The cell biology of acute itch

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Itch, the irritation we feel and the relief that comes from scratching, is an evolutionary warning system and defense against harmful environmental agents. Although once considered a subtype of pain, itch is now recognized as a unique sense, with its own distinct physiology and cell receptors. Here, we discuss recent advances in our understanding of itch and the molecular players that mediate this sensory modality.

Introduction

The average human is covered in 1.8 to 2.0 m² of skin (Ogden et al., 2004). With such a large surface area, a sensory modality we call itch has evolved to alert us to potentially dangerous external stimuli. Unlike the sensation of pain, where an organism will actively try and withdraw from an unpleasant stimulus, itch compels the affected to seek out the source and respond with a scratch. Acute itch serves us well in guarding against environmental threats; however, chronic or severe itch (pruritus) is a burdensome illness that affects millions every year (Nutten, 2015). Fortunately, great strides have been made over the past few decades in understanding the cellular biology that underlies both acute and chronic itch, providing hope for new medical treatments.

Compared with its sensory cousin, pain, the understanding of itch is still nascent. New discoveries within the past few years have brought excitement, however. Work uncovering receptors, agonists, and the interplay of different cell types has begun to widen the field and offer new avenues for study. In this review, we will look at the cell biology of itch, with an emphasis on the receptors, cell types, and pruriceptors that are involved in the processing of itch, focusing on the periphery and how itch is coded in the spinal cord.

The peripheral components of itch

Histaminergic peripheral neurons. Histamine was first used at the turn of the previous century to study skin vasculature. Application of histamine to the skin produces what cardiologists termed the triple response, with redness, flare, and swelling around the site of histamine injection (Lewis, 1926). Along with these noted changes in vasculature, histamine also produces itch (Simone et al., 1987), and many itch-inducing stimuli, such as insect bites (Horsmanheimo et al., 1996), are mediated through the endogenous release of histamine. A variety of cell types are capable of producing histamine, including mast cells, keratinocytes, and neurons.

There are four known histamine receptor subtypes, H1R, H2R, H3R, and H4R, and all are bound to G proteins (G protein–coupled receptors [GPCRs]) (Strasser et al., 2013). H1R is coupled to Gq proteins, where the ligand-bound receptor leads to activation of the phospholipase C and phosphatidylinositol signaling pathways, with a consequent rise in intracellular calcium. Subsequent effects of H1R activation are cell type dependent. Histamine release can activate a subset of peripheral sensory neurons, as peripheral blockade eliminates itch (Shelley and Melton, 1950; Roberson et al., 2013). Activated pruriceptors release neuropeptides, such as substance P and calcitonin gene–related peptide (CGRP; McCoy et al., 2013), 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 (Andoh et al., 1998), further studies in human skin using microdialysis showed little effect at physiological concentrations (Weidner et al., 2000).

Early efforts in drug discovery found that antihistamines are effective antipruritic agents and work by competing with histamine for its endogenous receptor (Wells et al., 1945). Studies with histamine receptor subtypes, H2R and H3R, have yet to reveal a role for either in itch. Both are expressed in a variety of tissue types, where activation of H2R on parietal cells causes gastric acid secretion, and H3R expression in the central nervous system is involved in neurotransmitter release (Black et al., 1972; Morisset et al., 2000). As for H4R, more recent evidence has shown some early success with H4R antagonists in treating inflammatory diseases, including chronic pruritus (Dunford et al., 2007; Thurmond et al., 2008). Histamine has been implicated in a host of diseases involving itch. Studies with patients suffering from atopic dermatitis found a 60% increase in skin histamine levels compared with normal patients’ skin (Johnson et al., 1960). Similarly, histamine was also found to be elevated in some patients suffering from chronic urticaria, a condition marked by an itchy rash and more commonly referred to as hives (Phanuphak et al., 1980).

Initial work by physiologists trying to elucidate the peripheral afferents responsible for itch proposed that itch was a
modified form of pain (Von Frey, 1922). Low-level activation of nociceptors would produce itch, whereas higher intensities would evoke pain. This intensity hypothesis, whereby pain and itch are coded by the same nociceptors, has lost ground to studies providing evidence for specific C-fibers that encode itch. Experiments using increasing amounts of electrical stimulation of nonglabrous skin in humans found concurrent increases in itch intensity (Tuckett, 1982) with no reported changes in pain ratings. Similar studies looking at pain and itch modulation using mustard oil or histamine saw distinct effects, where pain could not be converted to itch or vice versa (Handwerker et al., 1991).

The selectivity model, whereby a subset of neurons are selective for itch but also capable of algogenic responses, has recently garnered support (Schmelz et al., 2003). Two studies found that vesicular glutamate transporter 2 (VGLUT2) plays an important role in modulating both itch and pain (Lagerström et al., 2010; Liu et al., 2010). Deletion of the gene for VGLUT2 in mice resulted in a decrease in both pain but was accompanied by a marked increase in basal itch behavior, with adult mice displaying skin lesions caused by increased scratching (Lagerström et al., 2010). However, this enhanced itch behavior could be reduced with antihistamines, implicating histamine in the transmission of VGLUT2-regulated itch. Loss of VGLUT2 led to hypersensitivity to multiple pruritogens, including mast cell activator compound 48/80 (Liu et al., 2010). Interestingly, injection of capsaicin in VGLUT2 knockout (KO) mice evoked itch rather than pain. This phenotypic switch in behavior points to VGLUT2 contributing to pain transmission, whereas its loss leads to disinhibition of itch in these neurons (Liu et al., 2010).

Nonhistaminergic itch. The flare that follows neuropeptide release is a hallmark of histamine-induced itch. However, another well-known pruritogen is the tiny hairs or spicules derived from the plant cowhage (Mucuna pruriens). Cowhage is capable of producing a strong dose-dependent itch in animals and humans without any vasodilation. The active component of cowhage spicules is the proteinase mucunain (Shelley and Arthur, 1955; Reddy et al., 2008). Unlike histamine, cowhage spicules activate mechanoreceptive polymodal C-fibers in humans (Johane et al., 2007; Namer et al., 2008). These experiments, along with those done in animal models (Tuckett and Wei, 1987; Johane et al., 2008), provide evidence that cowhage and histamine activate separate and distinct populations of C-fibers.

Cowhage has more recently been used to explore Aδ fiber–mediated itch. Unlike C-fibers, Aδ fibers are thinly myelinated, possess a higher conduction velocity, and along with pain are thought to transmit mild pressure and cold sensations. Interestingly, selective blockade of Aδ fibers has no effect on capsaicin-induced pain and only a minor effect on histamine-induced itch, whereas cowhage-induced itch is almost completely lost (Ringkamp et al., 2011), revealing the complexity of peripheral pruritceptive neurons.

A GPCR family defines a class of histamine-independent itch receptors. Mas-related G protein–coupled receptors (Mrgrps) comprise a group of ~50 GPCRs expressed primarily in dorsal root and trigeminal ganglia (Dong et al., 2001). Four families of Mrgrps have been shown to play a role in itch: MrgrpA, MrgrpB, MrgrpC, and MrgrpD. Although histamine– and compound 48/80–induced itch was maintained in Mrgrp cluster KO animals, scratching behavior caused by the antimalarial drug chloroquine and bovine adrenal medulla 8-22 peptide was significantly reduced (Liu et al., 2009). Further experiments, using heterologous expression systems, identified MrgrpA3 and its human homolog MrgrpX1 as the receptor mediating chloroquine itch and MrgrpC11 as the receptor activated by bovine adrenal medulla 8-22 (Liu et al., 2009).

The peptide SLIGRL-NH2, a synthesized unmasked N terminus (tethered ligand) of protease-activated receptor 2 (PAR2), can result in robust itch when injected into animals and humans, pointing to PAR2 as a target for itch studies (Steinhoff et al., 2003; Shimada et al., 2006). More recently, however, SLI GRL was identified as an agonist specific for MrgrpC11 (Liu et al., 2011a). Liu et al. (2011a) demonstrated comparable scratching behavior between wild-type and PAR2 KO mice. Moreover SLIGRL elicited very little scratch behavior from MrgrpC11 KO mice, supporting its role as the primary receptor for SLI GRL. Although activated by distinct agonists, both MrgrpA3 and MrgrpC11 have been shown to rely on transient receptor potential cation channel ankyrin 1 (TRPA1) to transduce itch (Wilson et al., 2011). Further work with Mrgrps has implicated MrgrpD in mediating the itch and pricking sensation found after consumption of the sports supplement β-alanine (Liu et al., 2012). These findings point to the important role the Mrgrp family has in contributing to itch.

The discovery of Mrgrps has also provided additional evidence for the labeled line theory of itch, whereby dedicated itch-specific pruritogenic fibers transmit information to the spinal cord. Using a mouse line in which the transient receptor potential cation channel vanilloid 1 (TRPV1) was knocked out, Han et al. (2013) reintroduced TRPV1 via an MrgrpA3 driver. When the potent TRPV1 agonist capsaicin was injected, scratching was observed but not nociceptive behavior. As TRPV1 was expressed only on MrgrpA3+ neurons, this result demonstrated that MrgrpA3+ neurons are selective for itch and not pain. Moreover, when these MrgrpA3+ neurons were ablated, itch behavior was reduced but thermal and mechanical allodynia was maintained.

Identifying populations of itch neurons. In an elegant paper using an unbiased sampling of single-cell RNA-sequenced lumbar dorsal root ganglia (DRG) neurons, Usoskin et al. (2015) found 11 different expression classes comprising four distinct clusters of neurons. One cluster of nonpeptidergic (NP) nociceptors appears to play a role in pruritus because of its expression of a wide assortment of itch receptors. This cluster was identified based on unique expression of Plexin C1, purinergic receptor 3, the neurotrophin receptor tyrosine kinase, CGRP, and somatostatin.

Surprisingly, the study found low levels of histamine receptor expression across the NP cluster, with only NP2 (9%) and NP3 (8%) at detectable levels for H1. However, Mrgrps were found to have expression overlap with histamine-positive NP clusters. Moreover, Mrgrps had high expression overlap with TRPA1 (51% NP1) and TRPV1 (58% NP3), known downstream mediators of Mrgrp and histaminergic itch, respectively (Imamachi et al., 2009; Wilson et al., 2011). Cytokine receptors Oncostatin M and interleukin (IL)-31 were highly expressed (75% and 58%, respectively) on the NP3 cluster, implicating this cluster as associated with inflammatory itch. Collectively, the data in this study provide further evidence demonstrating distinctive types of itch neurons in the somatosensory system.

Nonneuronal cell biology of itch

Keratinocytes. As the primary cell type found in skin, keratinocytes are capable of producing a variety of defenses against
pathogens. In response to noxious stimuli, keratinocytes can release a host of inflammatory mediators, including nerve growth factor, IL-6, and serotonin, sensitizing peripheral neurons (Luo et al., 2015). Keratinocytes have also been shown to directly activate neurons via the release of the cytokine thymic stromal lymphopoietin, triggering itch behavior (Fig. 1; Wilson et al., 2013). Keratinocytes interact with the immune system via the release of chemoattractants, such as monocyte chemoattractant protein 1, chemokine ligand 5, and IL-8, recruiting immune cells to the site of injury or pruritogenic stimuli. These chemoattractants were found to be elevated in patients with atopic dermatitis and psoriasis, implicating keratinocytes in the pathology of itch (Giustizieri et al., 2001).

**Mast cells.** Unlike other granulocytes that freely circulate in the bloodstream, mast cells reside in connective tissue. Their location and function as sentinel cells allow for interaction with other cell types, including keratinocytes, sensory neurons, and vascular epithelium (Fig. 1; Galli et al., 2011). Mast cells and their products are best known for their association with IgE-mediated allergic disorders, including itch, eczema, rhinitis, and asthma. Three broad categories of mediators are capable of being released from activated mast cells in a time-dependent manner. These include preformed mediators (histamine, tryptase, serotonin), lipid mediators (leukotrienes and prostaglandins, released within minutes), and cytokines, chemokines, and growth factors (IL-6, chemokine ligand 5, nerve growth factor, and VEGF, hours after activation; Theoharides et al., 2015). As the primary reservoir of histamine in the skin, drugs targeting mast cells, including mast cell stabilizers, are effective in treating itch- and allergen-induced asthma, conjunctivitis, and mastocytosis (Horan et al., 1990). More recently, our laboratory identified a novel mast cell–specific receptor, Mas-related G protein–coupled receptor B2 (MrgprB2), and its human ortholog, MrgprX2, in pseudo-allergenic activation of mast cells (McNeil et al., 2015), opening up a new target in the treatment of mast cell–related disorders.

**The central components of itch.** Pain and itch are distinct sensations. Early studies saw itch as a subset of pain, where sensory neuron firing frequency could distinguish itch from pain. However, more recent work points to a labeled line theory in which itch has a distinct population of spinal neurons that encode itch.

The dorsal horn of the spinal cord receives sensory input from the periphery, including pain and itch, and is divided into distinct layers, or laminae. The C- and Aδ fibers that transmit pain and itch terminate in lamina I and II of the dorsal horn. Compared with the study of peripheral afferents, the cell biology underlying spinal pruriceptors is still emerging. Work using recordings from cat spinal cord identified neurons in the spinothalamic tract (STT) that were selective to activation by histamine (Andrew and Craig, 2001). The STT is home to many second-order neuron types, connecting the dorsal horn to the thalamus. Studies of histamine-responsive STT neurons showed them to have low conduction velocity, with no spontaneous activity, and projections to lateral thalamic nuclei, properties that are markedly different from both nociceptive spinal and wide-dynamic-range neurons (Andrew and Craig, 2001).

The findings outlined earlier in this review offer evidence for separate histamine and cowhage projections to the dorsal horn. Studies examining dorsal horn neurons have also uncovered distinct histamine- and cowhage-responsive populations of neurons in the STT (Fig. 2). Antidromic stimulation, in which axon conduction occurs opposite of the normal direction, was used to identify a population of STT neurons when histamine and cowhage was applied to their receptive field (Davidson et al., 2012). STT recordings found that 20% of neurons responded to histamine and 13% responded to cowhage, with only 2% of neurons responding to both. 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.

**STT neurons and the scratch reflex.** Scratching in response to histamine injection has been shown to reduce spinal neuronal activity in mice (Akiyama et al., 2012). In primates, scratching of cutaneous receptive fields results in consistent STT neuronal firing. However, in histamine-evoked scratching, the opposite has been found, where recordings from these same STT neurons exhibited a reduction in action potential discharge (Davidson et al., 2009). In studies of human...
subjects, histamine-evoked itch can be reduced via scratching the receptive field, but with a recovery in itching minutes later (Yosipovitch et al., 2007). Consistent with the human data, Davidson et al. saw a similar rebound of firing in primate STT neurons after scratching had ceased (Davidson et al., 2009). The switch to an inhibitory phenotype in STT neurons was dependent on histamine, as scratching caused by capsaicin injection only increased their firing. These results suggest that activation of prurinergic fibers is required for the relief one finds in scratching an itch.

Gastrin-releasing peptide. Further evidence for a distinct itch pathway has been provided by the identification of gastrin-releasing peptide (GRP) and its receptor (GRPR) as transducers of itch. Early work with GRP homologs bombesin and neuregulin B found both to produce scratching behavior when injected intrathecally (Gmerek and Cowan, 1983; Van Wimersma Greidanus and Maigret, 1991). Their human ortholog, the neuropeptide GRP, was first identified as mediating the release of gastric acid in the stomach. The GRPR is highly expressed in the stomach, as well as the pancreas and central nervous system, where receptor activation plays a role in modulating circadian rhythms. Studies in mice revealed expression of GRP in small- and medium-diameter dorsal root ganglia containing CGRP and substance P (Sun and Chen, 2007). These GRP+ fibers terminated in lamina I and II of the dorsal horn, whereas no GRP was detected in the spinal cord. However, Sun and Chen (2007) saw GRPR expression in lamina I and II of the dorsal horn, and scratching behavior was reduced in mice lacking GRPR. Interestingly, responses to noxious thermal and mechanical stimuli were unchanged in GRPR KO mice, with no deficits seen in motor activity, indicating that GRPR is not involved in pain transduction (Sun et al., 2009).

Itch after morphine treatment has long been reported in the clinic, with spinal application providing robust pruritus (Hales, 1980). Opioids provide pain relief by activating the µ-opioid receptor (MOR), leading to presynaptic γ-aminobutyric acid release, decreasing neuronal hyperexcitability (Kieffer, 1999). It was thought that pain inhibition unmasks itch signals in the spinal cord, as pain has been shown to reduce itch behavior. This selectivity hypothesis has been brought into question with the finding that morphine activates a subset of spinal neurons expressing a heteromer of the G protein–coupled receptor consisting of MOR and GRPR subunits (Liu et al., 2011b). This MOR1D–GRPR complex was located primarily in lamina I of the spinal cord. Furthermore, loss of GRPR had no effect on morphine-induced analgesia, nor did MOR inhibition effect GPR-induced scratching. This study provided proof for the direct action of MOR on itch behavior while providing more evidence for the role of GRPR as an itch receptor.

B-type natriuretic polypeptide. A more recent article identified another neuropeptide that plays a role in the transmission of itch in the spinal cord. Earlier work with TRPV1-deficient mice had shown deficits in scratching behavior when exposed to many different pruritogens (Mishra et al., 2011). Because of this finding, Mishra and Hoon (2013) used a differential microarray–based screen and found the neuropeptide B-type natriuretic polypeptide (BNP) selectively expressed in TRPV1+ and MrgrPA3/C11+ DRG neurons. When BNP was injected intrathecally, mice displayed a robust itch phenotype. Scratching behavior was lost in BNP KO mice injected with a variety of pruritogens, including histamine, chloroquine, serotonin, and compound 48/80. However, these mice had normal responses to thermal and mechanical stimuli. The primary receptor for BNP, NPRA, was found to be expressed in the outer
Interneurons modulate itch. Interneurons in the spinal cord play an important role in relaying sensory information from peripheral afferents to the thalamus. In a study looking at interneurons, Ross et al. (2010) found that loss of the transcription factor Bhlhb5 yielded an increase in itch behavior when Bhlhb5 KO mice were exposed to pruritogens. Loss of Bhlhb5 in the superficial lamina of the dorsal horn resulted in pathological itch, results that implicate the importance of inhibitory interneurons (Els) controls itch transmission to the brain. Histamine and nonhistaminergic pathways are regulated downstream of Nppa+ interneurons (Mishra and Hoon, 2013), gated by Bhlhb5 inhibitory interneurons, and converge in the dorsal horn on GRPR+ (Sun et al., 2009) and TR4+ excitatory interneurons. Mechanical itch is gated via excitatory input under the control of NPY+ interneurons (Bourane et al., 2015).

Light touch of hairy skin evokes a type of acute itch termed mechanical itch. Mechanical itch was thought to be under the control of mechanoreceptor-specific afferents, but the specific circuits involved were unknown. However, Bourane et al. (2015) have recently identified an important subset of interneurons that play a role in inhibiting mechanical itch. By expressing the diphtheria toxin receptor in a subset of interneurons that expressed neuropeptide Y (NPY), mice developed touch-evoked itch; however, chloroquine- and compound 48/80-evoked itch were unaffected (Bourane et al., 2015). NPY ablation was histamine independent, as histamine H1/H4 receptor antagonists had no effect on touch-evoked itch. Interestingly, NPY-ablated mice showed similar sensitivity to high-intensity force and pain, providing evidence for a pathway specific to light touch that also gates mechanical itch.

Studies have also identified excitatory interneurons in regulating itch in the spinal cord. Mice lacking the testicular orphan nuclear receptor (TR4) gene had complete loss of itch behavior when exposed to pruritogens such as histamine and chloroquine (Wang et al., 2013). Interestingly, these animals developed normal heat and mechanical hypersensitivity to a complete Freund’s adjuvant model of inflammation, but developed marked thermal hypersensitivity in a chronic constriction injury model of neuropathic pain. Immunohistochemistry revealed a loss of excitatory interneurons in the superficial dorsal horn of TR4 conditional KO mice. Moreover, by using a variety of markers, Wang et al. (2013) saw a 76.6% decrease of GRP-positive cells and an 83% decrease in GRPR-positive cells in the TR4 conditional KO mice. Although not specific for itch, TR4 interneurons provide further confirmation for the pivotal role interneurons have in regulating itch.

A new role for glia. Much focus over the past decade has involved understanding and integrating peripheral and central circuits involved in itch. However, a recent article has provided evidence for glial cells, specifically astrocytes, in mediating pruritus. Using a mouse model of atopic dermatitis, Shiratori-Hayashi et al. (2015) observed astrocytes in the spinal dorsal horn with enlarged cell bodies and overly arborized processes, hallmarks of astrogliosis. Astrogliosis is normally a result of infection or injury; however, the chronic scratching found in atopic dermatitis was also capable of shifting these cells to an abnormal state. The astrocyte marker GFAP was also found to be increased in segments of the spinal cord innervated from skin lesions caused by scratching. When TRPV1+ C-fibers were ablated using resiniferatoxin, mice with atopic dermatitis had fewer scratching bouts and reduced GFAP expression, providing a link between peripheral skin lesions caused by chronic itch and the astrogliosis found in the dorsal horn of the spinal cord. Although the study focused on the role of astrocytes in a chronic model of itch, the findings provide evidence for the importance of nonneuronal cells in contributing to pruritus.
Conclusion
Progress has been made in identifying distinct receptors and sensory neurons that encode itch, which was formerly thought to be a submodality of pain. Characterization of primary afferents expressing Mrgrps and GRP, as well as those spinal neurons that are positive for GRPR, BNP, and NPY, have broadened our understanding of the cell types underlying itch. The focus of this review has been acute itch, and questions still remain about whether pathological or chronic itch alters the expression and molecular underpinnings of the mechanisms outlined in this review. However, the research outlined here provides hope for the future, as the identification of unique itch pathways will aid in the development of novel clinical therapies for those suffering from debilitating pruritus.

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