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New insights into the mechanisms behind mechanical itch

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Abstract

Gentle tactile stimuli, such as insects crawling on the skin, can cause itching sensation called mechanical itch. Recent studies have begun to shed light on the neural mechanisms of mechanical itch. Interestingly, the neural pathway for mechanical itch is apparently different from that for chemical itch triggered by the activation of pruriceptors with various mediators. Mechanical itch dysesthesia is frequently seen in patients with chronic itch. Mechanisms of this dysesthesia are plausibly involved in central sensitization. In this review, we summarize the current knowledge of mechanical itch under normal and pathological conditions.

Keywords

Chemical itch; sensitization; disinhibition; GRPR; LTMR

1. Introduction

Itch is an unpleasant cutaneous sensation that can be induced by chemical substances, referred to as chemical itch or by gentle touch and pressure, referred to as mechanical itch. In human psychophysics, mechanical itch is assessed by using a wide range of mechanical stimuli, such as cotton wisp, brush, and von Frey filaments, which activate low threshold mechanoreceptors (LTMRs).[1] In the last decades, the mechanisms underlying chemical itch have been well studied. However, very little was known about the mechanisms behind mechanical itch partially due to the lack of animal models for mechanical itch. Recently, we proposed a mouse model for studying mechanical itch (touch-evoked itch).[2] In this model, very weak von Frey filament is applied to the murine rostral back to elicit itch-related behavior (scratching). Since its first publication, this model, with some modifications, has been widely used to investigate the molecular and cellular mechanisms underlying mechanical itch.

Sensitization of mechanical itch is frequently observed under pathological conditions.[3–5] The normally non-itchy mechanical stimuli near a site of itch or to the skin of patients with

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Conflict of interest

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chronic itch can elicit itch, a phenomenon known as itchy skin or alloknesis.[1,6] Likewise, touch-evoked itch is frequently observed in the mouse models of chronic itch (e.g., dry skin, atopic dermatitis, and psoriasis).[7–9] Mechanical itch caused by innocuous mechanical stimuli such as from clothing often represents a bothersome clinical problem that reduces the quality of life in patients with chronic itch.[10,11] Recent studies have provided new insight into the mechanisms of mechanical itch sensitization.[7,9,12,13]

Hyperknesis is defined as an increased sensitivity of itch induced by either chemical or pinprick stimuli.[1] Punctate pricking stimuli immediately below the mechanical pain threshold often produce mild itch in healthy subjects.[14,15] The same stimuli can elicit increased itch in patients with chronic itch. Punctate stimuli-evoked itch is thought to be mediated by Aδ-/polymodal C-fibers, based on the onset of reaction.[16–18] Since light tactile stimuli-evoked itch is mediated by Aβ-fibers as described in the next section, punctate stimuli-evoked itch is conceivably transmitted via a pathway distinct from that of itch evoked by light tactile stimuli. This review uses the term “mechanical itch” to describe itch evoked by light tactile stimuli. This is generally in accordance with the recent papers.[13,19,20]

In this review, we will summarize the current knowledge about the newly revealed neural pathway for mechanical itch (Fig. 1) and the molecular mechanisms of mechanical itch sensitization (Fig. 2).

2. Excitatory mechanical itch pathway

2-1 Sensory Neurons Mediating Mechanical Itch

Very low-intensity of mechanical stimuli can elicit itch in humans and scratching in mice.[13,14,19,21] These innocuous mechanical stimuli activate cutaneous Aβ-, Aδ-, and/or C-LTMRs.[22] The role of LTMRs in mechanical itch has been assessed in mouse models. Touch-evoked scratching is usually observed immediately after the stimulus, implying a role of Aβ-LTMRs in mechanical itch (Fig. 1). This idea is further supported by a recent study using the targeted delivery of a sodium channel blocker, QX-314. Aβ-fibers can be silenced by a localized co-injection of QX-314 and Toll-like receptor5 (TLR5) agonist, flagellin.[23] Activation of TLR5 with flagellin leads to the selective entry of QX-314 into Aβ-fibers and subsequent blockade of sodium currents in those fibers.[13,23] Following Aβ-fiber silencing, scratching induced by weak (0.7mN) von Frey filament stimulation was attenuated in naïve mice.[13] Moreover, co-treatment of flagellin and QX-314 also reduced touch-evoked scratching in histamine-sensitized mice and mice with atopic dermatitis-like skin inflammation. Taken together, these data suggest that TLR5-expressing Aβ-LTMRs transmit mechanical itch. In contrast, C-LTMRs are likely dispensable for mechanical itch.[13] C-LTMRs are a small subset of Nav1.8-expressing neurons. Mice depleted of Nav1.8-expressing neurons showed normal touch-evoked scratching.[13]

2-2 Excitatory Spinal Interneurons Mediating Mechanical Itch

Within the spinal cord, excitatory interneurons that receive input from LTMRs are located in laminae IIi-IV.[24,25] A subpopulation of excitatory interneurons that express the neuropeptide urocortin 3 (Ucn3) was distributed in the laminae IIi to the dorsal laminae III.[13] Ucn3-

expressing interneurons in the dorsal spinal cord were categorized into two types based on their location and type of sensory inputs.[13] Type 1 Ucn3-expressing interneurons are located in laminae vIIi-dIII and receive monosynaptic inputs from Aβ-LTMRs. Type 2 Ucn3-expressing interneurons are located in laminae IIo-dIIi and receive sensory inputs mainly from Aδ- and/or C-LTMRs. Considering the contribution of TLR5-expressing Aβ-LTMRs to mechanical itch, the type 1 Ucn3-expressing interneurons play a functional role in mechanical itch (Fig. 1). This concept was further supported by the inhibition of touch-evoked scratching by ablation or chemogenetic silencing of Ucn3-expressing neurons in the spinal cord. Interestingly, the ablation of Ucn3-expressing neurons did not affect touch, pain, or temperature sensations, implying that these neurons may represent a unique subpopulation of excitatory interneurons that predominantly mediate mechanical itch.

It has also been reported that neuropeptide Y1 receptor (NPY1R)-expressing interneurons are excitatory and involved in mechanical itch (Fig. 1).[20,26] NPY1R-expressing neurons are located within laminae I-VI and X in the rat lumbar spinal cord.[27] In the spinal cord of $NPY1R^{Cre}$ knock-in mice, $NPY1R^{Cre}$ neurons are distributed throughout laminae I-IV and enriched in laminae IIi and III. The $NPY1R^{Cre}$ neurons receive input from cutaneous LTMRs, including Aδ- and Aβ-LTMRs. Ablation of spinal $NPY1R^{Cre}$ neurons reduced touch-evoked scratching. Moreover, designer receptors exclusively activated by designer drugs-based chemogenetic silencing of the spinal $NPY1R^{Cre}$ neurons also reduced touch-evoked scratching, while chemogenetic activation of the same neurons increased spontaneous and touch-evoked scratching. These data suggest that NPY1R-expressing interneurons receive input from LTMRs and contribute to the transmission of mechanical itch. Interestingly, only ~15% of Ucn3-expressing interneurons expressed NPY1R in the dorsal spinal cord.[13] In the future, it will be highly worthwhile to unravel the functional relationship between NPY1R- and Ucn3-expressing excitatory interneurons.

In addition to the role in mechanical itch, NPY1R-expressing neurons are presumably implicated in the transmission of general light touch and possibly pain. NPY1R-expressing neurons could be morphologically divided into at least seven distinct populations in the rat spinal cord.[27] Recent single-cell RNA sequencing study classified the spinal excitatory neurons into 15 clusters, and *Npy1r* were detected in three clusters: Glut2, Glut8, and Glut9.[28] Considering that NPY1R-expressing neurons comprise a heterogeneous population, these neurons are implicated in multiple spinal functions. Some $NPY1R^{Cre}$ neurons expressed makers of excitatory neurons that regulate mechano-transmission, such as retinoid-related orphan receptor α^+ and $cMaf^+$ neurons[29,30]. $NPY1R^{Cre}$ neurons-ablated mice or mice lacking NPY1R in dorsal horn neurons exhibited decreased sensitivity to von Frey hair stimulation of the hindpaw glabrous skin, suggesting their role in light touch. On the other hand, the majority of NPY1R-expressing neurons in lamina II contained somatostatin (SST) , which is involved in mechanical pain.[26,31,32] Transcriptional profiling of SST interneurons revealed that *Npy1r* was enriched in the SST dorsal horn population.[33] Moreover, neuropeptide Y (NPY)-saporin treatment reduced NPY1R-expressing spinal neurons and decreased inflammatory pain as well as mechanical hypersensitivity in a rat model of neuropathic pain.[26,33,34] Therefore, the neurons co-expressing SST and NPY1R may regulate mechanical hypersensitivity in neuropathy. Further studies are required to

identify molecular markers for a population of NPY1R-expressing neurons that predominantly mediate mechanical itch.

2-3 Spinal Projection Neurons Mediating Mechanical Itch

Spinal projection neurons mediating mechanical itch have not been identified yet. Nociceptive and pruritic information are transmitted from the spinal cord to the brain through the anterolateral tract (ALT).[35–37] ALT projection neurons are concentrated in lamina I and scattered throughout lamina III-IV. The majority of lamina I projection neurons express the neurokinin 1 receptor (NK1R).[35,38] The primary ligand for NK1R is substance P, and intrathecal injection of substance P-saporin conjugate (SP-SAP) can ablate spinal NK1R.[39] Ablation of spinal NK1R by intrathecal injection of SP-SAP reduced chemical itch in rodents.[20,40] While NK1R and $NPY1R^{Cre}$ expression partially overlapped, the same SP-SAP treatment failed to attenuate touch-evoked scratching in wild-type mice or $NPY1R^{Cre}$ neuron-activated mice.[20] Therefore, neither $NK1R^{+}$ projection neurons nor $NK1R^{+}$ $NPY1R^{Cre}$ neurons are presumably required for mechanical itch under physiological conditions (Fig. 1).

3. Inhibitory Pathway for Mechanical Itch

3-1 Merkel Cells

In the epidermis, Merkel cells and Aβ slowly adapting (SA)-LTMRs together compose touch-domes, which detect and transmit touch signals (Fig. 1).[22,41,42] Piezo2 channels, Piezo-type mechanosensitive ion channel component 2, expressed by Merkel cells and Aβ SA-LTMRs are required for the detection of touch stimuli.[41,42] A recent study has addressed the involvement of Merkel cells in mechanical itch.[7] Genetic ablation of Merkel cells or Piezo2 channels expressed by Merkel cells elicited touch-evoked scratching, implying that mechanical itch is constitutively suppressed by Merkel cells or Piezo2 channels expressed by Merkel cells under physiological conditions. Interestingly, the ablation of Merkel cells did not affect chemical itch induced by histamine and chloroquine or mechanical and thermal pain. Thus, Merkel cells unlikely regulate either chemical itch, or mechanical and thermal pain. Previous studies have reported that Merkel cells undergo turnover under physiological conditions.[43,44] How the turnover of Merkel cells affects mechanical itch is still an open question.

3-2 Sensory Neurons Modulating Mechanical Itch

Recently, we have reported that TLR5-expressing Aβ-fibers are involved in the inhibition of mechanical itch (Fig. 1).[12] Following the silencing of TLR5-expressing Aβ-fibers by co-injection of flagellin and QX-314 to the shaved rostral back skin, mechanical stimuli adjacent to the site of co-injection elicited scratching. Importantly, the same stimuli to the injection site failed to elicit scratching, suggesting that TLR5-expressing Aβ-fibers in the site of injection also contribute to transmitting mechanical itch. Distinct subsets of TLR5-expressing Aβ-fibers may be responsible for transmitting and gating mechanical itch. The previous study has shown that Aβ-fibers can inhibit the responses of dorsal horn neurons evoked by stimulating separate neighboring Aβ-fibers.[45] Taken together, co-injection of flagellin and QX-314 likely silences TLR5-expressing Aβ-fibers at the injection site without

affecting TLR5-expressing Aβ-fibers adjacent to the injection site and disinhibits dorsal horn neurons receiving mechanical itch inputs from neighboring TLR5-expressing Aβ-fibers adjacent to the injection site. This interpretation is also consistent with the observation that mechanical stimuli to peri-affected skin, but not directly to pathological skin elicited scratching in mice with dry skin or psoriasis that exhibit loss of or reduced activity of Aβ-fibers.[2,7,12,46]

3-3 Spinal Inhibitory Interneurons for Mechanical Itch

NPY is expressed by inhibitory interneurons that are localized in laminae I-IV of the spinal cord.[19,47,48] NPY-expressing neurons account for ~15% or ~45% of the inhibitory neurons in the dorsal horn of rats or mice, respectively. They constitute a different population from the neuronal nitric oxide synthase-, galanin-, or parvalbumin-expressing inhibitory interneurons and receive inputs from Aβ-, Aδ-, and C-LTMRs as well as C-nociceptors. Ablation or silencing of NPY-expressing neurons in the spinal cord increased touch-evoked scratching.[1932] Conversely, chemogenetic activation of NPY-expressing neurons decreased touch-evoked scratching.[20] Therefore, NPY-expressing inhibitory interneurons appear to gate transmission of mechanical itch in the spinal cord. In addition to the involvement of mechanical itch, NPY-expressing neurons also slightly regulate mechanical pain and gentle touch.[20]

NPY-expressing inhibitory interneurons regulate both Ucn3- and NPY1R-expressing excitatory interneurons (Fig. 1).[13,20] The cell bodies of Ucn3- and NPY1R-expressing neurons displayed synaptic contacts from NPY-expressing neurons. NPY silences NPY1R-expressing neurons through Gi-signaling. The depletion of the NPY1R in dorsal horn neurons disinhibited NPY1R-expressing neurons and increased touch-evoked scratching. Additionally, chemogenetic activation of NPY-expressing inhibitory interneurons decreased touch-evoked scratching, and the NPY1R antagonist canceled this inhibition. These results suggest that NPY is released from NPY-expressing inhibitory interneurons to regulate NPY1R-expressing excitatory interneurons. On the other hand, optogenetic activation of NPY-expressing neurons induced the release of gamma aminobutyric acid (GABA) and/or glycine to regulate Ucn3-expressing excitatory interneurons.[13] However, whether GABA and/or glycine regulates Ucn3-expressing excitatory interneurons under physiological conditions needs to be tested.

4. Parallel Pathways for Transmitting Mechanical and Chemical Itch

Mechanical and chemical itch are apparently transmitted by separate neural pathways (Fig. 1).[19] Chemical itch is mediated by polymodal pruriceptive fibers via a wide array of receptors in the peripheral nervous system, while Aβ-LTMR fibers mediate mechanical itch.[6,13] In the spinal cord, gastrin-releasing peptide receptor (GRPR)-expressing excitatory interneurons play a central role in chemical itch. By contrast, GRPR-expressing excitatory interneurons are dispensable for mechanical itch. In line with this concept, the portion of Ucn3- and NPY1R-expressing excitatory interneurons are involved in the transmission of mechanical itch, but not chemical itch.[13,20] Ablation of Ucn3- or NPY1R-expressing excitatory interneurons diminished mechanically-evoked scratching without affecting

pruritogens-evoked scratching. However, NPY1R-expressing excitatory interneurons are also likely slightly involved in chemical itch. Some of them co-expressed somatostatin and gastrin-releasing peptide (GRP) observed in excitatory interneurons for chemical itch.[20] In accordance with this finding, a recent study has demonstrated that intrathecal injection of NPY or NPY1R agonist LP-NPY reduced the duration of histamine- and compound 48/80-induced scratching, without affecting the frequency of scratching.[49] Moreover, the reduction of scratching duration was abolished by injection of the selective NPY1R antagonist BIBO3304. Thus, the NPY1R is apparently involved in chemical itch as well as mechanical itch. NPY1R-expressing excitatory interneurons that co-express somatostatin and GRP appear to mediate chemical itch under the control of NPY-expressing inhibitory interneurons.

5. Sensitization of Mechanical Itch

5-1 Hypersensitivity of Itch Pathway Neurons

Here we propose a potential mechanism underlying mechanical itch sensitization based on the recent findings as well as the central sensitization theory that represents hyperexcitability of spinal neurons caused by excessive C-fiber inputs or a decrease in inhibitory transmission (Fig. 2).[50] Ongoing inputs from primary sensory neurons mediating chemical itch produce hypersensitivity of excitatory interneurons that are involved in feedforward activation of projection neurons and receive inputs from primary sensory neurons mediating light tactile stimuli. Consequently, the projection neurons that normally mediate chemical itch acquire the increased responsiveness to light tactile stimuli. Previous studies indicate that ongoing inputs from pruriceptive primary sensory neurons are required for the development of alloknesis.[51,52] Human subjects with allergic contact dermatitis (ACD) showed persistent itch and mechanically-evoked itch in the surrounding skin. The mechanically-evoked itch was reversely blocked by numbing the ACD site with cold. Moreover, ACD caused an increase in the incidence of spontaneous activity of Mas-related G-protein coupled receptor member A3 (MrgprA3)-expressing sensory neurons that represent a subset of pruriceptive sensory neurons in mice.[53] Taken together, ongoing inputs from MrgprA3-expressing sensory neurons are likely responsible for the development of alloknesis. It has been reported that pruriceptive projection neurons acquire the enhanced responsiveness to light tactile stimuli after pruritic responses.[54,55] In nonhuman primates, spinothalamic tract neurons developed enhanced responses to innocuous mechanical stimuli after a response to histamine. Likewise, intrathecal application of morphine enhanced the responses to innocuous mechanical stimuli in rat trigeminothalamic tract neurons.[56] In line with these findings, $NK1R^+$ spinal projection neurons are responsible for mechanical itch in a mouse model of atopic dermatitis, while they are dispensable for mechanical itch under the physiological conditions.[9,20]

Direct activation of LTMRs may contribute to mechanical itch sensitization. It has been demonstrated that hydrogen sulfide donor induces mechanical itch via the $Ca_v3.2$ T-type calcium channel.[57] Considering that $Ca_v3.2$ is exclusively expressed by Aδ- and C-LTMRs[58], hypersensitivity of Aδ- and C-LTMRs may contribute to the sensitization of mechanical itch under certain conditions. However, the $Ca_v3.2$ inhibitor failed to inhibit

touch-evoked scratching in a mouse model of type I diabetes.[59] Further research should be undertaken to investigate whether hydrogen sulfide, Cav3.2, Aδ-LTMRs, and C-LTMRs contribute to mechanical itch sensitization under chronic itch conditions.

5-2 Disinhibition of Neural Pathway for Mechanical Itch

While it is still uncertain whether disinhibition of itch pathways contributes to itch sensitization in chronic itch patients, dysfunction of the inhibitory pathway for chemical itch was observed in the patients with atopic dermatitis.[60] Likewise, recent mouse studies suggest dysfunction of the inhibitory pathway for mechanical itch under the chronic itch condition and its possible role in sensitization of mechanical itch (Fig. 2). As mentioned in section 3-1, a recent study demonstrated that Merkel cells are involved in the inhibition of mechanical itch.[7] Interestingly, the number of Merkel cells was decreased in mice with dry skin or aged mice that displayed touch-evoked scratching. Moreover, chemogenetic activation of Merkel cells inhibited touch-evoked scratching via the increase in the firing rate of Aβ-LTMRs in mice with dry skin. Thus, dysfunction of Merkel cell-Aβ-LTMRs signaling appears to contribute to mechanical itch in aged skin or dry skin. However, this finding is apparently contrary to previous observations of the increased number of Merkel cells in the skin of the patients with psoriasis or prurigo nodularis.[61,62] Further studies are required to confirm whether Merkel cells contribute to the disinhibition of mechanical itch in the pathological condition.

We have recently demonstrated that TLR5-expressing Aβ-fibers contribute to inhibition of mechanical itch. The number of TLR5-expressing Aβ-fibers was decreased in the epidermis of mice with psoriasis.[12] This finding also accords with previous observations, which showed that myelinated nerve fibers exhibited demyelination in the lesional skin of patients with atopic dermatitis.[63,64] It is interesting to investigate whether the Aβ-fibers are impaired in the skin of the patients with other itch conditions.

Impaired Aβ-fibers presumably contribute to the reduced activity of inhibitory interneurons that signal mechanical itch. While there is no direct evidence demonstrating that inhibitory interneurons are suppressed under chronic itch conditions, a recent study demonstrated that inhibitory inputs to Ucn3-expressing excitatory interneurons are decreased in mice with atopic dermatitis.[13]

While the disinhibition of the mechanical itch pathway causes spontaneous itch, it is unknown how itch signals are generated under the condition of disinhibition. Pan et al., demonstrated that Aβ-LTMRs are responsible for mediating mechanical itch.[13] Therefore, it seems fair to assume that skin stretch or skin movement excites Aβ-LTMRs to elicit mechanical itch.[24] Future studies are required to understand the generation mechanisms of mechanical itch by identifying subtype of Aβ-LTMRs that mediate mechanical itch.

6. Conclusion

In this review, we highlight new insights into the neural mechanisms of mechanical itch. Despite significant progress in the study of the mechanisms of mechanical itch, several questions remain to be answered: (i) which molecules stimulate the inhibitory pathway for

mechanical itch?; (ii) which molecules develop mechanical itch sensitization?; (iii) which projection neurons conduct mechanical itch signals?; (iv) do the mechanisms of mechanical itch differ in glabrous and hairy skins?; (v) which diseases cause chronic itch via mechanical itch sensitization? Insights from future studies could pave the way for new treatments for chronic itch.

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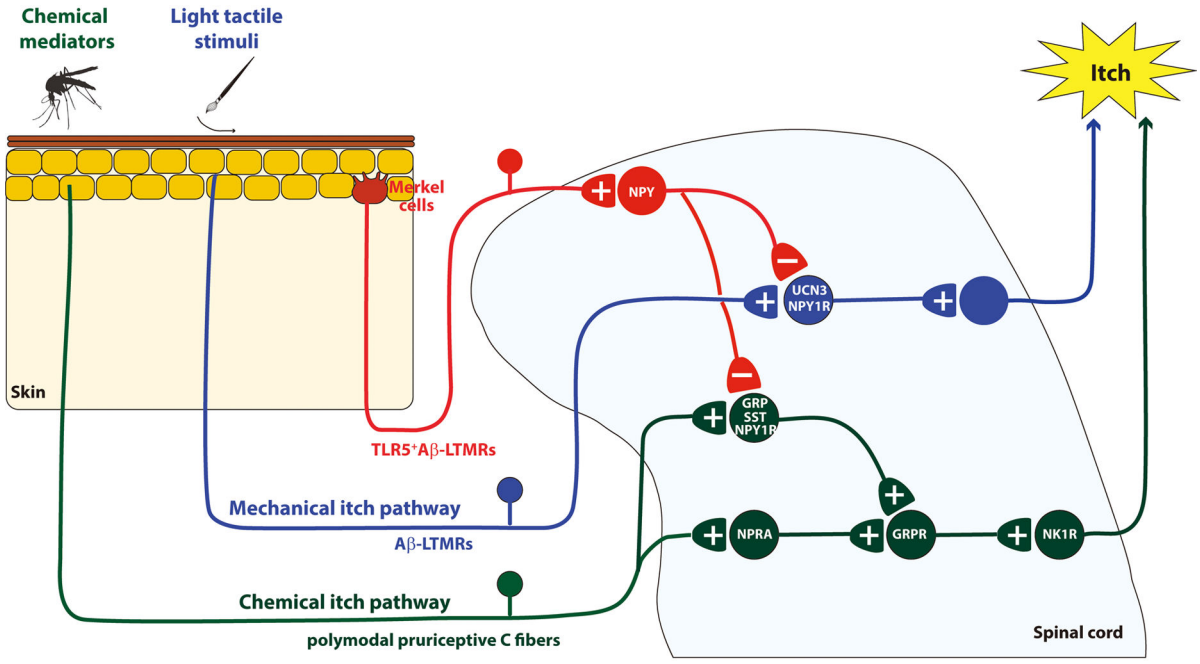

Fig. 1.

Schematic diagram of neural circuits for mechanical and chemical itch. +, - denote excitatory and inhibitory synapses, respectively. GRP, Gastrin Releasing Peptide; GRPR, Gastrin Releasing Peptide Receptor; LTMRs, Low-threshold mechanoreceptors; NK1R, Neurokinin 1 Receptor; NPRA, Natriuretic Peptide Receptor A; NPY, Neuropeptide Y; NPY1R, NPY1 receptor; SST, somatostatin; TLR5, Toll Like Receptor 5.

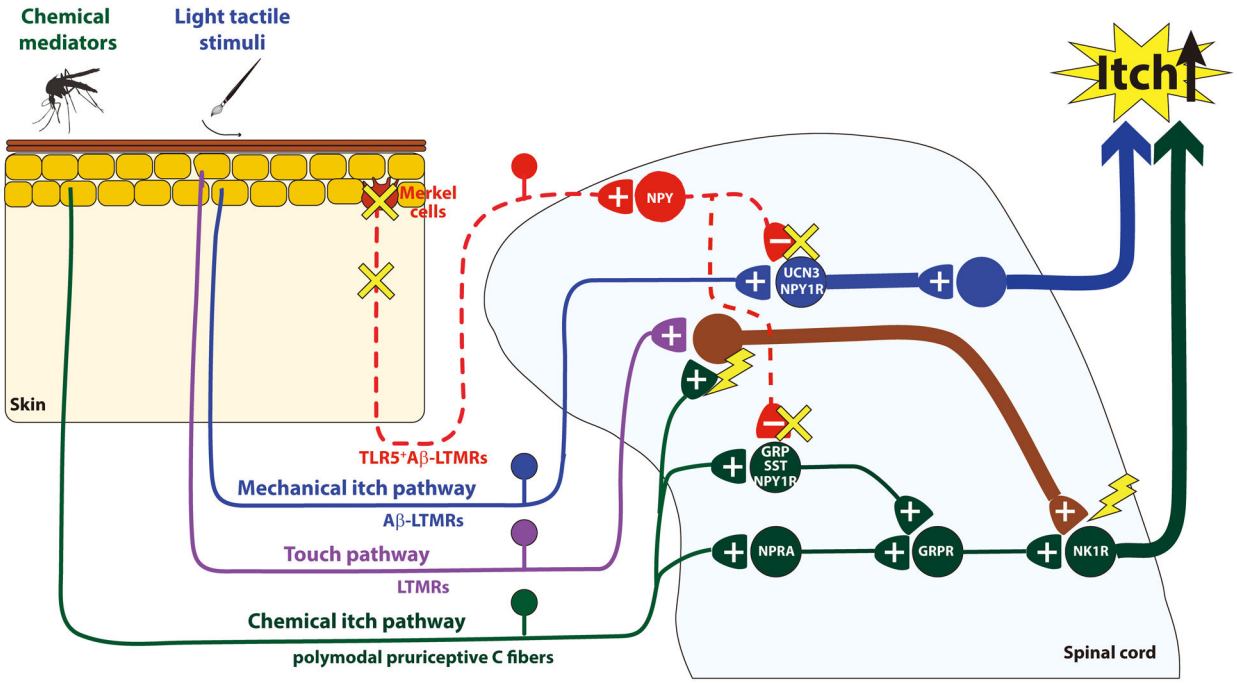

Fig. 2.

Schematic diagram of mechanisms underlying mechanical itch sensitization. Sustained activation of polymodal pruriceptive C fibers (green) sensitizes excitatory interneurons that receive convergent input from LTMRs (purple). Consequently, NK1R-expressing projection neurons (green) respond to light tactile stimuli, leading to mechanical itch sensitization. Alternatively, the disinhibition of NPY inhibitory circuits (red) may contribute to mechanical itch sensitization. +, - denote excitatory and inhibitory synapses, respectively. GRP, Gastrin Releasing Peptide; GRPR, Gastrin Releasing Peptide Receptor; LTMRs, Low-threshold mechanoreceptors; NK1R, Neurokinin 1 Receptor; NPRA, Natriuretic Peptide Receptor A; NPY, Neuropeptide Y; NPY1R, NPY1 receptor; SST, somatostatin; TLR5, Toll Like Receptor 5.