

Understanding neural mechanisms of mechanical itch



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Chronic itch, which is associated with many skin disorders and systemic diseases, is often difficult to treat and can greatly affect quality of life. Patients with chronic itch commonly have both peripheral and central sensitization of itch signaling pathways, which enables pruritogens to elicit an exaggerated itch response (known as chemical itch) and allows innocuous mechanical stimuli to evoke itch sensation (known as mechanical itch), resulting in persistent and ongoing itch. Fully understanding the mechanism of itch sensitization is critical for designing successful therapeutic strategies to treat chronic itch. In recent years, significant progress has been made in identifying the molecular, cellular, and circuit mechanisms underlying chemical itch.¹ However, understanding the pathways and mechanisms of mechanical itch associated with both acute and chronic itch is still in its early stages.

ACUTE MECHANICAL ITCH

Mechanical itch is a type of itch caused by light tactile stimuli on the skin, such as pressure, stroking, or vibration.¹ Studies have made significant progress in identifying the spinal circuits in mice that transmit and gate mechanical itch.^{2,3} A unique subpopulation of excitatory interneurons expressing neuropeptide urocortin 3 (*Ucn3*) in the inner lamina II and lamina III of the spinal cord has been identified as transmitting mechanical itch.³ Selectively ablating or silencing *Ucn3*⁺ neurons in the dorsal spinal cord by using intersectional genetic strategies abolishes gentle poking-evoked acute mechanical itch without affecting pruritogen-induced chemical itch or other somatosensory modalities, such as pain, touch, and temperature sensations.³ *Ucn3*⁺ excitatory interneurons in the dorsal spinal cord receive synaptic inputs from A β -low-threshold mechanoreceptors (A β -LTMRs), but the activation of *Ucn3*⁺ neurons is normally inhibited by neuropeptide Y-expressing (NPY⁺) inhibitory interneurons that receive inputs from

distinct A β -LTMRs.³ Activation of NPY⁺ inhibitory interneurons attenuates mechanical itch, whereas ablating these neurons results in spontaneous itch, which is abolished by ablating *Ucn3*⁺ interneurons.³ Thus, NPY⁺ inhibitory interneurons suppress mechanical itch through *Ucn3*⁺ interneurons (Fig 1). This feedforward inhibitory circuit in the spinal cord might explain the prevention of hypersensitivity to mechanical itch stimuli in most areas of the skin.

In the periphery, which population of primary sensory neurons is required for mechanical itch transmission? Spinal *Ucn3*⁺ neurons mainly receive monosynaptic inputs from Toll-like receptor 5-expressing (TLR5⁺) A β -LTMRs.³ Interestingly, intradermal injection of TLR5 agonist triggers itch behaviors in mice, and pharmacologic silencing of TLR5⁺ neurons abolishes mechanical itch.³ These results suggest that TLR5⁺ A β -LTMRs may mediate mechanical itch in the skin (Fig 1). However, TLR5 is also expressed in immune cells within the skin, and pharmacologic manipulations might affect these TLR5⁺ immune cells rather than sensory neurons. Thus, whether TLR5⁺ A β -LTMRs are solely responsible for mechanical itch remains unclear.

In addition to A β -LTMRs, a new pathway for transmitting mechanical itch via C-fibers has been discovered (Fig 1). Somatostatin and natriuretic peptide B coexpressing (*Sst*⁺/*Nppb*⁺) primary sensory neurons, which constitute a type of C-fiber chemical itch transmission neurons in the dorsal root ganglia (DRG), express mechanosensitive *Piezo1* channels and are responsible for poking-evoked acute mechanical itch in mice.⁴ Unlike A β -LTMR-mediated mechanical itch,³ high-threshold mechanical stimuli activate *Piezo1* channels in *Sst*⁺/*Nppb*⁺ sensory neurons and trigger C-fiber-dependent itch responses in mice.⁴ Deletion of *Piezo1* in *Sst*⁺/*Nppb*⁺ itch transmission neurons significantly attenuates acute mechanical itch. In contrast, mice with a gain-of-function *PIEZO1* allele display enhanced mechanical itch behaviors, suggesting a role for *Piezo1* channels in mechanical itch transmission.⁴ Notably, a small subset of *Sst*⁺/*Nppb*⁺ sensory neurons also express mechanosensitive *Piezo2* channels,⁴ implying that *Piezo2* channels in *Sst*⁺/*Nppb*⁺ neurons might partially contribute to mechanical itch transmission.

Interestingly, Mas-related G protein-coupled receptor D-expressing (*MrgprD*⁺) C-fiber polymodal nociceptors, which are required to transmit chemical itch and mechanical pain, also express mechanosensitive *Piezo1* and *Piezo2* channels, raising the possibility of their involvement in mechanical itch transmission.⁴ Nevertheless, further research is necessary to confirm this hypothesis.

Taken together, current findings suggest that various mechanical inputs in the peripheral nervous system may trigger mechanical itch via distinct pathways. This highlights the complexity of the neural pathways and mechanisms underlying acute mechanical itch sensation.

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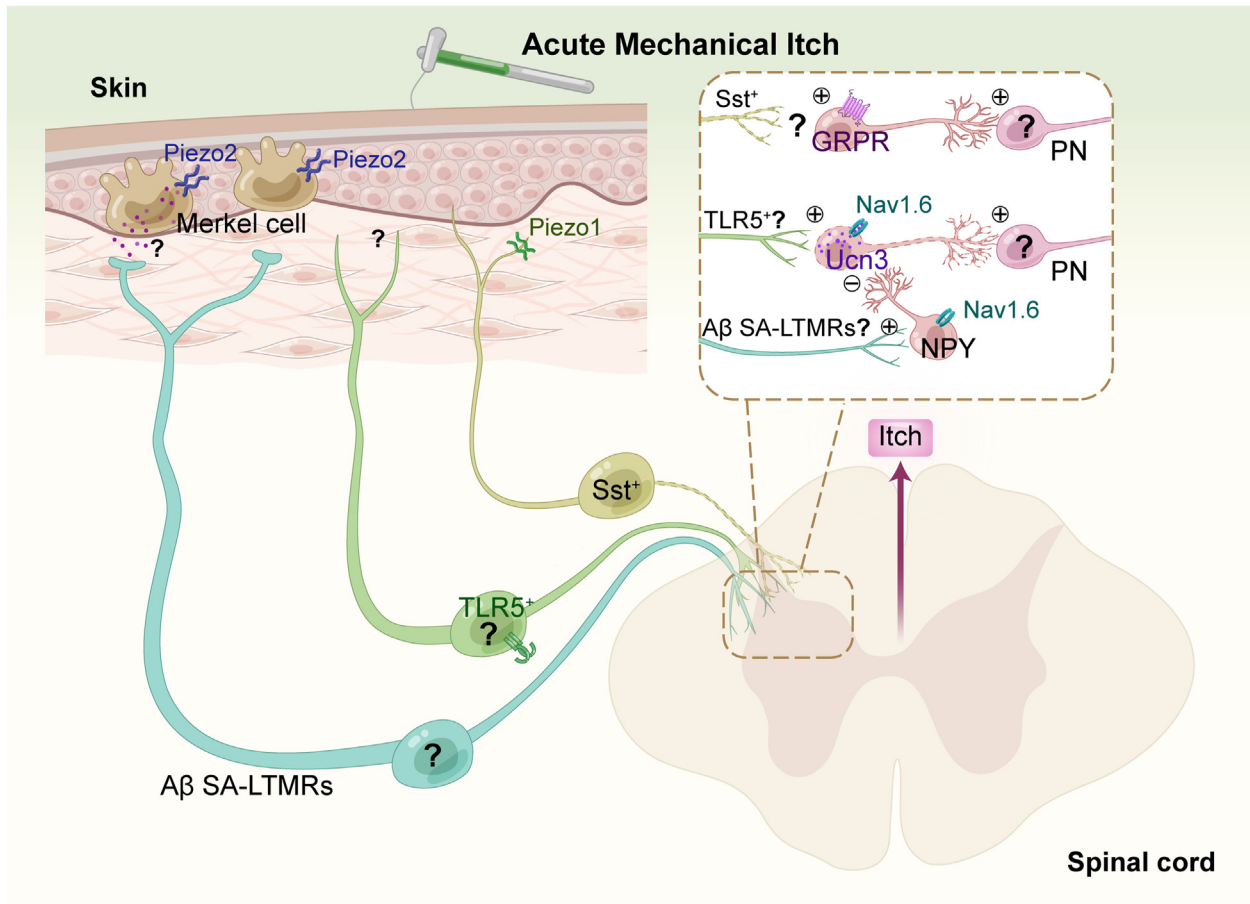


FIG 1. Schematic diagram showing neural pathways that transmit and gate acute mechanical itch. Three distinct neural pathways have been proposed; they include a cutaneous Piezo2-expressing Merkel cell complex (which might excite NPY⁺ inhibitory interneurons in the dorsal spinal cord via activation of unknown Aβ-LTMRs), Ucn3⁺ excitatory interneurons in the dorsal spinal cord (which may receive inputs from TLR5⁺ Aβ-LTMRs), and Piezo1-expressing Sst⁺/Nppb⁺ polymodal C-fiber chemical itch transmission neurons (which may couple downstream GRPR⁺ excitatory interneurons). Ucn3⁺ and GRPR⁺ neurons connect to unknown projection neurons (PNs) that transmit itch signals to the brain. Voltage-gated sodium channel Na_v1.6 is expressed in both Ucn3⁺ and NPY⁺ neurons in the spinal cord.

MECHANICAL ALLOKNESIS IN CHRONIC ITCH CONDITIONS

Peripheral mechanisms

Chronic mechanical itch, or mechanical alloknosis (mechanical itch sensitization, which is analogous to allodynia for pain), which is characterized by an abnormal sensitivity to mechanical stimuli, is a form of chronic itch that is associated with various skin disorders such as atopic dermatitis, psoriasis, and dry skin. The mechanisms involve release of endogenous pruritogens from immune cells, overactivation of sensory neurons in the skin, and changes in the activity of the central nervous system.^{1,5}

Recent studies have revealed the contributions of Aβ-LTMRs in mechanical alloknosis. One study has shown that silencing TLR5⁺ Aβ-LTMRs attenuates mechanical alloknosis in a mouse model of atopic dermatitis,³ suggesting that activation of Aβ-LTMR itch transmission neurons contributes to chronic mechanical itch (Fig 2). Another study has addressed the idea that loss of cutaneous Merkel cells, which are specialized mechanosensitive cells in the skin, results in mechanical alloknosis associated with aging and dry skin. Mice lacking Merkel cells or their

associated Piezo2 channels display mechanical alloknosis, whereas chemogenetic activation of Merkel cells prevents mechanical alloknosis in dry skin.⁶ The mechanism involves cutaneous Merkel cells sensing external mechanical stimuli via associated Piezo2 channels and activating innervating Aβ slowly adapting-LTMRs. The Merkel cell–Aβ slowly adapting-LTMR complex might activate downstream inhibitory interneurons in the spinal cord to suppress mechanical itch (Fig 2). Thus, the lack of Merkel cells in dry skin and aging individuals may lead to disinhibition of the mechanical itch pathway in the spinal cord, resulting in the development of mechanical alloknosis (Fig 2).

Emerging evidence suggests that aside from Aβ-LTMRs, C-fiber itch transmission neurons also play essential roles in mechanical alloknosis. Conditional knockout of *Piezo1* or blockade of Piezo1 channels in Sst⁺/Nppb⁺ C-polymodal itch transmission neurons attenuates mechanical alloknosis in a mouse model of atopic dermatitis,⁴ whereas ubiquitous gain-of-function mutation of *PIEZO1* develops mechanical alloknosis in mice.⁴ These findings suggest that overactivation of Piezo1 in Sst⁺/Nppb⁺

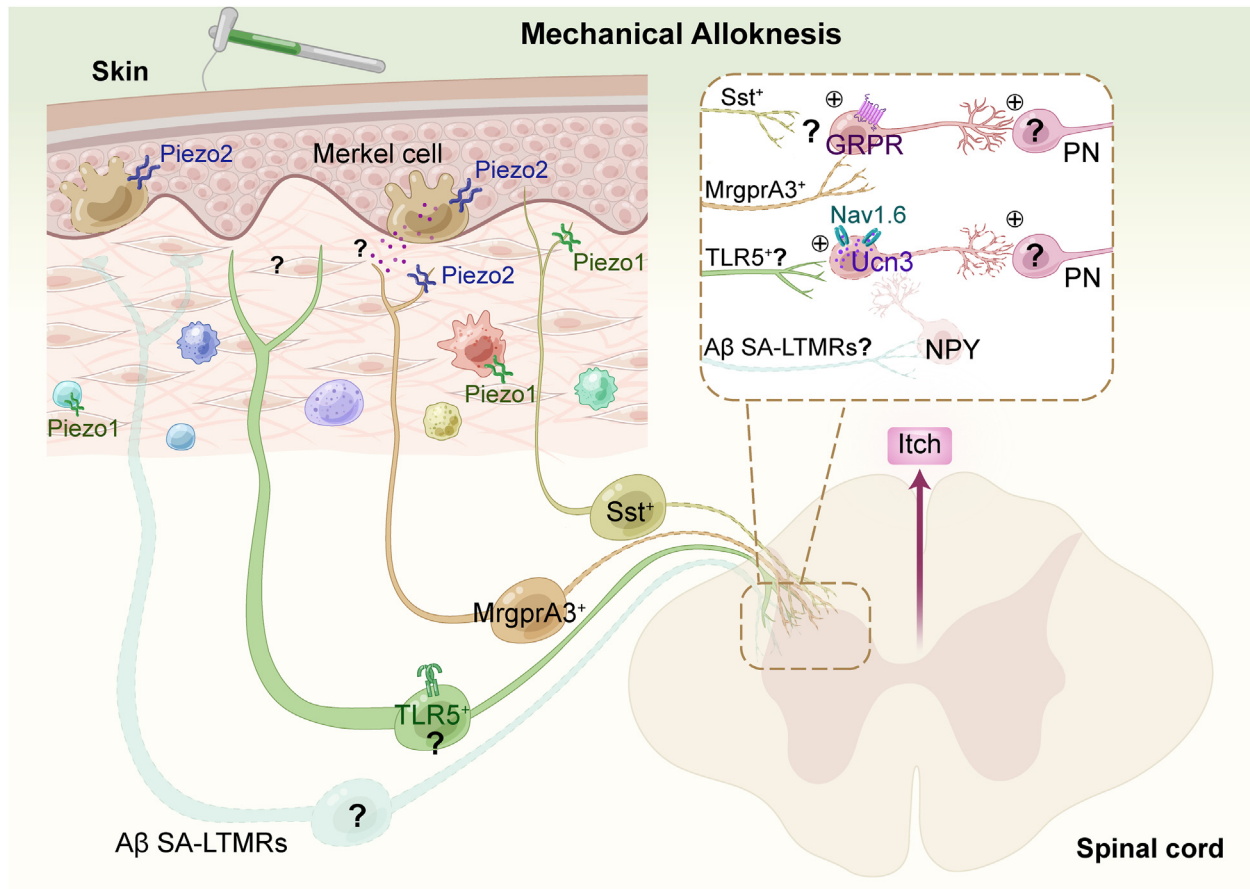


FIG 2. Schematic diagram showing neural pathways that modulate mechanical allodynia under chronic itch conditions. Three distinct neural pathways have been proposed for the development of mechanical allodynia; they include the Piezo1-dependent mechanical itch hypersensitivity in Sst^+ / $Nppb^+$ polymodal chemical itch transmission neurons, reduced synaptic inhibition from NPY^+ inhibitory interneurons and increased intrinsic excitability of $Ucn3^+$ excitatory interneurons in the spinal cord, and a dynamic miswiring between Merkel cells and $MrgprA3^+$ chemical itch transmission neurons. Reduced expression of $Nav1.6$ in NPY^+ neurons and increased expression of $Nav1.6$ in $Ucn3^+$ neurons contribute to mechanical allodynia. Although Piezo1 is expressed in immune cells within the skin (particularly in macrophages and T cells), their potential role in mechanical allodynia development is not covered in this article.

C-polymodal itch transmission neurons may contribute to mechanical allodynia (Fig 2). Interestingly, chemical itch mediator histamine sensitizes Piezo1 channel activity, whereas deletion of *Piezo1* in DRG neurons attenuates histamine and IL-31-mediated chemical itch behaviors,⁴ reflecting the potential interaction between chemical itch and mechanical itch pathways in chronic itch.

Furthermore, the interaction between touch sensors and pruriceptors in the skin also plays a role in mechanical allodynia. In dry itchy skin, $MrgprA3^+$ chemical itch transmission neurons rewire toward Merkel cells in the skin, and mechanical stimulation of the skin activates Piezo2 channels on Merkel cells, causing $MrgprA3^+$ neurons to fire.⁷ This miswiring mechanism may contribute to the itch-scratch cycle in chronic itch conditions (Fig 2).

It is important to note that the peripheral mechanisms underlying chronic mechanical itch are complex. Decreased epidermal-innervating C/A δ fiber density, as well as increased mechanical itch, is observed in postherpetic patients,⁸ challenging the

contribution of C-fibers in chronic mechanical itch. Furthermore, studies have demonstrated that mechanosensitive Piezo1 channels detect mechanical cues in immune cells such as macrophages and T cells (Fig 2), and activation of Piezo1 in these cells is required to initiate immune responses.⁹ Thus, further research is needed to fully understand the contribution of different types of cells in the skin to the development of chronic mechanical itch.

Central mechanisms

Central sensitization, which is characterized by increased excitability of itch transmission neurons and enhanced synaptic transmission in the spinal cord and brain, plays a crucial role in chronic itch development. Recent studies have shown that spinal $Ucn3^+$ mechanical itch transmission neurons are necessary to transmit mechanical allodynia in various mouse models of chronic itch.³ Additionally, in chronic itch models, the intrinsic excitability of $Ucn3^+$ neurons is significantly elevated; this increase is mostly due to overexpression of the voltage-gated

sodium channel $\text{Na}_v1.6$.¹⁰ In contrast, spinal NPY^+ mechanical itch gating neurons have significantly lower levels of $\text{Na}_v1.6$ expression under chronic itch conditions, which silences NPY^+ neurons and opens the gate for mechanical itch transmission in the spinal cord.¹⁰ Further computational simulation showed that reduced $\text{Na}_v1.6$ conductance in NPY^+ models play a major role in opening the itch gate under chronic itch conditions.¹⁰ These findings suggest that mechanical allodynia is caused by disinhibition in the mechanical itch circuit and that $\text{Na}_v1.6$ channels may be a potential therapeutic target for treating chronic itch (Fig 2).

How the spinal circuits for C-fiber mechanical itch transmission work is currently unclear. However, it is known that in chemical itch transmission, spinal excitatory interneurons expressing gastrin-releasing peptide receptor (GRPR) are activated by the activation of $\text{Sst}^+/\text{Nppb}^+$ pruritic sensory neurons via monosynaptic and/or polysynaptic transmission.¹ Therefore, it is possible that GRPR^+ neurons in the spinal cord may also play a role in chronic mechanical itch transmission (Fig 2).

CONCLUDING REMARKS

Remarkable progress is being made in revealing the contributions of different types of nerve fibers and cells in the skin, DRG, and spinal cord to the development of acute and chronic mechanical itch. To further our understanding, future research should focus on developing more precise and selective strategies to identify and manipulate the neural circuits involved in mechanical itch transmission from skin to brain, which will help us better understand the contribution of different neuron populations in chronic itch. Additionally, investigating the molecular mechanisms of mechanical allodynia, including ion channels and neuropeptides, will allow for targeted treatment strategies for treating chronic itch. Potential therapeutic strategies may include targeting Piezo1/2 channels in $\text{Sst}^+/\text{Nppb}^+$ sensory neurons or $\text{Na}_v1.6$ channels in Ucn3^+ and NPY^+ neurons in the spinal cord. Furthermore, to fully comprehend the molecular and cellular mechanisms underlying chronic itch, it is crucial to explore the interactions between chemical itch and mechanical itch, as well as the interactions between the nervous system and other systems involved in chronic itch, such as the immune system.⁵ Finally, although the functions of Piezo1/2

ion channels in mechanical itch transmission have been identified in mice, there is currently no evidence showing that *PIEZO1/2* variants affect itch sensitivity in humans. Moreover, the sensory neurons in humans and rodents are different. Thus, linking animal research with clinical research in future studies will be necessary.

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