Recent Advances in the Study of Itching

Updated Neurophysiology of Itch

Akihiko Ikoma
Research and Development, Galderma Japan;
13–1 Nishigokencho, Shinjuku-ku, Tokyo 162–0812, Japan.
Received June 4, 2013

The unique physiological features of histamine-sensitive C-fibers and spinothalamic tract neurons support the hypothesis of itch specific pathway, whereas subsequent studies on cowhage-induced itch have provided evidence against it, suggesting the presence of multiple neural pathways for itch. Not only peripheral pruritogens but also spinal neural receptors are involved in the control of itch, and will be the target of treatment. Itch sensitization in chronic pruritus is another crucial factor that needs to be considered in the treatment. Neuropathic itch is the type of itch that occurs when nerve fibers are damaged or injured and spontaneous firing of nerves takes place, and plays a major role in itch accompanying some pathological conditions such as herpes zoster. The complexity of itch is due to the broad range of mediators involved and the large variety of neural mechanisms behind.

Key words pruritogen; spinal receptor; itch sensitization; neuropathic itch

1. INTRODUCTION

Itch is defined in general as ‘an unpleasant sensation that induces desire to scratch.’ Itch is also a sensation that everyone feels more or less every day. However, chronic intense itch associated with diseases is agonizing and has a significant negative impact on quality of life. Also, scratching induced by itch causes skin inflammation, which then leads to worsening of itch, consequently resulting in a vicious cycle of itch and scratching. This vicious cycle is not limited to itch related to skin problems such as atopic dermatitis but also to itch of any origins such as systemic diseases or neuropathies. Combating itch and preventing the vicious cycle of itch and scratching are thus necessary in treatment of any types of itch. However, the presence of multiple neural pathways in itch induction makes therapeutic strategies for combating itch complicated.

2. NEURAL PATHWAYS FOR ITCH

Itch had been regarded for decades as a weak pain, in other words, as a sensation that occurs when weak signals are transmitted on neurons transmitting pain (=intensity hypothesis), until the neurons for histamine-induced itch were identified by microneurographical studies. Those studies have revealed that C- and spinothalamic neurons sensitive to transcutaneously applied histamine are obviously not identical to C- and spinothalamic neurons sensitive to painful stimuli in terms of their physiological characteristics such as sensitivity to mechanical stimuli and conduction velocities. After this finding, the hypothesis of itch-specific pathways drew more attention of neuroscientists. This hypothesis has further been supported by some subsequent findings such as the report on gastrin-releasing peptide (GRP) receptor in which the functional impairment of GRP receptor-positive neurons was found to cause loss of itch sensation, but not pain, in mouse models. The reported involvement of distinct subsets of transient receptors potential A1 (TRPA1)-positive neurons in chroloquine-induced itch also supports the specific hypothesis. However, there have also been findings against the specific theory such as the study on the neurons reactive to topically applied spicules of cowhage, which is a tropical bean plant known to cause itch in contact with the skin, reporting that they are different from histamine-sensitive neurons in their physiological features and are rather overlapped with the neurons that are reactive to pain-inducing stimuli. Thus, it is still controversial whether itch and pain are independent in terms of neural pathways, although it is at least clear that multiple neural pathways exist for itch induction.

By the way, it has not completely been verified that the cowhage-induced activation of the C-fibers that are sensitive to mechanical stimuli, contrary to histamine-sensitive C-fibers, and overlapped with the C-fibers involved in pain would really represent itch. Cowhage-induced itch is frequently accompanied by pain-related sensory components such as pricking, stinging, and burning. Therefore, the possibility cannot be excluded that the cowhage-induced activation of C-fibers involved in pain would merely represent such pain-related sensory components instead of itch. The simplest method to solve this question would be to demonstrate that itch similar to cowhage-induced itch in quality and intensity can be induced by mechanical stimuli. The reality is, however, that mechanical stimuli to skin such as touching skin with von-Frey filaments can only evoke tactile sensation, not itch. It is not only cowhage but also histamine, transcutaneous electrical stimulation and other stimuli that frequently induces both itch and pain at the same time. Regarding animal models, scratching in rodents does not always reflect itch but sometimes pain, although most animal studies employ scratching behavior as the sign representing itch. The recently-reported cheek application model in mice, in which itch causes scratching whereas pain...
causes wiping,\textsuperscript{21} seems an option to avoid misinterpretation of scratching. However, the question whether scratching on the cheek reflects pure itch or maybe reflects a mixed sensation of itch and pain still remains. Thus, the cheek application in mice is not a perfect solution to differentiate itch from pain. In that sense, the experimental method to evoke pure itch in healthy volunteers without any pain-related components simultaneously accompanying that we have very recently reported meets the required condition and can be applied to investigate differentiation between itch and pain.\textsuperscript{13}

3. PERIPHERAL PRURITOGENS

There is a lot of potential itch mediators (pruritogens) that have been reported so far. Among them, histamine released from mast cells is the best know pruritogen and in fact is the main role-player in itch of some diseases such as urticaria. Histamine receptors can be classified into four subtypes (H\textsubscript{1} to H\textsubscript{4}), among which H\textsubscript{1} seems the main one involved in itch in human beings, although H\textsubscript{2} also seems to play a role in itch in rodents according to some published reports.\textsuperscript{44} It is a frequent misinterpretation of histamine's role to see histamine as the main player in any types of itch. As histamine H\textsubscript{1} receptor blockers rarely bring a sufficient inhibition of itch in most pruritic diseases except for urticaria, it is unlikely for histamine to play a major role in itch in diseases.

Other mast cell mediators than histamine such as tryptase seem to be involved as peripheral pruritogens in itch of skin diseases such as atopic dermatitis. Among four known subtypes of protease-activated receptors (PAR\textsubscript{1} to PAR\textsubscript{3}), PAR\textsubscript{2} is highly expressed in keratinocytes and nerve endings in the lesional skin of atopic dermatitis. Moreover, locally applied PAR\textsubscript{2}-ligands induce itch in atopic dermatitis. This indicates the involvement of tryptase via PAR\textsubscript{2} in itch of atopic dermatitis.\textsuperscript{15}

Histamine-sensitive neurons are also sensitive to other mediators or substances that usually induce pain such as bradykinin and capsaicin. According to one of the published electrophysiological studies on histamine-sensitive neurons, histamine-sensitive but mechano-insensitive C-fibers slightly respond to bradykinin and capsaicin, whereas mechanosensitive and capsaicin-sensitive C-fibers involved in pain also slightly respond to histamine. Thus, it has been indicated by this study that intense activation of histamine-sensitive C-fibers involved in itch together with only weak activation of mechanosensitive C-fibers involved in pain leads to itch induction.\textsuperscript{86} Actually, intracutaneous application of prostaglandin E\textsubscript{2}, which causes a relatively intense activation of histamine-sensitive C-fibers involved in itch, is reported to induce itch in healthy volunteers.\textsuperscript{67}

Among other potential peripheral pruritogens, acetylcholine is known to induce itch when applied to the skin of patients with atopic dermatitis.\textsuperscript{18} As acetylcholine is released from sympathetic nerve endings innervating eccrine sweat glands, it is likely involved in itch that occurs often in patients with atopic dermatitis when they sweat. Cytokines also seem to function as peripheral pruritogens. Interleukin (IL)-31, mainly produced by Th2 cells, has been shown to be involved in itch of model mice with dermatitis similar to atopic dermatitis, according to the studies demonstrating occurrence of dermatitis with enhanced scratching in transgenic mice overexpressing IL-31 and the elevated mRNA level of IL-31 in mice that scratch a lot.\textsuperscript{29}

4. SPINAL RECEPTORS FOR ITCH

Endogenous opioids such as enkephalins, dynorphins, and endomorphins have functions of neuromediators as well as hormones and immunomodulators. Their receptors are classified to three categories: \( \mu \), \( \kappa \), and \( \delta \). Opioid receptors are located in both peripheral and central nervous system. Their involvement in pain/itch induction has been investigated mainly in the central nervous system, mostly related to morphine. Morphine is the best-known \( \mu \)-opioid receptor (MOR) agonist and has been used as pain killer for centuries. It is well known that epidural or spinal administration of morphine frequently causes segmental pruritus. Generalized itch sometimes accompanies systemic administration of morphine.\textsuperscript{20,21}

Although intracutaneous administration of morphine induces mast-cell degranulation and plasma levels of histamine are elevated after intravenous administration of morphine,\textsuperscript{22} this effect is not attenuated by naloxone, an MOR antagonist, suggesting that morphine makes histamine released from mast cells independently of the MOR.\textsuperscript{23} On the contrary, itch after spinal administration of morphine seems histamine-independen-\textsuperscript{22} Antihistamines have no clinical effects on itch induced by spinally-applied morphine.\textsuperscript{26} Spinally applied morphine-induced itch often spreads rostrally from the injection site,\textsuperscript{25} and can be inhibited by MOR antagonists,\textsuperscript{26} suggesting that MOR at the spinal cord level plays a major role in morphine-induced itch. This is also supported by a study demonstrating that a peptidic MOR agonist evoked intense scratching in monkeys when applied intracutaneously, but not when applied intravenously.\textsuperscript{27} Another study in monkeys has suggested that MOR in the medullary dorsal horn plays a critical role.\textsuperscript{28}

The antipruritic potential of MOR antagonists such as naloxone and naltrexone is not limited to morphine-induced itch. Histamine-induced itch is significantly suppressed by naloxone without affecting histamine-induced wheal/flare reactions or alloknesis.\textsuperscript{29} This suggests the central mode of antipruritic effects of naltrexone. Naloxone and naltrexone are also effective to dialysis- and cholestasis-related itch, which are normally resistant to antihistamines and difficult to control.\textsuperscript{30,32} To be interesting, application of MOR antagonists to patients with cholestatic pruritus reportedly reduced itch but induced pain.\textsuperscript{35} This indicates the involvement of MOR in controlling the balance between itch and pain.

Recent studies have demonstrated that \( \kappa \)-opioid receptor (KOR) agonists suppress MOR agonist-induced pruritus. They inhibit itch that occurs after intrathecal application of morphine without affecting analgesic effects.\textsuperscript{34} Moreover, pre-clinical data has shown that KOR agonists do not only inhibit morphine-induced itch but also other types of itch.\textsuperscript{35} Today, selective KOR agonists such as nalfurafine have drawn attention as novel antipruritic drugs. Indeed, clinical data has successfully demonstrated the effects of nalfurafine on severe itch in patients undergoing hemodialysis.\textsuperscript{36,37} It remains to be verified if other subtypes of intractable itch such as cholestatic- and tumor-associated itch would also be the target of KORs antipruritic effects.

As mentioned before, gastrin-releasing peptide (GRP) receptor is regarded to be an index of itch-specific pathways.
GRP and GRP receptor are broadly expressed in the central nervous system and gastrointestinal tract. The role of GRP and GRP receptor in itch has been investigated in a few of recent studies. According to them, GRP receptor-mutant mice showed normal pain perception for mechanical and thermal stimuli, but less scratching when pruritogens such as compound 48/80, chloroquine, or protease-activated receptor-2 (PAR2) agonists were applied to the skin. Intrathecal administration of GRP receptor antagonists suppressed scratching induced by those pruritogens in wild-type mice. Moreover, mice in which lamina I neurons expressing GRP receptor were ablated by intrathecal application of bombesin-saporin lacked their scratching response to histamine, compound 48/80, serotonin, endothelin-1, chloroquine, and PAR2 agonists. This deficit of scratching was not observed when GRP receptor-expressing neurons were intact. Another study has shown coexpression of GRP with the Mas-related G protein-coupled receptor (Mrgpr) member A3 (MrgprA3) in DRG neurons. Mrgprs consist of more than 50 members and are exclusively expressed in peripheral sensory neurons. A previous study has shown that the targeted disruption of the Mrgpr gene cluster in mice reduces scratching responses to chloroquine, but not to histamine, as well as that MrgprA3, among the Mrgpr family, is crucial for chloroquine-induced itch. Thus, the mechanism of itch induced by chloroquine, which is a malaria drug known to induce itch adversely, might be explained like this; Chloroquine activates MrgprA3 on primary afferent nerve fibers in the skin, and makes GRP released from central endings of primary afferent nerves, which leads to activation of GRP receptor in post-synaptic neurons of the spinal cord and consequently causes itch. However, it is of note that no significant difference was observed between GRP receptor-mutant and wild-type mice in their scratching reaction to histamine, endothelin-1, or serotonin, indicating that GRP/GRP receptors are not the sole player of itch induction at the spinal cord. GRP receptor-expressing neurons are the key player rather than GRP and GRP receptors themselves.

Substance P (SP) is a neuropeptide belonging to the tachykinin family. Neurokinin-1 receptor (NK1R) among three types of SP’s receptors has the highest affinity for SP and is broadly expressed in the peripheral and central nervous system. There has been a lot of publications that indicate expression of NK1R have been reported in pruritic skin diseases such as atopic dermatitis, urticaria, and psoriasis, suggesting that SP is involved in itch induction in humans, too. However, SP-induced itch in humans seems to be at least partly mediated via histamine release from mast cells. Moreover, the physiological amount of SP in human skin induces vasodilatation and protein extravasation but not itch sensation. On the contrary to its peripheral functions, however, a recent publication suggests the involvement of NK1R in itch at the central level. This study has demonstrated that NK1R-deficient mice show no scratching reactions to spider venom, which is pruritogenic in wild-type mice. Moreover, spider venom-induced scratching is blocked by systemically-applied, but not locally-applied, NK1R antagonists, suggesting the involvement of NK1R in itch at the central level. The antipruritic potential of NK1R antagonists on some pruritic conditions such as Sézary syndrome and other types of chronic pruritus has been reported. The value of NK1R antagonists in antipruritic treatment remains to be confirmed in large-scale clinical studies.

N-Methyl-d-aspartate (NMDA) receptor is a glutamate receptor made of many subunits, which are categorized into three subtypes (NR1, NR2, and NR3), and broadly expressed in the peripheral and central nervous system. The synaptic plasticity of NMDA receptor is known to be the fundamental mechanism for learning and memory processes and also contributes to central sensitization of pain. In central sensitization, continuous inputs from the peripheral nerves for pain under certain conditions such as inflammation and injuries cause depolarization in the post-synaptic cells of the spinal cord, which then remove the Mg2+ blockade from NMDA receptors and activate them. The activation of NMDA receptors causes Ca2+ influx and intracellular signal transduction cascades, and leads to the phosphorylation of ion channels in NMDA and other receptors. Thus, the spinal neuron excitability is increased in a long term by activation of NMDA receptors, which is the central sensitization.

<table>
<thead>
<tr>
<th>Table 1. Pain Sensitization versus Itch Sensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post herpetic neuralgia</td>
</tr>
<tr>
<td>Pain induced by non-painful stimuli=alldynia</td>
</tr>
<tr>
<td>Enhanced pain induced by painful stimuli=hyperalgesia</td>
</tr>
<tr>
<td>Pain induced by itchy stimuli (e.g., histamine-induced pain)</td>
</tr>
</tbody>
</table>

5. ITCH SENSITIZATION

Patients with chronic pain, for instance, post-herpetic neuralgia often complain of pain induced by weak mechanical stimuli to the skin such as slight contact of clothes to the skin. Those patients also find pin-pricking stimuli to the skin extremely painful. These phenomena, called allodynia and pin-prick hyperalgesia respectively, have been explained by neural sensitization. The corresponding phenomena are observed in patients with chronic pruritus. For instance, patients with atopic dermatitis often experience itch induced by weak mechanical stimuli to the skin such as contact of wool fibers to the skin. A previous experimental study has shown that cutaneous application of histamine induces itch more intensely in skin lesion of patients with atopic dermatitis than in their non-affected skin or in healthy persons. These phenomena, corresponding to allodynia and hyperalgesia, are called al-
loknis and hyperknesis, respectively (Table 1). Neural sensiti-
zation can be categorized into two types, the peripheral one 
and the central one, based on the levels of sensitized nerves.

In the peripheral sensitization, inflammatory mediators 
such as bradykinin, prostaglandins, and neurotrophins have 
been demonstrated to decrease the threshold of stimuli to 
external stimuli in peripheral nerves. Sensitized peripheral 
nerves react to stimuli that normally bring no activation. Mor-
phological change of peripheral nerve endings in inflamma-
tory lesions might also contribute to peripheral sensitization 
as has been shown in a previous study reporting the sprouting 
of peripheral nerves in patients with allodynia and hyperal-
gesia. Elevated levels of neurotrophins and nerve sprouting 
into the epidermis are also observed in patients with atopic 
dermatitis and contact dermatitis, indicating the involve-
ment of peripheral sensitization in alloknesis and hyperknesis.

Central sensitization is known to play a major role in 
allodynia and hyperalgesia. As mentioned above in relation 
NMDA, ongoing activation of C-neurons lowers thresholds of 
secondary neurons in the spinal cord. Consequently, signals 
that are not intense enough to activate secondary neurons and 
signals conducted through other peripheral nerves will also 
activate secondary neurons. In allodynia, for example, signals 
conducted through A-beta nerves, which normally induce 
touch sensation, cause pain sensation under central sensitiza-
tion. On the other hand, ongoing activation of C nerves in 
patients with chronic pruritus has also been reported. This im-
plicates that central sensitization is also involved in provoking 
alokkesis and hyperknesis. Moreover, continuous activation 
of C nerves by electrical stimulation and mechanical stimula-
tion that evokes itch has reportedly induced alloknesis and 
hyperknesis, suggesting that peripheral sensitization under 
inflammatory conditions is not always necessary for allokkesis 
and hyperknesis. Thus, combination of peripheral and central 
sensitization seems to be the explanation of itch sensitization.

A previous experimental study has shown that itch can be 
evoked in patients with atopic dermatitis even by mechanical, 
electrical, thermal and low-pH stimuli that normally evoke 
pain and suppress itch. This finding is consistent with the 
clinical feature of chronic pruritus such as atopic dermatitis 
that patients are often urged to keep scratching once they start it, suggesting that scratching does not only inhibit but also generate itch. On the other hand, pain sensitization causes a contrastive phenomenon. It has been reported that histamine induces pain rather than itch in patients with chronic pain. Thus, neural sensitization can give mediators a different role from their original one. Inflammatory mediators that normally induce pain can induce itch in atopic dermatitis due to itch sensitization. For instance, a previous study has shown that acetylcholine induces itch in patients with atopic dermatitis although otherwise pain. This has a therapeutic implication that not only pruritogens but also algogens need to be targeted to treat in order to combat itch in chronic pruritus associated with itch sensitization.

6. NEUROPATHIC ITCH

Injuries or damages in nerve fibers can cause spontaneous firing without external stimuli, resulting in pain or itch sensa-
tion. This type of pain and itch, called neuropathic pain/itch, is often seen in patients with herpes zoster after acute skin

inflammation has disappeared. Neuropathic pain/itch is often 
associated with central sensitization, such as allodynia, hy-
peralgesia, alloknesis and hyperknesis. The reason why some 
patients with herpes zoster suffer neuropathic pain whereas 
others neuropathic itch has not been clarified. Notalgia pares-
thetica and brachioradial pruritus also belong to neuropathic 
itch. Clinical effects of gabapentin and pregabalin for neu-
ropathic pain/itch are worth to note. Both of the drugs were 
developed as anti-epileptic drugs, and today are widely used 
for neuropathic pain. Their analgesic effects are likely to 
be based on their binding to the α2δ subunit of voltage-gated calcium channels, especially at the spinal cord level, which then inhibits pre-synaptic Ca²⁺ influx and decreases glutamate release and synaptic transmission. It is reasonable to guess that gabapentin and pregabalin might also be effective for neuropathic itch. Actually, some clinical studies have already demonstrated antipruritic effects of gabapentin and pregabali-

REFERENCES

1) Ikoma A, Steinhoff M, Ständer S, Yosipovitch G, Schmelz M. The 

2) Schmelz M, Schmidt R, Bickel A, Handwerker HO, Torbøjørk HE. 
Specific C-receptors for itch in human skin. J Neurosci., 17, 8003– 
8008 (1997).

3) Andrew D, Craig AD. Spinothalamic lamina I neurons selectively 
sensitive to histamine: a central neural pathway for itch. Nat. Neuro-

4) Sun YG, Zhao QZ, Meng XL, Yin J, Liu XY, Chen ZF. Cellular 

5) Wilson SR, Gerhold KA, Bifolck-Fisher A, Liu Q, Patel KN, Dong 
X, Bautista DM. TRPA1 is required for histamine-independent, 
Mas-related G protein-coupled receptor-mediated itch. Nat. Neuro-

6) Namer B, Carr R, Johanek LM, Schmelz M, Handwerker HO, 

7) Reddy VB, Iuga AO, Shimada SG, LaMotte RH, Lerner EA. Cow-
hage-evoked itch is mediated by a novel cysteine protease: a ligand 

8) Ikoma A, Handwerker H, Miyachi Y, Schmelz M. Electrically 

9) Kosteletzky F, Namer B, Forster C, Handwerker HO. Impact of 
scratching on itch and sympathetic reflexes induced by cowhage 
(Mucuna pruriens) and histamine. Acta Derm. Venereol., 89, 271– 
277 (2009).

10) Sikand P, Shimada SG, Green BG, LaMotte RH. Similar itch and no
ceptive sensations evoked by punctate cutaneous application of 

11) Seo YJ, Kwon MS, Shim EJ, Park SH, Choi OS, Suh HW. Changes 
in pain behavior induced by formalin, substance P, glutamate and 
pro-inflammatory cytokines in immobilization-induced stress 

12) Shimada SG, LaMotte RH. Behavioral differentiation between itch 

13) Fukuoka M, Miyachi Y, Ikoma A. Mechanically evoked itch in hu-

14) Cowden JM, Zhang M, Dunford PJ, Thurmond RL. The histamine 
H4 receptor mediates inflammation and pruritus in Th2-dependent 

15) Steinhoff M, Neisius U, Ikoma A, Fartasch M, Heyer G, Skov PS, 
Luger TA, Schmelz M. Proteinase-activated receptor-2 mediates 


40) Zhao M. Plasticity of NMDA receptor NR2B subunit in memory and chronic pain. Mol. Brain, 2, 4 (2009).

41) Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in...


