A, Granstein RD. Inhibition of the induction of delayed-type and contact hypersensitivity by calcitonin gene-related peptide. J Immunol. 1995a; 154:3056–3061. [PubMed: 7897198]

Asahina A, Hosoi J, Murphy GF, Granstein RD. Calcitonin gene-related peptide modulates Langerhans cell antigen-presenting function. Proc Assoc Am Physicians. 1995b; 107:242–244. [PubMed: 8624859]

Bang R, Sass G, Kiemer AK, Vollmar AM, Neuhuber WL, Tiegs G. Neurokinin-1 receptor antagonists CP-96,345 and L-733,060 protect mice from cytokine-mediated liver injury. J Pharmacol Exp Ther. 2003; 305:31–39. [PubMed: 12649350]

Bar-Shavit Z, Goldman R, Stabinsky Y, Gottlieb P, Fridkin M, Teichberg VI, Blumberg S. Enhancement of phagocytosis - a newly found activity of substance P residing in its N-terminal tetrapeptide sequence. Biochem Biophys Res Commun. 1980; 94:1445–1451. [PubMed: 6156684]

Barker R, Larner A. Substance P and multiple sclerosis. Med Hypotheses. 1992; 37:40–43. [PubMed: 1373793]

Barros PO, Ferreira TB, Vieira MM, Almeida CR, Araujo-Lima CF, Silva-Filho RG, Hygino J, Andrade RM, Andrade AF, Bento CA. Substance P enhances Th17 phenotype in individuals with generalized anxiety disorder: an event resistant to glucocorticoid inhibition. J Clin Immunol. 2011; 31:51–59. [PubMed: 20865305]

Beinborn M, Blum A, Hang L, Setiawan T, Schroeder JC, Stoyanoff K, Leung J, Weinstock JV. TGF-beta regulates T-cell neurokinin-1 receptor internalization and function. Proc Natl Acad Sci U S A. 2010; 107:4293–4298. [PubMed: 20160079]

Benitez del Castillo JM, Wasfy MA, Fernandez C, Garcia-Sanchez J. An in vivo confocal masked study on corneal epithelium and subbasal nerves in patients with dry eye. Invest Ophthalmol Vis Sci. 2004; 45:3030–3035. [PubMed: 15326117]

Benitez-Del-Castillo JM, Acosta MC, Wassfi MA, Diaz-Valle D, Gegundez JA, Fernandez C, Garcia-Sanchez J. Relation between corneal innervation with confocal microscopy and corneal sensitivity with noncontact esthesiometry in patients with dry eye. Invest Ophthalmol Vis Sci. 2007; 48:173–181. [PubMed: 17197530]

Bignami F, Giacomini C, Lorusso A, Aramini A, Rama P, Ferrari G. NK1 receptor antagonists as a new treatment for corneal neovascularization. Invest Ophthalmol Vis Sci. 2014; 55:6783–6794. [PubMed: 25228541]

Blum AM, Metwali A, Crawford C, Li J, Qadir K, Elliott DE, Weinstock JV. Interleukin 12 and antigen independently induce substance P receptor expression in T cells in murine schistosomiasis mansoni. FASEB J. 2001; 15:950–957. [PubMed: 11292655]

Bockmann S. Substance P (NK(1)) receptor expression by human colonic epithelial cell line Caco-2. Peptides. 2002; 23:1783–1791. [PubMed: 12383866]

Brecha NC, Sternini C, Anderson K, Krause JE. Expression and cellular localization of substance P/neurokinin A and neurokinin B mRNAs in the rat retina. Vis Neurosci. 1989; 3:527–535. [PubMed: 2484823]

Brown SM, Lamberts DW, Reid TW, Nishida T, Murphy CJ. Neurotrophic and anhidrotic keratopathy treated with substance P and insulinlike growth factor 1. Arch Ophthalmol. 1997; 115:926–927. [PubMed: 9230840]

Bull HA, Hothersall J, Chowdhury N, Cohen J, Dowd PM. Neuropeptides induce release of nitric oxide from human dermal microvascular endothelial cells. J Invest Dermatol. 1996; 106:655–660. [PubMed: 8618000]

Caberlotto L, Hurd YL, Murdock P, Wahlin JP, Melotto S, Corsi M, Carletti R. Neurokinin 1 receptor and relative abundance of the short and long isoforms in the human brain. Eur J Neurosci. 2003; 17:1736–1746. [PubMed: 12752772]

Calvo CF, Chavanel G, Senik A. Substance P enhances IL-2 expression in activated human T cells. J Immunol. 1992; 148:3498–3504. [PubMed: 1375246]

Cao YQ, Mantyh PW, Carlson EJ, Gillespie AM, Epstein CJ, Basbaum AI. Primary afferent tachykinins are required to experience moderate to intense pain. Nature. 1998; 392:390–394. [PubMed: 9537322]

Carucci JA, Ignatius R, Wei Y, Cypess AM, Schaer DA, Pope M, Steinman RM, Mojsov S. Calcitonin gene-related peptide decreases expression of HLA-DR and CD86 by human dendritic cells and dampens dendritic cell-driven T cell-proliferative responses via the type I calcitonin gene-related peptide receptor. J Immunol. 2000; 164:3494–3499. [PubMed: 10725702]

Castagliuolo I, Riegler M, Pasha A, Nikulasson S, Lu B, Gerard C, Gerard NP, Pothoulakis C. Neurokinin-1 (NK-1) receptor is required in Clostridium difficile- induced enteritis. J Clin Invest. 1998; 101:1547–1550. [PubMed: 9541482]

Castagliuolo I, Valenick L, Liu J, Pothoulakis C. Epidermal growth factor receptor transactivation mediates substance P-induced mitogenic responses in U-373 MG cells. J Biol Chem. 2000; 275:26545–26550. [PubMed: 10846186]

Castellani ML, Vecchiet J, Salini V, Conti P, Theoharides TC, Caraffa A, Antinolfi P, Tete S, Ciampoli C, Cuccurullo C, Cerulli G, Felaco M, Boscolo P. Stimulation of CCL2 (MCP-1) and CCL2 mRNA by substance P in LAD2 human mast cells. Transl Res. 2009; 154:27–33. [PubMed: 19524871]

Chang MM, Leeman SE. Isolation of a sialogogic peptide from bovine hypothalamic tissue and its characterization as substance P. J Biol Chem. 1970; 245:4784–4790. [PubMed: 5456150]

Chang MM, Leeman SE, Niall HD. Amino-acid sequence of substance P. Nat New Biol. 1971; 232:86–87. [PubMed: 5285346]

Chauhan VS, Sterka DG Jr. Gray DL, Bost KL, Marriott I. Neurogenic exacerbation of microglial and astrocyte responses to Neisseria meningitidis and Borrelia burgdorferi. J Immunol. 2008; 180:8241–8249. [PubMed: 18523290]

Chernova I, Lai JP, Li H, Schwartz L, Tuluc F, Korchak HM, Douglas SD, Kilpatrick LE. Substance P (SP) enhances CCL5-induced chemotaxis and intracellular signaling in human monocytes, which express the truncated neurokinin-1 receptor (NK1R). J Leukoc Biol. 2009; 85:154–164. [PubMed: 18835883]

Chikama T, Fukuda K, Morishige N, Nishida T. Treatment of neurotrophic keratopathy with substance-P-derived peptide (FGLM) and insulin-like growth factor I. Lancet. 1998; 351:1783–1784. [PubMed: 9635953]

Cho KJ, Trzaska KA, Greco SJ, McArdle J, Wang FS, Ye JH, Rameshwar P. Neurons derived from human mesenchymal stem cells show synaptic transmission and can be induced to produce the neurotransmitter substance P by interleukin-1 alpha. Stem Cells. 2005; 23:383–391. [PubMed: 15749933]

Christian C, Gilbert M, Payan DG. Stimulation of transcriptional regulatory activity by substance P. Neuroimmunomodulation. 1994; 1:159–164. [PubMed: 7489329]

Cunin P, Caillon A, Corvaisier M, Garo E, Scotet M, Blanchard S, Delneste Y, Jeannin P. The tachykinins substance P and hemokinin-1 favor the generation of human memory Th17 cells by inducing IL-1beta, IL-23, and TNF-like 1A expression by monocytes. J Immunol. 2011; 186:4175–4182. [PubMed: 21368235]

Cursiefen C. Immune privilege and angiogenic privilege of the cornea. Chem Immunol Allergy. 2007; 92:50–57. [PubMed: 17264482]

Cury PR, Canavez F, de Araujo VC, Furuse C, de Araujo NS. Substance P regulates the expression of matrix metalloproteinases and tissue inhibitors of metalloproteinase in cultured human gingival fibroblasts. J Periodontal Res. 2008; 43:255–260. [PubMed: 18179473]

De Felipe C, Herrero JF, O'Brien JA, Palmer JA, Doyle CA, Smith AJ, Laird JM, Belmonte C, Cervero F, Hunt SP. Altered nociception, analgesia and aggression in mice lacking the receptor for substance P. Nature. 1998; 392:394–397. [PubMed: 9537323]

Delgado M, Chorny A, Gonzalez-Rey E, Ganea D. Vasoactive intestinal peptide generates CD4+CD25+ regulatory T cells in vivo. J Leukoc Biol. 2005a; 78:1327–1338. [PubMed: 16204628]

Delgado M, Gonzalez-Rey E, Ganea D. VIP/PACAP preferentially attract Th2 effectors through differential regulation of chemokine production by dendritic cells. FASEB J. 2004a; 18:1453–1455. [PubMed: 15231725]

Delgado M, Gonzalez-Rey E, Ganea D. The neuropeptide vasoactive intestinal peptide generates tolerogenic dendritic cells. J Immunol. 2005b; 175:7311–7324. [PubMed: 16301637]

Delgado M, Leceta J, Ganea D. Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide promote in vivo generation of memory Th2 cells. FASEB J. 2002; 16:1844–1846. [PubMed: 12223451]

Delgado M, Leceta J, Gomariz RP, Ganea D. Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide stimulate the induction of Th2 responses by up-regulating B7.2 expression. J Immunol. 1999a; 163:3629–3635. [PubMed: 10490956]

Delgado M, Munoz-Elias EJ, Gomariz RP, Ganea D. Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide prevent inducible nitric oxide synthase transcription in macrophages by inhibiting NF-kappa B and IFN regulatory factor 1 activation. J Immunol. 1999b; 162:4685–4696. [PubMed: 10202009]

Delgado M, Munoz-Elias EJ, Gomariz RP, Ganea D. VIP and PACAP inhibit IL-12 production in LPS-stimulated macrophages. Subsequent effect on IFNgamma synthesis by T cells. J Neuroimmunol. 1999c; 96:167–181. [PubMed: 10337915]

Delgado M, Reduta A, Sharma V, Ganea D. VIP/PACAP oppositely affects immature and mature dendritic cell expression of CD80/CD86 and the stimulatory activity for CD4(+) T cells. J Leukoc Biol. 2004b; 75:1122–1130. [PubMed: 15020654]

Depino AM, Earl C, Kaczmarczyk E, Ferrari C, Besedovsky H, del Rey A, Pitossi FJ, Oertel WH. Microglial activation with atypical proinflammatory cytokine expression in a rat model of Parkinson's disease. Eur J Neurosci. 2003; 18:2731–2742. [PubMed: 14656322]

Derocq JM, Segui M, Blazy C, Emonds-Alt X, Le Fur G, Brelire JC, Casellas P. Effect of substance P on cytokine production by human astrocytic cells and blood mononuclear cells: characterization of novel tachykinin receptor antagonists. FEBS Lett. 1996; 399:321–325. [PubMed: 8985172]

Ding W, Stohl LL, Wagner JA, Granstein RD. Calcitonin gene-related peptide biases Langerhans cells toward Th2-type immunity. J Immunol. 2008; 181:6020–6026. [PubMed: 18941191]

Eglezos A, Andrews PV, Boyd RL, Helme RD. Effects of capsaicin treatment on immunoglobulin secretion in the rat: further evidence for involvement of tachykinin-containing afferent nerves. J Neuroimmunol. 1990; 26:131–138. [PubMed: 1688877]

Elekes K, Helyes Z, Nemeth J, Sandor K, Pozsgai G, Kereskai L, Borzsei R, Pinter E, Szabo A, Szolcsanyi J. Role of capsaicin-sensitive afferents and sensory neuropeptides in endotoxin-induced airway inflammation and consequent bronchial hyperreactivity in the mouse. Regul Pept. 2007; 141:44–54. [PubMed: 17291600]

Engel MA, Khalil M, Mueller-Tribbensee SM, Becker C, Neuhuber WL, Neurath MF, Reeh PW. The proximodistal aggravation of colitis depends on substance P released from TRPV1-expressing sensory neurons. J Gastroenterol. 2012; 47:256–265. [PubMed: 22080974]

Erdelyi B, Kraak R, Zhivov A, Guthoff R, Nemeth J. In vivo confocal laser scanning microscopy of the cornea in dry eye. Graefes Arch Clin Exp Ophthalmol. 2007; 245:39–44. [PubMed: 16874525]

Feistritzer C, Clausen J, Sturn DH, Djanani A, Gunsilius E, Wiedermann CJ, Kahler CM. Natural killer cell functions mediated by the neuropeptide substance P. Regul Pept. 2003; 116:119–126. [PubMed: 14599723]

Fiebich BL, Schleicher S, Butcher RD, Craig A, Lieb K. The neuropeptide substance P activates p38 mitogen-activated protein kinase resulting in IL-6 expression independently from NF-kappa B. J Immunol. 2000; 165:5606–5611. [PubMed: 11067916]

Foldenauer ME, McClellan SA, Berger EA, Hazlett LD. Mammalian target of rapamycin regulates IL-10 and resistance to Pseudomonas aeruginosa corneal infection. J Immunol. 2013; 190:5649–5658. [PubMed: 23626014]

Fong TM, Anderson SA, Yu H, Huang RR, Strader CD. Differential activation of intracellular effector by two isoforms of human neurokinin-1 receptor. Mol Pharmacol. 1992; 41:24–30. [PubMed: 1310144]

Forster R, Davalos-Misslitz AC, Rot A. CCR7 and its ligands: balancing immunity and tolerance. Nat Rev Immunol. 2008; 8:362–371. [PubMed: 18379575]

Fox FE, Kubin M, Cassin M, Niu Z, Hosoi J, Torii H, Granstein RD, Trinchieri G, Rook AH. Calcitonin gene-related peptide inhibits proliferation and antigen presentation by human peripheral blood mononuclear cells: effects on B7, interleukin 10, and interleukin 12. J Invest Dermatol. 1997; 108:43–48. [PubMed: 8980285]

Fu WX, Qin B, Zhou AP, Yu QY, Huang QJ, Liang ZF. Regulation of NK92-MI cell cytotoxicity by substance P. Scand J Immunol. 2011; 74:107–113. [PubMed: 21375557]

Fukuda M, Kuwayama Y, Shiosaka S, Ishimoto I, Shimizu Y, Takagi H, Inagaki S, Sakanaka M, Semba E, Takatsuki K, Tohyama M. Demonstration of a substance P-like immunoreactivity in retinal cells of the rat. Neurosci Lett. 1981; 23:239–242. [PubMed: 6167910]

Gad M, Pedersen AE, Kristensen NN, Fernandez Cde F, Claesson MH. Blockage of the neurokinin 1 receptor and capsaicin-induced ablation of the enteric afferent nerves protect SCID mice against T-cell-induced chronic colitis. Inflamm Bowel Dis. 2009; 15:1174–1182. [PubMed: 19326358]

Gasteiger G, Rudensky AY. Interactions between innate and adaptive lymphocytes. Nat Rev Immunol. 2014; 14:631–639. [PubMed: 25132095]

Germonpre PR, Bullock GR, Lambrecht BN, Van De Velde V, Luyten WH, Joos GF, Pauwels RA. Presence of substance P and neurokinin 1 receptors in human sputum macrophages and U-937 cells. Eur Respir J. 1999; 14:776–782. [PubMed: 10573219]

Goetzl EJ, Voice JK, Shen S, Dorsam G, Kong Y, West KM, Morrison CF, Harmar AJ. Enhanced delayed-type hypersensitivity and diminished immediate-type hypersensitivity in mice lacking the inducible VPAC(2) receptor for vasoactive intestinal peptide. Proc Natl Acad Sci U S A. 2001; 98:13854–13859. [PubMed: 11698667]

Gonzalez-Rey E, Chorny A, Fernandez-Martin A, Ganea D, Delgado M. Vasoactive intestinal peptide generates human tolerogenic dendritic cells that induce CD4 and CD8 regulatory T cells. Blood. 2006a; 107:3632–3638. [PubMed: 16397128]

Gonzalez-Rey E, Fernandez-Martin A, Chorny A, Delgado M. Vasoactive intestinal peptide induces CD4+,CD25+ T regulatory cells with therapeutic effect in collagen-induced arthritis. Arthritis Rheum. 2006b; 54:864–876. [PubMed: 16508968]

Grace PM, Hutchinson MR, Maier SF, Watkins LR. Pathological pain and the neuroimmune interface. Nat Rev Immunol. 2014; 14:217–231. [PubMed: 24577438]

Grace PM, Maier SF, Watkins LR. Opioid-induced central immune signaling: implications for opioid analgesia. Headache. 2015; 55:475–489. [PubMed: 25833219]

Grady EF, Garland AM, Gamp PD, Lovett M, Payan DG, Bunnett NW. Delineation of the endocytic pathway of substance P and its seven-transmembrane domain NK1 receptor. Mol Biol Cell. 1995; 6:509–524. [PubMed: 7545030]

Greeno EW, Mantyh P, Vercellotti GM, Moldow CF. Functional neurokinin 1 receptors for substance P are expressed by human vascular endothelium. J Exp Med. 1993; 177:1269–1276. [PubMed: 7683033]

Guo CJ, Lai JP, Luo HM, Douglas SD, Ho WZ. Substance P up-regulates macrophage inflammatory protein-1beta expression in human T lymphocytes. J Neuroimmunol. 2002; 131:160–167. [PubMed: 12458047]

Guo W, Wang H, Watanabe M, Shimizu K, Zou S, LaGraize SC, Wei F, Dubner R, Ren K. Glial-cytokine-neuronal interactions underlying the mechanisms of persistent pain. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2007; 27:6006–6018. [PubMed: 17537972]

Hartung HP, Toyka KV. Activation of macrophages by substance P: induction of oxidative burst and thromboxane release. Eur J Pharmacol. 1983; 89:301–305. [PubMed: 6191998]

Hazlett LD, McClellan SA, Barrett RP, Liu J, Zhang Y, Lighvani S. Spantide I decreases type I cytokines, enhances IL-10, and reduces corneal perforation in susceptible mice after Pseudomonas aeruginosa infection. Invest Ophthalmol Vis Sci. 2007; 48:797–807. [PubMed: 17251480]

Hegde A, Zhang H, Moochhala SM, Bhatia M. Neurokinin-1 receptor antagonist treatment protects mice against lung injury in polymicrobial sepsis. J Leukoc Biol. 2007; 82:678–685. [PubMed: 17565047]

Ho WZ, Lai JP, Zhu XH, Uvaydova M, Douglas SD. Human monocytes and macrophages express substance P and neurokinin-1 receptor. J Immunol. 1997; 159:5654–5660. [PubMed: 9548509]

Hokfelt T, Johansson O, Ljungdahl A, Lundberg JM, Schultzberg M. Peptidergic neurones. Nature. 1980; 284:515–521. [PubMed: 6154244]

Holzer P. Local effector functions of capsaicin-sensitive sensory nerve endings: involvement of tachykinins, calcitonin gene-related peptide and other neuropeptides. Neuroscience. 1988; 24:739–768. [PubMed: 3288903]

Hong HS, Kim S, Nam S, Um J, Kim YH, Son Y. Effect of substance P on recovery from laser-induced retinal degeneration. Wound Repair Regen. 2015; 23:268–277. [PubMed: 25682893]

Hong HS, Lee J, Lee E, Kwon YS, Ahn W, Jiang MH, Kim JC, Son Y. A new role of substance P as an injury-inducible messenger for mobilization of CD29(+) stromal-like cells. Nature medicine. 2009; 15:425–435.

Hosoi J, Murphy GF, Egan CL, Lerner EA, Grabbe S, Asahina A, Granstein RD. Regulation of Langerhans cell function by nerves containing calcitonin gene-related peptide. Nature. 1993; 363:159–163. [PubMed: 8483499]

Huang GT, Lee HW, Lee HS, Lee GH, Huh SY, Choi GW, Park SH. Localization of substance P-induced upregulated interleukin-8 expression in human dental pulp explants. Int Endod J. 2008; 41:100–107. [PubMed: 18005045]

Ikeda Y, Takei H, Matsumoto C, Mase A, Yamamoto M, Takeda S, Ishige A, Watanabe K. Administration of substance P during a primary immune response amplifies the secondary immune response via a long-lasting effect on CD8+ T lymphocytes. Arch Dermatol Res. 2007; 299:345–351. [PubMed: 17643253]

Inomata T, Mashaghi A, Di Zazzo A, Dana R. Ocular surgical models for immune and angiogenic responses. Journal of biological methods. 2015; 2

Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. Nat Immunol. 2015; 16:343–353. [PubMed: 25789684]

Janelsins BM, Mathers AR, Tkacheva OA, Erdos G, Shufesky WJ, Morelli AE, Larregina AT. Proinflammatory tachykinins that signal through the neurokinin 1 receptor promote survival of dendritic cells and potent cellular immunity. Blood. 2009; 113:3017–3026. [PubMed: 18987361]

Janelsins BM, Sumpter TL, Tkacheva OA, Rojas-Canales DM, Erdos G, Mathers AR, Shufesky WJ, Storkus WJ, Falo LD Jr. Morelli AE, Larregina AT. Neurokinin-1 receptor agonists bias therapeutic dendritic cells to induce type 1 immunity by licensing host dendritic cells to produce IL-12. Blood. 2013; 121:2923–2933. [PubMed: 23365459]

Jeon HK, Jung NP, Choi IH, Oh YK, Shin HC, Gwag BJ. Substance P augments nitric oxide production and gene expression in murine macrophages. Immunopharmacology. 1999; 41:219–226. [PubMed: 10428650]

Jimeno R, Leceta J, Garin M, Ortiz AM, Mellado M, Rodriguez-Frade JM, Martinez C, Perez-Garcia S, Gomariz RP, Juarranz Y. Th17 polarization of memory Th cells in early arthritis: the vasoactive intestinal peptide effect. J Leukoc Biol. 2015; 98:257–269. [PubMed: 25957307]

Jin Y, Hong HS, Son Y. Substance P enhances mesenchymal stem cells-mediated immune modulation. Cytokine. 2015; 71:145–153. [PubMed: 25461392]

Joachim RA, Sagach V, Quarcoo D, Dinh T, Arck PC, Klapp BF. Upregulation of tumor necrosis factor-alpha by stress and substance p in a murine model of allergic airway inflammation. Neuroimmunomodulation. 2006; 13:43–50. [PubMed: 16837794]

Jones MA, Marfurt CF. Peptidergic innervation of the rat cornea. Exp Eye Res. 1998; 66:421–435. [PubMed: 9593636]

Kan A, Hodgkin P. Mechanisms of cell division as regulators of acute immune response. Systems and synthetic biology. 2014; 8:215–221. [PubMed: 25136383]

Katsanos GS, Anogeianaki A, Orso C, Tete S, Salini V, Antinolfi PL, Sabatino G. Impact of substance P on cellular immunity. J Biol Regul Homeost Agents. 2008; 22:93–98. [PubMed: 18597700]

Kavelaars A, Broeke D, Jeurissen F, Kardux J, Meijer A, Franklin R, Gelfand EW, Heijnen CJ. Activation of human monocytes via a non-neurokinin substance P receptor that is coupled to Gi protein, calcium, phospholipase D, MAP kinase, and IL-6 production. J Immunol. 1994; 153:3691–3699. [PubMed: 7930588]

Keeble J, Blades M, Pitzalis C, Castro da Rocha FA, Brain SD. The role of substance P in microvascular responses in murine joint inflammation. Br J Pharmacol. 2005; 144:1059–1066. [PubMed: 15700029]

Kimbrell DA, Beutler B. The evolution and genetics of innate immunity. Nat Rev Genet. 2001; 2:256–267. [PubMed: 11283698]

Kincy-Cain T, Bost KL. Increased susceptibility of mice to Salmonella infection following in vivo treatment with the substance P antagonist, spantide II. J Immunol. 1996; 157:255–264. [PubMed: 8683123]

Kitamura H, Kobayashi M, Wakita D, Nishimura T. Neuropeptide signaling activates dendritic cell-mediated type 1 immune responses through neurokinin-2 receptor. J Immunol. 2012; 188:4200–4208. [PubMed: 22474018]

Knodell RG, Handwerger BS, Morley JE, Levine AS, Brown DM. Separate influences of insulin and hyperglycemia on hepatic drug metabolism in mice with genetic and chemically induced diabetes mellitus. J Pharmacol Exp Ther. 1984; 230:256–262. [PubMed: 6379147]

Ko JA, Yanai R, Nishida T. Up-regulation of ZO-1 expression and barrier function in cultured human corneal epithelial cells by substance P. FEBS Lett. 2009; 583:2148–2153. [PubMed: 19446555]

Kohara H, Tajima S, Yamamoto M, Tabata Y. Angiogenesis induced by controlled release of neuropeptide substance P. Biomaterials. 2010; 31:8617–8625. [PubMed: 20708795]

Koizumi H, Yasui C, Fukaya T, Ueda T, Ohkawara A. Substance P induces inositol 1,4,5-trisphosphate and intracellular free calcium increase in cultured normal human epidermal keratinocytes. Exp Dermatol. 1994; 3:40–44. [PubMed: 7520337]

Koon HW, Zhao D, Zhan Y, Simeonidis S, Moyer MP, Pothoulakis C. Substance P-stimulated interleukin-8 expression in human colonic epithelial cells involves protein kinase Cdelta activation. J Pharmacol Exp Ther. 2005; 314:1393–1400. [PubMed: 15917399]

Kramer MS, Cutler N, Feighner J, Shrivastava R, Carman J, Sramek JJ, Reines SA, Liu G, Snavely D, Wyatt-Knowles E, Hale JJ, Mills SG, MacCoss M, Swain CJ, Harrison T, Hill RG, Hefti F, Scolnick EM, Cascieri MA, Chicchi GG, Sadowski S, Williams AR, Hewson L, Smith D, Carlson EJ, Hargreaves RJ, Rupniak NM. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science. 1998; 281:1640–1645. [PubMed: 9733503]

Kramer MS, Winokur A, Kelsey J, Preskorn SH, Rothschild AJ, Snavely D, Ghosh K, Ball WA, Reines SA, Munjack D, Apter JT, Cunningham L, Kling M, Bari M, Getson A, Lee Y. Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression. Neuropsychopharmacology. 2004; 29:385–392. [PubMed: 14666114]

Krause JE, Chirgwin JM, Carter MS, Xu ZS, Hershey AD. Three rat preprotachykinin mRNAs encode the neuropeptides substance P and neurokinin A. Proc Natl Acad Sci U S A. 1987; 84:881–885. [PubMed: 2433692]

Kroegel C, Giembycz MA, Barnes PJ. Characterization of eosinophil cell activation by peptides. Differential effects of substance P, melittin, and FMET-Leu-Phe. J Immunol. 1990; 145:2581–2587. [PubMed: 1698858]

Kubilus JK, Linsenmayer TF. Developmental corneal innervation: interactions between nerves and specialized apical corneal epithelial cells. Invest Ophthalmol Vis Sci. 2010; 51:782–789. [PubMed: 19741242]

Labbe A, Liang Q, Wang Z, Zhang Y, Xu L, Baudouin C, Sun X. Corneal nerve structure and function in patients with non-sjogren dry eye: clinical correlations. Invest Ophthalmol Vis Sci. 2013; 54:5144–5150. [PubMed: 23833066]

Lai JP, Douglas SD, Ho WZ. Human lymphocytes express substance P and its receptor. J Neuroimmunol. 1998; 86:80–86. [PubMed: 9655475]

Lai JP, Ho WZ, Kilpatrick LE, Wang X, Tuluc F, Korchak HM, Douglas SD. Full-length and truncated neurokinin-1 receptor expression and function during monocyte/macrophage differentiation. Proc Natl Acad Sci U S A. 2006; 103:7771–7776. [PubMed: 16675550]

Lai JP, Lai S, Tuluc F, Tansky MF, Kilpatrick LE, Leeman SE, Douglas SD. Differences in the length of the carboxyl terminus mediate functional properties of neurokinin-1 receptor. Proc Natl Acad Sci U S A. 2008; 105:12605–12610. [PubMed: 18713853]

Lai JP, Zhan GX, Campbell DE, Douglas SD, Ho WZ. Detection of substance P and its receptor in human fetal microglia. Neuroscience. 2000; 101:1137–1144. [PubMed: 11113362]

Lambrecht BN, Germonpre PR, Everaert EG, Carro-Muino I, De Veerman M, de Felipe C, Hunt SP, Thielemans K, Joos GF, Pauwels RA. Endogenously produced substance P contributes to lymphocyte proliferation induced by dendritic cells and direct TCR ligation. Eur J Immunol. 1999; 29:3815–3825. [PubMed: 10601989]

Lembeck F, Holzer P. Substance P as neurogenic mediator of antidromic vasodilation and neurogenic plasma extravasation. Naunyn Schmiedebergs Arch Pharmacol. 1979; 310:175–183. [PubMed: 93706]

Levite M. Neuropeptides, by direct interaction with T cells, induce cytokine secretion and break the commitment to a distinct T helper phenotype. Proc Natl Acad Sci U S A. 1998; 95:12544–12549. [PubMed: 9770522]

Lewis KM, Turner RJ, Vink R. Blocking neurogenic inflammation for the treatment of acute disorders of the central nervous system. International journal of inflammation. 2013; 2013:578480. [PubMed: 23819099]

Li WW, Guo TZ, Shi X, Sun Y, Wei T, Clark DJ, Kingery WS. Substance P spinal signaling induces glial activation and nociceptive sensitization after fracture. Neuroscience. 2015; 310:73–90. [PubMed: 26386297]

Li Y, Douglas SD, Ho W. Human stem cells express substance P gene and its receptor. J Hematother Stem Cell Res. 2000; 9:445–452. [PubMed: 10982242]

Lieb K, Fiebich BL, Berger M, Bauer J, Schulze-Osthoff K. The neuropeptide substance P activates transcription factor NF-kappa B and kappa B-dependent gene expression in human astrocytoma cells. J Immunol. 1997; 159:4952–4958. [PubMed: 9366421]

Lighvani S, Huang X, Trivedi PP, Swanborg RH, Hazlett LD. Substance P regulates natural killer cell interferon-gamma production and resistance to Pseudomonas aeruginosa infection. Eur J Immunol. 2005; 35:1567–1575. [PubMed: 15832292]

Lipton JM, Catania A. Anti-inflammatory actions of the neuroimmunomodulator alpha-MSH. Immunol Today. 1997; 18:140–145. [PubMed: 9078687]

Liu D, Jiang LS, Dai LY. Substance P and its receptors in bone metabolism. Neuropeptides. 2007; 41:271–283. [PubMed: 17655927]

Liu J, Chen M, Wang X. Calcitonin gene-related peptide inhibits lipopolysaccharide-induced interleukin-12 release from mouse peritoneal macrophages, mediated by the cAMP pathway. Immunology. 2000; 101:61–67. [PubMed: 11012754]

Liu JY, Hu JH, Zhu QG, Li FQ, Sun HJ. Substance P receptor expression in human skin keratinocytes and fibroblasts. Br J Dermatol. 2006; 155:657–662. [PubMed: 16965412]

Lo SY, Brett CL, Plemel RL, Vignali M, Fields S, Gonen T, Merz AJ. Intrinsic tethering activity of endosomal Rab proteins. Nat Struct Mol Biol. 2012; 19:40–47.

Lotz M, Carson DA, Vaughan JH. Substance P activation of rheumatoid synoviocytes: neural pathway in pathogenesis of arthritis. Science. 1987; 235:893–895. [PubMed: 2433770]

Lu TS, Avraham HK, Seng S, Tachado SD, Koziel H, Makriyannis A, Avraham S. Cannabinoids inhibit HIV-1 Gp120-mediated insults in brain microvascular endothelial cells. J Immunol. 2008; 181:6406–6416. [PubMed: 18941231]

Lucas K, Karamichos D, Mathew R, Zieske JD, Stein-Streilein J. Retinal laser burn-induced neuropathy leads to substance P-dependent loss of ocular immune privilege. J Immunol. 2012; 189:1237–1242. [PubMed: 22745377]

Luger TA, Scholzen TE, Brzoska T, Bohm M. New insights into the functions of alpha-MSH and related peptides in the immune system. Ann N Y Acad Sci. 2003; 994:133–140. [PubMed: 12851308]

Luo W, Sharif TR, Sharif M. Substance P-induced mitogenesis in human astrocytoma cells correlates with activation of the mitogen-activated protein kinase signaling pathway. Cancer Res. 1996; 56:4983–4991. [PubMed: 8895754]

Maghni K, Michoud MC, Alles M, Rubin A, Govindaraju V, Meloche C, Martin JG. Airway smooth muscle cells express functional neurokinin-1 receptors and the nerve-derived preprotachykinin-a gene: regulation by passive sensitization. Am J Respir Cell Mol Biol. 2003; 28:103–110. [PubMed: 12495938]

Marriott I, Bost KL. IL-4 and IFN-gamma up-regulate substance P receptor expression in murine peritoneal macrophages. J Immunol. 2000; 165:182–191. [PubMed: 10861051]

Marriott I, Bost KL. Expression of authentic substance P receptors in murine and human dendritic cells. J Neuroimmunol. 2001; 114:131–141. [PubMed: 11240024]

Marshall GE, Shehab SA, Spike RC, Todd AJ. Neurokinin-1 receptors on lumbar spinothalamic neurons in the rat. Neuroscience. 1996; 72:255–263. [PubMed: 8730722]

Mashaghi A, Dekker C. Systems and synthetic biology approaches to cell division. Systems and synthetic biology. 2014; 8:173–178. [PubMed: 25136378]

Mathers AR, Tckacheva OA, Janelsins BM, Shufesky WJ, Morelli AE, Larregina AT. In vivo signaling through the neurokinin 1 receptor favors transgene expression by Langerhans cells and promotes the generation of Th1- and Tc1-biased immune responses. J Immunol. 2007; 178:7006–7017. [PubMed: 17513750]

Matis WL, Lavker RM, Murphy GF. Substance P induces the expression of an endothelial-leukocyte adhesion molecule by microvascular endothelium. J Invest Dermatol. 1990; 94:492–495. [PubMed: 1690249]

McClellan SA, Zhang Y, Barrett RP, Hazlett LD. Substance P promotes susceptibility to Pseudomonas aeruginosa keratitis in resistant mice: anti-inflammatory mediators downregulated. Invest Ophthalmol Vis Sci. 2008; 49:1502–1511. [PubMed: 18385069]

McConalogue K, Corvera CU, Gamp PD, Grady EF, Bunnett NW. Desensitization of the neurokinin-1 receptor (NK1-R) in neurons: effects of substance P on the distribution of NK1-R, Galphaq/11, G-protein receptor kinase-2/3, and beta-arrestin-1/2. Mol Biol Cell. 1998; 9:2305–2324. [PubMed: 9693383]

McConalogue K, Dery O, Lovett M, Wong H, Walsh JH, Grady EF, Bunnett NW. Substance P-induced trafficking of beta-arrestins. The role of beta-arrestins in endocytosis of the neurokinin-1 receptor. J Biol Chem. 1999; 274:16257–16268. [PubMed: 10347182]

McGeer PL, McGeer EG. Glial reactions in Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society. 2008; 23:474–483. [PubMed: 18044695]

McGregor GP, Bloom SR. Radioimmunoassay of substance P and its stability in tissue. Life sciences. 1983; 32:655–662. [PubMed: 6188020]

Mei G, Xia L, Zhou J, Zhang Y, Tuo Y, Fu S, Zou Z, Wang Z, Jin D. Neuropeptide SP activates the WNT signal transduction pathway and enhances the proliferation of bone marrow stromal stem cells. Cell Biol Int. 2013; 37:1225–1232. [PubMed: 23893958]

Metwali A, Blum AM, Ferraris L, Klein JS, Fiocchi C, Weinstock JV. Eosinophils within the healthy or inflamed human intestine produce substance P and vasoactive intestinal peptide. J Neuroimmunol. 1994; 52:69–78. [PubMed: 7515901]

Michaels LA, Ohene-Frempong K, Zhao H, Douglas SD. Serum levels of substance P are elevated in patients with sickle cell disease and increase further during vaso-occlusive crisis. Blood. 1998; 92:3148–3151. [PubMed: 9787150]

Michel JP, Sakamoto N, Bouvier R, Tommasi M, Pearson J. Substance P-immunoreactive astrocytes related to deep white matter and striatal blood vessels in human brain. Brain Res. 1986; 377:383–387. [PubMed: 2425903]

Mikami N, Matsushita H, Kato T, Kawasaki R, Sawazaki T, Kishimoto T, Ogitani Y, Watanabe K, Miyagi Y, Sueda K, Fukada S, Yamamoto H, Tsujikawa K. Calcitonin gene-related peptide is an important regulator of cutaneous immunity: effect on dendritic cell and T cell functions. J Immunol. 2011; 186:6886–6893. [PubMed: 21551361]

Mikami N, Sueda K, Ogitani Y, Otani I, Takatsuji M, Wada Y, Watanabe K, Yoshikawa R, Nishioka S, Hashimoto N, Miyagi Y, Fukada S, Yamamoto H, Tsujikawa K. Calcitonin gene-related peptide regulates type IV hypersensitivity through dendritic cell functions. PLoS One. 2014; 9:e86367. [PubMed: 24466057]

Mikami N, Watanabe K, Hashimoto N, Miyagi Y, Sueda K, Fukada S, Yamamoto H, Tsujikawa K. Calcitonin gene-related peptide enhances experimental autoimmune encephalomyelitis by promoting Th17-cell functions. Int Immunol. 2012; 24:681–691. [PubMed: 22843730]

Miller A, Costa M, Furness JB, Chubb IW. Substance P immunoreactive sensory nerves supply the rat iris and cornea. Neurosci Lett. 1981; 23:243–249. [PubMed: 6167911]

Milner P, Bodin P, Guiducci S, Del Rosso A, Kahaleh MB, Matucci-Cerinic M, Burnstock G. Regulation of substance P mRNA expression in human dermal microvascular endothelial cells. Clin Exp Rheumatol. 2004; 22:S24–27. [PubMed: 15344593]

Monastyrskaya K, Hostettler A, Buergi S, Draeger A. The NK1 receptor localizes to the plasma membrane microdomains, and its activation is dependent on lipid raft integrity. J Biol Chem. 2005; 280:7135–7146. [PubMed: 15590676]

Mosley RL, Benner EJ, Kadiu I, Thomas M, Boska MD, Hasan K, Laurie C, Gendelman HE. Neuroinflammation, Oxidative Stress and the Pathogenesis of Parkinson's Disease. Clinical neuroscience research. 2006; 6:261–281. [PubMed: 18060039]

Mukherjee S, Liu X, Arasaki K, McDonough J, Galan JE, Roy CR. Modulation of Rab GTPase function by a protein phosphocholine transferase. Nature. 2011; 477:103–106. [PubMed: 21822290]

Muller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. Exp Eye Res. 2003; 76:521–542. [PubMed: 12697417]

Munoz M, Rosso M. The NK-1 receptor antagonist aprepitant as a broad spectrum antitumor drug. Invest New Drugs. 2010; 28:187–193. [PubMed: 19148578]

Murphy JE, Roosterman D, Cottrell GS, Padilla BE, Feld M, Brand E, Cedron WJ, Bunnett NW, Steinhoff M. Protein phosphatase 2A mediates resensitization of the neurokinin 1 receptor. Am J Physiol Cell Physiol. 2011; 301:C780–791. [PubMed: 21795521]

Murris-Espin M, Pinelli E, Pipy B, Leophonte P, Didier A. Substance P and alveolar macrophages: effects on oxidative metabolism and eicosanoid production. Allergy. 1995; 50:334–339. [PubMed: 7573817]

Nakamura M, Chikama T, Nishida T. Up-regulation of integrin alpha 5 expression by combination of substance P and insulin-like growth factor-1 in rabbit corneal epithelial cells. Biochem Biophys Res Commun. 1998a; 246:777–782. [PubMed: 9618288]

Nakamura M, Kawahara M, Morishige N, Chikama T, Nakata K, Nishida T. Promotion of corneal epithelial wound healing in diabetic rats by the combination of a substance P-derived peptide (FGLM-NH2) and insulin-like growth factor-1. Diabetologia. 2003; 46:839–842. [PubMed: 12764579]

Nakamura M, Nagano T, Chikama T, Nishida T. Up-regulation of phosphorylation of focal adhesion kinase and paxillin by combination of substance P and IGF-1 in SV-40 transformed human corneal epithelial cells. Biochem Biophys Res Commun. 1998b; 242:16–20. [PubMed: 9439602]

Namba K, Kitaichi N, Nishida T, Taylor AW. Induction of regulatory T cells by the immunomodulating cytokines alpha-melanocyte-stimulating hormone and transforming growth factor-beta2. J Leukoc Biol. 2002; 72:946–952. [PubMed: 12429716]

Nawa H, Hirose T, Takashima H, Inayama S, Nakanishi S. Nucleotide sequences of cloned cDNAs for two types of bovine brain substance P precursor. Nature. 1983; 306:32–36. [PubMed: 6195531]

Nessler S, Stadelmann C, Bittner A, Schlegel K, Gronen F, Brueck W, Hemmer B, Sommer N. Suppression of autoimmune encephalomyelitis by a neurokinin-1 receptor antagonist--a putative role for substance P in CNS inflammation. J Neuroimmunol. 2006; 179:1–8. [PubMed: 16904192]

Niizeki H, Kurimoto I, Streilein JW. A substance p agonist acts as an adjuvant to promote hapten-specific skin immunity. J Invest Dermatol. 1999; 112:437–442. [PubMed: 10201526]

Nilsson J, von Euler AM, Dalsgaard CJ. Stimulation of connective tissue cell growth by substance P and substance K. Nature. 1985; 315:61–63. [PubMed: 2581142]

Nio DA, Moylan RN, Roche JK. Modulation of T lymphocyte function by neuropeptides. Evidence for their role as local immunoregulatory elements. J Immunol. 1993; 150:5281–5288. [PubMed: 8515059]

Nishida T, Nakamura M, Konma T, Ofuji K, Nagano K, Tanaka T, Enoki M, Reid TW, Brown SM, Murphy CJ, Mannis MJ. Neurotrophic keratopathy--studies on substance P and the clinical significance of corneal sensation. Nihon Ganka Gakkai Zasshi. 1997; 101:948–974. [PubMed: 9436358]

Nishimura K, Warabi K, Roush ED, Frederick J, Schwinn DA, Kwatra MM. Characterization of GRK2-catalyzed phosphorylation of the human substance P receptor in Sf9 membranes. Biochemistry. 1998; 37:1192–1198. [PubMed: 9477943]

Nong YH, Titus RG, Ribeiro JM, Remold HG. Peptides encoded by the calcitonin gene inhibit macrophage function. J Immunol. 1989; 143:45–49. [PubMed: 2543703]

O'Connor TM, O'Connell J, O'Brien DI, Goode T, Bredin CP, Shanahan F. The role of substance P in inflammatory disease. J Cell Physiol. 2004; 201:167–180. [PubMed: 15334652]

Okayama Y, Ono Y, Nakazawa T, Church MK, Mori M. Human skin mast cells produce TNF-alpha by substance P. Int Arch Allergy Immunol. 1998; 117(Suppl 1):48–51. [PubMed: 9758897]

Ostrowski SM, Belkadi A, Loyd CM, Diaconu D, Ward NL. Cutaneous denervation of psoriasiform mouse skin improves acanthosis and inflammation in a sensory neuropeptide-dependent manner. J Invest Dermatol. 2011; 131:1530–1538. [PubMed: 21471984]

Ottosson A, Edvinsson L. Release of histamine from dural mast cells by substance P and calcitonin gene-related peptide. Cephalalgia: an international journal of headache. 1997; 17:166–174. [PubMed: 9170339]

Pascual DW, Xu-Amano JC, Kiyono H, McGhee JR, Bost KL. Substance P acts directly upon cloned B lymphoma cells to enhance IgA and IgM production. J Immunol. 1991; 146:2130–2136. [PubMed: 1706387]

Pavlova MN, Kaz'min AI, Abal'masova EA, Barer FS. Pathomorphological characteristics of the intervertebral disks in scoliosis of varying etiology. Ortopediia travmatologiia i protezirovanie. 1976:1–7.

Payan DG. Receptor-mediated mitogenic effects of substance P on cultured smooth muscle cells. Biochem Biophys Res Commun. 1985; 130:104–109. [PubMed: 2411258]

Payan DG, Brewster DR, Goetzl EJ. Specific stimulation of human T lymphocytes by substance P. J Immunol. 1983; 131:1613–1615. [PubMed: 6194207]

Pelayo JC, Poole DP, Steinhoff M, Cottrell GS, Bunnett NW. Endothelin-converting enzyme-1 regulates trafficking and signalling of the neurokinin 1 receptor in endosomes of myenteric neurones. J Physiol. 2011; 589:5213–5230. [PubMed: 21878523]

Pickel VM, Reis DJ, Leeman SE. Ultrastructural localization of substance P in neurons of rat spinal cord. Brain Res. 1977; 122:534–540. [PubMed: 843902]

Qazi Y, Hamrah P. Corneal Allograft Rejection: Immunopathogenesis to Therapeutics. J Clin Cell Immunol. 2013; 2013

Quinlan KL, Naik SM, Cannon G, Armstrong CA, Bunnett NW, Ansel JC, Caughman SW. Substance P activates coincident NF-AT- and NF-kappa B-dependent adhesion molecule gene expression in microvascular endothelial cells through intracellular calcium mobilization. J Immunol. 1999; 163:5656–5665. [PubMed: 10553096]

Ramalho R, Almeida J, Beltrao M, Pirraco A, Costa R, Sokhatska O, Guardao L, Palmares C, Guimaraes JT, Delgado L, Moreira A, Soares R. Substance P antagonist improves both obesity and asthma in a mouse model. Allergy. 2013; 68:48–54. [PubMed: 23176443]

Rameshwar P, Ganea D, Gascon P. Induction of IL-3 and granulocyte-macrophage colony-stimulating factor by substance P in bone marrow cells is partially mediated through the release of IL-1 and IL-6. J Immunol. 1994; 152:4044–4054. [PubMed: 7511664]

Rameshwar P, Gascon P. Substance P (SP) mediates production of stem cell factor and interleukin-1 in bone marrow stroma: potential autoregulatory role for these cytokines in SP receptor expression and induction. Blood. 1995; 86:482–490. [PubMed: 7541664]

Rameshwar P, Gascon P, Ganea D. Stimulation of IL-2 production in murine lymphocytes by substance P and related tachykinins. J Immunol. 1993; 151:2484–2496. [PubMed: 7689609]

Rameshwar P, Joshi DD, Yadav P, Qian J, Gascon P, Chang VT, Anjaria D, Harrison JS, Song X. Mimicry between neurokinin-1 and fibronectin may explain the transport and stability of increased substance P immunoreactivity in patients with bone marrow fibrosis. Blood. 2001a; 97:3025–3031. [PubMed: 11342427]

Rameshwar P, Zhu G, Donnelly RJ, Qian J, Ge H, Goldstein KR, Denny TN, Gascon P. The dynamics of bone marrow stromal cells in the proliferation of multipotent hematopoietic progenitors by substance P: an understanding of the effects of a neurotransmitter on the differentiating hematopoietic stem cell. J Neuroimmunol. 2001b; 121:22–31. [PubMed: 11730936]

Razavi R, Chan Y, Afifiyan FN, Liu XJ, Wan X, Yantha J, Tsui H, Tang L, Tsai S, Santamaria P, Driver JP, Serreze D, Salter MW, Dosch HM. TRPV1+ sensory neurons control beta cell stress and islet inflammation in autoimmune diabetes. Cell. 2006; 127:1123–1135. [PubMed: 17174891]

Reinke EK, Johnson MJ, Ling C, Karman J, Lee J, Weinstock JV, Sandor M, Fabry Z. Substance P receptor mediated maintenance of chronic inflammation in EAE. J Neuroimmunol. 2006; 180:117–125. [PubMed: 16942803]

Ren K, Dubner R. Interactions between the immune and nervous systems in pain. Nature medicine. 2010; 16:1267–1276.

Rochlitzer S, Veres TZ, Kuhne K, Prenzler F, Pilzner C, Knothe S, Winkler C, Lauenstein HD, Willart M, Hammad H, Muller M, Krug N, Lambrecht BN, Braun A. The neuropeptide calcitonin gene-

related peptide affects allergic airway inflammation by modulating dendritic cell function. Clin Exp Allergy. 2011; 41:1609–1621. [PubMed: 21752117]

Roosterman D, Cottrell GS, Schmidlin F, Steinhoff M, Bunnett NW. Recycling and resensitization of the neurokinin 1 receptor. Influence of agonist concentration and Rab GTPases. J Biol Chem. 2004; 279:30670–30679. [PubMed: 15128739]

Rozsa AJ, Beuerman RW. Density and organization of free nerve endings in the corneal epithelium of the rabbit. Pain. 1982; 14:105–120. [PubMed: 7177676]

Rupniak NM, Kramer MS. Discovery of the antidepressant and anti-emetic efficacy of substance P receptor (NK1) antagonists. Trends Pharmacol Sci. 1999; 20:485–490. [PubMed: 10671176]

Scholzen TE, Steinhoff M, Sindrilaru A, Schwarz A, Bunnett NW, Luger TA, Armstrong CA, Ansel JC. Cutaneous allergic contact dermatitis responses are diminished in mice deficient in neurokinin 1 receptors and augmented by neurokinin 2 receptor blockage. FASEB J. 2004; 18:1007–1009. [PubMed: 15084523]

Scicchitano R, Biennenstock J, Stanisz AM. In vivo immunomodulation by the neuropeptide substance P. Immunology. 1988; 63:733–735. [PubMed: 2452790]

Serra MC, Bazzoni F, Della Bianca V, Greskowiak M, Rossi F. Activation of human neutrophils by substance P. Effect on oxidative metabolism, exocytosis, cytosolic Ca2+ concentration and inositol phosphate formation. J Immunol. 1988; 141:2118–2124. [PubMed: 2459200]

Serra MC, Calzetti F, Ceska M, Cassatella MA. Effect of substance P on superoxide anion and IL-8 production by human PMNL. Immunology. 1994; 82:63–69. [PubMed: 7519174]

Severini C, Improta G, Falconieri-Erspamer G, Salvadori S, Erspamer V. The tachykinin peptide family. Pharmacological reviews. 2002; 54:285–322. [PubMed: 12037144]

Shaik-Dasthagirisaheb YB, Varvara G, Murmura G, Saggini A, Potalivo G, Caraffa A, Antinolfi P, Tete S, Tripodi D, Conti F, Cianchetti E, Toniato E, Rosati M, Conti P, Speranza L, Pantalone A, Saggini R, Theoharides TC, Pandolfi F. Vascular endothelial growth factor (VEGF), mast cells and inflammation. Int J Immunopathol Pharmacol. 2013; 26:327–335. [PubMed: 23755748]

Shimizu Y. Localization of neuropeptides in the cornea and uvea of the rat: an immunohistochemical study. Cell Mol Biol. 1982; 28:103–110. [PubMed: 6177417]

Simeonidis S, Castagliuolo I, Pan A, Liu J, Wang CC, Mykoniatis A, Pasha A, Valenick L, Sougioultzis S, Zhao D, Pothoulakis C. Regulation of the NK-1 receptor gene expression in human macrophage cells via an NF-kappa B site on its promoter. Proc Natl Acad Sci U S A. 2003; 100:2957–2962. [PubMed: 12594338]

Skidgel RA, Engelbrecht S, Johnson AR, Erdos EG. Hydrolysis of substance p and neurotensin by converting enzyme and neutral endopeptidase. Peptides. 1984; 5:769–776. [PubMed: 6208535]

Sonea IM, Palmer MV, Akili D, Harp JA. Treatment with neurokinin-1 receptor antagonist reduces severity of inflammatory bowel disease induced by Cryptosporidium parvum. Clin Diagn Lab Immunol. 2002; 9:333–340. [PubMed: 11874873]

Star RA, Rajora N, Huang J, Stock RC, Catania A, Lipton JM. Evidence of autocrine modulation of macrophage nitric oxide synthase by alpha-melanocyte-stimulating hormone. Proc Natl Acad Sci U S A. 1995; 92:8016–8020. [PubMed: 7544012]

Stevenson W, Chauhan SK, Dana R. Dry eye disease: an immune-mediated ocular surface disorder. Arch Ophthalmol. 2012; 130:90–100. [PubMed: 22232476]

Stucchi AF, Shofer S, Leeman S, Materne O, Beer E, McClung J, Shebani K, Moore F, O'Brien M, Becker JM. NK-1 antagonist reduces colonic inflammation and oxidative stress in dextran sulfate-induced colitis in rats. Am J Physiol Gastrointest Liver Physiol. 2000; 279:G1298–1306. [PubMed: 11093954]

Sturiale S, Barbara G, Qiu B, Figini M, Geppetti P, Gerard N, Gerard C, Grady EF, Bunnett NW, Collins SM. Neutral endopeptidase (EC 3.4.24.11) terminates colitis by degrading substance P. Proc Natl Acad Sci U S A. 1999; 96:11653–11658. [PubMed: 10500232]

Sun J, Ramnath RD, Tamizhselvi R, Bhatia M. Neurokinin A engages neurokinin-1 receptor to induce NF-kappaB-dependent gene expression in murine macrophages: implications of ERK1/2 and PI 3-kinase/Akt pathways. Am J Physiol Cell Physiol. 2008a; 295:C679–691. [PubMed: 18596216]

Sun J, Ramnath RD, Zhi L, Tamizhselvi R, Bhatia M. Substance P enhances NF-kappaB transactivation and chemokine response in murine macrophages via ERK1/2 and p38 MAPK signaling pathways. Am J Physiol Cell Physiol. 2008b; 294:C1586–1596. [PubMed: 18434625]

Takashima A. Harnessing DCs by substance P. Blood. 2013; 121:2815–2816. [PubMed: 23580632]

Tancowny BP, Karpov V, Schleimer RP, Kulka M. Substance P primes lipoteichoic acid- and Pam3CysSerLys4-mediated activation of human mast cells by up-regulating Toll-like receptor 2. Immunology. 2010; 131:220–230. [PubMed: 20497485]

Taracanova A, Theoharides T. Substance P and IL-33 Synergistically Stimulate Mast Cells to Release IL-1β and TNF-α implicated in psoriasis; inhibition by the flavonoid methoxyluteolin. The FASEB Journal. 2015; 29

Taylor A, Namba K. In vitro induction of CD25+ CD4+ regulatory T cells by the neuropeptide alpha-melanocyte stimulating hormone (alpha-MSH). Immunol Cell Biol. 2001; 79:358–367. [PubMed: 11488983]

Taylor AW. Modulation of regulatory T cell immunity by the neuropeptide alpha-melanocyte stimulating hormone. Cell Mol Biol (Noisy-le-grand). 2003; 49:143–149. [PubMed: 12887097]

Taylor AW, Yee DG, Nishida T, Namba K. Neuropeptide regulation of immunity. The immunosuppressive activity of alpha-melanocyte-stimulating hormone (alpha-MSH). Ann N Y Acad Sci. 2000; 917:239–247. [PubMed: 11268350]

Tebas P, Spitsin S, Barrett JS, Tuluc F, Elci O, Korelitz JJ, Wagner W, Winters A, Kim D, Catalano R, Evans DL, Douglas SD. Reduction of soluble CD163, substance P, programmed death 1 and inflammatory markers: phase 1B trial of aprepitant in HIV-1-infected adults. Aids. 2015; 29:931–939. [PubMed: 25915168]

Tervo K, Tervo T, Eranko L, Eranko O. Substance P immunoreactive nerves in the rodent cornea. Neurosci Lett. 1981; 25:95–97. [PubMed: 6168984]

Thornton E, Vink R. Treatment with a substance P receptor antagonist is neuroprotective in the intrastriatal 6-hydroxydopamine model of early Parkinson's disease. PLoS One. 2012; 7:e34138. [PubMed: 22485158]

Todd AJ, McGill MM, Shehab SA. Neurokinin 1 receptor expression by neurons in laminae I, III and IV of the rat spinal dorsal horn that project to the brainstem. Eur J Neurosci. 2000; 12:689–700. [PubMed: 10712649]

Tran MT, Lausch RN, Oakes JE. Substance P differentially stimulates IL-8 synthesis in human corneal epithelial cells. Invest Ophthalmol Vis Sci. 2000; 41:3871–3877. [PubMed: 11053288]

Tuluc F, Meshki J, Spitsin S, Douglas SD. HIV infection of macrophages is enhanced in the presence of increased expression of CD163 induced by substance P. J Leukoc Biol. 2014; 96:143–150. [PubMed: 24577568]

Tumati S, Largent-Milnes TM, Keresztes AI, Yamamoto T, Vanderah TW, Roeske WR, Hruby VJ, Varga EV. Tachykinin NK(1) receptor antagonist co-administration attenuates opioid withdrawal-mediated spinal microglia and astrocyte activation. Eur J Pharmacol. 2012; 684:64–70. [PubMed: 22724132]

Twardy BS, Channappanavar R, Suvas S. Substance P in the corneal stroma regulates the severity of herpetic stromal keratitis lesions. Invest Ophthalmol Vis Sci. 2011; 52:8604–8613. [PubMed: 21969295]

US VE, Gaddum JH. An unidentified depressor substance in certain tissue extracts. J Physiol. 1931; 72:74–87. [PubMed: 16994201]

van der Kleij HP, Ma D, Redegeld FA, Kraneveld AD, Nijkamp FP, Bienenstock J. Functional expression of neurokinin 1 receptors on mast cells induced by IL-4 and stem cell factor. J Immunol. 2003; 171:2074–2079. [PubMed: 12902513]

Vigna SR. Phosphorylation and desensitization of neurokinin-1 receptor expressed in epithelial cells. J Neurochem. 1999; 73:1925–1932. [PubMed: 10537050]

Vilisaar J, Kawabe K, Braitch M, Aram J, Furtun Y, Fahey AJ, Chopra M, Tanasescu R, Tighe PJ, Gran B, Pothoulakis C, Constantinescu CS. Reciprocal Regulation of Substance P and IL-12/IL-23 and the Associated Cytokines, IFNgamma/IL-17: A Perspective on the Relevance of This Interaction to Multiple Sclerosis. Journal of neuroimmune pharmacology: the official journal of the Society on NeuroImmune Pharmacology. 2015; 10:457–467. [PubMed: 25690155]

Villani E, Galimberti D, Viola F, Mapelli C, Ratiglia R. The cornea in Sjogren's syndrome: an in vivo confocal study. Invest Ophthalmol Vis Sci. 2007; 48:2017–2022. [PubMed: 17460255]

Villani E, Magnani F, Viola F, Santaniello A, Scorza R, Nucci P, Ratiglia R. In vivo confocal evaluation of the ocular surface morpho-functional unit in dry eye. Optom Vis Sci. 2013; 90:576–586. [PubMed: 23670123]

Vink R, van den Heuvel C. Substance P antagonists as a therapeutic approach to improving outcome following traumatic brain injury. Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics. 2010; 7:74–80. [PubMed: 20129499]

Voedisch S, Rochlitzer S, Veres TZ, Spies E, Braun A. Neuropeptides control the dynamic behavior of airway mucosal dendritic cells. PLoS One. 2012; 7:e45951. [PubMed: 23049899]

Voice J, Donnelly S, Dorsam G, Dolganov G, Paul S, Goetzl EJ. c-Maf and JunB mediation of Th2 differentiation induced by the type 2 G protein-coupled receptor (VPAC2) for vasoactive intestinal peptide. J Immunol. 2004; 172:7289–7296. [PubMed: 15187104]

Walters N, Trunkle T, Sura M, Pascual DW. Enhanced immunoglobulin A response and protection against Salmonella enterica serovar typhimurium in the absence of the substance P receptor. Infect Immun. 2005; 73:317–324. [PubMed: 15618168]

Watanabe M, Nakayasu K, Iwatsu M, Kanai A. Endogenous substance P in corneal epithelial cells and keratocytes. Jpn J Ophthalmol. 2002; 46:616–620. [PubMed: 12543186]

Weinstock JV. Substance P and the regulation of inflammation in infections and inflammatory bowel disease. Acta physiologica. 2015; 213:453–461. [PubMed: 25424746]

Weinstock JV, Blum A, Metwali A, Elliott D, Arsenescu R. IL-18 and IL-12 signal through the NF-kappa B pathway to induce NK-1R expression on T cells. J Immunol. 2003a; 170:5003–5007. [PubMed: 12734344]

Weinstock JV, Blum A, Metwali A, Elliott D, Bunnett N, Arsenescu R. Substance P regulates Th1-type colitis in IL-10 knockout mice. J Immunol. 2003b; 171:3762–3767. [PubMed: 14500676]

Weinstock JV, Blum A, Walder J, Walder R. Eosinophils from granulomas in murine schistosomiasis mansoni produce substance P. J Immunol. 1988; 141:961–966. [PubMed: 2456338]

Whyteside AR, Turner AJ, Lambert DW. Endothelin-converting enzyme-1 (ECE-1) is post-transcriptionally regulated by alternative polyadenylation. PLoS One. 2014; 9:e83260. [PubMed: 24497914]

Wozniak A, McLennan G, Betts WH, Murphy GA, Scicchitano R. Activation of human neutrophils by substance P: effect on FMLP-stimulated oxidative and arachidonic acid metabolism and on antibody-dependent cell-mediated cytotoxicity. Immunology. 1989; 68:359–364. [PubMed: 2480329]

Xanthos DN, Sandkuhler J. Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. Nat Rev Neurosci. 2014; 15:43–53. [PubMed: 24281245]

Xu Q, Fitzsimmons B, Steinauer J, O'Neill A, Newton AC, Hua XY, Yaksh TL. Spinal phosphinositide 3-kinase-Akt-mammalian target of rapamycin signaling cascades in inflammation-induced hyperalgesia. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2011; 31:2113–2124. [PubMed: 21307248]

Yadav M, Goetzl EJ. Vasoactive intestinal peptide-mediated Th17 differentiation: an expanding spectrum of vasoactive intestinal peptide effects in immunity and autoimmunity. Ann N Y Acad Sci. 2008; 1144:83–89. [PubMed: 19076367]

Yamada N, Yanai R, Inui M, Nishida T. Sensitizing effect of substance P on corneal epithelial migration induced by IGF-1, fibronectin, or interleukin-6. Invest Ophthalmol Vis Sci. 2005; 46:833–839. [PubMed: 15728538]

Zhang D, Yeh HH. Substance-P-like immunoreactive amacrine cells in the adult and the developing rat retina. Brain Res Dev Brain Res. 1992; 68:55–65. [PubMed: 1381664]

Zhang X, Chen Q, Chen W, Cui L, Ma H, Lu F. Tear dynamics and corneal confocal microscopy of subjects with mild self-reported office dry eye. Ophthalmology. 2011; 118:902–907. [PubMed: 21146227]

Zhao D, Kuhnt-Moore S, Zeng H, Pan A, Wu JS, Simeonidis S, Moyer MP, Pothoulakis C. Substance P-stimulated interleukin-8 expression in human colonic epithelial cells involves Rho family small GTPases. Biochem J. 2002; 368:665–672. [PubMed: 12169092]

Ziche M, Morbidelli L, Masini E, Amerini S, Granger HJ, Maggi CA, Geppetti P, Ledda F. Nitric oxide mediates angiogenesis in vivo and endothelial cell growth and migration in vitro promoted by substance P. J Clin Invest. 1994; 94:2036–2044. [PubMed: 7525653]

Ziche M, Morbidelli L, Pacini M, Geppetti P, Alessandri G, Maggi CA. Substance P stimulates neovascularization in vivo and proliferation of cultured endothelial cells. Microvasc Res. 1990; 40:264–278. [PubMed: 1701206]

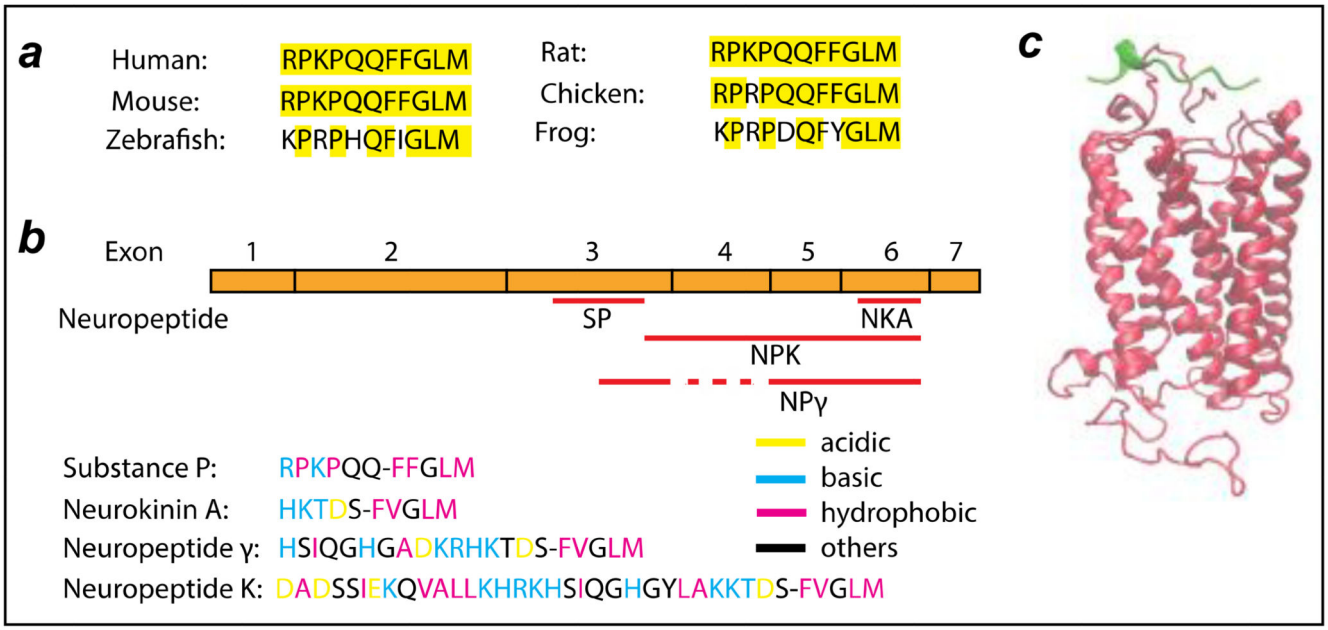

Figure 1.

Molecular properties of substance P. (a) Primary sequence of Substance P is conserved across species. (b) TAC1 gene encodes substance P along with three other neuropeptides with significant similarities in primary sequences. One-letter notation is used for aminoacids. (c) Structure of NK1R bound to substance P (PDB = 2KS9).

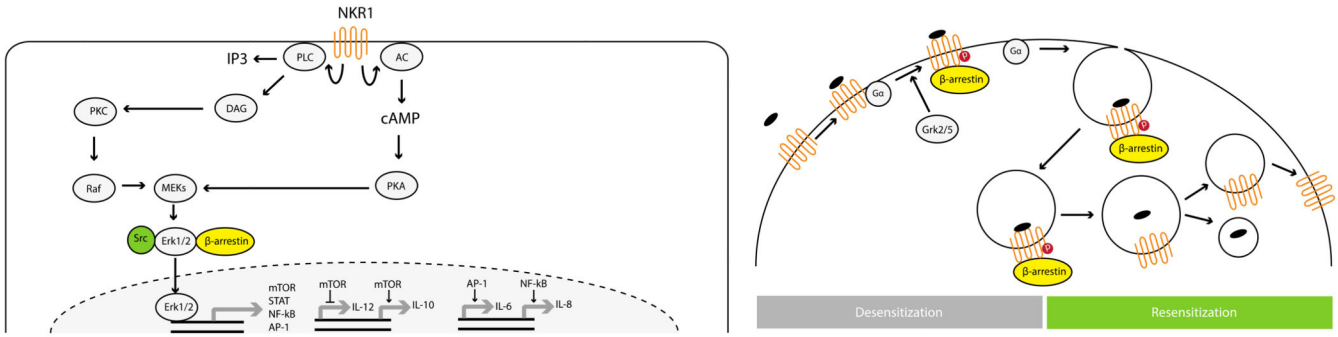

Figure 2.

NK1R signaling and regulation. (left) NK1R associated signaling pathways control the expression of cytokines and transcription factors with critical involvement in immune regulation. (right) High concentration of SP initiates a desensitization process involving phosphorylation of NK1R and its prolonged binding to ß-arrestin. The phosphorylated NK1R can be recycled via endocytosis and acidification within endosomes.

Table 1

Immunomodulatory effects of SP as compared to a few other neuropeptides. + indicates activation; − denotes inhibition.

Neuropeptide	Dendritic cell Macrophage	Lymphocyte			
		Th1	Th2	Treg	Th17
Substance P	+ (1)	+ (2)			
+(3)					
NKA	+ (4)	+(5)			
CGRP	− (6)	− (7)		+(8)	+ (9)
+(10)					
a-MSH	− (11)	− (12)		+(13)	+ (14)
VIP	−(15)	− (16)		+(17)	+(18)
+(19)					

(1)(Jeon et al, 1999; Kavelaars et al, 1994; Voedisch et al, 2012), (2)(Janelsins et al, 2009; Janelsins et al, 2013; Takashima, 2013), (3)(Barros et al, 2011; Cunin et al, 2011), (4)(Sun et al, 2008a), (5)(Kitamura et al, 2012), (6)(Asahina et al, 1995b; Carucci et al, 2000; Fox et al, 1997; Hosoi et al, 1993; Mikami et al, 2011; Nong et al, 1989; Rochlitzer et al, 2011; Voedisch et al, 2012), (7)(Asahina et al, 1995a; Liu et al, 2000; Mikami et al, 2011; Mikami et al, 2014), (8)(Ding et al, 2008; Mikami et al, 2011; Takashima, 2013), (9)(Takashima, 2013), (10)(Mikami et al, 2012), (11) (Lipton & Catania, 1997; Luger et al, 2003; Star et al, 1995), (12)(Taylor et al, 2000), (13)(Takashima, 2013), (14)(Namba et al, 2002; Takashima, 2013; Taylor & Namba, 2001; Taylor, 2003; Taylor et al, 2000), (15)(Delgado et al, 2005b; Delgado et al, 1999b; Delgado et al, 2004b; Voedisch et al, 2012), (16)(Delgado et al, 2005b; Delgado et al, 1999c; Goetzl et al, 2001), (17)(Delgado et al, 2004a; Delgado et al, 2002; Delgado et al, 1999a; Takashima, 2013; Voice et al, 2004), (18)(Delgado et al, 2005a; Gonzalez-Rey et al, 2006a; Gonzalez-Rey et al, 2006b; Takashima, 2013), (19)(Jimeno et al, 2015; Yadav & Goetzl, 2008)

Table 2

Immunomodulatory role of the substance P: lessens from disease models

Disease model	Administration of SP	Blockage of NK1R/SP/NEP system: knockout (KO) or pharmacological blockade (PB)	Reference
Arthritis	Pro-inflammatory	Anti-inflammatory (KO)	(Keeble et al, 2005; Knodell et al, 1984)
Type 1 diabetes	Reversal of diabetes (Intrapancreatic in NOD mice)		(Razavi et al, 2006)
Inflammatory bowel disease		Anti-inflammatory (KN, PB)	(Engel et al, 2012; Gad et al, 2009; Sonea et al, 2002; Stucchi et al, 2000)
Colitis		Anti-inflammatory (PB)	(Sturiale et al, 1999; Weinstock et al, 2003b)
Psoriasis		Anti-inflammatory (PB)	(Ostrowski et al, 2011)
Contact dermatitis		Anti-inflammatory (PB, KO)	(Niizeki et al, 1999; Scholzen et al, 2004)
Asthma	Pro-inflammatory (Intranasal)	Anti-inflammatory (PB)	(Elekes et al, 2007; Joachim et al, 2006; Ramalho et al, 2013)
Immune mediated liver disease		Anti-inflammatory (PB)	(Bang et al, 2003)
Lung injury in sepsis		Anti-inflammatory (PB)	(Hegde et al, 2007)
Experimental Autoimmune Encephalitis (EAE)		Anti-inflammatory (PB, KO)	(Nessler et al, 2006; Reinke et al, 2006)
Infections			(Castagliuolo et al, 1998; Kincy-Cain & Bost, 1996; Walters et al, 2005)
Enterocolitis		Anti-inflammatory (KO)	
Salmonella enterica infection		Protective through promoting IgA generation (KO) Increased susceptibility through suppression of IL-12 and IFN-γ (PB)	
Pseudomonas aeruginosa corneal infection	Pro-inflammatory (Intraperitoneal)	Increased resistance in susceptible mice (PB) Increased susceptibility in resistant mice (PB)	(McClellan et al, 2008)
HSV-1 corneal infection		Anti-inflammatory (PB)	(Twardy et al, 2011)
Corneal Neovascularization (CNV) -suture model -alkali burn model		Anti-inflammatory (PB)	(Bignami et al, 2014)