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Forum Minireview

Analysis of the Mechanism for the Development of Allergic Skin Inflammation and the Application for Its Treatment: Mechanisms and Management of Itch in Atopic Dermatitis

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Abstract. Although the identification of neural pathways for histamine-induced itch was a breakthrough in itch research, other pathways also seem to be involved in itch. In regard to itch of atopic dermatitis, neural sensitization complicates its mechanisms. Inflammatory mediators such as bradykinin that, normally, do not induce itch can function as pruritogens under neural sensitization, which also affects the treatment to a considerable extent. Complete inhibition of skin inflammation is, for now, the most effective way to suppress itching in atopic dermatitis, since there might be countless potential mediators inducing itch. Centrally acting anti-pruritic drugs as well as drugs against neural sensitization are prospective treatments for itch of atopic dermatitis.

Keywords: histamine, itch sensitization, alloknesis, nerve growth factor, opioid, allergic inflammation

Introduction

Itch is generally recognized to be 'an unpleasant sensation that induces desire to scratch'. Although felt more or less by everyone in everyday life, chronic itch in pruritic diseases such as atopic dermatitis is quite annoying and is very damaging to the quality of life. Moreover, itch induces scratching and thereby worsens the condition of the skin, resulting in a vicious itch–scratching cycle. It is, therefore, widely accepted that control of itch is the most important issue in the treatment of atopic dermatitis. Compared with pain research, less attention has been paid to itch research, which has impeded the development of treatments for itching. In the last ten years, however, itch has been gradually recognized as a research topic. Our understanding has been greatly renovated by many new findings on itch mechanisms (1). In this article, the neurophysiological mechanisms and treatment of itch will be reviewed, with a particular focus on itch associated with atopic dermatitis.

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Itch-specific neural pathways (Fig. 1)

Histamine has been well known for more than a half century to be a potent itch mediator in human beings. The neural pathway for histamine-induced itch, however, was not clear and the 'intensity theory' that itch is felt when weak signals are transmitted in pain-conducting nerves was generally believed in, for a number of reasons, including the following: patients with spinal cord injury lose both itch and pain and intracutaneous injection of histamine induces itch in low concentration but causes pain in high concentration. However, this theory failed to explain the contradictory fact that morphine inhibits pain but induces itch.

It was ten years ago that a study employing microneurography finally denied this theory and gave rise to the 'specific theory'. Peripherally, nerves responsive to histamine have been found among the C-nerves. Although most C-nerves are polymodal, that is, responsive to mechanical and heat stimuli, histamine-responsive ones are not mechano-sensitive (2). Besides mechano-insensitivity, the difference from pain C-nerves is also demonstrated by a high threshold to electrical stimuli, a large innervating area, a slow conduction velocity, and less spontaneous activation

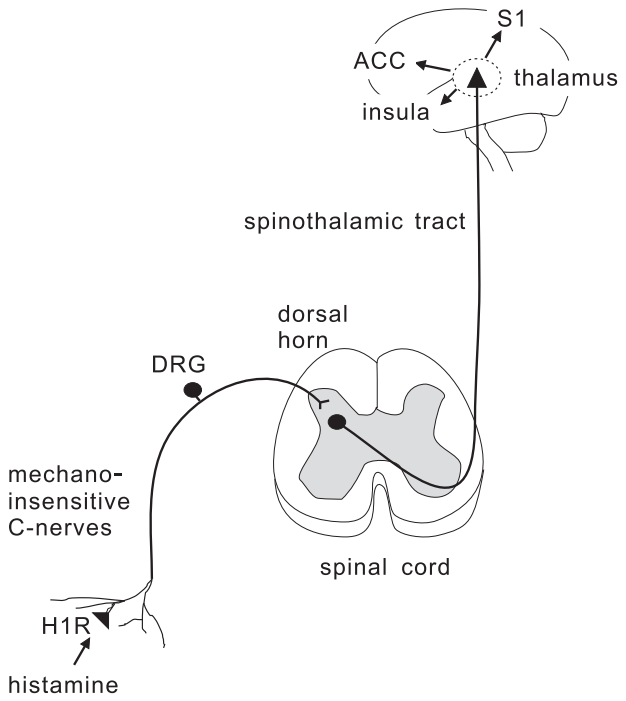

Fig. 1. Itch-specific neural pathway for histamine-induced itch. H1R: histamine H_1 receptor, DRG: dorsal root ganglion, ACC: anterior cingulated cortex, S1: primary somatosensory cortex.

of itch C-nerves. A later study in cats has shown that histamine-sensitive nerves are found in the spinothalamic tract but are not mechano-sensitive, different from most of other spinothalamic nerves (3). Moreover, they project mainly to the ventral posterior inferior (VPI) nucleus and the ventral periphery of the ventral posterior lateral (vVPL) nucleus of the lateral thalamus, whereas pain nerves project mainly to the nucleus submedius (SM) of the medial thalamus. Thus, the peripheral and central presence of itch-specific nerves has been demonstrated.

There is another recent study supporting specificity of itch nerves. Gastrin-releasing peptide receptor (GRPR) mutant mice showed normal responses to painful stimuli compared to wild-type mice, whereas scratching behavior induced by itchy stimuli was significantly reduced in GRPR mutant mice (4). Gastrin-releasing peptide (GRP) is expressed in a small subset of dorsal root ganglion neurons, while expression of GRPR is restricted to lamina I of the dorsal spinal cord at which itch and pain nerves terminate. This suggests that GRP and GRPR transmit itch specifically.

Other itch pathways

Although demonstration of the presence of itch-specific neural pathways as well as identification of histamine-sensitive itch nerves is a breakthrough for itch research, one cannot explain every type of itch by the histamine pathways. For example, histamine-induced itch always accompanies flare that is induced by axon-reflex of histamine-sensitive C-nerves. However, itch without flare is often experienced. Cowhage (*Mucuna pruriens*), whose sheath has small spicules on the surface containing pruritogens, also induces itch without flare. It has been reported that cowhage-induced itch, but not histamine-induced itch, is reduced in human skin by capsaicin-induced desensitization (5). A study of primate spinothalamic tract has shown the presence of nerves responsive to either cowhage or histamine, but not to both (6). It is therefore suggested that cowhage-induced itch is transmitted by another pathway different from histamine-sensitive nerves.

Another piece of evidence supporting the presence of other itch pathways is electrically evoked itch in human wrist skin. Pure and intense itch sensation can be evoked repeatedly by this method. Although a long time-lag between electrical stimulation and itch sensation is consistent with the feature of C-nerves, itch is evoked by very weak electricity and does not accompany flare, which is different from histamine-sensitive C-nerves (7).

Thus, it is highly possible that there are more than one neural pathway for itch.

Cerebral function for itch

Following many brain imaging studies on pain, the number of such studies on itch is gradually increasing. It is generally accepted that spatial, temporal, and intensity aspects of pain perception are processed in the primary and secondary somatosensory cortex (S1 and S2, respectively), whereas affective and motivational aspects are processed in the anterior cingulate cortex (ACC) and insular cortex (8). The activation of the thalamus, prefrontal cortex, premotor areas, and cerebellum is also commonly observed at pain sensation (9, 10). On the other hand, it has been shown by studies on itch using positron emission tomography (PET) that the prefrontal cortex, premotor areas, S1, and ACC are activated in response to histamine-induced itch (11, 12). Ipsilateral activation of premotor areas might reflect desire to scratch (13). However, a large overlap has been found between pain- and itch-related brain areas and their difference is not clear yet. One of the obstacles to brain-imaging studies on itch is the shortage of suitable itchy stimuli available for humans. Itch induced by application of histamine or histamine-releasing substances cannot be controlled, which is not suitable for functional magnetic resonance imaging. In this sense, the newly developed experimental method to evoke itch

electrically in humans will apparently be useful for brain imaging studies on itch (7).

Itch sensitization in atopic dermatitis

Patients with chronic pain such as post-herpetic neuralgia often complain of pain that is evoked by weak mechanical stimuli like light contact of clothes to the skin. They sometimes describe light pin-pricking stimuli to the skin to be unendurably intense pain. These phenomena, called allodynia and pin-prick hyperalgesia, respectively, are caused by neural sensitization, that is, lowering of neural thresholds. Comparable phenomena can be observed in patients with itchy diseases such as atopic dermatitis. Patients with atopic dermatitis often find weak mechanical stimuli like contact of wool fibers to their eczematous skin to be itchy. It has been shown that intracutaneous application of histamine induces significantly more intense itch in their eczematous skin than in their non-affected skin or in healthy individuals (14). These phenomena are parallel to allodynia and hyperalgesia and are called alloknesis and hyperknesis, respectively.

Inflammatory mediators in skin such as adenosine triphosphate (ATP), bradykinin, serotonin, prostaglandins, and neurotrophins not only activate but also acutely sensitize primary afferent nerves. Sensitized nerves then react to those stimuli that would normally induce no activation. One example of this is transient receptor potential vanilloid-1 (TRPV1) located in free nerve endings that is normally activated by a temperature of 42°C, but by activated at 35°C in the presence of ATP or bradykinin (15). Sprouting of epidermal nerve fibers caused by increased neurotrophins, found in patients with atopic dermatitis, might also contribute to sensitization (16). Increased serum level of nerve growth factors (NGF) has also been reported to correlate with the severity of atopic dermatitis (17).

On the other hand, ongoing activation of C-nerves for pain lowers thresholds of spinal processing neurons for pain in the spinal cord (18). As a result of this, signals conducted through other peripheral nerves such as A-β nerves can also activate central neurons for pain, which accounts for touch-evoked pain, that is, allodynia. Not only itch in inflammatory skin diseases like atopic dermatitis but also itch evoked by continuous transcutaneous electrical stimulation also accompanies alloknesis (7). This implicates the involvement of central neural sensitization, caused by ongoing activation of C-nerves for itch, in alloknesis.

Due to the combination of peripheral and central neural sensitization, various painful stimuli do not inhibit but rather induce itch. It has been shown that itch can be evoked in patients with atopic dermatitis by mechanical, electrical, thermal, and low-pH stimuli that are normally painful (19). This finding is consistent with one of the well-known clinical features of patients with atopic dermatitis that they cannot stop scratching once they start it. This suggests that scratching, which normally induces pain, does not inhibit but, to the contrary, generate itch. It is of note that neural sensitization in patients with chronic pain causes histamine to induce exclusively pain instead of itch (20). Thus, due to neural sensitization, pain can convert to itch, and vice versa.

Pruritogens in atopic dermatitis

Histamine is the best known itch mediator in humans and plays a significant role in itch of urticaria. Although only a weak itch in their non-lesional skin, histamine induces very intense itch in lesional skin of patients with atopic dermatitis due to neural sensitization (14). This suggests that histamine still functions as a potent pruritogen in atopic dermatitis. However, it must also be admitted that antihistamines are not very effective for itch of atopic dermatitis. Histamine-sensitive C-nerves are also responsive to other mediators including pain mediators such as bradykinin and capsaicin (21). On the other hand, histamine activates polymodal C-nerves for pain, although weakly. Since prostaglandin E2, which activates histamine-sensitive C-nerves moderately but polymodal C-nerves hardly, is reported to induce itch in human skin (22), the balance of itch and pain nerve activation seems to play the key role in determination of final perception, that is, itch or pain.

There have been many studies searching for pruritogens of atopic dermatitis other than histamine. Among mast cell mediators except for histamine, tryptase is regarded to be a highly potential itch mediator. Protease activated receptor-2 (PAR2), on which tryptase works as ligand, is densely found on nerve endings of atopic dermatitis, and moreover, application of an artificial ligand for PAR2 to atopic dermatitis induces itch (23).

Acetylcholine, released from sympathetic nerves innervating eccrine sweat glands, induces itch in atopic dermatitis, suggesting the involvement of acetylcholine in sweat-associated itch of patients with atopic dermatitis (24). By the way, acetylcholine induces pain when applied to healthy skin. Bradykinin also induces itch in atopic dermatitis, while inducing pain in healthy skin. This difference between atopic dermatitis and healthy skin can perhaps be explained by neural sensitization.

Interleukin-31 (IL-31), released from helper T cells type 2 (Th2), seems to be indirectly involved in itch of atopic dermatitis, since IL-31 transgenic mice develop

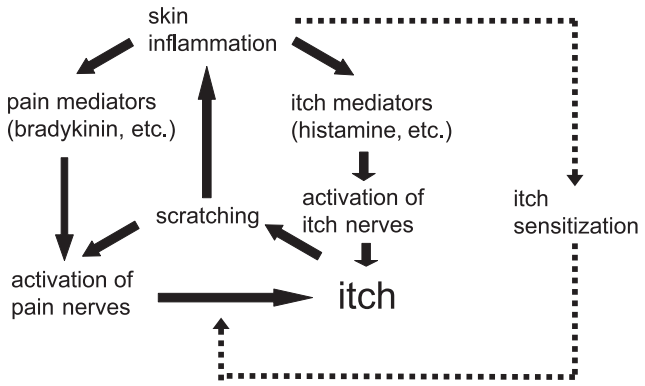

Fig. 2. Involvement of neural itch sensitization in itch of atopic dermatitis

skin lesions similar to atopic dermatitis and scratching frequency of atopic dermatitis model mice is correlated to the mRNA level of IL-31 (25).

Current treatment of itch in atopic dermatitis

Antihistamines, that is, H_1-receptor blockers, are commonly used for any type of itch, not to mention atopic dermatitis. Histamine induces very intense itch in atopic dermatitis due to neural sensitization, for which antihistamines are effective. In effect, however, antihistamines do not inhibit pruritus of atopic dermatitis sufficiently, since there are many other itch-causing substances.

In addition, neural sensitization, which causes non-pruritic mediators such as bradykinin to induce itch, cannot be ignored in the treatment of pruritus of atopic dermatitis. Since there might be countless potential pruritogens that must be overcome, it would make more sense to suppress skin inflammation by using a topical steroid or tacrolimus rather than to prepare antagonists to all of them in order to control itch of atopic dermatitis (Fig. 2).

New strategies for itch of atopic dermatitis

Since neural sensitization plays an important role in pruritus of atopic dermatitis, successful inhibition of sensitization must be effective. In this sense, nerve growth factor (NGF) is one of the important targets since it is known to induce acute neural sensitization as well as sprouting of nerve endings into the epidermis. Anti-NGF treatment has been proved to be effective in patients with pain as well as in pain model mice. Anti-NGF approaches against pruritus have been successfully applied in animal models of atopic dermatitis (26). It is interesting to note that semaphorin 3A, which inhibits NGF-induced sprouting of nerves, has recently been shown to inhibit mice scratching and improve skin condition (27).

Drugs to inhibit itch centrally are being awaited. The opioid system is regarded to be the key factor related to this. Morphine, which is an opioid μ-receptor agonist, is known to suppress pain but induces itch frequently as a side effect. On the other hand, naltrexone and naloxone, opioid μ-receptor antagonists, have been reported to be effective for pruritus associated with renal failure and cholestatic liver diseases. Thus, the opioid system seems to control the balance of itch and pain centrally. Recently, an opioid κ-receptor agonist has been shown to have an anti-pruritic effect (28) and is now being expected to centrally inhibit itch associated with renal failure, liver diseases, and also, atopic dermatitis.

Post-herpetic neuralgia, which is due to nerve damage, is mostly painful but sometimes itchy. This kind of itch is not due to itch mediator release but to self activation of damaged nerves and is called neuropathic itch, which is normally resistant to antihistamines and topical steroid application. Gabapentin, which can block nerve signal transmission, has successfully been used to reduce neuropathic itch as well as pain (29) and might be effective for itch of atopic dermatitis. Thus, many hints to develop itch treatment are hidden in pain studies, since there are many common mechanisms behind these two sensations.

It must also be mentioned that the treatment of itch in atopic dermatitis does not only consist of medication but also of patient education to teach how to prevent itch. The latter includes the choice of clothes material, hair style, and so on, in which neural sensitization must be taken into consideration.

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