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Commentary

Understanding the switch from pain-to-itch in dermatitis

Junichi Hachisuka[a,b], Sarah E. Ross[a,b,c,*]

[a] Department of Neurobiology, University of Pittsburgh, 200 Lothrop Street, Pittsburgh, PA 15213, USA
[b] Pittsburgh Center for Pain Research, University of Pittsburgh, 200 Lothrop Street, Pittsburgh, PA 15213, USA
[c] Department of Anesthesiology, University of Pittsburgh, 200 Lothrop Street, Pittsburgh, PA 15213, USA

Severe chronic itch is debilitating symptom that results from a large number of pathological conditions including skin disorders, organ failure, and even some types of cancers [1]. In particular, conditions that are associated with inflammation of the skin—such as atopic dermatitis and contact dermatitis—commonly result in itch that is difficult to treat. Moreover, excessive scratching causes skin damage and release of inflammatory mediators that exacerbates itch, resulting in a pathological itch-scratch cycle. However, currently there are no effective drugs for the treatment of itch in dermatitis. While antihistamines reduce itch caused by hives, they have limited efficacy for most other types of itch, including atopic and contact dermatitis.

Recently, there has been a surge of interest in the field of itch, and a large number of new pruritogens (itch-inducing agents) and their receptors have been identified. Of these, histamine is the prototypical pruritogen, which is released from dermal mast cells and activates mechano-insensitive C-fibers to produce itch [2]. In addition to histamine, there are numerous other pruritogens such as cowhage, chloroquine, bovine adrenal medulla 8-22 (BAM8-22), and serotonin, that likely cause itch via the activation of a distinct population (or populations) of primary afferents [3–8]. These agents cause acute itch in humans and/or trigger vigorous scratching behavior when injected into the skin of mice. However, we still do not understand which factors are responsible for itch in disease states like dermatitis, highlighting the pressing need for a better understanding of mechanisms underlying chronic itch.

Just as people who suffer from chronic pain often experience hyperalgesia and allodynia, people suffering from chronic itch often experience hyperknesis and alloknesis. This 'itchy-skin' is commonly seen in dermatitis, where numerous innocuous stimuli—light touch, gentle brushing or contact with wool fiber—cause extraneous itch [9,10]. Moreover, substances such as bradykinin, which are normally experienced as painful, inappropriately cause itch rather than pain for people with atopic dermatitis [11].

Although this pain-to-itch phenomenon is important to understand, whether it can be modeled, and therefore studied, in mice was hitherto unknown. Now in this volume of Neuroscience Letters, Fu et al. show that it can. In this study, Lamotte's group develop a mouse model of contact dermatitis and then show that, in mice with dermatitis, the algogen bradykinin causes an abnormal itch behavior, indicating that sensory input that ought to be painful is experienced as itch.

Figuring out whether a mouse is experiencing itch or pain requires a behavioral assay that can distinguish between these aversive sensations, and such an assay did not exist until recently. In traditional pain assays, algogens are injected into the paw (where mice are unable to show itch behavior by scratching), whereas in traditional itch assays, pruritogens are injected into the skin at nape of the neck (where mice are unable to show pain behavior by licking). As a result, these assays do not allow pain and itch to be differentiated. What Lamotte and colleagues realized several years ago is that if you inject an aversive chemical into the skin of the cheek, you observe two different types of responses that are easy to tell apart [12]. Agents that cause itch give rise to scratching with the hindpaw, whereas agents that cause pain give rise to wiping with the forepaw. In this study, Lamotte's group used this cheek model to assess the degree of itch and pain induced by two substances that normally cause itch (histamine and BAM8-22) and one that normally evokes pain (bradykinin). As expected, histamine and BAM8-22 caused mainly scratching, indicative of itch, whereas bradykinin caused mainly wiping, indicative of pain.

Next, the authors made a model of acute contact dermatitis using repeated exposure to a hapten called squaric acid dibutylester (SADBE) to trigger an immune response in the skin. In mice with SADBE-mediated contact dermatitis, some pruritogens caused more itch than normal. But this hypersensitivity to pruritogens was not true across the board—BAM8-22-induced itch was abnormally elevated, but histamine-induced itch was unchanged. These data suggest that contact dermatitis selectively enhances non-histaminergic itch. Furthermore, these findings further underscore the idea that non-histaminergic itch might play a larger role than histaminergic itch for may types of dermatitis, possibly explaining why antihistamines are ineffective at treating itch in atopic dermatitis.

* Corresponding author at: Department of Neurobiology, University of Pittsburgh, 200 Lothrop Street, Pittsburgh, PA 15213, USA. Tel.: +1 412 624 9178.
E-mail address: saross@pitt.edu (S.E. Ross).

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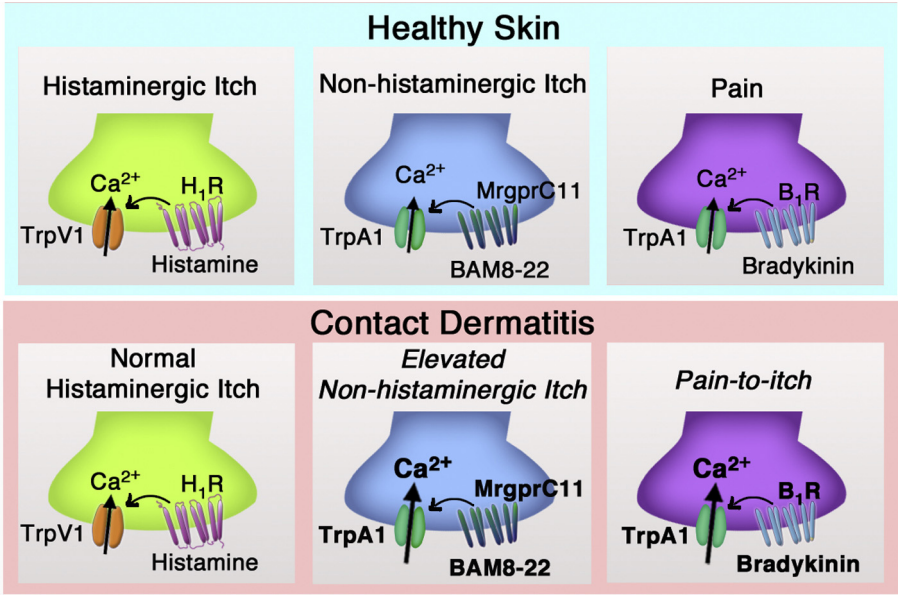

Fig. 1. Amplified non-histaminergic itch and pain-to-itch in contact dermatitis. Histamine receptor signaling requires TrpV1, whereas BAM8-22-mediated signaling and bradykinin-mediated signaling require TrpA1. In skin that is inflamed due to contact dermatitis, histaminergic itch is normal, whereas BAM8-22-mediated itch is amplified. In addition, bradykinin, which normally causes pain, now causes pain and itch. Thus, TrpA1-coupled pathways may be sensitized in contact dermatitis.

Fu et al. also found that application of bradykinin, which is known as pain inducer, caused not only wiping but also scratching in their model of acute contact dermatitis. Thus, as was previously observed in humans with atopic dermatitis, mice with contact dermatitis showed a pain-to-itch phenomenon in which substances that ordinarily evoke pain now evoke abnormal itch.

These findings fit very nicely into an emerging idea about the central role for TrpA1 in chronic itch. Over the past few years, it has become increasingly clear that metabotropic receptors for aversive chemicals, including the receptors for histamine, BAM8-22 and bradykinin, do not work on their own—rather, for these receptors to trigger an action potential in sensory neurons, they must couple to an ion channel that mediates a depolarization potential [13]. Importantly, it appears that Trp channels provide this function. Moreover, different receptors appear to be coupled to different Trp channels: the receptor for histamine is coupled to TrpV1 [14,15], whereas the receptors for BAM8-22 (MrgprC11) and bradykinin (B2R) are coupled to TrpA1 [16,17]. Thus, the findings here that BAM8-22 and bradykinin, but not histamine, are sensitized in chronic itch are consistent with the idea that TrpA1-coupled receptors, but not TrpV1-coupled receptors, mediate this condition. Thus, this study provides yet more evidence in support of the concept that that TrpA1 is a central ion channel underlying chronic itch (Fig. 1).

The fundamental role for TrpA1 in chronic itch has recently been revealed by two groups who have used several different animal models of chronic itch. In particular, allergic contact dermatitis was modeled by repeated exposure of the mice to urushiol (allergen found in poison ivy, poison oak, and sumac) or the chemical allergen oxazolone, which caused itchy skin accompanied by edema formation and increases in skin thickness [18]. Dry skin-induced itch was modeled through the repeated application of acetone/ether followed by water (AEW model) to disrupt barrier integrity of the skin, resulting in spontaneous itch [19]. Importantly, irrespective of which model was used, in all of these experiments *TrpA1* knockout mice consistently showed a significant decrease in scratching behavior as well as reduced severity of dermatitis relative to wild type controls. Moreover, acute inhibition of TrpA1 with TrpA1 antagonists also reduced scratching behavior in these animal models of chronic itch. These studies raise the possibility that TrpA1, in particular, is sensitized in several types of chronic itch. And now, the findings by Fu et al. in this issue of Neuroscience Letters substantiate this idea by revealing that chronic itch results in amplified signaling that may to be specific to TrpA1-coupled receptors.

What remains to be addressed is mechanism that underlies the switch from pain to itch, particularly whether it is a peripheral or central phenomenon. One possibility is that chronic itch results in the selective sensitization of peripheral sensory neurons that are tuned to detect itch such that these itch afferents are now abnormally responsive to the algogen bradykinin. Alternatively, the bradykinin-induced itch may be a form of central sensitization due to changes in the activity of spinal circuits that process pain and itch signals. Although the answer to this question is still unknown, at least we now have a mouse model with which to address it.

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