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INVITED REVIEW

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

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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

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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 sensitivity 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].

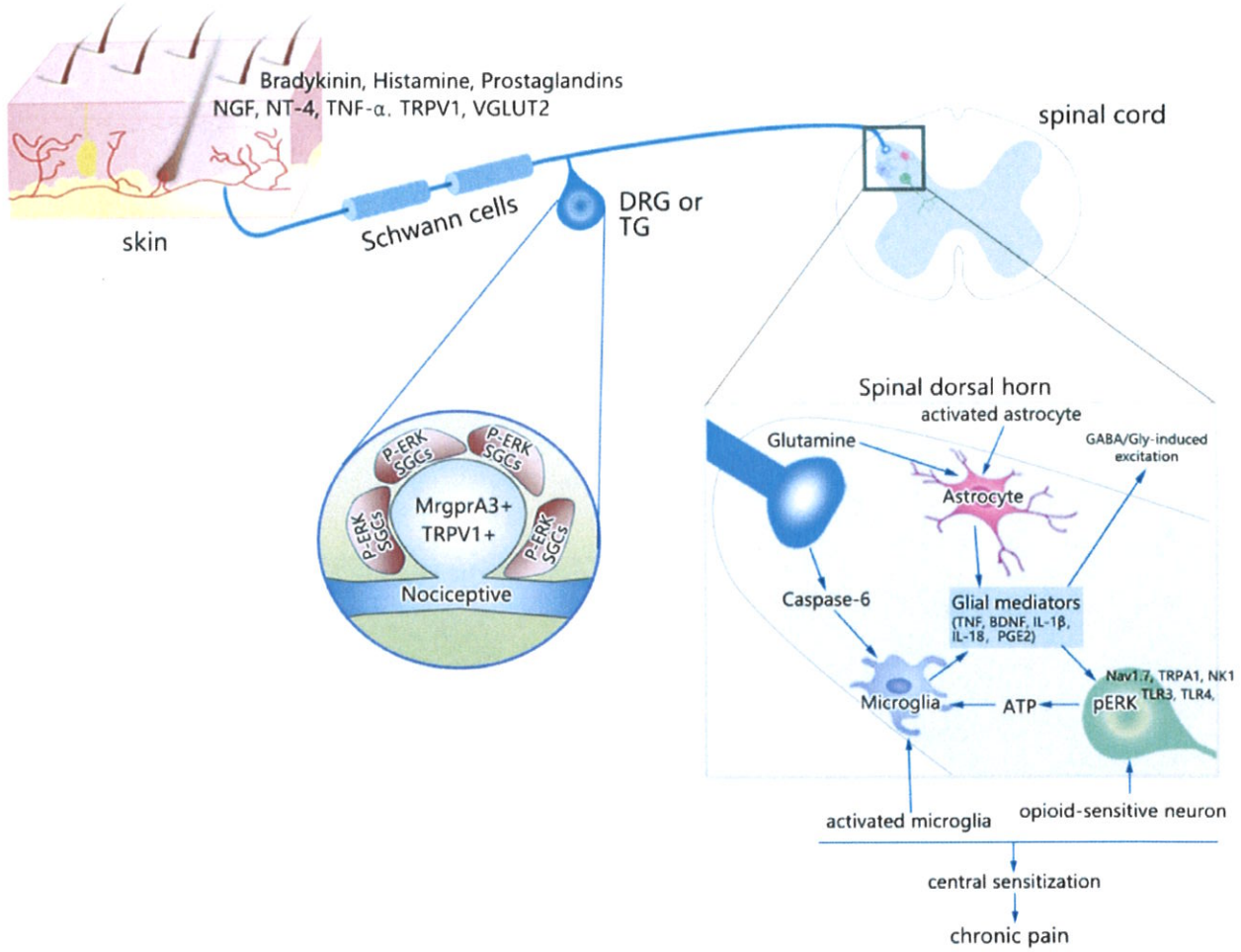

Fig. 1 Peripheral and central mechanisms of sensitization of pain processing. In the periphery, inflammatory mediators can activate and sensitize nerve endings of the primary nociceptive neurons (MrgprA3$^+$/TRPV1$^+$) in the dorsal root ganglia (DRG) or trigeminal ganglia (TG). Nerve growth factor (NGF) 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

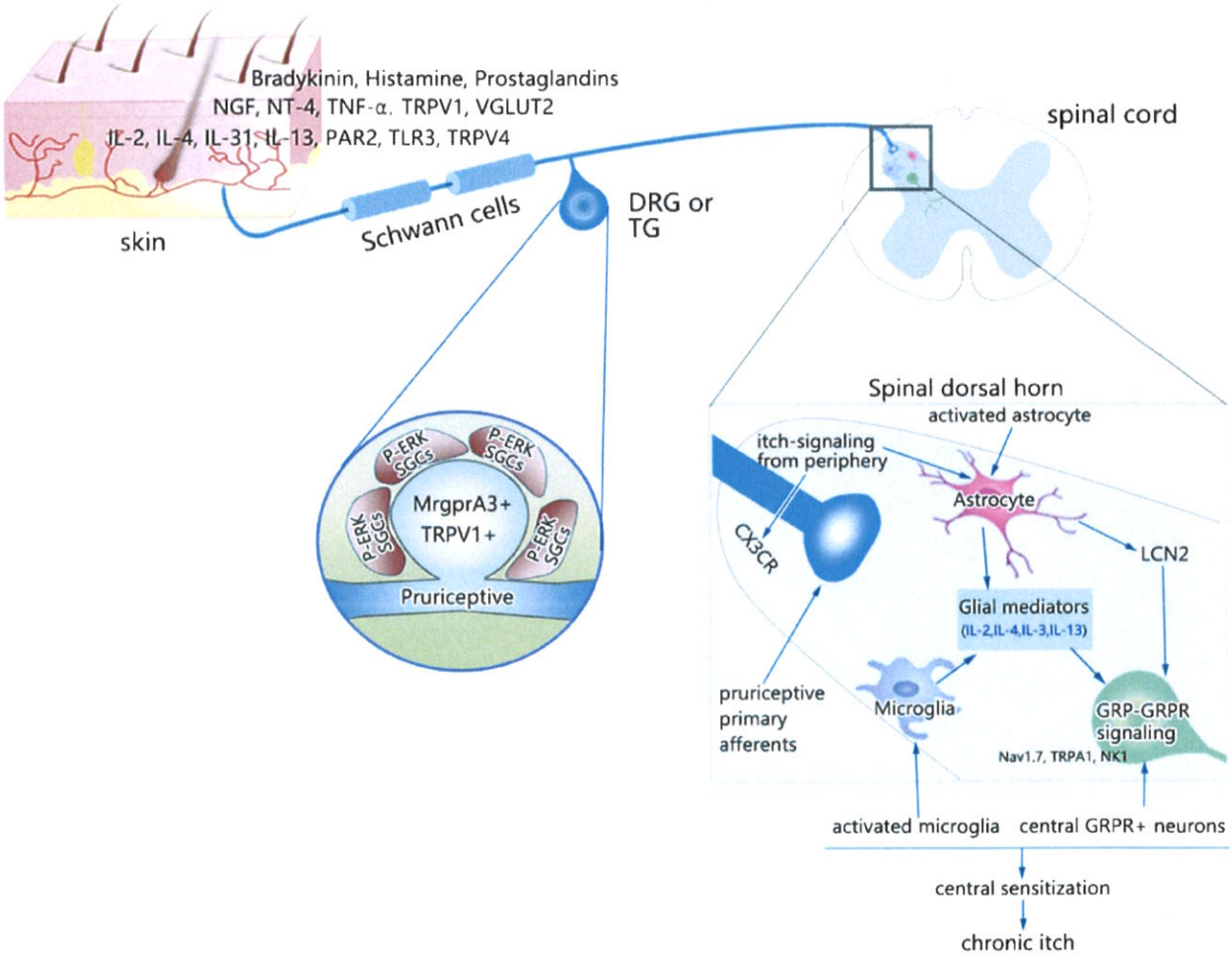

Fig. 2 Peripheral and central mechanisms of sensitization of itch processing. In the periphery, inflammatory and immune mediators can activate and sensitize nerve endings of the primary pruriceptive neurons ($MrgprA3^+/TRPV1^+$) in the dorsal root ganglia (DRG) or trigeminal ganglia (TG). In addition 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.

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Declarations

The authors declare no competing interests.

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