Substance P and neurokinin 1 receptor are new targets for the treatment of chronic pruritus*

S. Ständer1 and G. Yosipovitch2

1Center for Chronic Pruritus, Department of Dermatology, University Hospital Münster, Münster, Germany
2Miami Itch Center, Dr Phillip Frost Department of Dermatology and Cutaneous Surgery, Miller School of Medicine, University of Miami, Miami, FL, U.S.A.

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Summary

Background Chronic pruritus is a distressing symptom associated with various dermatological conditions and systemic diseases. Current treatment options are often inadequate, resulting in impaired quality of life for many patients. An understanding of the underlying mechanisms of itch across pruritic conditions is important for development of effective, targeted treatments for chronic pruritus.

Objectives To provide an overview of the pathogenesis of chronic pruritus, focusing on the role of substance P (SP) and neurokinin 1 receptor (NK1R) in itch signalling, and to describe data supporting NK1R antagonism as a potential strategy for the treatment of chronic pruritus.

Methods A PubMed search was conducted to determine what data were available that investigated the role of SP and NK1R in itch signalling.

Results SP is a neuropeptide that is a mediator of itch signalling. One of the target receptors for SP is NK1R, which is expressed in the central nervous system and on multiple cell types involved in the initiation and transmission of itch. Studies demonstrating that SP and NK1R are overexpressed across multiple chronic itch-inducing conditions and that NK1R antagonism disrupts itch signalling and reduces itch provide a rationale for targeting this pathway as a potential treatment of chronic pruritus across multiple diseases.

Conclusions A large and growing body of evidence, including recent phase II clinical studies of NK1R antagonists, demonstrate that SP and NK1R play an important role in itch signalling. Additional studies are ongoing to further evaluate the use of NK1R antagonists for the treatment of chronic pruritus.

What’s already known about this topic?

- Chronic pruritus has a significant impact on quality of life.
- Current treatment options for chronic pruritus are inadequate.
- Substance P (SP) and neurokinin 1 receptor (NK1R) have been shown to play a role in itch signalling, and may be a rational target for addressing chronic pruritus.
- NK1R antagonists are being evaluated as potential treatment for chronic pruritus.

What does this study add?

- This review provides a compilation of the most up-to-date data elucidating the role of SP and NK1R in itch signalling, which supports targeting this pathway as a potential treatment of chronic pruritus.
- NK1R antagonism disrupts itch signalling and reduces itch.
- A summary of the latest data on NK1R antagonists in the treatment of pruritus is provided.
Chronic pruritus is a common symptom associated with various dermatological conditions and systemic diseases and no known underlying condition in some cases. Chronic pruritus is classified by clinical presentation (e.g. association with diseased/inflamed or normal/noninflamed skin, and presence of secondary scratch lesions) and underlying cause (e.g. dermatological, systemic, neurological, psychogenic/psychosomatic, mixed or undetermined origin). As current treatments are often inadequate, chronic pruritus can be distressing for patients and frequently results in impaired quality of life comparable with that of chronic pain.

The lifetime prevalence of chronic pruritus in the general population is estimated to be 22–26%, i.e. approximately one in four people. Prevalence estimates vary depending on underlying conditions, with 87% of patients with atopic dermatitis and 83–84% of patients with psoriasis reporting itch on a daily basis, and 35% of patients on haemodialysis and 45% of patients with HIV reporting chronic itch.

To develop effective treatments for chronic pruritus, it is important to understand the underlying mechanisms of itch and potential commonalities across pruritic conditions that can be targeted. This review provides a general overview of the pathogenesis of chronic pruritus, focusing on the role of substance P (SP) and one of its target receptors, neurokinin 1 receptor (NK1R), in itch signalling, and describes data supporting NK1R antagonism as a potential strategy for treatment of chronic pruritus associated with various underlying conditions.

Pathogenesis of chronic pruritus

Research over the last decade has greatly increased understanding of itch pathways, including the nerve fibres and neuropeptides involved in itch perception and transmission. The histaminergic pathway is primarily mediated by a subpopulation of unmyelinated, mechano-insensitive C-fibres that respond to histamine, whereas the nonhistaminergic pathway involves polymodal mechano- and heat-sensitive C-fibres and Aδ-fibres. In addition to their afferent function in transmitting sensory information to the spinal cord, these cutaneous nerve fibres are also involved in peripheral sensitization as they release neuropeptides, such as calcitonin gene-related peptide (CGRP) and SP upon neural activation in response to itch mediators.

Although both histamine-dependent and histamine-independent pathways are important for transmission of itch signals, the nonhistaminergic pathway appears to have a greater role in conditions associated with chronic pruritus. This is consistent with clinical observations that some forms of itch, such as urticaria and insect bites, are responsive to antihistamines, while antihistamines are generally ineffective at reducing chronic pruritus associated with atopic dermatitis and systemic diseases. Current research is focused on identifying novel targets for treatment of chronic pruritus, which include neural targets such as neurokinin antagonists, μ- and κ-opioid receptor agonists, and immune targets such as interleukin (IL) antagonists (e.g. IL-31, IL-4, IL-13 and IL-17a) and Janus kinase inhibitors. This review will focus on the role of SP and NK1R in itch signalling and the relevance of this pathway for the treatment of chronic pruritus.

Substance P and neurokinin 1 receptor

SP is a member of the tachykinin family of peptides and acts as a neurotransmitter or modulator in the mammalian peripheral and central nervous system (CNS). SP is produced and secreted by nerve fibres and binds to NK1R and another class of receptors involved in itch signalling, the mas-related G protein-coupled receptors (Mrgprs). NK1R is a tachykinin receptor and belongs to the G protein-coupled receptor family, known to activate signal transduction pathways within the cell. The NK1R has two isoforms, a full form and a truncated form that is missing the last 96 amino acids of the C-terminus. SP has higher affinity for the full form, although differences in expression and signalling pathways between each isoform remain to be clarified. NK1R is expressed in the central and peripheral nervous system, including the superficial lamina I dorsal horn neurons of the spinal cord, and on multiple skin cell types involved in the initiation and transmission of itch, including keratinocytes, fibroblasts and mast cells.

The sensory neuron-specific G protein-coupled receptors, also known as Mrgprs, were discovered in 2001 and include 50 distinct sequences in mice and 18 genes and pseudogenes in humans. Although activation of Mrgprs in mice has been shown to be involved in both nociception and itch signalling, the role of Mrgprs in itch signalling in humans is less clear. SP binds to and activates mouse MrgprA1, mouse MrgprB2 and human MrgprX2, and was reported to induce itch in mice by activating MrgprA1, rather than NK1R, on sensory neurons. However, NK1R antagonists were recently shown to block both the NK1R and MrgprB2 in mice but only NK1R and not MrgprX2 in humans. MrgprX2 is expressed on dorsal root ganglion neurons and mast cells and is reported to mediate SP-induced IgE-independent mast cell degranulation, indicating that this receptor may be responsible for the proinflammatory properties of SP. As mast cells are not thought to have a primary role in SP-induced scratching, MrgprX2 may be more relevant for SP-induced inflammation and less relevant for SP-induced itch, at least in humans. Broad expression of the NK1R in the CNS, and specifically on spinal interneurons involved in transmission of the itch signal to the brain, supports a prominent role for the NK1R in itch signalling. Expression of MrgprX2 on peripheral dorsal root ganglion and mast cells suggest it may play a role in itch initiation but would still require NK1R expressing neurons to pass the signal to the brain. Further research is needed to clarify the roles of these two receptors in itch signalling.
Role of substance P and neurokinin 1 receptor in itch signalling

An overview of the role of SP and NK₁R in itch signalling is provided in Figure 1. SP is released from the primary sensory nerves in the skin into the surrounding tissue upon neuronal activation. The role of SP in keratinocytes, fibroblasts and mast cells appears to be predominantly related to induction of inflammation and includes vasodilation of short duration leading to mast cell degranulation, nerve growth factor expression in keratinocytes and neurogenic inflammation associated with erythema, wheals and pruritus. SP is reported to promote skin inflammation by inducing expression of nerve growth factor and leukotriene B₄ in keratinocytes and release of proinflammatory mediators from mast cells. These data support a role for SP in itch induction; however, further research is necessary to elucidate fully the role of NK₁R in the skin.

SP and NK₁R have been shown to play a prominent role in transmission of the itch signal carried by peripheral sensory nerve fibres through the dorsal root ganglion to the spinal cord where the nerve fibres synapse with second-order neurons. SP is released from the presynaptic terminals of the peripheral neurons to bind to the NK₁R on the postsynaptic terminals of superficial lamina dorsal horn neurons of the spinal cord. A large percentage (89–94%) of ascending projection neurons, including spinothalamic and spinoparabrachial projection neurons, express NK₁R; inhibition of these neurons reduces scratching in response to itch mediators in mice. The spinothalamic tract provides direct spinal input to the thalamus, and the spino-parabrachial neurons project to both the thalamus and midbrain, including periaqueductal grey matter and the lateral parabrachial area. These data support a role for NK₁R-expressing spinal neurons in relaying itch information from the dorsal horn to higher centres in the brain.

Fig 1. Role of substance P (SP) and neurokinin 1 receptor (NK₁R) in itch signalling. SP is a neuropeptide that binds to and activates NK₁R. SP and NK₁R are expressed on multiple cell types involved in the initiation and transmission of an itch signal in the skin, peripheral nervous system, dorsal root ganglion, spinal cord and regions of the brain. The NK₁R is abundant in the anterior cingulate cortex (ACC), caudate and putamen (areas that are highly associated with itch). The itch stimulus originates in the skin and is transmitted through itch-selective sensory nerve fibres to the spine and brain (1). The itch signal is carried by peripheral sensory nerve fibres through the dorsal root ganglion (2) to the spinal cord, where SP is released from the presynaptic terminals of the peripheral sensory neurons and binds to NK₁R on the postsynaptic terminals of the spinal cord neurons (3). The itch signal travels from the spinal cord up to the regions of the brain involved in itch processing (4). In response to the itch signal, a motor response is generated that results in scratching behaviour. PAG, periaqueductal grey; PB, parabrachial area.
Putative mechanisms of neurokinin 1 receptor in chronic pruritus

To develop antipruritic therapies, it is important to understand similarities and differences across pruritic diseases. Initial evidence for the role of SP in itch came from a study in which intradermal injection of SP produced flare, wheal and itch in humans. Further evidence supporting a role of SP in chronic pruritus came from studies evaluating expression of sensory neuropeptides such as SP and CGRP, and their cognate receptors in patients with various dermatological conditions. These studies demonstrated increased expression of SP-positive nerve fibres and overexpression of NK₁R in lesional skin compared with nonlesional skin or healthy controls (Table 1). In patients with psoriasis, the number of SP-positive nerve fibres in lesional skin was shown to correlate with pruritus intensity.

A recent study used RNA sequencing to evaluate gene expression profiles in pruritic and nonpruritic skin of patients with psoriasis and atopic dermatitis, to identify differentially expressed genes with a potential role in chronic pruritus. For differentially expressed genes of interest, protein expression was examined using immunohistochemistry. Consistent with previous studies, the number of SP-expressing nerve fibres was increased in pruritic skin, with increased SP expression in nerve fibres close to the dermoepidermal junction; NK₁R was also overexpressed in the epidermis of pruritic skin.

Preclinical studies provided support for the functional role of increased expression of SP and NK₁R observed in pruritic conditions. In mice, cutaneous injection of SP resulted in dose-dependent increases in scratching at the injection site. In humans, application of SP to the skin produced the sensation of itch, and intradermal injection of SP was associated with pruritus in healthy volunteers and patients with psoriasis. In another study in mice, skin scratching resulted in an increased number of SP-immunoreactive cutaneous nerve fibres, indicating that scratching behaviour may contribute to the increased number of SP-positive nerve fibres in patients with chronic pruritus. These data support a role for SP and NK₁R as important mediators of itch in dermatological conditions.

Neural sensitization in chronic pruritus and its association with the neurokinin 1 pathway

Chronic pruritus is associated with increased sensitivity of itch-signalling pathways, sometimes resulting in spontaneous itching, alloknesis (itch elicited by an innocuous touch stimulus) or hyperknesis (enhanced itch to a normally itchy substance). Studies have reported spontaneous firing of itch-selective C-fibres and increased susceptibility to mechanically evoked itch in patients with chronic pruritus. Preclinical studies showed reduced behavioural signs of ongoing itch, alloknesis and hyperknesis, and reduced chemically induced scratching after inhibition of NK₁R-expressing spinal neurons in a mouse model of atopic dermatitis, indicating an important role for NK₁R-expressing spinal neurons in itch signalling and sensitization.

It is unclear whether the neuronal sensitization in chronic pruritus results from central or peripheral mechanisms, or a combination of both. Andersen et al. proposed that sensitization to chemical and mechanical stimuli in normal skin could be due to central mechanisms, whereas further sensitization in lesional skin could be due to peripheral sensitization related to ongoing inflammation, itch and pain. These data suggest the NK₁R signalling pathway is involved in itch sensitization in pruritic conditions; therefore, drugs targeting this pathway are potentially promising for treating chronic itch.

Table 1 Studies investigating the role of substance P (SP)/neurokinin 1 receptor (NK₁R) in dermatological diseases

| Disease          | Key results and references                                                                 |
|------------------|-------------------------------------------------------------------------------------------|
| Psoriasis        | Compared with nonpruritic skin, SP-positive nerve fibres (close to dermoepidermal junction) and NK₁R were overexpressed in pruritic skin. |
|                 | Higher numbers of SP-immunoreactive nerve fibres and cells observed in lesional vs. nonlesional psoriatic and healthy control skin; number of SP-positive nerve fibres correlated with pruritus intensity. |
| AD               | Compared with nonpruritic skin, SP-positive nerve fibres (close to dermoepidermal junction) and NK₁R were overexpressed in pruritic skin. |
|                 | SP-positive nerve fibres present in lesional skin from patients with AD but not in healthy controls. |
|                 | Increased density of SP-positive sensory nerve fibres in biopsies from skin of patients with AD. |
| Chronic pruritus | Density of dermal SP-positive nerve fibres were significantly higher in affected area than control area. |

PN, prurigo nodularis; AD, atopic dermatitis. *PN is also called chronic prurigo (of the nodular type) or chronic nodular prurigo.
Therapeutic potential of neurokinin 1 receptor antagonism in pruritus

The efficacy of aprepitant (a first-in-class, oral, selective, high-affinity NK₁R antagonist) in chemotherapy-induced nausea and vomiting, the only currently approved indication for an NK₁R antagonist, could provide insight into potential efficacy in pruritus.²⁴ NK₁R antagonists have been shown to act centrally to prevent chemotherapy-induced nausea and vomiting by binding to NK₁R in regions of the brain and brainstem responsible for vomiting and blocking their activation by SP.²⁵ Therefore, it is possible that a similar effect of NK₁R antagonism in regions of the brain responsible for itch processing could result in effective antipruritic therapy. As preclinical studies demonstrated that NK₁R antagonists had to cross the blood–brain barrier (BBB) to be effective antiemetics,²⁶ the same may be true, at least with respect to the central effects, for antipruritics. Both aprepitant and serlopitant, a novel NK₁R antagonist under investigation specifically for pruritus, have been shown to cross the BBB.²⁷,²⁸

As evidence that stimulation of NK₁R is an important pathway for pruritus perception, recent studies have shown that blocking the itch signal through NK₁R antagonism can disrupt itch signalling and reduce itch.

A small (n = 20) proof-of-concept study in patients with treatment-refractory chronic pruritus, including 13 patients with prurigo nodularis (PN), reported that aprepitant caused a marked reduction of itch intensity [from mean visual analogue scale (VAS) score of 8.4 at baseline to 4.9 after treatment].²⁹ In this study, the underlying condition was identified as renal disease for five patients, multifactorial for seven (including renal disease in three) and unknown for eight. However, aprepitant was ineffective for treating pruritus in a randomized multicentre, double-blind, crossover phase II study that compared aprepitant with placebo in 58 patients with atopic dermatitis (NCT03568331). The results of these studies are expected to provide additional clarification of the antipruritic potential of these agents.²⁷,²⁸

Summary and conclusion

SP and NK₁R play an important role in itch signalling. This is supported by a large and growing body of evidence demonstrating that (i) NK₁R is broadly expressed in multiple cell types in the skin, such as keratinocytes and mast cells, as well as the CNS; (ii) in many pruritic dermatological conditions, based on immunohistochemical studies, overexpression of NK₁R is seen in the epidermis and increased numbers of SP-expressing nerve fibres and inflammatory cells are found in the skin; (iii) SP binding to NK₁R-bearing neurons in the dorsal horn of the spine is a key relay point in itch signalling; and (iv) the blocking of NK₁R via the use of NK₁R antagonists interrupts transmission of the itch signal. In proof-of-concept and phase II clinical studies, NK₁R antagonists reduced itch in patients with treatment-refractory chronic pruritus and PN.²⁹ Additional studies are ongoing to further evaluate the safety and efficacy of these agents for treatment of chronic pruritus.

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