Potential New Therapeutic Targets for Pathological Pruritus

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Very few approved medications are indicated for the treatment of pruritus, and drug development for pruritic diseases is awaited. During the past two decades, progress has been made in understanding the molecular basis of the physiology and pathophysiology of pruritus. Newly identified potential targets for pathological pruritus include receptors (histamine H4 receptor, leukotriene B4 receptors, interleukin-31 receptor A, bombesin BB2 receptor, toll-like receptor 3, α-adrenoceptor, and opioid μ- and κ-receptors), channels (transient receptor potential (TRP) V3 and TRPA1 channels), and enzymes (histidine decarboxylase, sphingomyelin glucosylceramide deacylase, 5-lipoxygenase, leukotriene A4 hydrolase, and autotaxin). The development of specific, effective blockers and agonists/antagonists of these targets is awaited.

Key words pruritic disease; itch mediator; keratinocyte; primary sensory neuron; dorsal horn neuron; itch inhibitory system

Table 1. Potential New Therapeutic Targets for Pathological Pruritus

<table>
<thead>
<tr>
<th>Mediator/stimulant</th>
<th>Enzyme</th>
<th>Receptor/channel</th>
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</thead>
<tbody>
<tr>
<td>Periphery</td>
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<tr>
<td>Histamine (keratinocyte)</td>
<td>Histidine decarboxylase (keratinocyte)</td>
<td>H1 receptor (primary afferent)</td>
</tr>
<tr>
<td>Histamine (mast cell)</td>
<td>Histidine decarboxylase (mast cell)</td>
<td>H4 receptor (primary afferent, other cells)</td>
</tr>
<tr>
<td>Proteinase (mast cell, other cells)</td>
<td>Sphingomyelin glucosylceramide deacylase (keratinocyte)</td>
<td>PAR2 receptor (primary afferent, keratinocyte)</td>
</tr>
<tr>
<td>Sphingosylphosphorylcholine (keratinocyte)</td>
<td>5-Lipoxygenase and LTA4 hydrolase (keratinocyte)</td>
<td>BLT1 receptor (primary afferent)</td>
</tr>
<tr>
<td>LTB4 (keratinocyte)</td>
<td>5-Lipoxygenase and LTA4 hydrolase (mast cell)</td>
<td>BLT2 receptor (T lymphocyte)</td>
</tr>
<tr>
<td>LTB4 (mast cell)</td>
<td>Autotaxin (liver?)</td>
<td>Not determined (primary afferent, keratinocyte)</td>
</tr>
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<td>Lysophosphatic acid (blood)</td>
<td></td>
<td>Interleukin-31 receptor A and oncostatin M receptor (primary afferent, keratinocyte)</td>
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<tr>
<td>Interleukin-31 (T lymphocyte)</td>
<td></td>
<td>TRPV3 (primary afferent, keratinocyte)</td>
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<tr>
<td>Warm temperature?</td>
<td></td>
<td>TRPA1 (primary afferent)</td>
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<tr>
<td>Oxidant</td>
<td></td>
<td></td>
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<tr>
<td>Dorsal horn</td>
<td></td>
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<tr>
<td>GRP (sensory neuron, dorsal horn neuron)</td>
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<td>BB2 receptor (dorsal horn neuron)</td>
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<tr>
<td>Noradrenaline (descending neuron)</td>
<td></td>
<td>Toll-like receptor 3 (sensory neuron)</td>
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LTA4, leukotriene A4; LTB4, leukotriene B4; GRP, gastrin-releasing peptide.

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an important site of action of antipruritic drugs. Here I review the molecular targets that have been shown to be associated with pathological pruritus (Table 1).

2. TARGETS IN THE PERIPHERY

2.1. Histamine and Histidine Decarboxylase

Histamine is a major itch mediator associated with mast cell-mediated acute responses in the skin and conjunctiva. Histamine H1 receptor antagonists and mast cell stabilizers are usually used to treat itching in immediate allergy. In animal experiments, H1 receptor antagonists exert a significant, although partial, inhibition of the itch-related response, hind-paw scratching, to passive cutaneous anaphylaxis and immediate pollen allergy in the conjunctiva.2,3

Single topical application of sodium laurate, an alkaline surfactant, induces delayed scratching in mice, although topical application of a neutral surfactant or sodium hydroxide solution does not induce delayed scratching.4 Sodium laurate-induced delayed scratching is almost completely inhibited by a histamine H1 receptor antagonist, but it is not affected by deficiency in mast cells.5 In the normal skin, histamine is mainly present in mast cells in the dermis and a trace of histamine is present in the epidermis. Topical application of sodium laurate increases histamine production in the epidermal keratinocytes, which may be due to enhanced processing of 74-kDa to 53-kDa histidine decarboxylase, the latter of which is a key enzyme for histamine production, in the epidermal keratinocytes.6 Since there are no histamine-containing granules in the keratinocytes and histamine is spontaneously released without being stored, histidine decarboxylase is also a potential target for the prevention of alkaline surfactant-induced delayed itching. Consistent with this view, sodium laurate-induced delayed scratching is inhibited by the topical application of agents that suppress the increase in 53-kDa histidine decarboxylase in the keratinocytes.7

Binding affinities of histamine H1 and H2 receptors for histamine are much higher than those of histamine H3 and H2 receptors.8,9 Intradermal injections of H2 receptor agonists increase scratching behaviors in mice, but it remains unknown whether the H2 receptor is involved in pathological itching. Systemic administration of a histamine H2 receptor antagonist reduces scratching induced by allergic dermatitis and passive cutaneous anaphylaxis in mice.10 Intradermal injection of an H2 receptor agonist elicits scratching, which is markedly inhibited by an H2 receptor antagonist and H2 receptor deficiency.9 Histamine-independent scratching is also inhibited by an H2 receptor antagonist.10,11 Thus, the histamine H2 receptor in the periphery and/or central nervous system is a potential target for pruritic diseases.

2.2. Proteinases and Proteinase-Activated Receptor 2 (PAR2)

Proteinases (endopeptidases), but not exopeptidases, have long been known to cause itching when injected intradermally in humans.12 Pruritogenic mechanisms of proteinases include the activation of the PAR-1,13,14 the degranulation of mast cells,15–17 and the production of pruritogenic peptides.18,19 The proteinase receptor PAR2 may be involved in itching and scratching in atopic dermatitis,18,19 urticaria,18,20,21 dermatophyte infection,20,31 and contact with cowhage seed pod.20 Some mast cells in the human skin express PAR2, the stimulation of which results in histamine release.20,21 However, histamine does not play an important role in proteinase receptor PAR2-mediated scratching in mice,16 and separate sensory neurons may play a role in histamine- and proteinase receptor-mediated itching.22–28 The responses of dorsal horn neurons to intradermal injection of a PAR2 agonist, but not histamine, are enhanced under dry skin conditions.29 Tryptase, a PAR2 agonist proteinase, increases in mast cells in the lesional skin of chronic dermatitis.20,21 Thus, the proteinase receptor PAR2 is a potential therapeutic target for pruritic diseases, including H1 antagonist-resistant dermatitis. Proteinases are involved in itching in several pruritic diseases. However, it may be difficult for specific proteinase inhibitors to inhibit itching in a broad spectrum of pruritic diseases because there are many types of pruritogenic proteinases.

2.3. Lipid Mediators

Stratum corneum lipids, especially ceramides, play a pivotal role in maintaining the water barrier of the skin. Ceramides are produced from sphingomyelin and glucocerebroside by sphingomyelinase and glucocerebrosidase, respectively, in the stratum corneum and the superficial layers of the epidermis. In patients with atopic dermatitis, the amount of ceramide in the stratum corneum decreases, and there is an inverse correlation between ceramide and sphingosylphosphorylcholine (SPC) levels in the lesional stratum corneum.30 In the epidermis of patients with atopic dermatitis, the activity of sphingomyelin glucosylceramide deacylase is increased, and sphingomyelin and glucocerebroside are converted to SPC and glucosylsphingosine, respectively, by this enzyme, which results in the decrease in ceramide, leading to skin dryness and the disruption of the skin barrier.30 SPC downregulates filaggrin gene transcription, which also leads to skin dryness and the disruption of the skin barrier.31 SPC is also increased in the lesional epidermis of mice with chronic allergic dermatitis.32 Intradermal injection of SPC, but not of sphingomyelin and sphingosine, elicits scratching in mice.32–34 SPC may act on the epidermal keratinocytes, dendritic cells, primary sensory neurons, and mast cells in the skin.33–36 Naturally occurring δ-erythrob SPC, but not ω-three SPC, induces scratching after intradermal injection, raising the possibility that SPC acts on a specific receptor to induce itching.31 However, SPC receptors remain unclear, although some candidates were reported. It is expected that the suppression of the increased activity of sphingomyelin glucosylceramide deacylase results in not only the decrease in SPC (relieving itch) but also the increase in ceramides in the stratum corneum and epidermis (improving skin dryness and barrier disruption) in patients with atopic dermatitis. Therefore, sphingomyelin glucosylceramide deacylase is a more attractive therapeutic target for SPC-mediated itching in atopic dermatitis.

SPC acts on keratinocytes to produce leukotriene (LT) B4, which is involved in SPC-induced scratching.34 LT B4 elicits hind-paw scratching at relatively low doses after administration to the skin and conjunctiva in mice.35,37 LT B4 was shown to be involved in scratching in mice with chronic allergic dermatitis and allergic conjunctivitis.3,32,38 but not in those with acute cutaneous allergy.39 There are two LT B4 receptor subtypes, BLT1 and BLT2, which have high and low binding affinities for LT B4, respectively.40 The BLT1 receptor is expressed mainly in leukocytes, and the BLT2 receptor is expressed more ubiquitously.40 Dorsal root ganglion neurons, mainly transient receptor potential (TRP) VI-positive small neurons, express the BLT1 receptor, and LT B4 administration
increases intracellular Ca\(^{2+}\) ions in cultured dorsal ganglion neurons.\(^{43}\) When LTB\(_4\) production is localized in the epidermis (e.g., dermatophyte infection), BLT\(_1\) receptors on primary afferents may be involved in LTB\(_4\)-mediated itching. LTB\(_4\) synthesis is catalyzed by 5-lipoxygenase and LTA\(_4\) hydrolase. Scratching induced by passive cutaneous anaphylaxis is suppressed by an LTA\(_4\) hydrolase inhibitor, suggesting that mast cell-derived LTB\(_4\) is involved in itching.\(^{45}\) When LTB\(_4\) is produced in the dermis (e.g., mast cells), it may act as a leukocyte chemoattractant via BLT\(_2\) receptor stimulation, and leukocyte-released superoxide may induce itching.\(^{46}\) Nonelective LTB\(_4\) antagonists are more desirable than the selective BLT\(_1\) or BLT\(_2\) antagonists because both BLT\(_1\) and BLT\(_2\) receptors can be involved in LTB\(_4\)-mediated itching. A 5-lipoxygenase inhibitor relieves pruritus in Sjögren–Larsson syndrome\(^{44}\) and has a tendency to improve pruritus in atopic dermatitis.\(^{45}\) In animal experiments, a 5-lipoxygenase inhibitor inhibits scratching in mice with acute ocular or cutaneous allergy and chronic allergic dermatitis.\(^{33,38,39}\) Thus, 5-lipoxygenase and LTA\(_4\) hydrolase are also potential therapeutic targets for pruritus in allergic inflammation.

Intradermal injection of 12(S)-hydroperoxyeicosatetraenoic acid, a 12-lipoxygenase metabolite, induces scratching with a potency similar to that of LTB\(_4\).\(^{40}\) This action has been shown to be mediated by the BLT\(_2\) receptor.\(^{47}\)

Lysophosphatidic acid is a phospholipid mediator with many biological functions and disease implications. Lysophosphatidic acid is produced both in cells and biological fluids; it is predominantly produced by autotaxin (lysophospholipase D), a plasma enzyme in the blood.\(^{48}\) The serum levels of autotaxin activity and autotaxin protein are enhanced, and there is a significant correlation between the intensity of itch perception and serum autotaxin activity in patients with pruritic cholestasis.\(^{49}\) Biliary drainage treatment relieves cholestatic pruritus and serum autotaxin activity.\(^{49}\) The serum levels of histamine, tryptase, substance P, \(\mu\)-opioid activity, and bile salt are not correlated with the intensity of itch perception.\(^{49}\) Intradermal injection of lysophosphatidic acid induces scratching in mice.\(^{49,50}\) Autotaxin activity in the serum is not increased in patients with other pruritic diseases, such as uremia, Hodgkin’s disease, or atopic dermatitis.\(^{51}\) These findings raise the possibility that lysophosphatidic acid and autotaxin are potential therapeutic targets for cholestatic pruritus.

2.4. Cytokines Interleukin (IL)-31 is preferentially produced by activated CD4\(^+\) T cells. IL-31 transgenic mice show severe scratching and skin lesions.\(^{52}\) Subcutaneous infusion of IL-31 protein using a mini-osmotic pump also increases scratching.\(^{52}\) IL-31 mRNA increases in the skin of patients with atopic dermatitis\(^{53,54}\) and mice with chronic allergic dermatitis.\(^{55}\) Repeated intraperitoneal injections of anti-IL-31 monoclonal antibody decrease scratching behavior in mice with chronic allergic dermatitis.\(^{56}\) These findings taken together suggest that IL-31 is involved in promoting pruritus in chronic allergic dermatitis, especially atopic dermatitis. IL-31 signaling occurs through a functional complex of IL-31 receptor A with the oncostatin M receptor. Although oncostatin M receptor expression is ubiquitous, IL-31 receptor A has much higher expression in the dorsal root ganglia compared with other tissues.\(^{51}\) Oncostatin M receptor is expressed mainly in the nonpeptidergic unmynelinated sensory neurons,\(^{57}\) and IL-31 receptor A is expressed in the small-sized neurons expressing oncostatin M receptor.\(^{58}\) Therefore, it is possible that IL-31 acts on pruriceptive primary afferents as an itch mediator. However, since the stimulation of toll-like receptor 2 upregulates IL-31 receptor A with oncostatin M receptor in cultured human keratinocytes,\(^{59}\) epidermal keratinocytes may also play a role in IL-31-mediated itching in atopic dermatitis. Thus, IL-31 and IL-31 receptor A may be potential therapeutic targets for pruritus in atopic dermatitis.

2.5. Channels Primary sensory neurons expressing TRPV1 channels play an important role in itch signaling.\(^{60}\) TRPV1 channels are indispensable to current generation following the stimulation of itch-related G-protein-coupled receptors. Histamine stimulation of H\(_1\) receptor produces TRPV1 currents through the phospholipase A\(_2\)-12-lipoxygenase and phospholipase C\(\beta\) signaling systems.\(^{60,61}\) Similarly, proteinase stimulation of the PAR\(_2\) receptor produces TRPV1 currents through a phospholipase C–protein kinase C pathway.\(^{62}\) Therefore, TRPV1 channel blockers may relieve itching in a broad spectrum of pruritic diseases. However, the TRPV1 channel may not be an adequate therapeutic target for pruritic diseases because it plays a key role in sensing heat pain, and systemic administration of TRPV1 channel blockers may suppress the withdrawal reflex induced by noxious heat stimulation.

The TRPV3 channel is activated at innocuous warm temperature and is expressed in primary sensory neurons and keratinocytes.\(^{63,64}\) A gain-of-function mutation in the TRPV3 channel causes spontaneous scratching and dermatitis in mice.\(^{65}\) In contrast, a deficiency of the TRPV3 channel suppresses spontaneous scratching in mice with skin dryness, without affecting cutaneous barrier disruption and a decrease in stratum corneum hydration.\(^{66}\) Thus, the TRPV3 channel may be a potential therapeutic target for pruritus of xero-derma.

TRPA1 channels are expressed in a subset of TRPV1-positve sensory neurons and are involved in cold sensing.\(^{67,68}\) The TRPA1 channel has been shown to be involved in itch signaling. For example, chloroquine (an antimalaria drug) and bovine adrenal medulla peptide 8–22 (a pruriceptive opioid peptide) act on Mas-related G protein-coupled receptor (Mrgpr) A3 and MrgprC11, respectively, on primary sensory neurons to induce scratching in mice, and TRPA1 is required for the Mrgpr-mediated signaling.\(^{69}\) TRPA1 currents are sensitized by PAR\(_2\) receptor stimulation.\(^{70}\) TRPA1 has been shown to be involved in oxidant-induced scratching.\(^{71}\) Although the TRPA1 channel seems to be an interesting target for pruritus, it remains unknown whether it is involved in pathological pruritus.

3. TARGETS IN THE CENTRAL NERVOUS SYSTEM

3.1. Itch Transmitters Neuromedin B and gastrin-releasing peptide (GRP), mammalian homologues of amphibian bombesin, have high binding affinities for bombesin BB\(_1\) and BB\(_2\) receptors, respectively. GRP is expressed in a small subset of peptidergic primary afferent neurons and a subset of neurons in the superficial dorsal horn.\(^{72,73}\) Intrathecal administration of a bombesin-saporin conjugate produces the selective ablation of BB\(_2\) receptor-expressing spinal neurons, without effect on BB\(_1\) receptor-expressing spinal neurons.\(^{74}\) This treatment markedly reduces scratching responses to intradermal
injections of many pruritogenic substances such as histamine, compound 48/80, serotonin, endothelin-1, PAR2 agonist, and chloroquine.75 BB2 receptor mutation and intrathecal injection of a BB2 receptor antagonist reduce scratching responses of mice to intradermal injections of compound 48/80, PAR2 agonist, and chloroquine, whereas these manipulations do not affect pain responses.76 Serum levels of GRP correlate with the itching score in patients with atopic dermatitis.76 GRP-positive nerve fibers are increased in the skin of patients with atopic dermatitis and mice with chronic allergic dermatitis,76,77 and GRP released from primary afferents may degranulate mast cells.78 GRP and BB2 receptor seem to be interesting targets for pruritus, although their roles in pathological pruritus remain unclear. In addition, glutamate rather than GRP has been shown to be the principal excitatory transmitter between C-fiber primary afferents and BB2 receptor-expressing dorsal horn neurons.79 Neuromedin B is mainly expressed in small-sized sensory neurons.72 Intracerebroventricular injections of neuromedin B (and of GRP) elicits scratching in rats,80 but intrathecal injection of neuromedin B elicits pain-like behaviors.81 Toll-like receptors mediate innate immune responses and recognize pathogen-associated molecule patterns. Although toll-like receptors are mainly expressed by immune cells, some members are expressed in primary sensory neurons and have been shown to be implicated in itching. Toll-like receptor 3 is expressed in a subset of small-sized dorsal root ganglion neurons that are positive for GRP and the TRPV1 channel.82 A deficiency of toll-like receptor 3 reduces scratching responses to compound 48/80 and chloroquine and spontaneous scratching in mice with dry skin.83 Toll-like receptor 3 deficiency inhibits long-term potentiation in the dorsal horn neurons, suggesting involvement in the regulation of central sensitization.83 Toll-like receptor 7 has been implicated in itching induced by imiquimod, an immune response modifier.83

3.2. Itch-Inhibitory System

Itch perception is suppressed by various stimuli from the external environment; for example, itching is inhibited by counterstimuli including noxious stimuli, innocuous vibration, and warming stimulation applied to the itching area and vibration of the opposite side of the body.84,85 Distraction with noncontact stimulation also inhibits itching in humans86 and scratching behaviors in mice.87,88 These findings suggest the presence of itch-inhibitory systems in the central nervous system.

Subpopulations of wide dynamic range neurons and nociceptive-specific neurons in the superficial dorsal horn mainly receive itch signals from the periphery.89-91 Histamine-evoked firing of primate spinothalamic tract neurons and murine superficial dorsal horn neurons is inhibited by scratching of the skin.92,93 The spontaneous activity of superficial dorsal horn neurons increases in mice with chronic dry skin, and the increased activity is also suppressed by scratching.94 This suppression is blocked by local administration of antagonists of glycine or γ-aminobutyric acid.94 and a subset of inhibitory interneurons in the dorsal horn is involved in the inhibitory regulation of itching.95 The scratching-induced suppression is inhibited by cold block and spinal transection at the upper spinal cord level, suggesting that this suppression is regulated by the descending inhibitory system.94

Depletion of noradrenaline in the spinal cord enhances scratching behaviors induced by acute allergy and pruritogen injection in mice.96,97 Intrathecal injection of a nonselective α-1-adrenoceptor antagonist, but not of selective α1- or α2-adrenoceptor antagonists, also enhances the scratching behaviors.96,98 These findings suggest that the descending noradrenergic system exerts tonic inhibition on itch signaling in the spinal cord. Both α1- and α2-adrenoceptor antagonists act on the spinal cord to inhibit pruritogen-induced scratching.97,98 Thus, the descending noradrenergic system and α1,2-adrenoceptors in the spinal cord are potential therapeutic targets for pruritus treatment.

3.3. Opioids

An adverse effect of opioid analgesics (μ-opioid receptor agonists) includes pruritus, which is relieved by opioid μ-receptor antagonists.99 Opioid μ-receptor antagonists have been used in the treatment of pruritus in dermatologic and systemic diseases.100 Nalfurafine, a selective opioid κ-receptor agonist, has recently been approved for the treatment of chronic uremic pruritus in Japan.101 Thus, opioid μ- and κ-receptors are potential therapeutic targets for pruritus. In the spinal cord, the opioid μ-receptor isoform MOR1D heterodimerizes with the bombesin BB2 receptor, and the stimulation of MOR1D by morphine produces an effect similar to the stimulation of the BB2 receptor.102 Analgesia induced by intracisternal injection of morphine is antagonized by naloxonazine, an opioid μ1-receptor antagonist, but scratching induced by intracisternal morphine is not inhibited by naloxonazine.103 These opioid μ-receptor subtypes are potential therapeutic targets for pruritus.

4. CONCLUSION

Very few approved medications are indicated for the treatment of pruritus. There are no uniformly effective interventions to treat itching in all pruritic diseases, because no single mediator or mechanism is responsible for all pruritus. Therefore, precise information is needed on the details of the mechanisms of itching in pruritic diseases. During the past two decades, progress has been made in understanding the molecular basis of the physiology and pathophysiology of pruritus, although further research is needed. Specific, effective blockers and agonist/antagonists of newly identified targets are indispensable to corroborate their significance in the treatment of pathological pruritus, and their development is awaited.

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