Pflügers Archiv - European Journal of Physiology (2021) 473:1603–1615
https://doi.org/10.1007/s00424-021-02599-y

INVITED REVIEW

# Common and discrete mechanisms underlying chronic pain and itch: peripheral and central sensitization

**Chengjin Li[1] · Hee Jin Kim[2] · Seung Keun Back[3] · Heung Sik Na[4]**

Received: 2 December 2020 / Revised: 26 May 2021 / Accepted: 22 June 2021 /Published online: 10 July 2021


## Abstract

Normally, an obvious antagonism exists between pain and itch. In normal conditions, painful stimuli suppress itch sensation, whereas pain killers often generate itch. Although pain and itch are mediated by separate pathways under normal conditions, most chemicals are not highly specific to one sensation in chronic pathologic conditions. Notably, in patients with neuropathic pain, histamine primarily induces pain rather than itch, while in patients with atopic dermatitis, bradykinin triggers itch rather than pain. Accordingly, repetitive scratching even enhances itch sensation in chronic itch conditions. Physicians often prescribe pain relievers to patients with chronic itch, suggesting common mechanisms underlying chronic pain and itch, especially peripheral and central sensitization. Rather than separating itch and pain, studies should investigate chronic itch and pain including neuropathic and inflammatory conditions. Here, we reviewed chronic sensitization leading to chronic pain and itch at both peripheral and central levels. Studies investigating the connection between pain and itch facilitate the development of new therapeutics against both chronic dysesthesias based on the underlying pathophysiology.

**Keywords** Central sensitization · Peripheral sensitization · Chronic pain · Chronic itch

## Introduction

Chronic pain and itch are common, complex, and devastating clinical challenges with a profound impact on patients, their families, and societies in most modern countries. Pain and itch-related diseases are the leading cause of disability and social burden globally. Despite the clinical importance, our knowledge about these dysesthesias is preliminary. Pain and itch are obviously distinct but reciprocal sensations. Pain elicits withdrawal responses, while itch (also known as pruritus) leads to scratching responses. Under physiological conditions, an antagonistic interaction exists between pain and itch. Scratch-induced painful stimuli often inhibit itch sensation. Conversely, pain killers like opioid analgesics elicit itch sensation. However, pain and itch also share many similarities, especially in chronic pathophysiological conditions that lead to the sensitization of nociceptive pathways. This sensitization is characterized by plastic changes in primary afferents (peripheral sensitization) and synaptic transmission in the central nervous system (central sensitization). Thus, in chronic pathological conditions, painful stimuli can trigger itch, whereas some pain killers are often prescribed for chronic itch. In this review, we will discuss chronic sensitization as the common mechanism underlying chronic pain and itch.

Chronic pain such as long-lasting inflammatory and neuropathic pain is characterized by spontaneous burning pain, hyperalgesia, and allodynia. Unfortunately, chronic pain often persists even after the precipitating event has resolved. Furthermore, neuropathic pain is poorly treated by currently available medications and, thus, is considered as the most intractable clinical problem [103, 155]. Chronic itch is another unpleasant

✉ Seung Keun Back
skback@konyang.ac.kr

✉ Heung Sik Na
hsna@korea.ac.kr

1 Jiangxi Provincial Key Lab of System Biomedicine, Jiujiang University, 17 Lufeng Road, Jiujiang 332000, China

2 Division of Biological Science and Technology, Science and Technology College, Yonsei University Wonju Campus, Wonju, Korea

3 Department of Biomedical Laboratory Science, College of Medical Science, Konyang University, Daejeon 35365, Korea

4 Neuroscience Research Institute and Department of Physiology, Korea University College of Medicine, Seoul 02841, Korea

sensation threatening patients and their family well-being. Based on the underlying diseases, chronic itch conditions can be divided into four subtypes: dermatologic, systemic, neuropathic, and psychogenic [53]. Dermatologic itch arises from skin diseases such as atopic dermatitis (AD), eczema, and psoriasis. Systemic itch is always accompanied by systemic disorders, such as renal and hepatic diseases, HIV/AIDS, and metabolic disorders (cholestatic pruritus and uremic pruritus) [10, 130, 154]. Neuropathic itch results from traumatic injuries or disorders of the nervous system associated with nerve compression, irritation, multiple sclerosis, brain tumors, and cerebral hemorrhage. Psychogenic itch is attributed to psychological or psychiatric disorders (obsessive–compulsive disorders and delusions of parasitosis). Chronic itch is often intractable and has a profound effect on patient's life.

## Anatomical defects in ascending pathways of pain and itch

Pain and itch are distinct sensations associated with ascending pathways. However, anatomical ascending pathways involving both sensations are intimately related in the nervous system [68] and influence each other [25, 123, 152]. Pain and itch signals are transmitted to the superficial dorsal horn of the spinal cord, which is a pivotal center for integrating signals, and then further transmitted to the brain via the spinothalamic tract (STT) [24, 162]. In chronic pathological conditions, however, there seems to be interference in distinct pathways for the transmission of both pain and itch. Scratching-evoked pain stimuli can be perceived as itch in these conditions. In patients with chronic itch, normally painful electrical, chemical (bradykinin or acetylcholine), mechanical, and thermal stimulation results primarily in itch rather than pain [63, 64, 66, 102, 124]. Thus, scratching produces an "itch-scratch-itch" vicious cycle to exacerbate itch sensation in these patients [71]. Interestingly, itch stimuli induce burning pain rather than itch in patients with neuropathy [15, 21]. In fact, physicians often prescribe pain medications, such as gabapentin, to control chronic itch. These abnormal interactions between pain and itch are due, in part, to the changes in neuronal transmission (neural plasticity) in pathologic conditions.

## Peripheral sensitization

Pain and itch share largely overlapping mediators and their receptors (Figs. 1, 2 and Table 1). Inflammatory mediators such as bradykinin, serotonin, histamine, and prostaglandins sensitize pruriceptors [146] as well as nociceptors [85]. The inflammatory mediators are complicated by their interactions. Combinations of prostaglandin E2 and histamine show supra-additive effects [122]. Proteinase-activated receptor 2 (PAR-2) has been known to sensitize the capsaicin receptor TRPV1 [147]. All these studies suggest a possible cross-talk between pain and itch signals under pathophysiological conditions.

Skin injury and inflammation result in recruitment of immune cells (e.g., T lymphocytes, diverse innate immune cells) into the affected skin areas. Activated immune cells release endogenous mediators increasing the excitation of pruriceptors or nociceptors [17, 75]. Increased excitability of sensory nerve endings in response to these mediators is called peripheral sensitization [75, 131]. This peripheral sensitization plays a prominent role in the manifestation of both chronic pain and itch [17, 68].

Many pruritogens are likely to be involved in peripheral sensitization [63, 67, 92, 128]. In mice exhibiting dry skin, the levels of MrgprA3 and TLR3 expression are significantly increased in sensory neurons [107, 185]. In patients with chronic itch, the level of PAR2 expression has been found to be upregulated in the affected skin [8, 161]. In addition, multiple cytokines (e.g., IL-2, IL-4, IL-13, and IL-31) have been reported to contribute to chronic itch [13, 112, 126, 149]. IL-31, released from T cells, appears to be strongly linked to chronic itch [112]. Transgenic mice over-expressing IL-31 developed chronic itch with obvious skin problems such as alopecia and eczematous lesions [34, 157]. In the majority of dogs with AD, canine IL-31 was also increased [43]. In clinical studies, an increased number of IL-31-producing T cells and elevated IL-31 mRNA expression were found in the skin and serum of patients with chronic itch [39, 157, 165]. Moreover, it has been reported that blood levels of β-endorphin and IL-31 significantly correlated with itch severity in AD patients [100]. Immunohistochemical analysis revealed an increase in IL-31 and β-endorphin levels and co-localization in patients' skin [100]. TRPV3 and TRPV4 have also been demonstrated as important transducers in peripheral sensitization [3, 86, 133, 197].

Brain-derived neurotrophic factor (BDNF), neurotrophins 3 (NT-3) and 4 (NT-4), and glia cell-derived neurotrophic factor, important modulators in intraepidermal nerve fibers, may also play a role in chronic itch [50, 62, 147]. Sensory nerve fibers mediating itch signals may become sensitized under chronic pathophysiological conditions. In both patients and animals with AD, the sprouting of epidermal nerve fibers (or hyper-innervation) increased the excitability or decreased the threshold of primary sensory neurons [87, 168]. In patients diagnosed with prurigo nodularis, electrophysiological recordings demonstrated aberrant firing behavior of mechano-insensitive C-fibers, indicating sensitization [145]. Itch sensation can be evoked by transcutaneous electrical stimulation in humans. The threshold for electrically evoked itch has been reported to be significantly lower in the skin of patients with AD [66, 67, 128]. The dose of histamine required to elicit itch sensation in lesional skin

of AD patients is lower than in normal healthy skin [65]. Furthermore, in chronic pathological itch, the population of pruriceptors is enlarged and also exhibits enhanced response to pruritogens [120]. In dry skin-induced chronic itch, the numbers of primary sensory neurons responding to PAR2 agonist and 5-HT are increased, which is closely associated with enhanced scratching response to these pruritogens [4]. Many previous studies have demonstrated that intradermal nerve fiber density is increased in patients with prurigo nodularis and AD [1, 87].

In chronic pain condition, peripheral sensitization is defined as reduced threshold and/or increased responsiveness of peripheral nociceptive neurons in response to stimulation of their receptive fields. Sensitized nerves show ectopic action potential, enhanced signaling, and conduction via normal pathways [77]. Furthermore, signaling from nerves that are not nociceptive in nature, such as Aβ myelinated fibers, can converge onto nociceptive central pathways following sufficient tissue injuries and result in pain perception (allodynia) [96, 129, 141].

## Molecular mechanism of peripheral sensitization in both chronic pain and itch

### Nerve growth factor

Nerve growth factor (NGF) and artemin that are secreted from mast cells [51, 140] and fibroblasts [118], respectively, induce long-term structural reorganization of nociceptors [57] or pruriceptors [112]. In addition, cumulative evidence suggests that NGF plays a prominent role in the sensitization of primary afferents in both chronic itch and pain [53, 76, 192]. In clinical studies, expression of NGF and its receptor TrkA was found to increase in patients with prurigo nodularis [82], psoriasis, and AD [36, 51, 169, 171, 172, 190]. Increases in serum and local NGF have been known to trigger sprouting of epidermal nerve fibers in pruritic contact dermatitis, AD, and prurigo nodularis [69, 87, 171]. Anti-NGF therapy effectively inhibited epidermal hyperinnervation, skin lesioning, and scratching behavior in animal studies [170]. Increased epidermal NGF expression has been shown in NC/Nga mice, a mouse model of AD [166, 168]. It is interesting that TLR3$^{-/-}$mice with dry skin show lack of NGF upregulation and less severe scratching behaviors, compared with wild-type mice with the same skin disease [171].

NGF is also implicated in chronic pain conditions [14, 28, 180]. NGF is increased in injured and inflamed tissues, and activation of TrkA on nociceptive neurons triggers and potentiates pain signaling via multiple mechanisms [57]. In clinical studies, blockade of NGF with specific antibodies induced analgesia [97, 142]. In complex chronic pain conditions like vulvar dysesthesia, the sprouting of epidermal nerve fibers appears to be initiated by increased NGF levels. Anti-NGF strategies have already been shown to prevent epidermal nerve sprouting and chronic pain in both clinical [191] and animal [52] studies.

As described above, NGF is one of the key molecules underlying the pathogenesis of chronic pain and itch, and anti-NGF strategies may facilitate the treatment of both chronic pain and itch.

### Substance P and calcitonin gene-related peptide

NGF is known to upregulate neuropeptides, especially substance P (SP) and calcitonin gene-related peptide (CGRP) [176]. Excessive release of SP and CGRP from sensory nerve endings induces cutaneous neurogenic inflammation (CNI) on the local skin innervated by nerve endings [45, 58, 138]. SP plays an important role in the manifestation of chronic pain in rodents [94]. In addition, SP has also been reported to be associated with the severity of skin disease in AD patients [171]. SP activates mast cell degranulation and chemokine production and thereby contributes to neuronal sensitization and itch sensation [193]. The effect of CGRP on peripheral neuronal sensitization has also been reported in rodents [116, 164]. Interestingly, increased SP levels coexist with reduced CGRP levels in the NC/Nga mice [83]. Given that thermal pain sensitivity is correlated with CGRP levels [116], and pain sensitivity is negatively correlated with *s*ensitivity in itch models [48], one might speculate about the preferred role of CGRP and SP in nociception and itch, respectively.

### Cutaneous neurogenic inflammation and TRPs

During chronic inflammation, long-lasting changes occur in the expression and function of ion channels such as TRPV1 and TRPA1. Long-term changes associated with these ion channels are related to abnormal hyperexcitabilities of neurons and development of chronic pain [90]. Cutaneous neurogenic inflammation (CNI), characterized by a multi-cellular network with multiple, multidirectional interactions, leads to chronic inflammation [45, 46]. Indeed, CNI is frequently involved in chronic inflammatory skin disorders, including psoriasis, AD [89, 156], sensitive skin [29], and hypertrophic scars [2, 91]. TRPV1 and TRPA1 are known to be involved in CNI and pain manifestation [46]. Activation of TRPV1 induces the release of SP [9] and CGRP [23] from sensory nerve endings, leading to neurogenic inflammation and edema [138, 161, 178, 199]. During CNI, endogenous mediators such as eicosanoids, acidosis, ATP, histamine, bradykinin, and NGF sensitize or activate TRPV1 on epidermal nerve

terminals. In turn, activated TRV1 contributes to the self-regulation of CNI [138].

Similar to TRPV1, the activation of TRPA1 mediates skin inflammation by increasing inflammatory mediators, such as growth factors, bradykinins, proteases, and inflammatory cytokines [30, 35, 46, 113, 179]. These mediators potentiate neurogenic skin inflammation by enhancing cellular responses and, therefore, contribute to enhancement or maintenance of CNI [18, 70]. TRPA1 is required for AD and histamine-independent itch [46]. Indeed, oxazolone-induced TRPA1 activation triggers chronic dermatitis and upregulates inflammatory cytokines (i.e., IL-1β, IL-4, IL-16, and CXCL-2) and neuropeptides (i.e., SP and endothelin) in mice. All these substances are known to be involved not only in sensory dysesthesia, but also in structural changes including epidermal nerve sprouting and resultant increase in nerve fiber density [109]. TRPA1-deficient mice show diminished SP- and oxazolone-evoked scratching behaviors [109]. Histamine-independent itch elicited by chloroquine, BAM8–22, or AEW was abrogated in TRPA1-deficient mice, which exhibited impaired scratching behavior and epidermal thickening [183, 185]. Moreover, within the AD skin of patients and mice, TSLP released from keratinocytes potentiated TRPA1 activity via TSLPR, thereby inducing (or enhancing) skin inflammation and eliciting robust itch sensation [117, 184, 198].

TRPA1 is co-expressed with TRPV1 in a subset of nociceptive sensory neurons expressing neuropeptides such as SP and CGRP [46, 163, 175]. Indeed, the activation of TRPA1 stimulates SP and CGRP release with subsequent signs of CNI, such as edema and leukocyte infiltration [114, 151, 163, 173]. TRPA1 modulates inflammatory gene expression in keratinocytes by increasing the expression of IL-1α and IL-1β [12], resulting in the secretion of PGE2 [72]. Both IL-1 and PGE2 are known to be involved in skin inflammation leading to decreased mechanical and thermal thresholds of the sensory nerve endings, which facilitates CNI [20]. In addition, the activation of TRPA1 in keratinocytes increased the expression of inflammatory cytokines such as IL-1β, TNF-α, and IL-6 in a mouse model of allergic contact dermatitis [12, 194]. The mediators not only enhanced the activity of TRPA1 but also prevented the desensitization of TRPA1, which consequently aggravated chronic pain conditions [35, 125]. These findings indicate that TRPA1 mediates the synthesis of several cytokines from keratinocytes that directly trigger or enhance CNI by acting on neighboring target cells [46]. In addition to keratinocytes, TRPA1 acts on skin immune cells, but it appears to play an anti-inflammatory role in monocytes/macrophages [19].

## Peripheral glial cells

Glial cells in the peripheral nerve system consist of satellite glial cells (SGCs) in the dorsal root ganglia and trigeminal ganglia and Schwann cells (Figs. 1 and 2). Emerging evidence suggested that SGCs play a potential role in the development of persistent pain such as inflammatory and neuropathic pain [37, 54, 55, 73, 106, 127, 195]. Following hindpaw inflammation induced by CFA injection, structural and functional coupling among SGCs has been known to develop [37]. Axotomy induces outgrowth of perineuronal SGCs sheaths and then allows to formation of new gap junctions among the approximal SGSs wrapping each own neuronal processes [54]. It has been reported that the types of DRG neurons surrounded by activated SGCs are changed early from early small- and medium-sized neurons later with large diameter neuron as time spent following nerve injury [106]. In the previous study using an animal model of intervertebral foraminal stenosis and low back pain, the authors have shown that a chronic compression of the DRG (CCD) increases the excitability of neuronal cell bodies. Rapid alterations in inwardly rectifying potassium currents of SGCs after CCD seem to be involved in the development of neuronal hyperexcitability in the CCD model of neuropathic pain [195]. Changes in SGC potassium ion buffering capacity and glutamate recycling can lead to neuropathic pain-like behavior in animal models [127]. SGCs have also been suggested as potential contributors in cisplatin-induced neuropathic pain [132].

Schwann cells also play roles in the development and maintenance of neuropathic pain [143, 181]. The Schwann cells respond to nerve injury as the ways to change their phenotypes and proliferate and interact with nociceptive neurons by releasing glial mediators (cytokines, chemokines, growth factors, and biologically active small molecules) [181]. Additionally, it has been reported that receptors expressed in active Schwann cells are involved in different pain conditions[181]. In the patients with nerve injuries, distal Schwann cells undergo atropy due to disconnection with proximal neurons, resulting depletion of neurotrophic growth factors, changes in the extracellular matrix, and loss of Schwann cell basal lamina[143].

Dysfunction of Schwann cells has also been linked to the pathogenesis of chronic itch in prurigo nodularis[6]. After hydroxyethyl starch (HES) infusion therapy in the patients with severe hemorrhage, protracted itch is a common adverse symptom. Exploratory studies explained that this is a consequence of HES accumulation in the Schwann cells leading to functional disturbances[115, 158]. In the patients suffering from hepatic pruritus, increased serum lysophosphatidic acid activates SGCs and Schwann cell[137]. In addition, TRPV4 has been suggested as a prurinergic receptor-operated channel in SGCs of sensory ganglia[133].

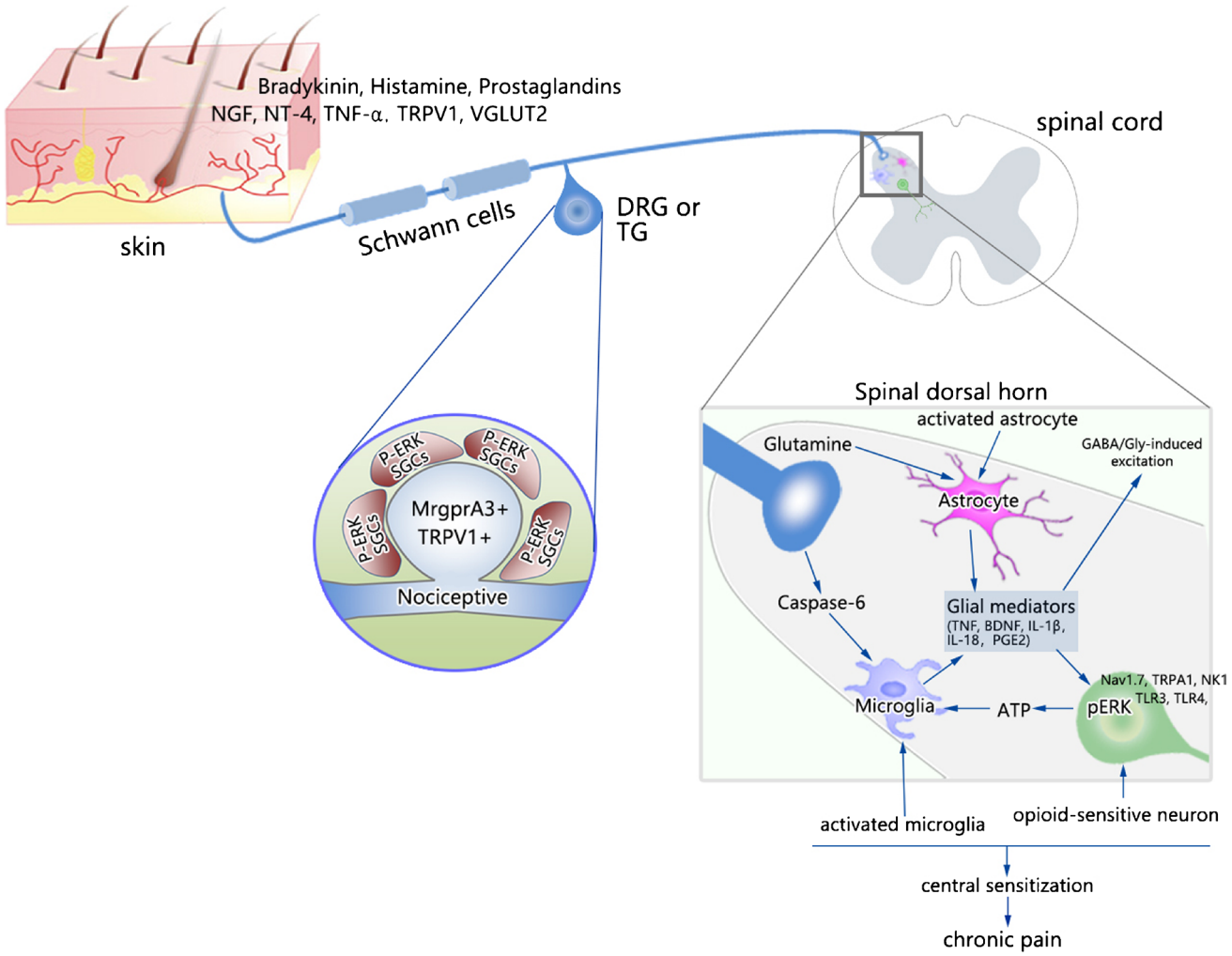


**Fig. 1** Peripheral and central mechanisms of sensitization of pain processing. In the periphery, inflammatory mediators can activate and sensitize nerve endings of the primary nociceptive neurons ($MrgprA3^{+}/TRPV1^{+}$) in the dorsal root ganglia (DRG) or trigeminal ganglia (TG). Nerve growth factor (NGF) and peripheral glia, such as Schwann cells and satellite glial cells induce long term changes in neuronal sensitivities along with structural alterations (e.g., collateral sprouting). In the spinal cord, spinal dorsal horn neuron can be sensitized by inflammatory or immune mediators, such as TNF-α, BDNF, IL-1β, IL-18, and PGE2 that are released from activated glial cells. *Abbreviation: BDNF, brain-derived neurotrophic factor; NK1, neurokinin 1; NT-4, neurotrophin-4; PGE2, prostaglandin E2; TLR3, toll-like receptor 3; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; VGLUT2, vesicular glutamate transporter 2

## Central sensitization

Chronic pain and itch are maintained in part via central sensitization, which is defined as an increased neuronal responsiveness in the central nervous system in response to afferent inputs following painful or pruritic insults [186, 187]. Spinal cord long-term potentiation is an important form of spinal cord synaptic plasticity contributing to central sensitization and pain and itch [76, 108, 111, 188]. Similar to peripheral sensitization, central sensitization occurs not only in neurons, but also in glial cells, by regulating the expression of chronic itch or pain-sensing molecules in the central nervous system (Figs. 1, 2, and Table 1).

## Central sensitization-associated signs

During pain signal processing, repeated activities involving chemonociceptors can sensitize spinal cord dorsal horn neurons, thereby leading to hypersensitivity in response to input from the primary afferents, which is called hyperalgesia [88]. There are two types of mechanical hyperalgesia: allodynia and punctate hyperalgesia. Non-noxious touch stimuli can lead to allodynia or pain sensation, which is mediated by myelinated mechanoreceptor units, although it requires ongoing activity of primary afferent C-nociceptors. The second type of mechanical hyperalgesia results in "punctate hyperalgesia" or the perception of slightly painful pin prick

as more painful in the secondary zone around a focus of insult. It does not require ongoing activity of primary nociceptors for its maintenance. It can persist for hours following a trauma, usually much longer than touch or brush-evoked hyperalgesia [95].

In chronic itch processing, striking phenomena involving a pattern of central sensitization have been described. Alloknesis and hyperknesis typically occur within the region of itch provocation, and in the skin immediately surrounding the provocation site, which is termed "itchy skin" [153]. During alloknesis, innocuous mechanical touch frequently elicits itch sensation around the pruritogen injection site on human skin [60, 61, 153]. Recently, Carstens' group [53] developed a mouse model of alloknesis demonstrating that exposure to innocuous mechanical stimuli (light touch by von Frey filaments) on the skin near the pruritogen injection sites or the lesional dry skin region induces scratching behavior. Consistent with the previous human psychophysical findings of μ-opioid antagonist-attenuated alloknesis [60], μ-opioid antagonists inhibited touch-evoked scratching in mice, suggesting the reliability of the animal model. It is thought that morphine-induced itch is developed by the

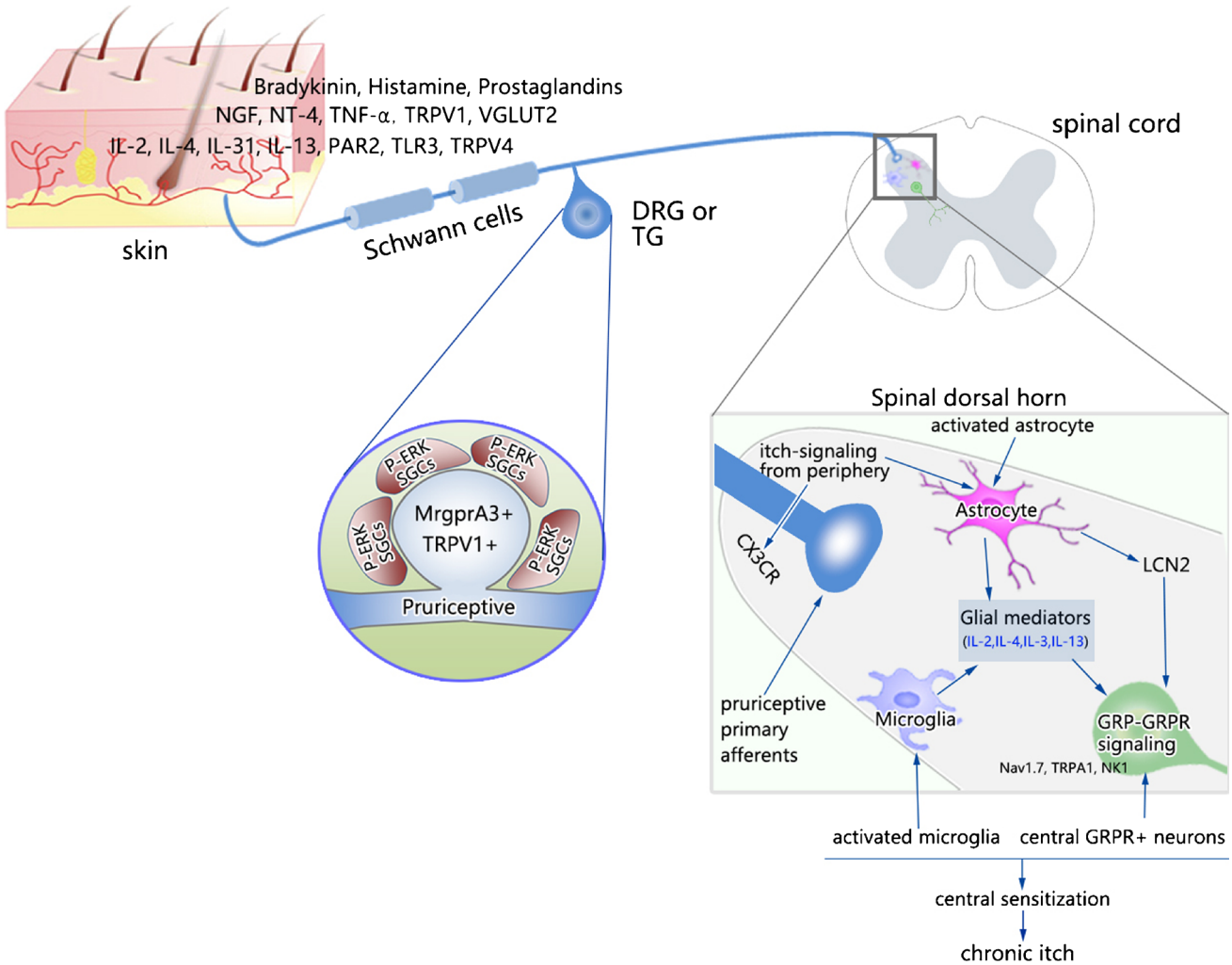


**Fig. 2** Peripheral and central mechanisms of sensitization of itch processing. In the periphery, inflammatory and immune mediators can activate and sensitize nerve endings of the primary pruriceptive neurons ($MrgprA3^+/TRPV1^+$) in the dorsal root ganglia (DRG) or trigeminal ganglia (TG). In addition to acute sensitization, nerve growth factor (NGF) and peripheral glia, such as Schwann cells and satellite glial cells induce long-term changes in neuronal sensitivities along with structural alterations. In the spinal cord, spinothalamic neurons ($GRPR^+$) transmitting itch signals can be sensitized by inflammatory cytokines, such as IL-2, IL-4, IL-3, and IL-13, released from activated glial cells. *Abbreviation: BDNF, brain-derived neurotrophic factor; CX3CR, C-X-C motif chemokine receptor 3; GRP, gastrin-releasing peptide; GRPR, gastrin-releasing peptide receptor; LCN2, lipocalin-2; NK1, neurokinin 1; NT-4, neurotrophin-4; PAR2, protease-activated receptor 2; PGE2, prostaglandin E2; TLR3, toll-like receptor 3; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; TRPV4, transient receptor potential vanilloid 4; VGLUT2, vesicular glutamate transporter 2

cross-activation of GRPR with an isoform of the μ-opioid receptor (MOR), MOR1D [16, 105]. Very similar to allodynia, alloknesis requires ongoing activities in low threshold mechanoreceptors (Aβ-fibers) [59, 153]. Additionally, hyperknesis is an exaggerated itch response to normally pruritic or mild punctate pain stimuli [7, 11]. The itch-associated dysesthesias are noticeably analogous to dysesthesias occurring in various experimental and clinical pain conditions [5, 68, 148].

## Possible mechanisms of central sensitization in chronic pain and itch

### Pain-sensing molecules driving central sensitization

Central sensitization is maintained by ongoing stimuli, such as spontaneous activities arising from sensory fibers or locally released immune mediators, which are responsible for the maintenance and spread of neuropathic pain beyond the initial injury site [47]. Postsynaptic glutamate N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy- 5-methyl-4-isoxazolepropionic acid (AMPA) receptors mediate the induction and maintenance of central sensitization [74, 99].

### Central itch-sensing molecules driving central sensitization

In non-human primates suffering from idiopathic chronic itch [121], both gastrin-releasing peptide (GRP) and its receptor GRPR are significantly upregulated in the spinal cord, which in turn enhance the central sensitization.

### Altered synaptic transmission

In pathophysiological conditions, decreased inhibitory synaptic transmission (referred to as "disinhibition") in the spinal cord has also been known to mediate central sensitization. In the neuronal pathways relaying pain signals, a reduction or loss of inhibitory synaptic transmission has also been implicated in the genesis of central sensitization and chronic pain [99]. Factors such as TNF, IL-1β, IL-6, CCL2, IFN-γ, and ROS decrease inhibitory signaling pathways in the spinal dorsal horn via deactivation of GABAergic and glycinergic inhibitory interneurons as well as inhibitory descending projections [44, 47, 56, 84, 177]. In addition, it has been suggested that activation of NK1 receptors in the locus coeruleus induces analgesia via noradrenergic-mediated descending inhibition in a rat model of neuropathic pain [119].

In the neural pathway of chronic itch, central sensitization also occurs with the disinhibition of Bhlhb5$^+$ inhibitory interneurons in the spinal dorsal horn, as shown in Bhlhb5 and Vglut2 knockout mice [93, 104, 139].

### Glial activation-driven central sensitization by neuroinflammation

Accumulating evidence suggests that synaptic hyperexcitability in the spinal dorsal horn might not be attributed to simple changes in neurons, but rather multiple alterations in glial cells [76]. Microglia and astrocytes in the spinal dorsal horn play a role in chronic pain and itch, respectively [174]. Neuroinflammation by glial cells induces central sensitization and widespread chronic pain and itch [75, 76]. In the pathogenesis of chronic pain [26, 42, 136], tissue or nerve injury releases glial activators, which in turn bind to their own receptors on the microglia and astrocytes in the spinal cord or brain [76, 78, 80, 81]. Upon glial activation, the glial receptors induce intracellular signal transduction and activation of protein kinases (phosphorylation of mitogen-activated protein kinase and Src kinase), leading to the release of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), chemokines (CCL2 and CXCL1), and BDNF, leading to neuroinflammation, which, in turn, sustains central sensitization [40, 76, 79]. However, these glial mediators contribute to the central sensitization via alterations in excitatory or inhibitory synaptic transmission [40, 41]. Following astrogliosis, excitatory synaptic transmission is enhanced, following the persistent downregulation of the spinal astrocyte glutamate transporters after peripheral nerve injury, leading to excitotoxicity and resultant nociceptive hypersensitivity [134, 189].

The central glial cells play a role in prolonged or chronic itch [150, 196]. Intramedullary cavernous hemangiomas were associated with chronic neuropathic itch in the corresponding dermatome and characterized by gliosis and hemosiderin deposition after hemorrhage [27, 32, 98]. Moreover, in NC/Nga mice, central astrocytes contribute to modulation of chronic itch via LCN2-signaling with GRPR$^+$ neurons [49, 110, 150]. In addition, astrocytes in the spinal dorsal horn carry enlarged cell bodies and extensively arborized processes in AD mice [150]. Recent studies suggest that the transcription factor signal transducer and activator of transcription 3 (STAT3) [150] and the toll-like receptor 4 (TLR4) [110] are selectively activated and expressed in reactive astrocytes in the animals suffering from chronic itch. STAT3-dependent reactive astrogliosis in the spinal dorsal horn contributes to the pathogenesis of chronic itch via conditional disruption of astrocytic STAT3 or pharmacological inhibition of spinal STAT3-attenuated chronic itch in mice [150].

## Similar patterns of central sensitization in chronic pain and itch

The striking similarities between chronic pain and itch sensations suggest similar mechanisms of central sensitization (Figs. 1, 2 and Table 1). In neuropathic conditions such as postherpetic neuralgia, diabetic neuropathy, meralgia paresthetica, nostalgia paresthetica, and brachioradial pruritus, the patients suffer from both pain and itch sensations [148]. It is remarkable that patients with nostalgia paresthetica or brachioradial pruritus complain of a predominantly chronic itch sensation, while patients suffering from postherpetic neuralgia, diabetic neuropathy, or meralgia paresthetica primarily manifest chronic pain symptoms [148]. Interestingly, the same medications are often prescribed to treat chronic pain and itch. For example, gabapentin [33, 144] or clonidine [38] is usually used to treat both chronic neuropathic pain and itch, suggesting shared mechanisms underlying chronic pain and itch. In TLR3$^{-/-}$ mice, excitatory synaptic transmission and long-term potentiation in the intact spinal cord have been reported to be impaired. Chronic pain or itch was substantially reduced in these mice. All these findings demonstrate a critical role of TLR3 in central sensitization leading to chronic pain and chronic itch sensations [107].

The population of SP receptor NK1-expressing neurons, most of which are known to be spinothalamic tract (STT) neurons, has been implicated in both chronic itch and pain sensations [159, 160]. Selective ablation of STT neurons expressing NK1 receptor leads to robust inhibition of alloknesis in AD mice, potentially implicating both ascending pathways [167]. However, ablation of spinal NK1 neurons also reduces spinal sensitization and prevents development of chronic pain [182].

TLRs, Nav1.7, and TRPA1 play an important role in central sensitization by conducting and transmitting the signals for chronic dysesthesias [22, 31, 75, 101]. TLR4 released by spinal astrocytes also plays a possible role in developing or maintaining chronic itch [135].

**Table 1** Similarities and Differences between chronic pain and chronic itch, covering chronic sensitization (peripheral sensitization and central sensitization) and symptoms/response, as well as therapeutic treatments. *Abbreviation: *BDNF*, brain-derived neurotrophic factor; *Bhlhb5*, basic helix-loop-helix domain-containing protein class B 5; *CCL2*, C–C motif chemokine ligand 2; *CCL5*, C–C motif chemokine ligand 5; *CXCL*1, C-X-C motif chemokine ligand 1; *NGF*, nerve growth factor; *NK1*, neurokinin 1; *NT-4*, neurotrophin-4; *PAR2*, protease-activated receptor 2; *PGE2*, prostaglandin E2; *STAT3*, signal transducer and activator of transcription 3; *TLR3,* toll-like receptor 3; *TLR4*, toll-like receptor 4; *TNF-α*, tumor necrosis factor-α; *TRPA1*, transient receptor potential ankyrin 1; *TRPV1*, transient receptor potential vanilloid 1; *TRPV4*, transient receptor potential vanilloid 4; *VGLUT2*, vesicular glutamate transporter 2

| | | | Chronic pain | Chronic itch |
|---|---|---|---|---|
| Chronic sensitization | Peripheral sensitization | Similarities | Peripheral nerve fiber sprouting, Increase in neuronal excitability | |
| | | | Sharing mediators: NGF, NT-4, TNF-α, TRPV1, TRPA1, VGLUT2 | |
| | | | Cutaneous neurogenic inflammation | |
| | | | Schwann cells and satellite glial cells in the DRG | |
| | | Differences | | Mediators: IL-2, IL-4, IL-31, IL-13, PAR2, TLR3, TRPV4 |
| | Central sensitization | Similarities | Increase in CNS excitability | |
| | | | Microglia and astrocyte (overlapping mediators: BDNF, TNF-α) | |
| | | | Overlapping mediators: TLR3, TLR4, Nav1.7, TRPA1, NK1 | |
| | | Differences | Associated signs: hyperalgesia, allodynia | Associated signs: hyperknesis, alloknesis |
| | | | | Spinal GRPR |
| | | | Glial mediators: IL-1β, IL-6, IL-18, PGE2, CCL2, CCL5, CXCL1 | Glial mediators: IL-2, IL-4, IL-31, IL-13, STAT3, TLR4 |
| | | | GABAergic & glycinergic inhibitory interneurons, Descending inhibition | Bhlhb5 + inhibitory interneurons |
| Symptoms/responses | | Similarities | Persistent intractable clinical symptoms | |
| | | Differences | Withdrawal | Scratching |
| Therapeutics | | Similarities | Gabapentin, pregabalin, local anesthetics, clonidine, antidepressant, local cold application | |
| | | Differences | NSAIDs, μ-opioid (morphine) | Anti-IL-4, anti-IL-13, anti-IL-31, κ-opioid agonist (butorphanol), μ-opioid antagonist (naltrexone) antihistamines |

## Conclusion

Despite of many current literatures that have gone on here, we still do not exactly understand how we recognized pain and itch as distinct sensations with different qualities in the same chronic sensitization. This would be a good theme in the next further studies. Literatures suggest that both chronic pain and itch may share strikingly similar underlying mechanisms. Especially, peripheral and central sensitization leads to the development and persistence of chronic dysesthesias. The similarities between chronic itch and pain suggest the need to combine studies investigating both itch and pain and, thereby, facilitate the development of new therapeutics against both two chronic dysensthesias.

**Funding** This research was supported by the National Science Foundation for Young Scientists of China program, funded by the National Natural Science Foundation of China (NSFC), Project No. 81901150 (H0903).

#### Declarations

The authors declare no competing interests.

## References

1. Abadia Molina F et al (1992) Increased sensory neuropeptides in nodular prurigo: a quantitative immunohistochemical analysis. Br J Dermatol 127(4):344–351
2. Akaishi S, Ogawa R, Hyakusoku H (2008) Keloid and hypertrophic scar: neurogenic inflammation hypotheses. Med Hypotheses 71(1):32–38
3. Akiyama T et al (2016) Involvement of TRPV4 in serotonin-evoked scratching. J Invest Dermatol 136(1):154–160
4. Akiyama T, Carstens MI, Carstens E (2010) Enhanced scratching evoked by PAR-2 agonist and 5-HT but not histamine in a mouse model of chronic dry skin itch. Pain 151(2):378–383
5. Andersen HH et al (2017) Antipruritic effect of pretreatment with topical capsaicin 8% on histamine- and cowhage-evoked itch in healthy volunteers: a randomized, vehicle-controlled, proof-of-concept trial. Br J Dermatol 177(1):107–116
6. Andersen HH, Arendt-Nielsen L, Gazerani P (2016) Glial cells are involved in itch processing. Acta Derm Venereol 96(6):723–727
7. Andersen HH, Elberling J, Arendt-Nielsen L (2015) Human surrogate models of histaminergic and non-histaminergic itch. Acta Derm Venereol 95(7):771–777
8. Andersen HH, Yosipovitch G, Galor A (2017) Neuropathic symptoms of the ocular surface: dryness, pain, and itch. Curr Opin Allergy Clin Immunol 17(5):373–381
9. Andreev YA, Vassilevski AA, Kozlov SA (2012) Molecules to selectively target receptors for treatment of pain and neurogenic inflammation. Recent Pat Inflamm Allergy Drug Discov 6(1):35–45
10. Arndt J, Smith N, Tausk F (2008) Stress and atopic dermatitis. Curr Allergy Asthma Rep 8(4):312–317
11. Atanassoff PG et al (1999) Enhancement of experimental pruritus and mechanically evoked dysesthesiae with local anesthesia. Somatosens Mot Res 16(4):291–298
12. Atoyan R, Shander D, Botchkareva NV (2009) Non-neuronal expression of transient receptor potential type A1 (TRPA1) in human skin. J Invest Dermatol 129(9):2312–2315
13. Azim AAA et al (2015) Role of Interleukin-2 in uremic pruritus among attendants of al-zahraa hospital dialysis unit. Indian J Dermatol 60(2):211–211
14. Barcena de Arellano ML et al (2011) Influence of nerve growth factor in endometriosis-associated symptoms. Reprod Sci 18(12):1202–10
15. Baron R et al (2001) Histamine-induced itch converts into pain in neuropathic hyperalgesia. NeuroReport 12(16):3475–3478
16. Barry DM, Munanairi A, Chen ZF (2018) Spinal mechanisms of itch transmission. Neurosci Bull 34(1):156–164
17. Basbaum AI et al (2009) Cellular and molecular mechanisms of pain. Cell 139(2):267–284
18. Bautista DM, Pellegrino M, Tsunozaki M (2013) TRPA1: a gatekeeper for inflammation. Annu Rev Physiol 75:181–200
19. Billeter AT et al (2015) TRPA1 mediates the effects of hypothermia on the monocyte inflammatory response. Surgery 158(3):646–654
20. Binshtok AM et al (2008) Nociceptors are interleukin-1beta sensors. J Neurosci 28(52):14062–14073
21. Birklein F et al (1997) Effects of cutaneous histamine application in patients with sympathetic reflex dystrophy. Muscle Nerve 20(11):1389–1395
22. Black JA et al (2012) Expression of Nav1.7 in DRG neurons extends from peripheral terminals in the skin to central preterminal branches and terminals in the dorsal horn. Mol Pain 8:82
23. Boillat A, Alijevic O, Kellenberger S (2014) Calcium entry via TRPV1 but not ASICs induces neuropeptide release from sensory neurons. Mol Cell Neurosci 61:13–22
24. Brodal P (2005) The neurobiology of pain. Tidsskr Nor Laegeforen 125(17):2370–2373
25. Brull SJ et al (1999) Attenuation of experimental pruritus and mechanically evoked dysesthesiae in an area of cutaneous allodynia. Somatosens Mot Res 16(4):299–303
26. Calvo M, Dawes JM, Bennett DL (2012) The role of the immune system in the generation of neuropathic pain. Lancet Neurol 11(7):629–642
27. Carstens E (2008) Scratching the brain to understand neuropathic itch. J Pain 9(11):973–974
28. Chevalier X, Eymard F, Richette P (2013) Biologic agents in osteoarthritis: hopes and disappointments. Nat Rev Rheumatol 9(7):400–410
29. Costa A et al (2014) Neuromodulatory and anti-inflammatory ingredient for sensitive skin: in vitro assessment. Inflamm Allergy Drug Targets 13(3):191–198
30. Dai Y et al (2007) Sensitization of TRPA1 by PAR2 contributes to the sensation of inflammatory pain. J Clin Invest 117(7):1979–1987
31. Devigili G et al (2014) Paroxysmal itch caused by gain-of-function Nav1.7 mutation. Pain 155(9):1702–7
32. Dey DD, Landrum O, Oaklander AL (2005) Central neuropathic itch from spinal-cord cavernous hemangioma: a human case, a possible animal model, and hypotheses about pathogenesis. Pain 113(1–2):233–237
33. Dhand A, Aminoff MJ (2014) The neurology of itch. Brain 137(Pt 2):313–322
34. Dillon SR et al (2004) Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. Nat Immunol 5(7):752–760

35. Diogenes A, Akopian AN, Hargreaves KM (2007) NGF upregulates TRPA1: implications for orofacial pain. J Dent Res 86(6):550–555
36. Dou YC et al (2006) Increased nerve growth factor and its receptors in atopic dermatitis: an immunohistochemical study. Arch Dermatol Res 298(1):31–37
37. Dublin P, Hanani M (2007) Satellite glial cells in sensory ganglia: their possible contribution to inflammatory pain. Brain Behav Immun 21(5):592–598
38. Elkersh MA et al (2003) Epidural clonidine relieves intractable neuropathic itch associated with herpes zoster-related pain. Reg Anesth Pain Med 28(4):344–346
39. Ezzat MH, Hasan ZE, Shaheen KY (2011) Serum measurement of interleukin-31 (IL-31) in paediatric atopic dermatitis: elevated levels correlate with severity scoring. J Eur Acad Dermatol Venereol 25(3):334–339
40. Gao YJ et al (2009) JNK-induced MCP-1 production in spinal cord astrocytes contributes to central sensitization and neuropathic pain. J Neurosci 29(13):4096–4108
41. Gao YJ et al (2010) The c-Jun N-terminal kinase 1 (JNK1) in spinal astrocytes is required for the maintenance of bilateral mechanical allodynia under a persistent inflammatory pain condition. Pain 148(2):309–319
42. Gao YJ, Ji RR (2010) Chemokines, neuronal-glial interactions, and central processing of neuropathic pain. Pharmacol Ther 126(1):56–68
43. Gonzales AJ et al (2013) Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. Vet Dermatol 24(1):48-53.e11–2
44. Gosselin RD et al (2005) Constitutive expression of CCR2 chemokine receptor and inhibition by MCP-1/CCL2 of GABA-induced currents in spinal cord neurones. J Neurochem 95(4):1023–1034
45. Gouin O et al (2015) Self-maintenance of neurogenic inflammation contributes to a vicious cycle in skin. Exp Dermatol 24(10):723–726
46. Gouin O et al (2017) TRPV1 and TRPA1 in cutaneous neurogenic and chronic inflammation: pro-inflammatory response induced by their activation and their sensitization. Protein Cell 8(9):644–661
47. Grace PM et al (2014) Pathological pain and the neuroimmune interface. Nat Rev Immunol 14(4):217–231
48. Green AD et al (2006) Influence of genotype, dose and sex on pruritogen-induced scratching behavior in the mouse. Pain 124(1–2):50–58
49. Green D, Dong X (2015) Supporting itch: a new role for astrocytes in chronic itch. Nat Med 21(8):841–842
50. Grewe M et al (2000) Neurotrophin-4 production by human epidermal keratinocytes: increased expression in atopic dermatitis. J Invest Dermatol 114(6):1108–1112
51. Groneberg DA et al (2005) Gene expression and regulation of nerve growth factor in atopic dermatitis mast cells and the human mast cell line-1. J Neuroimmunol 161(1–2):87–92
52. Halvorson KG et al (2005) A blocking antibody to nerve growth factor attenuates skeletal pain induced by prostate tumor cells growing in bone. Cancer Res 65(20):9426–9435
53. Han L, Dong X (2014) Itch mechanisms and circuits. Annu Rev Biophys 43:331–355
54. Hanani M et al (2002) Glial cell plasticity in sensory ganglia induced by nerve damage. Neuroscience 114(2):279–283
55. Hanani M (2010) Satellite glial cells in sympathetic and parasympathetic ganglia: in search of function. Brain Res Rev 64(2):304–327
56. Harvey RJ et al (2004) GlyR alpha3: an essential target for spinal PGE2-mediated inflammatory pain sensitization. Science 304(5672):884–887
57. Hefti FF et al (2006) Novel class of pain drugs based on antagonism of NGF. Trends Pharmacol Sci 27(2):85–91
58. Herbert MK, Holzer P (2002) Neurogenic inflammation. I. Basic mechanisms, physiology and pharmacology. Anasthesiol Intensivmed Notfallmed Schmerzther 37(6):314–25
59. Heyer G et al (1995) Histamine-induced itch and alloknesis (itchy skin) in atopic eczema patients and controls. Acta Derm Venereol 75(5):348–352
60. Heyer G et al (1997) Opiate and H1 antagonist effects on histamine induced pruritus and alloknesis. Pain 73(2):239–243
61. Hojland CR et al (2015) A human surrogate model of itch utilizing the TRPA1 agonist trans-cinnamaldehyde. Acta Derm Venereol 95(7):798–803
62. Hon KL et al (2007) Pathophysiology of nocturnal scratching in childhood atopic dermatitis: the role of brain-derived neurotrophic factor and substance P. Br J Dermatol 157(5):922–925
63. Hosogi M et al (2006) Bradykinin is a potent pruritogen in atopic dermatitis: a switch from pain to itch. Pain 126(1–3):16–23
64. Ikoma A et al (2003) Neurophysiology of pruritus: interaction of itch and pain. Arch Dermatol 139(11):1475–1478
65. Ikoma A et al (2003) Neuronal sensitization for histamine-induced itch in lesional skin of patients with atopic dermatitis. Arch Dermatol 139(11):1455–1458
66. Ikoma A et al (2004) Painful stimuli evoke itch in patients with chronic pruritus: central sensitization for itch. Neurology 62(2):212–217
67. Ikoma A et al (2005) Electrically evoked itch in humans. Pain 113(1–2):148–154
68. Ikoma A et al (2006) The neurobiology of itch. Nat Rev Neurosci 7(7):535–547
69. Ikoma A et al (2011) Anatomy and neurophysiology of pruritus. Semin Cutan Med Surg 30(2):64–70
70. Inoue K et al (2002) Functional vanilloid receptors in cultured normal human epidermal keratinocytes. Biochem Biophys Res Commun 291(1):124–129
71. Ishiuji Y et al (2008) Repetitive scratching and noxious heat do not inhibit histamine-induced itch in atopic dermatitis. Br J Dermatol 158(1):78–83
72. Jain A et al (2011) TRP-channel-specific cutaneous eicosanoid release patterns. Pain 152(12):2765–2772
73. Jasmin L et al (2010) Can satellite glial cells be therapeutic targets for pain control? Neuron Glia Biol 6(1):63–71
74. Ji RR et al (2003) Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci 26(12):696–705
75. Ji RR (2015) Neuroimmune interactions in itch: do chronic itch, chronic pain, and chronic cough share similar mechanisms? Pulm Pharmacol Ther 35:81–86
76. Ji RR et al (2018) Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology 129(2):343–366
77. Ji RR, Chamessian A, Zhang YQ (2016) Pain regulation by non-neuronal cells and inflammation. Science 354(6312):572–577
78. Ji RR, Donnelly CR, Nedergaard M (2019) Astrocytes in chronic pain and itch. Nat Rev Neurosci 20(11):667–685
79. Ji RR, Suter MR (2007) p38 MAPK, microglial signaling, and neuropathic pain. Mol Pain 3:33
80. Jiang F et al (2009) Spinal astrocyte and microglial activation contributes to rat pain-related behaviors induced by the venom of scorpion Buthus martensi Karch. Eur J Pharmacol 623(1–3):52–64
81. Jin SX et al (2003) p38 mitogen-activated protein kinase is activated after a spinal nerve ligation in spinal cord microglia and dorsal root ganglion neurons and contributes to the generation of neuropathic pain. J Neurosci 23(10):4017–4022
82. Johansson O, Liang Y, Emtestam L (2002) Increased nerve growth factor- and tyrosine kinase A-like immunoreactivities in

prurigo nodularis skin – an exploration of the cause of neurohyperplasia. Arch Dermatol Res 293(12):614–619
83. Katsuno M et al (2003) Neuropeptides concentrations in the skin of a murine (NC/Nga mice) model of atopic dermatitis. J Dermatol Sci 33(1):55–65
84. Kawasaki Y et al (2008) Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord. J Neurosci 28(20):5189–5194
85. Kidd BL, Urban LA (2001) Mechanisms of inflammatory pain. Br J Anaesth 87(1):3–11
86. Kim S et al (2016) Facilitation of TRPV4 by TRPV1 is required for itch transmission in some sensory neuron populations. Sci Signal 9(437):ra71
87. Kinkelin I et al (2000) Increase in NGF content and nerve fiber sprouting in human allergic contact eczema. Cell Tissue Res 302(1):31–37
88. Koltzenburg M (2000) Neural mechanisms of cutaneous nociceptive pain. Clin J Pain 16(3 Suppl):S131–S138
89. Kubanov AA, Katunina OR, Chikin VV (2015) Expression of neuropeptides, neurotrophins, and neurotransmitters in the skin of patients with atopic dermatitis and psoriasis. Bull Exp Biol Med 159(3):318–322
90. Kuruvilla M, Kalangara J, Lee FEE (2019) Neuropathic pain and itch mechanisms underlying allergic conjunctivitis. J Investig Allergol Clin Immunol 29(5):349–356
91. Kwak IS et al (2014) Immunohistochemical analysis of neuropeptides (protein gene product 9.5, substance P and calcitonin gene-related peptide) in hypertrophic burn scar with pain and itching. Burns 40(8):1661–7
92. van Laarhoven AI et al (2013) Sensitivity to itch and pain in patients with psoriasis and rheumatoid arthritis. Exp Dermatol 22(8):530–534
93. Lagerstrom MC et al (2010) VGLUT2-dependent sensory neurons in the TRPV1 population regulate pain and itch. Neuron 68(3):529–542
94. Laird JM et al (2001) Role of central and peripheral tachykinin NK1 receptors in capsaicin-induced pain and hyperalgesia in mice. Pain 90(1–2):97–103
95. LaMotte RH et al (1991) Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. J Neurophysiol 66(1):190–211
96. LaMotte RH, Dong X, Ringkamp M (2014) Sensory neurons and circuits mediating itch. Nat Rev Neurosci 15(1):19–31
97. Lane NE et al (2010) Tanezumab for the treatment of pain from osteoarthritis of the knee. N Engl J Med 363(16):1521–1531
98. Lanotte M et al (2013) Central neuropathic itch as the presenting symptom of an intramedullary cavernous hemangioma: case report and review of literature. Clin Neurol Neurosurg 115(4):454–456
99. Latremoliere A, Woolf CJ (2009) Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 10(9):895–926
100. Lee CH et al (2012) Mechanistic correlations between two itch biomarkers, cytokine interleukin-31 and neuropeptide beta-endorphin, via STAT3/calcium axis in atopic dermatitis. Br J Dermatol 167(4):794–803
101. Lee JH et al (2014) A monoclonal antibody that targets a NaV1.7 channel voltage sensor for pain and itch relief. Cell 157(6):1393–1404
102. Liang J, He Y, Ji W (2012) Bradykinin-evoked scratching responses in complete Freund's adjuvant-inflamed skin through activation of B1 receptor. Exp Biol Med (Maywood) 237(3):318–326
103. Linderoth B, Meyerson B (2001) Peripheral and central nervous system stimulation in chronic therapy-resistant pain. Background, hypothetical mechanisms and clinical experiences. Lakartidningen 98(47):5328–34 (**5336**)
104. Liu Y et al (2010) VGLUT2-dependent glutamate release from nociceptors is required to sense pain and suppress itch. Neuron 68(3):543–556
105. Liu XY et al (2011) Unidirectional cross-activation of GRPR by MOR1D uncouples itch and analgesia induced by opioids. Cell 147(2):447–458
106. Liu FY et al (2012) Activation of satellite glial cells in lumbar dorsal root ganglia contributes to neuropathic pain after spinal nerve ligation. Brain Res 1427:65–77
107. Liu T et al (2012) TLR3 deficiency impairs spinal cord synaptic transmission, central sensitization, and pruritus in mice. J Clin Invest 122(6):2195–2207
108. Liu T et al (2012) TLR3 deficiency impairs spinal cord synaptic transmission, central sensitization, and pruritus in mice. J Clin Investig 122(6):2195–2207
109. Liu B et al (2013) TRPA1 controls inflammation and pruritogen responses in allergic contact dermatitis. FASEB J 27(9):3549–3563
110. Liu T et al (2016) Toll-like receptor 4 contributes to chronic itch, alloknesis, and spinal astrocyte activation in male mice. Pain 157(4):806–817
111. Liu B-W et al (2019) Altered expression of itch-related mediators in the lower cervical spinal cord in mouse models of two types of chronic itch. Int J Mol Med 44(3):835–846
112. Liu T, Ji R-R (2013) New insights into the mechanisms of itch: are pain and itch controlled by distinct mechanisms? Pflugers Arch 465(12):1671–1685
113. Malin S et al (2011) TRPV1 and TRPA1 function and modulation are target tissue dependent. J Neurosci 31(29):10516–10528
114. Meseguer V et al (2014) TRPA1 channels mediate acute neurogenic inflammation and pain produced by bacterial endotoxins. Nat Commun 5:3125
115. Metze D et al (1997) Persistent pruritus after hydroxyethyl starch infusion therapy: a result of long-term storage in cutaneous nerves. Br J Dermatol 136(4):553–559
116. Mogil JS et al (2005) Variable sensitivity to noxious heat is mediated by differential expression of the CGRP gene. Proc Natl Acad Sci U S A 102(36):12938–12943
117. Moniaga CS et al (2013) Protease activity enhances production of thymic stromal lymphopoietin and basophil accumulation in flaky tail mice. Am J Pathol 182(3):841–851
118. Murota H et al (2012) Artemin causes hypersensitivity to warm sensation, mimicking warmth-provoked pruritus in atopic dermatitis. J Allergy Clin Immunol 130(3):671-682.e4
119. Muto Y et al (2012) Activation of $NK_1$ receptors in the locus coeruleus induces analgesia through noradrenergic-mediated descending inhibition in a rat model of neuropathic pain. Br J Pharmacol 166(3):1047–1057
120. Nathan PW (1990) Touch and surgical division of the anterior quadrant of the spinal cord. J Neurol Neurosurg Psychiatry 53(11):935–939
121. Nattkemper LA et al (2013) Overexpression of the gastrin-releasing peptide in cutaneous nerve fibers and its receptor in the spinal cord in primates with chronic itch. J Invest Dermatol 133(10):2489–2492
122. Nicolson TA et al (2007) Prostaglandin E2 sensitizes primary sensory neurons to histamine. Neuroscience 150(1):22–30
123. Nilsson HJ, Levinsson A, Schouenborg J (1997) Cutaneous field stimulation (CFS): a new powerful method to combat itch. Pain 71(1):49–55

124. Nilsson HJ, Schouenborg J (1999) Differential inhibitory effect on human nociceptive skin senses induced by local stimulation of thin cutaneous fibers. Pain 80(1–2):103–112
125. Obata K et al (2005) TRPA1 induced in sensory neurons contributes to cold hyperalgesia after inflammation and nerve injury. J Clin Invest 115(9):2393–2401
126. Oh M-H et al (2013) TRPA1-dependent pruritus in IL-13-induced chronic atopic dermatitis. J Immunol 191(11):5371–5382 ((**Baltimore, Md. : 1950**))
127. Ohara PT et al (2009) Gliopathic pain: when satellite glial cells go bad. Neuroscientist 15(5):450–463
128. Ozawa M et al (2009) Neuroselective transcutaneous electrical stimulation reveals neuronal sensitization in atopic dermatitis. J Am Acad Dermatol 60(4):609–614
129. Peirs C, Seal RP (2016) Neural circuits for pain: recent advances and current views. Science 354(6312):578–584
130. Pogatzki-Zahn E et al (2008) Chronic pruritus: targets, mechanisms and future therapies. Drug News Perspect 21(10):541–551
131. Potenzieri C, Undem BJ (2012) Basic mechanisms of itch. Clin Exp Allergy 42(1):8–19
132. Poulsen JN et al (2015) Oxaliplatin enhances gap junction-mediated coupling in cell cultures of mouse trigeminal ganglia. Exp Cell Res 336(1):94–99
133. Rajasekhar P et al (2015) P2Y1 receptor activation of the trpv4 ion channel enhances purinergic signaling in satellite glial cells. J Biol Chem 290(48):29051–29062
134. Ramos KM et al (2010) Spinal upregulation of glutamate transporter GLT-1 by ceftriaxone: therapeutic efficacy in a range of experimental nervous system disorders. Neuroscience 169(4):1888–1900
135. Ransohoff RM (2016) How neuroinflammation contributes to neurodegeneration. Science 353(6301):777–783
136. Ren K, Dubner R (2010) Interactions between the immune and nervous systems in pain. Nat Med 16(11):1267–1276
137. Robering JW et al (2019) Lysophosphatidic acid activates satellite glia cells and Schwann cells. Glia 67(5):999–1012
138. Roosterman D et al (2006) Neuronal control of skin function: the skin as a neuroimmunoendocrine organ. Physiol Rev 86(4):1309–1379
139. Ross SE et al (2010) Loss of inhibitory interneurons in the dorsal spinal cord and elevated itch in Bhlhb5 mutant mice. Neuron 65(6):886–898
140. Rukwied RR et al (2013) NGF sensitizes nociceptors for cowhage- but not histamine-induced itch in human skin. J Invest Dermatol 133(1):268–270
141. Sandkuhler J (2009) Models and mechanisms of hyperalgesia and allodynia. Physiol Rev 89(2):707–758
142. Sanga P et al (2013) Efficacy, safety, and tolerability of fulranumab, an anti-nerve growth factor antibody, in the treatment of patients with moderate to severe osteoarthritis pain. Pain 154(10):1910–1919
143. Scheib J, Hoke A (2013) Advances in peripheral nerve regeneration. Nat Rev Neurol 9(12):668–676
144. Scheinfeld N (2003) The role of gabapentin in treating diseases with cutaneous manifestations and pain. Int J Dermatol 42(6):491–495
145. Schmelz M et al (2003) Active "itch fibers" in chronic pruritus. Neurology 61(4):564–566
146. Schmelz M et al (2003) Chemical response pattern of different classes of C-nociceptors to pruritogens and algogens. J Neurophysiol 89(5):2441–2448
147. Schmelz M (2010) Itch and pain. Neurosci Biobehav Rev 34(2):171–176
148. Schmelz M (2015) Itch and pain differences and commonalities. Handb Exp Pharmacol 227:285–301
149. Shang H et al (2016) IL-4 gene polymorphism may contribute to an increased risk of atopic dermatitis in children. Dis Markers 2016:1021942–1021942
150. Shiratori-Hayashi M et al (2015) STAT3-dependent reactive astrogliosis in the spinal dorsal horn underlies chronic itch. Nat Med 21(8):927–931
151. Silva CR et al (2011) The involvement of TRPA1 channel activation in the inflammatory response evoked by topical application of cinnamaldehyde to mice. Life Sci 88(25–26):1077–1087
152. Simone DA et al (2004) Comparison of responses of primate spinothalamic tract neurons to pruritic and algogenic stimuli. J Neurophysiol 91(1):213–222
153. Simone DA, Alreja M, LaMotte RH (1991) Psychophysical studies of the itch sensation and itchy skin ("alloknesis") produced by intracutaneous injection of histamine. Somatosens Mot Res 8(3):271–279
154. Singh F, Rudikoff D (2003) HIV-associated pruritus: etiology and management. Am J Clin Dermatol 4(3):177–188
155. Siniscalco D et al (2005) Neuropathic pain: is the end of suffering starting in the gene therapy? Curr Drug Targets 6(1):75–80
156. Smolyannikova VA et al (2015) Role of the skin expression of neuropeptides, neurotrophins and their receptors in the pathogenesis of dermatoses. Arkh Patol 77(4):33–39
157. Sonkoly E et al (2006) IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol 117(2):411–417
158. Stander S et al (2002) Hydroxyethyl starch does not cross the blood-brain or the placental barrierbut the perineurium of peripheral nerves in infused animals. Cell Tissue Res 310(3):279–287
159. Ständer S et al (2010) Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. PLoS ONE 5(6):e10968–e10968
160. Starnowska J et al (2017) Analgesic properties of opioid/NK1 multitarget ligands with distinct in vitro profiles in naive and chronic constriction injury mice. ACS Chem Neurosci 8(10):2315–2324
161. Steinhoff M et al (2003) Proteinase-activated receptor-2 mediates itch: a novel pathway for pruritus in human skin. J Neurosci 23(15):6176–6180
162. Steinhoff M et al (2006) Neurophysiological, neuroimmunological, and neuroendocrine basis of pruritus. J Invest Dermatol 126(8):1705–1718
163. Story GM et al (2003) ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. Cell 112(6):819–829
164. Sun RQ et al (2004) Calcitonin gene-related peptide receptor activation produces PKA- and PKC-dependent mechanical hyperalgesia and central sensitization. J Neurophysiol 92(5):2859–2866
165. Takaoka A et al (2005) Expression of IL-31 gene transcripts in NC/Nga mice with atopic dermatitis. Eur J Pharmacol 516(2):180–181
166. Tanaka A, Matsuda H (2005) Expression of nerve growth factor in itchy skins of atopic NC/NgaTnd mice. J Vet Med Sci 67(9):915–919
167. Todd AJ (2010) Neuronal circuitry for pain processing in the dorsal horn. Nat Rev Neurosci 11(12):823–836
168. Tominaga M et al (2007) A hypothetical mechanism of intraepidermal neurite formation in NC/Nga mice with atopic dermatitis. J Dermatol Sci 46(3):199–210
169. Tominaga M et al (2009) Psoralen-ultraviolet A therapy alters epidermal Sema3A and NGF levels and modulates epidermal innervation in atopic dermatitis. J Dermatol Sci 55(1):40–46
170. Tominaga M, Takamori K (2014) Itch and nerve fibers with special reference to atopic dermatitis: therapeutic implications. J Dermatol 41(3):205–212

171. Toyoda M et al (2002) Nerve growth factor and substance P are useful plasma markers of disease activity in atopic dermatitis. Br J Dermatol 147(1):71–79
172. Toyoda M et al (2003) Localization and content of nerve growth factor in peripheral blood eosinophils of atopic dermatitis patients. Clin Exp Allergy 33(7):950–955
173. Trevisani M et al (2007) 4-Hydroxynonenal, an endogenous aldehyde, causes pain and neurogenic inflammation through activation of the irritant receptor TRPA1. Proc Natl Acad Sci U S A 104(33):13519–13524
174. Tsuda M (2018) Modulation of Pain and Itch by Spinal Glia. Neurosci Bull 34(1):178–185
175. Vellani V et al (2010) Protease activated receptors 1 and 4 sensitize TRPV1 in nociceptive neurones. Mol Pain 6:61
176. Verge VM et al (1995) Differential influence of nerve growth factor on neuropeptide expression in vivo: a novel role in peptide suppression in adult sensory neurons. J Neurosci 15(3 Pt 1):2081–2096
177. Vikman KS, Duggan AW, Siddall PJ (2007) Interferon-gamma induced disruption of GABAergic inhibition in the spinal dorsal horn in vivo. Pain 133(1–3):18–28
178. Vincent L et al (2013) Mast cell activation contributes to sickle cell pathobiology and pain in mice. Blood 122(11):1853–1862
179. Wang S et al (2008) Phospholipase C and protein kinase A mediate bradykinin sensitization of TRPA1: a molecular mechanism of inflammatory pain. Brain 131(Pt 5):1241–1251
180. Watanabe T et al (2011) Nerve growth factor level in the prostatic fluid of patients with chronic prostatitis/chronic pelvic pain syndrome is correlated with symptom severity and response to treatment. BJU Int 108(2):248–251
181. Wei Z et al (2019) Emerging role of schwann cells in neuropathic pain: receptors, glial mediators and myelination. Front Cell Neurosci 13:116
182. Weisshaar CL, Winkelstein BA (2014) Ablating spinal NK1-bearing neurons eliminates the development of pain and reduces spinal neuronal hyperexcitability and inflammation from mechanical joint injury in the rat. J Pain 15(4):378–386
183. Wilson SR et al (2011) TRPA1 is required for histamine-independent, Mas-related G protein-coupled receptor-mediated itch. Nat Neurosci 14(5):595–602
184. Wilson SR et al (2013) The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. Cell 155(2):285–295
185. Wilson SR et al (2013) The ion channel TRPA1 is required for chronic itch. J Neurosci 33(22):9283–9294
186. Woolf CJ (1983) Evidence for a central component of post-injury pain hypersensitivity. Nature 306(5944):686–688
187. Woolf CJ, Salter MW (2000) Neuronal plasticity: increasing the gain in pain. Science 288(5472):1765–1769
188. Xie R-G et al (2018) Spinal CCL2 promotes central sensitization, long-term potentiation, and inflammatory pain via CCR2: Further insights into molecular, synaptic, and cellular mechanisms. Neurosci Bull 34(1):13–21
189. Xin WJ, Weng HR, Dougherty PM (2009) Plasticity in expression of the glutamate transporters GLT-1 and GLAST in spinal dorsal horn glial cells following partial sciatic nerve ligation. Mol Pain 5:15
190. Yamaguchi J et al (2009) Quantitative analysis of nerve growth factor (NGF) in the atopic dermatitis and psoriasis horny layer and effect of treatment on NGF in atopic dermatitis. J Dermatol Sci 53(1):48–54
191. Yeh JF et al (2017) Monoclonal antibodies for chronic pain: a practical review of mechanisms and clinical applications. Mol Pain 13:1744806917740233
192. Yosipovitch G, Berger T, Fassett MS (2020) Neuroimmune interactions in chronic itch of atopic dermatitis. Journal of the European Academy of Dermatology and Venereology : JEADV 34(2):239–250
193. Yosipovitch G, Greaves MW, Schmelz M (2003) Itch. Lancet 361(9358):690–4
194. Yusuf N et al (2009) Heat shock proteins HSP27 and HSP70 are present in the skin and are important mediators of allergic contact hypersensitivity. J Immunol 182(1):675–683
195. Zhang H et al (2009) Altered functional properties of satellite glial cells in compressed spinal ganglia. Glia 57(15):1588–1599
196. Zhang Y et al (2015) Microglia are involved in pruritus induced by DNFB via the CX3CR1/p38 MAPK pathway. Cell Physiol Biochem 35(3):1023–1033
197. Zhao P et al (2014) Cathepsin S causes inflammatory pain via biased agonism of PAR2 and TRPV4. J Biol Chem 289(39):27215–27234
198. Ziegler SF et al (2013) The biology of thymic stromal lymphopoietin (TSLP). Adv Pharmacol 66:129–155
199. Zygmunt PM et al (1999) Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. Nature 400(6743):452–457