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Molecular mechanisms of pruritus

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ABSTRACT

Pruritus is an unpleasant sensation that evokes the urgent desire to scratch. It is a symptom derived from many nervous system disorders that affects a large population of humans and is treated by a variety of pharmacological agents with variable access. Chronic itch is a huge unmet health problem which affect upward 20% of people worldwide. The mechanisms underlying the chronic pruritus are complex. Studies of the neurobiology, neurophysiology and cellular biology of itch have gradually been clarifying the mechanism of chronic itch both peripherally and centrally. The discussion has been focused on pruriceptive nerves and their receptors as well as the cytokines/chemokines that play major roles in itch induction. Though it is historically hypothesized that pain convey signal generated with the stimuli under high intensity, and itch transduces signal from the same nerves of pain but under low intensity, recently, with the identification of distinct itch specific sensory afferent fibers the theory has twisted the "intensity" to a existence of a complete separation of pain and itch pathways. This review helps to understand the unique properties of itch signaling pathways and their clinical importance of the itch perception and pruritic diseases.

1. Pruriceptive receptors and nerves in the skin

Pruriceptive itch originates following the activation of pruriceptive receptors on the peripheral sensory upon interaction with pruritogens which are released from surrounding cells [1]. The pruritogens include histamine released from mast cells from histamine receptors (H_1, H_2, H_3, and H_4) when they are activated under various inflammatory conditions such as the type I allergy [2], and proteases, including trypsin, tryptase, cathepsins, and kallikreins, which are pruritogens in inflammatory skin diseases such as atopic dermatitis (AD) [3]. Protease-activated receptor-2 (PAR_2) is one of the receptors activated by these proteases and PAR_2 expression at nerve endings in the skin is significantly increased in AD [3], which could serve as a promising therapeutic target for control of AD. Despite of being classified as pruriceptive receptors involved in itch induction, H_1 receptors and PAR_2, are also known to transduce pain, such as subcutaneous injection of histamine [4] and PAR_2 activation is sufficient to induce neuronal plasticity leading to a chronic pain state [5]. Moreover, histamine release from mast cells in the upper dermis leads to itch sensation, whereas histamine release in the deep dermis or subcutaneous tissue leads to angioedema, which is often accompanied by pain rather than itch [5]. Furthermore, endothelin-1 (ET-1) has been implicated in non-histaminergic itch, but we also reported recently that ET-1 could activate nociceptive neurons to result in simultaneous sensations of itch and pain, consistent with observations that ET-1 elicits both itch- and pain-related behaviors in animals and burning itch sensations in humans [6]. ET-1 is predominantly a pruritogen in humans, but also has brief algogenic activity, probably via activation of ET-A/and or ET-B receptors on C- and/or A-delta nociceptors. Recently, it is found that the hyperexcitability of $MRGPRA3^+$ neurons, essential for normal histamine-dependent itch behavior [7], and $MRGPRD^+$ neurons, which contribute to mechanically evoked pain [8] and histamine-independent itch [9] may contribute to the spontaneous itch- and pain-related behaviors accompanying contact hypersensitivity and/or other inflammatory diseases in humans.

Though itch and pain share largely overlapping mediators and receptors, the sensation caused by skin burn also depend upon its location, and the depth of the damage. When the damage is superficially limited or when the burn is almost healed, the main sensation is itch, whereas, when the damage is deeper, the main sensation is exclusively pain. The origin of pain is not only limited to a deeper level in the skin. A hypothesis has been drawn that nerve endings in the superficial layer of skin are involved in both itch and pain, and that the elongated fine nerves in the epidermis

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contribute to neural sensitization. However, it is noticed that the classification of pain and itch is not as simple as that, it is also noticed that morphine reduces pain but simultaneously induces itch, and that itch evoked by electrical stimulation does not convert into pain even at a higher frequency of stimulation [10]. The intensity theory seems to be in line with several other findings, such as vesicular glutamate transporter 2 seems to be important in transmission of pain and itch [11].

According to the myelination, diameter, and conduction velocity and type of transmitters released, sensory neurons are divided into several groups: fast-conducting, myelinated A-β fibers mediate the synaptic release of transmitters such as excitatory amino acids from small clear synaptic vesicles which cause cortical spreading depression, neuronal hyper-excitability and central sensitization; on the other hand, the slow transfer of signals via the A-δ and unmyelinated C fibers elicit the secretion of CGRP, substance P, neurokinin A [12]. Aδ and C nerves are mainly involved in the conduction of thermal and pain/itch sensation, whereas Aβ nerves conduct tactile sensation [12]. TRP family that are activated in warm (TRPV2, TRPV3 and TRPV4) or cold (TRPM8 and TRPA1) temperature ranges are involved in modulation of pruritus. TRPA1 mediates histamine-independent, MrgprA3 and C11-dependent itch [13]. Activated pruriceptors or nociceptors release neuropeptides. Recently, glutamate was found to work together with both substance P and CGRP to mediate tissue-injury associated pain. Activated pruriceptors release neuropeptides, such as substance P and CGRP [14], both of which contribute to the characteristic flare and wheal that is concomitant with itch. Although substance P was originally implicated in mediating itch via cutaneous activation of its receptor NK1 [15], further studies in human skin using microdialysis showed little effect at physiological concentrations [16]. Itch is also regulated by the VGLUT2-mediated transmission via the $Trpv1^+$ neurons, through CGRP and gastrin-releasing peptide receptor (GRPR) transmission. Thus, the complexicity of neuropeptides and small neurotransmitters mediate and modulate sensory transmission, such as different pain neurotransmitters combined can cooperate with each other to transmit or regulate various acute sensations, including itch, under certain conditions. The identification of a subset of neurons as the dedicated itch-specific prurinergic fibers, named as $MrgprA3^+$ neurons, is the first time that establish the existence of itch-specific nerves. In a mouse line that capsaicin receptor is only expressed in the MrgprA3 neurons, capsaicin was able to elicited scratching behaviors but not nocifensive behavior [7]. Moreover, it has been found that when the MrgprA3 neurons are depleted, itch behaviors are reduced but thermal and mechanical allodynia was maintained. These data supports the distinguishable pain and itch pathways are operating in sensory periphery systems.

Hypersensitivity of pruriceptors can be induced during the skin lesion by dysregulated cytokines from the environment. Several inflammatory cytokines have been shown to be regulators of periphery sensory nerve signaling sensitivity in pruritus. Although the immune cell-IL-31-neuron axis has been implicated in severe pruritus during atopic skin inflammation, only recently, the pruritus- and TH_2-associated novel cytokine IL-31 was found to induce a distinct transcriptional program in sensory neurons, leading to nerve elongation and branching both in vitro and in vivo. This finding will help us understand the clinical observation that patients with atopic dermatitis experience increased sensitivity to minimal stimuli inducing sustained itch [17]. Moreover, nerve growth factor and tumor growth factor have been found to potentiate the TRPV1 and TRPA1 function on the periphery nerve endings during inflammatory conditions. Co-trafficking of these pruriceptors to the surface of the cell plasma membrane are induced by tumor growth factor-α [18].

2. Dorsal horn of the spinal cord receptors for itch

Conquering of itch has been expanded significantly to the central nervous systems. Some rodent studies have demonstrated that neural pathways for itch ascend to the brain via the superficial layer of dorsal horn, including laminae I and II, in the spinal cord [19–22]. For example, GRP, which is a bombesin-like peptide, and its receptor, GRPR, are broadly expressed in the central nervous system. GRP exerts various physiological functions such as hormone secretion, blood flow regulation, and smooth muscle contraction through activation of GRPR, which located in a very small population of spinal cord nerve cells where pain and itch signals are transmitted from the skin to the brain [23]. In the dorsal horn of the spinal cord, GRP is distinctly localized in lamina I and the outer layer of lamina II (IIo). Interestingly, the descending 5-HT system facilitates GRP-GRPR signaling via 5-HT1A to augment itch-specific outputs, and a disruption of crosstalk between 5-HT1A and GRPR may be a useful antipruritic strategy. It has been found that a subset of VGLUT2-expressing nociceptors in the DRG and a subset of dorsal horn inhibitory interneurons expressing Bhlhb5 (B5-I neurons) specifically suppress itch signal transmission [24]. Dynorphin, which is released from B5-I neurons, is a key neuromodulator of pruritus. Numerous neural receptors in the spinal cord are apparently involved in pruritus, this also includes BNP (B-type natriuretic peptide) signaling pathway. BNP activates NPRA (natriuretic peptide receptor A)-expressing spinal interneurons. NPRA and GRPR systems contribute to spinal processing of itch. However, evidence has been shown that BNP–NPRA system may function upstream of the GRP-GRPR system to regulate itch in the mouse spinal cord though NPRA and GRPR antagonists may have antipruritic efficacy against centrally, but not peripherally, elicited itch. More recent findings using ISH, qPCR, and immunohistochemistry demonstrated that GRP is, indeed, not expressed in DRG neurons but rather is abundantly expressed in interneurons of the superficial dorsal horn, where it likely plays an integral part in the neuronal circuits that transmit itch messages. Ablation of GRPR in mice did not affect the responses to noxious thermal and mechanical stimuli as well as motor activity [25]. However, it is found that peripheral nerve injury induces a dramatic upregulation of GRP in DRG neurons, which may have important implications in conditions of neuropathic pain or itch [26]. Moreover, a mixed population of DRG neurons showed significantly increase of GRP expression after peripheral nerve injury. Future studies should investigate the circuits engaged by the spinal cord GRP interneurons, as well as the functional significance of the de novo expression of GRP in the DRG after nerve injury. Approximately 15% of lamina II neurons are hyperpolarized by kappa opioids, though the identity of these cells remains to be identified, it was concluded that GRP-evoked itch is attenuated by nalfurafine is consistent with the idea that kappa opioids directly inhibit GRPR-expressing spinal interneurons [27]. Intrathecal injection of GRP led to intense scratching, an effect largely reduced by either GRPR antagonists or PI3Kγ inhibitor or an Akt activator. In a dry skin model of itch, GRPR blockade or PI3Kγ inhibition also reversed the scratching behavior [28].

The spinothalamic tract (STT) is home to many second-order neuron types, connecting the dorsal horn to the thalamus. In STT, 20% of neurons responded to histamine and 13% responded to cowhage, with only 2% of neurons responding to both [29]. These histamine- and cowhage-responsive neurons terminated in a cluster of densely packed neurons, termed the ventral posterior nucleus, an area implicated in itch behavior. Similar to histamine-sensitive C-nerves in humans, histamine-sensitive STT tract neurons in cats do not respond to mechanical or thermal

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