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The multiple pathways for itch and their interactions with pain

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Abstract

Multiple neural pathways and molecular mechanisms responsible for producing the sensation of itch have recently been identified, including histamine-independent pathways. Physiological, molecular, behavioral and brain imaging studies are converging to describe these pathways and their close association with pain processing. Some conflicting results have arisen, and the precise relationship between itch and pain remains controversial. A better understanding of the generation of itch and of the intrinsic mechanisms that inhibit itch after scratching should facilitate the search for new methods to alleviate clinical pruritus (itch). In this review, we describe the current understanding of the production and inhibition of itch. A model of itch processing within the central nervous system (CNS) is proposed.

INTRODUCTION

Itch is an unpleasant sensory and emotional experience associated with an actual or perceived disruption to the skin that produces a desire to scratch. Acute itch is a daily experience that can usually be abolished by briefly scratching near the area of itching. But chronic itch can be debilitating and scratching provides little relief, and instead, exacerbates the problem^{1,2}. Advances in itch research have elucidated differences between itch and pain, but have also blurred their distinctions. Itch and pain appear to be independent sensations since nociceptive and pruriceptive stimuli (Glossary) each elicit unique behavioral responses³. Yet, itch is also inversely related to pain because itch is reduced by nociceptive counter-stimuli (e.g. scratching), and analgesic opioids often have the adverse side-effect of producing itch⁴. Itch and pain also have much in common: itch-producing agents activate nociceptive primary afferent fibers and can generate simultaneous pruritic and nociceptive sensations⁵. Moreover, surgical lesion of the anterolateral funiculus of the spinal cord relieves chronic pain and also abolishes itch⁶, and individuals with congenital insensitivity to pain are also insensitive to itch⁷. This suggests that the neural anatomy responsible for the distinct sensation of itch is closely shared with that for pain (Figure 1).

The histamine type-1 receptor (H1R) has been the primary target for pharmaceutical relief of pruritus⁸. However, other histamine receptors have recently been identified that may contribute to the generation of itch. Additionally, novel non-histaminergic pathways for itch have recently been identified. While pain and itch appear to be inextricably linked, multiple, independent pathways for itch have now been established, revealing that the neural processing of itch is more diverse and complex than previously appreciated.

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Several hypotheses have been proposed to describe the neural coding of itch. The specificity or 'labeled line' hypothesis posits a subset of neurons in series that respond specifically to stimuli that produce itch. This idea has gained traction, but the evidence has not been critically reexamined. Other hypotheses have posited that neurons excited by pruritic stimuli may also respond to noxious stimuli. In these cases, the distinct sensation of itch is postulated to emerge from a pattern⁹ or frequency of action potential discharge or otherwise from a population code across multiple neurons¹⁰. Here, we address the view that itch is processed within the nociceptive system by polymodal neurons. We also discuss the developing research indicating that itch can be signaled through non-histaminergic pathways in addition to a heterogeneous histaminergic system. Finally, the intrinsic neural mechanisms for the inhibition of itch by scratching and other counter-stimuli are reviewed.

Itch and pain: unique sensations, identical pathways?

Peripheral signaling of itch—In a seminal study, Schmelz and colleagues¹¹ provided evidence for the existence of a class of C-fibers that are mechanically insensitive (CMi), extremely slowly conducting, and excited by the application of histamine into the skin. The responses of CMi fibers to histamine matched the simultaneous sensation of itch in human subjects, suggesting a specific peripheral system for coding and transmitting itch. This labeled line hypothesis for itch was further supported by a study in which ten mechanically insensitive feline spinothalamic tract (STT) neurons were activated by histamine¹². Four of these neurons were tested for responses to the noxious agonist mustard oil, which activates Transient Receptor Potential (TRP) ankyrin-1 (TRPA1), and two did not respond, suggesting an itch specific pathway in the spinal cord. Importantly, responses to other noxious chemicals, including the TRP vanilloid-1 (TRPV1) agonist capsaicin, were not evaluated in either study. Therefore, claims of specific responses only to pruritogens were based on limited testing. Indeed, a subsequent study examined the responses of CMi fibers during the application of several nociceptive and pruriceptive compounds¹³. This study confirmed that many CMi fibers are strongly activated by histamine. However, histamine responsive CMi fibers were also activated by several nociceptive compounds including bradykinin and capsaicin, indicating that CMi_(hist+) fibers also act more generally as chemical nociceptors. In addition to the CMi_(hist+) fibers, mechanically-sensitive (polymodal) C-fibers may also respond to histamine in humans and monkeys, but the intensity and duration of their responses do not clearly match itch sensation^{14,9}.

The link between responses to histamine and capsaicin in the same primary afferent neuron has generated interest at the molecular level. TRPV1-deficient mice show a marked reduction in scratching relative to wild-type after an intradermal injection of histamine^{15,16}. Consistent with this, histamine induced a Ca²⁺ increase in dorsal root ganglion (DRG) neurons from wild-type but not TRPV1 knockout mice. Furthermore, capsazepine, a TRPV1 antagonist, reduced Ca²⁺ currents evoked by histamine. Finally, non-heterologous cells co-transfected with H1R and TRPV1 produced an inward current when histamine was applied, but histamine failed to elicit the current when TRPV1 was missing¹⁵. These results indicate that the presence of functional TRPV1 is required for histamine to excite sensory neurons.

The interaction between TRPV1 and the H1R is not well understood, but there is evidence pointing to several overlapping, intracellular signal transduction pathways (Figure 1). Phospholipase C (PLC) β 3 has been shown to be a critical mediator of the histamine induced Ca²⁺ increase in DRG neurons, and mice with a null mutation of PLC β 3 have marked deficits in scratching after histamine injection¹⁷. A byproduct of PLC activation, diacylglycerol, directly activates TRPV1¹⁸. Alternatively, TRPV1 may be activated by a phospholipase A₂ pathway that has also been shown to be involved in histamine-induced scratching^{15,19}. These studies demonstrate that DRG neurons responsive to histamine can

also be activated by capsaicin, noxious heat, bradykinin or other noxious stimuli. Thus, histamine-induced itch is likely signaled by a particular subpopulation of primary afferent chemo-nociceptors that are responsive to histamine.

Itch processing in the spinal cord—A subpopulation of neurons in the superficial and deep dorsal horn of rodent and primate spinal cord is excited by pruritic agents as well as by noxious mechanical, thermal or chemical stimuli^{20–26}. Using antidromic activation to identify STT neurons in monkeys, about one-quarter of neurons tested were found to be activated by either histamine or by cowhage when applied to the receptive field²⁶. Since all examined neurons were also activated by nociceptive stimuli including capsaicin, the findings suggest that the transmission of an itch signal in the spinal cord is carried by polymodal nociceptive neurons. The axons of STT neurons excited by pruritic stimuli terminated in the posterior and ventral posterior region of the thalamus.

The molecular mechanisms of itch in the dorsal horn have only recently begun to be examined. An important report identified a role of the gastrin-releasing peptide (GRP) receptor (GRPR) located on neurons within the superficial dorsal horn²⁷. Mice lacking this receptor exhibited a reduction in scratching elicited by several pruritic agents; in contrast, these mice responded normally in all tests of pain sensation. The results suggest a new pharmacologic approach to block itch without affecting pain sensation by antagonizing spinal GRPRs. Most primary afferent fibers that release GRP also expressed TRPV1, raising the question as to whether GRPR+ neurons in the spinal cord also play a role in signaling pain. This question was addressed recently using intrathecal injections of an endogenous ligand for GRPR, bombesin, conjugated to saporin, a toxin that leads to cell death upon receptor internalization²⁸. Injections of bombesin/saporin selectively ablated the GRPR+ cells from the dorsal horn, and markedly reduced scratching evoked by several pruritogens²⁸. Behavioral tests for nociceptive, inflammatory and neuropathic forms of pain suggested that the elimination of GRPR+ neurons had no effects on these types of pain. Based on the lack of modified pain behaviors it was concluded that GRPR+ neurons constituted a labeled line for pruriceptive information. This appears to contrast with the electrophysiological results discussed above, which demonstrate that virtually all spinal neurons responsive to pruritic agents also respond to nociceptive stimulation^{19–25}. It also raises the surprising question of whether TRPV1+ primary afferent fibers can signal non-nociceptive information (i.e., pruriceptive-only).

In the spinal cord, GRPR+ neurons receiving inputs from TRPV1+ and GRP+ polymodal fibers were destroyed by the bombesin/saporin treatment²⁸. This relatively small subpopulation of neurons contrasts with the much larger population of non-pruriceptive (nociceptive-only) spinal neurons that do not express GRPRs. It is possible that the larger non-pruriceptive population compensated for the loss of the subset of GRPR+ neurons to maintain normal pain behaviors. Therefore, while GRPR+ neurons clearly play a critical role in itch, these neurons must be further examined to determine whether they lack the ability to also be excited by nociceptive stimuli. Furthermore, GRPR knockout mice showed fewer deficits in scratching behaviors to various pruritogens compared with the mice with ablated GRPR neurons^{27,28}, indicating that additional, unidentified itch receptors may exist on GRPR+ dorsal horn neurons.

Two recent studies tested the role of vesicular glutamate transporter-2 (VGLUT2)-mediated glutamatergic neurotransmission by TRPV1+ primary afferent fibers in pain and itch^{29,30}. Knockout of *VGLUT2* in mice led to reduced pain behaviors, but increased basal and evoked itch, suggesting that glutamate release is dispensable for signaling itch and may otherwise inhibit itch sensation. In contrast, peptide neurotransmitters released from the central terminals, such as GRP, could be critical for itch transmission^{29,30}. Additional support for

peptide signaling in itch is provided by a study in which ablation of dorsal horn neurons expressing neurokinin-1 reduced pruritogen evoked scratching in rats³¹. Furthermore, in naked mole rats, which naturally lack substance-P in nociceptors and do not scratch to intradermal histamine, histamine-evoked scratching was rescued by spinal administration of substance-P³². These studies advance the intriguing hypothesis that, depending on the particular peripheral receptors activated, the composition of centrally released transmitters could be differentially regulated and this could signal specific sensory modality.

If itch is signaled by spinal projection neurons that receive inputs from fibers transmitting both pruritic and nociceptive information, how can itch be perceived as a distinct sensation from pain? Itch producing agents excite only a subpopulation of polymodal somatosensory neurons in the spinal cord and most nociceptive neurons do not respond to pruritogens. This leads to the possibility that neurons in supraspinal regions receive selective projections from the pruritogen responsive subpopulation of spinal projection neurons. Supraspinal neurons may distinguish between pruritic and nociceptive information based on the selective connectivity of pruritic input. A schema for itch encoded by functionally categorized populations of polymodal spinal cord projection neurons is illustrated in Figure 2.

Specificity within the itch pathways

Histaminergic vs. non-histaminergic itch—Itch can be generated by systemic, neuropathic, psychogenic and cutaneous disorders. Any of these classifications may have multiple etiologies and many of the specific pruritic mediators are putative or unknown^{1,33,34}. The histaminergic pathway is the best studied; it can be easily manipulated experimentally and in nature is activated by tissue damage, allergy and infection. Antagonists of H1R (antihistamines) are effective against some itches^{8,35}; however, many clinically relevant forms of pruritus (e.g. atopic dermatitis) are not blocked by antihistamines, pointing to the existence of a histamine-independent pruritic pathway^{1,35}. Furthermore, histamine produces a wheal and large area of neurogenically mediated vasodilatation called “flare”. This flare is produced by an axon reflex which occurs in the widely branching peripheral axons of CMi neurons after activation³⁶. However, itch can also be produced without flare by cutaneous electrical or mechanical stimuli, suggesting the existence of an itch pathway independent of histamine receptors and the class of CMi(hist+) neurons^{37,38}.

Spicules of cowhage produce itch and sensations of pricking and burning pain when inserted into the skin^{5,39}. Both the absence of flare and the failure of antihistamine to block cowhage evoked itch has been demonstrated, indicating that cowhage generates itch through a non-histaminergic system^{40,41}. In monkey and human, polymodal C-fibers respond to cowhage, but weakly or not at all to histamine, supporting the idea of separate histaminergic and non-histaminergic pathways^{9,42}. This separation is maintained in the primate spinal cord and ascending pathways to the brain; STT neurons responded either to histamine or to cowhage but not to both²⁶ (Figure 1).

Recently, the anti-malaria drug chloroquine, which often has the adverse side-effect of producing itch for which antihistamines are ineffective, was confirmed to be another histamine-independent pruritogen⁴³. When injected into the skin, chloroquine activates MrgprA3, a G-protein coupled receptor (GPCR) located on DRG neurons. Mice deficient in a cluster of Mrgpr genes, including MrgprA3, showed reduced scratching, and DRG from these mice failed to respond to chloroquine. In contrast, Mrgpr-deficient mice exhibited normal scratching to histamine and the responses to histamine were not impaired in Mrgpr-deficient DRG neurons, indicating that itch generated by activation of MrgprA3 is histamine-independent. Interestingly, the same DRG neurons responsive to chloroquine were also responsive to histamine and capsaicin, suggesting that the signaling of Mrgpr-

induced itch occurs in neurons that transduce multiple pruritic and nociceptive stimuli via independent mechanisms⁴³. The intracellular signaling of MrgprA3 and possible interactions with other pruritic and nociceptive receptor signaling is unknown.

Histamine receptors in cutaneous pruritus—Four types of histamine receptors have been cloned (H1R-H4R) and each is a 7-transmembrane GPCR⁴⁴. Receptor subtypes H1, H3, and H4 have been found in DRG^{45–49}. The most recently identified receptor, H4R, was detected in about one-third of DRG neurons and these possessed central projections to the superficial and deep dorsal horn⁴⁷. In mouse models of itch, intradermal injections of selective H1R and H4R agonists each evoked scratching behavior⁵⁰. However, no cross-inhibition of scratching occurred when an antagonist to H1R was given for H4R-evoked scratching or when the H4R antagonist was given for scratching evoked by H1R⁴⁴. Moreover, the frequency of scratching from histamine was completely abolished when H1R and H4R antagonists were delivered together, but not when either was delivered alone^{51,52}. Likewise, histamine-evoked scratching was abolished with an H1R antagonist in a H4R knockout mouse, but was only partially reduced in wild-type mice⁵¹. Finally, H4R antagonists reduced scratching in models of pruritus in which H1R antagonists either failed to reduce or incompletely abolished scratching behavior^{52,53}. These results suggest that H1R and H4R mediate pruritus independently. Cutaneously applied H3R antagonists evoked scratching in mice⁵⁴, but this was dependent on peripheral release of substance P⁵⁵, suggesting that H3R mediates itch indirectly. Indeed, H3R immunoreactivity in the epidermis could not be detected on C or Aδ fibers⁴⁹. In addition to roles in itch, histamine receptors are also involved in inflammation and the modification of behavioral responses to noxious stimuli, indicating that histamine receptors are not themselves ‘itch specific’^{56–58}.

Proteinase activated receptors in cutaneous pruritus—Itch can be elicited by activation of non-histaminergic receptors such as the proteinase activated receptors (PARs). Four members of the PAR family have been identified (PAR1-4) and each is a 7-transmembrane GPCR. PARs are activated by proteolytic cleavage of their extracellular N-terminus which, when cleaved, exposes a tethered ligand domain. This domain binds to a site on the receptor and causes auto-activation^{59–61}. PARs are expressed in many tissues throughout the body including on DRG and their peripheral fibers, keratinocytes, and immune cells in the dermis^{62–64}. PAR-2 was first identified as an important non-histaminergic pruritic mediator when it was found to be robustly expressed in the epidermis of individuals with atopic dermatitis, along with high levels of tryptase, an endogenous serine protease and PAR-2 agonist⁶⁵. PAR-2 is expressed in small DRG with unmyelinated fibers that can co-express the peptides substance P and Calcitonin Gene Related Peptide (CGRP)^{63,64,66}. These peptides are released after PAR-2 activation to generate local vasodilation by a neurogenic mechanism⁶⁷. However, a widespread flare response has not been reported when PAR-2 is activated in the epidermis, suggesting that PAR-2 may not be present on the CMi fibers that mediate flare. A biochemical study on the constituents of cowhage has determined that the active, itch-producing agent is a 36 kD cysteine protease named “mucunain”^{68,69}. Mucunain was found to activate PAR-2 and PAR-4⁶⁹.

PAR-1 and PAR-4 may play a role in the generation of itch, inflammation and pain^{70–73}. However, scratching evoked from PAR-1 and PAR-4 agonists is suppressed by antihistamine, suggesting an indirect action perhaps by PAR mediated degranulation of mast cells^{72,74}. Since PAR-3 does not evoke scratching in mice, only PAR-2 appears to mediate cutaneous itch directly, through a histamine-independent mechanism⁷². Activation of PAR-2 with tryptase or PAR-2-Activating Peptides (APs) elicits scratching in mice that is not blocked by antihistamines^{27,72–78}. Interestingly, c-fos+ neurons observed in the superficial dorsal horn after a PAR-2-AP injection were located in an anatomically distinct region compared with c-fos+ neurons after histamine injection⁷⁹. In contrast, PAR-2-AP,

histamine, and noxious chemicals applied to the cutaneous receptive fields of mouse superficial dorsal horn neurons excited the identical cells^{23,24}. The latter result suggests a possible convergence of itch pathways in the mouse that was not found in the primate STT²⁶. In addition to methodological or species differences that may explain this discrepancy²⁴, serine based APs for PAR-2 may initiate different intracellular signaling pathways than proteolytic cleavage of the receptor by a cysteine protease such as mucunain^{80,81}.

PAR-2 agonists increase intracellular Ca^{2+} in DRG for several minutes⁶³ and depolarize resting membrane potential via inhibition of a potassium current^{82,83}. Most TRPV1+ neurons in DRG express PAR-2, and activation of PAR-2 potentiates TRPV1 inward currents^{84,85}. PAR-2 activates PLC which activates protein kinase C; protein kinase A is also activated by PAR-2 and both signaling pathways sensitize TRPV1 and TRPV4^{86,87}. PAR-2 also sensitizes TRPA1⁸⁸. Finally, PAR-2 agonists induce thermal and mechanical hyperalgesia^{82,84,89}. Because itch evoked by cowhage occurs along with sensations of burning and stinging pain^{5,39}, the factors downstream of PAR-2 activation may play a role in both the modulation of nociception and itch. Therefore, while PAR-2 plays an important role in non-histaminergic itch, it is not itself an itch specific receptor (Figure 1).

Reduction of itch by counter-stimuli

Permanent relief from most everyday itches can be achieved with a brief scratch to the skin. However, in experimental models of pruritus the intensity of itch rebounds soon after scratching^{41,90,91}. Likewise, chronic pruritus can lead to repeated itch-scratch cycles that damage the skin, raise the risk of infection and increase patient distress^{92,93}. An understanding of the neural circuits and transmitters that underlie the reduction of itch obtained by counter-stimuli, like scratching, is important because elements of the intrinsic itch-control circuitry could potentially be manipulated to block itch.

Psychophysical experiments indicate central modulation of itch—Noxious counter-stimuli including scratch, pin-prick, capsaicin injection, electrical stimulation, heat and cold have each been shown to block itch even when applied several centimeters distal to the area of itching^{41,90,91,94–101}. This indicates that effective counter-stimuli need not act directly on the same primary afferent fibers responsible for signaling itch. The $\text{CMI}_{(\text{hist}+)}$ fibers that correlate with itch sensation^{11,13} are particularly unlikely to be involved in blocking itch by nature of their insensitivity to mechanical stimuli. Rather, scratching and other counter-stimuli activate mechanically-sensitive polymodal C and A δ fibers which likely inhibit itch through a central mechanism. Polymodal C-fibers respond to pruritic stimuli in primates^{9,42}, but their small cutaneous receptive fields¹⁰² suggest that effective counter-stimuli applied centimeters distally activate separate nociceptive fibers. Itch cannot be elicited from a zone of capsaicin-induced secondary hyperalgesia, indicating that capsaicin-sensitive nociceptors can induce a central inhibitory process that prevents itch¹⁰¹. Together, these observations are consistent with the idea that nociceptors excited by counter-stimuli engage mechanisms within the CNS to block the transmission of itch.

Several hypotheses have been proposed to explain the inhibition of itch by counter-stimuli^{10,20}. One explanation is that the itch signal could be “occluded” or masked by the additional activation of pain signaling neurons⁹. However, this does not explain how a brief scratch can permanently eliminate an everyday itch after the occluding (scratch-activated) neurons are no longer excited. More likely, there is a direct central interaction between nociceptive and pruriceptive systems. Another hypothesis is that descending inhibition from the midbrain, similar to that described for the inhibition of pain, can block itch at the level of the spinal cord^{20,103}. Alternatively, the central terminals of pruriceptive DRG neurons may

be modulated by retrograde signaling (e.g. cannabinoid or nitric oxide signaling) from dorsal horn neurons activated by counter-stimuli. Finally, inhibitory interneurons capable of blocking the itch signal may be activated by nociceptive input. These hypotheses are not mutually exclusive and the mechanism of inhibition may depend on the specific class of pruritogen.

CNS mechanisms for inhibition of itch—Neurons in the dorsal horn responsive to pruritic agents have been examined for a reduction of the pruritogen-evoked response during the application of a counter-stimulus. In rats, a histamine-evoked discharge recorded from isolated dorsal horn neurons was briefly reduced when noxious heat or scratching was applied to the receptive field²⁰. Inhibition of histamine-evoked activity in the dorsal horn was observed when descending pathways originating from the periaqueductal gray (PAG) were electrically stimulated¹⁹. Histamine-evoked activity was likewise inhibited when cold was applied near the site of histamine application in rats¹⁰⁴. These studies demonstrated that activity evoked by histamine in dorsal horn neurons could be inhibited by various noxious counter-stimuli and the stimulation of descending pathways. However, unlike primates and mice, histamine does not elicit scratching behavior in rats²². Therefore, it is unclear whether the spinal neurons in these studies contributed to itch.

Recently, primate STT neurons responding to histamine were found to have a reduced firing rate after scratching the skin, despite showing excitation to scratching before the histamine response¹⁰⁵. In contrast, scratching during a capsaicin response was additively excitatory, suggesting a state-dependent inhibition that occurs only during itch. The result indicates that excitation of nociceptive primary afferent fibers by scratching during itch engages an inhibitory mechanism that acts at the level of the spinal cord (Figure 3). Experiments to determine the microcircuitry of the dorsal horn have recently begun to elucidate the synaptic connectivity of inhibitory interneurons. For instance, stimulation of C-fibers was shown to activate inhibitory interneurons in the substantia gelatinosa of the dorsal horn¹⁰⁰. These inhibitory interneurons made direct connections onto lamina I neurons that were excited by input from extremely slowly conducting (possibly CMi) C-fibers¹⁰⁶. Therefore, the circuit organization for the inhibition of itch by noxious counter-stimuli exists. Indeed, a subpopulation of inhibitory interneurons located within the dorsal horn was recently found to play a key role in blocking itch¹⁰⁷. The survival of these neurons requires the expression of the basic helix-loop-helix transcription factor *Bhlhb5* during development. When *Bhlhb5* expression was prevented in mice, self-inflicted lesions from scratching occurred. The results suggest that tonic activity in these *Bhlhb5*-expressing inhibitory neurons is important in preventing pruritus¹⁰⁷. Furthermore, glutamatergic input from polymodal fibers onto inhibitory spinal neurons is implicated by the heightened itch behaviors of mice with genetic ablation of *VGLUT2*^{29,30}. When capsaicin was injected into wild-type mice, *c-fos* expression was increased in a population of spinal neurons expressing neuropeptide Y (NPY), a marker for a subset of inhibitory neurons³⁰. However, in mice lacking *VGLUT2*, the number of *c-fos*-labeled NPY+ interneurons after capsaicin injection was reduced relative to the wild-type³⁰. These results suggest that polymodal fibers possess synaptic inputs to inhibitory interneurons that block itch.

The effects of counter-stimuli on brain activity during itch have been examined using imaging techniques. In one study, a painfully cold stimulus was delivered to the skin to reduce histamine evoked itch while measurements of cerebral blood flow were taken by positron emission tomography¹⁰³. Activity around the PAG was observed in the presence of itch and pain together, but not in the presence of either itch or pain alone. Additionally, other areas previously activated during the itch-alone condition were reduced during the counter-stimulus⁹⁷. The authors concluded that the midbrain may act in a state-dependent manner to reduce itch, becoming active only during simultaneous painful and pruritic stimuli. Blood-

oxygen-level-dependent (BOLD) responses to the suppression of itch by scratching have recently been examined using fMRI¹⁰⁸. Passive scratching of the skin (by an investigator) in the absence of itch was shown to both activate and deactivate certain motor and sensory brain regions^{108,109}. During itch, however, passive scratching activated the putamen, an area that was not active during scratching without itch, and also produced changes in activity levels in other areas¹⁰⁸. These results suggest that the brain receives different signals from the spinal cord during itch and pain states, and that the combination of itch and pain may lead to unique patterns of activation.

Conclusion

Itch is a frequently occurring but poorly understood somatosensory experience. Much has been learned recently, beginning with the finding of a population of C-fibers with responses matching the sensation of itch in human when activated by histamine¹⁰. More remains to be determined about the anatomy of itch including the potential role of A δ fibers, other ascending pathways in the spinal cord, and the identification of which diencephalic and cortical neurons respond to cutaneously applied pruritic agents (Box 1). The identification of multiple histamine receptors and non-histaminergic receptors in the periphery have expanded our knowledge of the multiple, independent means of itch transduction and have provided a rationale for why H1R antihistamines are not clinically effective for every itch. In the spinal cord, the discovery of a role for GRPR in mediating itch sensations has provided the first molecular marker of central pruritic neurons and a new pharmacological target for blocking pruritus.

Box 1

Outstanding questions

- It is currently unknown whether H1R and H4R are co-localized on the same, or separate, primary afferent fibers. Specifically, the histamine receptor expression profile in CMI_(hist+) fibers and in histamine-responsive polymodal C-fibers should be determined. The extent of overlap in the intracellular mediators activated by H1R or H4R in pruritic neurons is likewise unknown.
- Receptors for itch: only a handful of pruritic receptors have been identified on peripheral terminals and only one receptor, the gastrin-releasing peptide receptor, has been identified in the spinal cord. There are likely to be additional peripheral non-histaminergic receptors and evidence points to additional spinal receptors involved in itch sensation as well.
- The intracellular signaling cascades in dorsal root ganglia following activation of pruritic GPCRs are not well known. Intracellular signaling cascades could be a determinant of neuronal firing pattern and possibly of selective transmitter release. Knowledge of these signaling cascades could provide insight into how polymodal neurons signal pain or itch.
- Several ascending pathways in addition to the spinothalamic tract travel within the anterolateral funiculus. These pathways project axons to the hypothalamus, reticular formation, the midbrain and other supraspinal regions. These pathways have not been examined for responses to pruritic agents, but may be important contributors to the sensory, affective and motivational aspects of itch.
- Functional assessment of the responses of individual supraspinal neurons to itch producing agents has not been performed. Specifically, it is unknown which thalamic neurons respond to pruritic agents and what their projection targets

might be. Additionally, whether any responses in individual supraspinal pruritic responsive neurons are modulated by counter-stimuli is unknown.

The aversive nature of itch motivates scratching, which sometimes can provide relief. The utility of scratching lies in its ability to remove offending debris or parasites from the skin and is sometimes described as pleasurable or rewarding. However, this aspect of itch has not been empirically explored. Finally, the labeled line hypothesis has been a catalyst for research on itch, but has not been supported by recent electrophysiological studies. Pruritogen responsive neurons are known to also respond to nociceptive chemicals, when adequately tested. This suggests that polymodal nociceptors in the periphery and central nervous system are important in encoding the itch experience.

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Glossary

Antidromic activation	An electrophysiological technique used to identify the location of an axon that is far from its soma. A small current is injected near the axon generating an action potential that travels retrogradely toward the cell body. A recording electrode records the action potential as it invades the soma. This technique permits investigators to functionally characterize a neuron and determine the projection target of its axon
Axon reflex	The membrane depolarization of primary afferent terminals due to signal transduction can spread to the far reaching branches of the peripheral axon. The spreading depolarization leads to the release of peptides and neurotransmitters within the peripheral tissues and can have effects on blood vessels and immune cells in the skin causing neurogenic inflammation
Cowhage	The spicules covering the pod of the tropical legume <i>Mucuna pruriens</i> . Contained within these spicules is the proteolytic enzyme mucunain and also serotonin. These spicules produce itch and sensations of pricking and burning pain when inserted into the skin
c-Fos	A proto-oncogene belonging to the immediate early gene family of transcription factors. Immunological identification of c-fos protein can be used as an indicator of neural activity
Labeled line code	The hypothesis that a specific quality of sensation (e.g. hot, cold, itch or pain) is encoded by a dedicated group of neurons that respond to and encode a single quality and signal that quality in series to the brain
Nociceptive	Related to the neural mechanisms involved in the detection, encoding and transmission of noxious stimuli (from the Latin word nocere, to injure)
Pattern/Frequency code	The hypothesis that qualities of sensation are encoded by polymodal neurons that transmit information about a particular quality via the temporal pattern or frequency of discharge of action potentials

Population code	The hypothesis that qualities of sensation are encoded by multiple polymodal neurons. By virtue of being active simultaneously, subsets of these neurons are able to generate information about the specific quality of sensation
Pruriceptive	Related to the neural mechanisms involved in the detection, encoding and transmission of the sensation of itch or itch behavior (from the Latin prurire, to itch)
Substance P/ Calcitonin Gene Related Peptide (CGRP)	Neuropeptides released from peripheral terminals and central terminals of nociceptive neurons during ongoing signal transduction. Both play a role in neurogenic inflammation and pain. The receptor for Substance P is neurokinin-1 and for CGRP is the CGRP receptor
Transient Receptor Potential (TRP) Channels	A family of diversely functioning six-transmembrane polypeptide subunits with intracellular N- and C-termini that assemble as tetramers to form cation-permeable pores. TRP channels are involved in sensory transduction of a wide variety of stimuli and are expressed throughout the body including on sensory nerve terminals in the skin

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Figure 1.

A schematic illustrating multiple anatomical pathways for itch, including transduction at the peripheral terminals in the skin, synaptic transmission in the spinal cord, and central projections to the thalamus. **(A)** Polymodal C-fibers are activated in the epidermis by the non-histaminergic pruritogen, cowhage. **Box A:** Cowhage releases mucunain, a protease that cleaves and activates the Protease Activated Receptor 2 (PAR-2) located in the peripheral terminal. Activation of PAR-2 activates Phospholipase-C (PLC) which, in turn, sensitizes Transient Receptor Potential Vanilloid-1 and Ankyrin-1 (TRPV1 and TRPA1). Additionally, PAR-2 leads to membrane depolarization by inhibiting a voltage-gated K⁺ channel. **(B)** Histamine, typically released by mast cells in the dermis, activates a population of mechanically-insensitive C-fibers (CMi). These fibers innervate a broad territory and, upon activation, release pro-inflammatory mediators such as Calcitonin-Gene-Related-Peptide (CGRP) into the skin leading to vasodilation and widespread flare. **Box B:** Histamine receptor-1 activates PLCβ3 and phospholipase A2 (PLA₂) leading to sensitization of TRPV1. The presence of TRPV1 is required for the histamine evoked response (i.e. TRPV1 and the histamine receptor-1 act together as an “AND-GATE” to produce a response to histamine). The chloroquine receptor, MgrprA3 is present on histamine responsive fibers, but may have independent, intracellular signaling mechanisms. The bradykinin receptors (B1 and B2) are also expressed on histamine responsive DRG. **(C)** Both non-histaminergic C-polymodal fibers and histamine-responsive CMi fibers terminate centrally in the dorsal horn of the spinal cord. Each excites distinct populations of spinothalamic tract neurons that maintain separate histaminergic and non-histaminergic channels in primates. Little is known of itch responsive thalamic neurons. **Box C:** Polymodal C-fibers and CMi fibers release excitatory neurotransmitters as well as peptide neuromodulators such as substance-P (SP), CGRP, and the gastrin-releasing-peptide (GRP). The central terminals of primary afferent neurons form synapses with spinal interneurons possessing the Gastrin-Related-Peptide-Receptor (GRPR).

Figure 2.

A simple model of somatosensory encoding for itch, pain and touch by functionally distinct polymodal spinal neurons. **Bottom:** The skin is exposed to various stimuli: pruritogenic, noxious and tactile. These stimuli activate different subpopulations of spinothalamic tract (STT) neurons. **Middle:** STT neurons are either pruriceptive (pruri) or not-pruriceptive (non-pruri) and either of the wide dynamic range (WDR) or high threshold (HT) type. The smaller subpopulation of STT neurons that are pruriceptive are represented by smaller circles, and the larger population of STT neurons that are nociceptive (non-pruriceptive) are represented by larger circles. The output from selective activation of these four types of neurons could distinctively encode touch, pain and itch. Tactile stimuli activate WDR, but not HT neurons. Noxious stimuli activate all four types of neurons. Itch producing stimuli activate only the pruriceptive subpopulation of neurons. **Top:** When only the pruriceptive STT neurons are activated (i.e., in the absence of activation of the other nociceptive STT neurons), then itch is signaled. Pruriceptive neurons may also contribute to tactile and nociceptive processing, but without complementary activity in the nociceptive-type neurons, activation of pruriceptive STT neurons produces itch. Thus, the absence of activation of certain subpopulations of STT neurons is hypothesized to be important in transmitting specific sensory information to the brain.

Figure 3.

A schematic of a current working model for the inhibition of pruriceptive spinothalamic tract neurons by scratching. **(A)** Itch and scratch stimuli activate dorsal root ganglion (DRG) neurons which synapse in the dorsal horn of the spinal cord. Pruritic information ascends in the spinothalamic tract (STT). Descending modulation of pruriceptive spinal neurons may arise from neurons in the periaqueductal grey (PAG). **(B)** From the boxed region in (A): Pruritogen-responsive primary afferent fibers are hypothesized to synapse (directly or indirectly) onto STT neurons and make another synapse onto an inhibitory interneuron (black). The synapse to the STT neuron drives action potential production, but the synapse onto the inhibitory interneuron is proposed to be too weak to drive action potential production alone. However, simultaneous activation of the pruritogen-responsive primary afferent fiber along with activation of a nociceptive fiber that also synapses onto the same inhibitory interneuron would provide an adequate stimulus. This “AND-gate” inhibitory interneuron is proposed to have strong inputs to the STT neuron and can block the response evoked by histamine. This is consistent with the idea that scratching produces central inhibition only during an itch. Also depicted is the possible involvement of a descending pathway hypothesized to originate from the PAG (green). Other possibilities such as inhibition of central terminals by retrograde signaling from dorsal horn neurons exist, but are not illustrated.