

Review

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Histamine-induced itch and its relationship with pain

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Abstract

Itch is one of the major complications of skin diseases. Although there are various substances that induce itch or pruritus, it is evident that histamine is the best known endogenous agent that evokes itch. Even though histamine-induced itch has been studied for some time, the underlying mechanism of itch is just beginning to emerge. Although various downstream signaling pathways of histamine receptors have been revealed, more studies are required to determine the cause of histamine-induced itch. It appears that itch and pain involve different neuronal pathways. Pain generally inhibits itch, which indicates an inter-communication between the two. Complex interactions between itch and pain may be expected based on reports on disease states and opioids. In this review, we discuss the molecular mechanism and the pharmacological aspects of histamine-induced itch. Especially, the underlying mechanism of TRPV1 (an anti-pruritus target) has been determined to some extent.

Introduction

Itch is a sensation felt on skin, which causes the desire to scratch. Although itch might constitute an alert system against certain stimuli like mosquito bites, it can become stressful and exhausting when excessive. Indeed, patients with severe pruritus often find it difficult to lead a normal life due to itch-associated psychological disturbances, such as, depression or sleep deprivation [1,2]. Atopic dermatitis patients suffer from severe itch, and this disease is inadequately addressed by currently available medications. Therefore, an understanding of the mechanism of itch is essential in order to treat severe symptoms.

Although numerous substances are known to cause pruritus, such as, substance P, cytokines, proteases and so forth (for a detailed review on pruritogenic agents, see [3,4]), histamine is best known to evoke experimental itch when applied to the skin [5-9]. Recent itch-related studies have

focused on non-histaminergic itch symptoms, but it is also of considerable importance that we understand the manner in which histamine induces itch. In this regard, it is worth mentioning that antihistamines are among the most widely-used drugs in the United States [10]. Therefore, in this review, we will focus mainly on experimental findings concerning histamine-induced itch.

Histamine and itch

Histamine is released from mast cells when tissues are inflamed or stimulated by allergens [11,12], and once released, histamine induces itch is triggered by the excitation of a subset of unmyelinated C-fibers [13]. Histamine receptors are known to mediate histamine-induced responses, and are members of the G-protein-coupled receptors. Four subtypes of histamine receptors have been identified to date, and histamine receptor subtype I (H1R) has been studied most extensively in the context of hista-

mine-induced itch. In fact, H1R blockers (antihistamines) are widely used to manage and alleviate itch symptoms [14]. However, the itch-reducing efficacies of these classical H1R antihistamines are debatable because some believe that the effect is attributable to sedation rather than to H1R antagonism [15]. It appears that H1R antagonism does, at least to some extent, attenuate histamine-induced itch, because non-sedative second generation H1R antihistamines are beneficial for the management of itch symptoms [16]. However, in contrast to the proven relation between H1R and itch induction, the involvement of histamine receptor subtype II (H2R) is less convincing. It is generally believed that H2R is at best, only marginally involved in histamine-induced itch process [17,18]. For instance, dimaprit (a H2R agonist) failed to cause scratching, and cimetidine (a H2R antagonist) failed to suppress histamine-induced itch in BalbC mice [19]. On the other hand, it is intriguing that histamine receptor subtype III (H3R) "antagonists" aggravate itch symptoms, which appears to contradict the aforementioned histamine-induced itch pathway [20]. For example, the blockade of H3R by H3R-specific antagonists (thioperamide or AQ0145) was found to significantly increase the incidence of scratching behavior in mice [21]. Furthermore, intradermal injections of iodophenpropit or clobenpropit (also H3R antagonists) caused significant increases in scratching behavior in both mast cell-deficient and wild-type mice [22]. Currently, it appears that the itch elicited by H3 antagonism is mediated by substance P, another itch-inducing agent [23]. However, it could also be mediated by mixed responses from H3R and histamine receptor subtype IV (H4R), since clobenpropit (a H3R antagonist) is also an agonist of H4R [24]. H4R agonists cause scratching responses in mice, and are attenuated by pretreating animals with a selective H4R antagonist, like JNJ7777120 [25]. It is also noteworthy that scratching behaviors are almost completely abolished when H1R/H4R antagonists or H1 antagonist are co-administered to H4R-knockout mice, which suggests that H1R and H4R are key components of the itch response [25].

Summarizing, it appears that activated H1R and H4R are involved in the induction of itch, whereas H3R acts in the reverse manner. On the other hand, it appears that H2R has a minor role at most.

The histamine signaling pathway in sensory neurons

H1R is coupled with $G\alpha_q$ proteins, and this interaction activates phospholipase C (PLC) [26]. In line with this, it has been reported that histamine elevates calcium levels in rat cultured sensory neurons, and that this elevation is blocked by U73122 (a PLC inhibitor) [27]. Moreover, it was recently found that PLC β 3 (and not the other PLC iso-types) specifically mediates histamine-induced calcium

responses via H1R in cultured sensory neurons [28]. On the other hand, stimulation of phospholipase A₂ (PLA₂) by H1R was found to mediate histamine-induced sensory neuron excitation [29,30]. Furthermore, Shim and colleagues showed that histamine induces itch by activating PLA₂, lipoxygenase, and the TRPV1 signaling pathway [30]. Histamine induces inward currents that are blocked by antagonists of TRPV1, a nonselective cation channel stimulated by capsaicin [30,31]. They also demonstrated that TRPV1 activation in sensory neurons by histamine is mediated by the synthesis of 12-HPETE – a metabolite of 12-lipoxygenase and an endogenous TRPV1 activator [30,32]. Moreover, histamine-induced scratching is greatly reduced when inhibitors or blockers of H1R, PLA₂, 12-lipoxygenase, or TRPV1 have been pre-treated. More importantly, histamine-induced scratching is significantly lower in TRPV1-deficient mice [30]. In line with this, the direct intradermal injection of 12-HPETE (an endogenous TRPV1 activator) was found to evoke scratching behaviors in mice [33]. However, this 12-HPETE/TRPV1 linkage is somewhat controversial, since 12-HPETE-induced scratching in mice is not blocked by the TRPV1 antagonist capsazepine [34]. However, 12-HPETE-induced scratching is reduced by topical application of capsaicin [33], which is also known to cause desensitization of TRPV1. More studies are required to determine whether 12-HPETE/TRPV1 activation mechanisms participate in H1R-related itch pathways.

It is well-known that H2R is involved in gastric acid secretion, wherein the coupling of H2R and $G\alpha_s$ leads to cAMP production [26]. However, as mentioned above, the role of H2R in itch appears minor. H3R, on the other hand, is linked to $G\alpha_{i/o}$ and the activation of H3R mainly inhibits cAMP formation [35], but various down-stream signals are also generated, such as, the activations of mitogen-activated protein kinase (MAPK), PLA₂, and others (For a detailed review, see [36]). However, it should be noted that H3R is predominantly expressed in the central nervous system, and was first identified in brain [37]. Although its existence in perivascular nerve terminals has been suggested [38], it appears that H3R is not present in the peripheral nervous system – at least in mice [23]. Therefore, the role of H3R in the mediation of histamine-induced itch seems minor. However, interestingly, H3R is regarded as a novel target for the treatment of obesity and cognitive disorders [39,40].

The importance of H4R in terms of itch is becoming more evident [41,42]. It is well known that the activation of H4R increases intracellular Ca²⁺ levels; possibly in a phospholipase C-dependent manner in mast cells [43]. Moreover, the existence of H4R in sensory neurons is suggested by the observation that an intradermally administered H4R-specific agonist elicited scratching in mice, which

were completely inhibited by pretreatment of H4R antagonist, JNJ7777120 [25]. Thus, it seems likely that the activation of H4R results in the excitation of itch-mediating histamine-sensitive afferents by increasing intracellular Ca^{2+} levels, as mentioned above for the H1R pathway.

Neurophysiology of itch fibers

Most C fibers are polymodal nociceptors that respond to noxious mechanical and heat stimuli (CMH units). These CMH units are mainly related to nociception, but are largely insensitive to or only weakly activated by histamine [44]. In addition, histamine-sensitive C-fibers do not respond to mechanical stimulation, which indicates that these itch-mediating fibers differ from polymodal C-fibers [45]. Indeed, these itch-mediating C fibers only comprise about five percent of afferent C-fibers in human cutaneous nerves [5]. Histamine activates a subset of C-fibers that innervate the superficial layer of skin and transmit electrical signals to the superficial layer of the dorsal horn of the spinal cord [5]. These signals then ascend to the thalamus through contralateral spinothalamic tracts and are eventually conducted to the somatosensory and cingulate cortex [46]. Interestingly, it was found that gastrin-releasing peptide plays a key role in mediating itch sensation, rather than pain, by interacting with gastrin-releasing peptide receptor (GRPR) at the spinal level [47]. Furthermore, the induction of scratching behavior in response to pruritogenic stimuli was significantly diminished in GRPR knockout mice, but pain-related behavioral responses to noxious stimuli were normal [47]. In addition, direct spinal injection of a GRPR antagonist considerably inhibited scratching behaviors [47]. Again, these results provide support for the presence of a distinct itch-mediating pathway. On the other hand, the itch elicited by cowhage (a non-histaminergic pruritogen) appears to be mediated through other distinct primary afferents [48] and through cowhage-specific non-histaminergic spinothalamic tracts [49]. Therefore, it seems that different types of itch-mediating neurons coexist in the periphery. Recently, the active compound in cowhage was identified as a novel cysteine protease "mucunain", which is a ligand for protease-activated receptors-2 and 4 [50]. Nakano *et al* recently similarly concluded that different types of dorsal horn neurons are associated with histamine-induced and protease-activated receptor-2-mediated itch [51]. Thus, it seems that there exist dedicated itch-mediating neuronal pathways. Moreover, the recent identification of the coexistence of histamine-sensitive and insensitive (or protease-related) pathways may provide some insight into the mechanism of itch.

Painful stimuli inhibits itch sensation

We all share the experience that scratching relieves itching. Furthermore, itch is also relieved when noxious heat is administered [52]. In other words, itch can be suppressed

by painful mechanical and thermal stimuli. As stated above, itch- and pain-inducing stimuli activate distinct populations of sensory fibers, and thus, it is likely that painful stimuli modulate itch sensations centrally and not at the peripheral level. Histamine was found not to induce itch when a noxious thermal stimulus was administered within 10 cm, or to reduce itch severity if a noxious stimulus was administered more than 10 cm away [53]. Noxious cold also reduces pruritus when administered to fingertips contralateral to a pruritic stimulus [54]. Moreover, various other painful stimuli, such as, noxious heat or scratching, are known to inhibit histamine-induced itch via central mechanisms [55-57].

In fact, capsaicin, the active ingredient of hot pepper, is used as an anti-pruritic agent [58]. Capsaicin activates the nonselective cation channel TRPV1, which is regarded to induce nociception [31]. Thus, it is assumed that the anti-pruritic effect of capsaicin is attributable to its algescic effect. However, it should be noted that TRPV1 is expressed in some histamine-sensitive itch-mediating fibers as well as nociceptive C-fibers [30], which raises the question; What types of processes are involved in the sensation experienced when capsaicin is applied to the skin? In most cases, pain is likely to be the predominant perception, since approximately 80% of the primary afferent C-fibers are polymodal nociceptors [59-61]. In fact, the clinical limitation of topical capsaicin administered as an anti-pruritic agent is that it produces unbearable, burning pain [58]. Furthermore, even if capsaicin excites TRPV1 in itch fibers, the itch sensation may not dominate since itch-mediating fibers comprise only small proportion of C fibers [5]. Thus, although capsaicin may activate both pain and itch through TRPV1 receptors in their respective neurons, it is highly likely that capsaicin preferentially activates nociceptive fibers.

However, it should also be noted that repeated and prolonged applications of topical capsaicin are required to effectively reduce itch [62,63]. This method of application is believed to fully desensitize and deplete neuropeptides, such as, substance P in sensory afferents, and to thus delay the interconnection between skin and sensory neurons [58]. Indeed, it has been shown that repetitive application of topical capsaicin prevents histamine-induced itch under experimental conditions [64]. In this regard, it can also be considered that the anti-pruritic effect of capsaicin may stem from peripheral desensitization of sensory neurons and central mechanisms.

Itch can also be suppressed by cold stimuli [65-67], and in particular the anti-pruritic effect of menthol is interesting [65], because menthol activates cold receptor TRPM8 [68,69]. However, although TRPM8 is a wonderful molecular target, the mechanism whereby cold and menthol

mitigates itch has yet to be determined. TRPA1, which is activated by noxious cold ($<17^{\circ}\text{C}$), is also a viable target [70]. but no concrete relationship between itch and TRPA1 has been established. On the other hand, warming appears to aggravate itch. Indeed, histamine-induced response is potentiated by warming [67], but no clear explanation has been offered as to how these thermal stimuli interact with itch at the molecular level. It is noteworthy that some TRP channels, like TRPV3 [71,72] respond to warming, which suggests that they participate in itch induction. However, no studies to date have focused specifically on this topic.

Unfortunately, the relationships between itch and exogenous stimuli in disease states appear anything but straightforward. For instance, the itch-inhibitory effects of repetitive scratching and noxious heat are ineffective in patients with atopic dermatitis [73]. Similarly, the inhibitory effect of topical capsaicin on histamine-induced itch was found to be ineffective in atopic dermatitis patients, but effective in healthy controls [64], indicating that other factors are involved in disease states. Moreover, in contrast to our general understanding that cooling alleviates itch, short-term low-intensity cooling increases the intensity of histamine-induced itch above the scratch threshold in man [74,75].

Interestingly, as a corollary to the suppression of itch by painful stimuli, the reduction of pain by opioids may induce itch [76]. Patients spinally administered μ -opioid agonists frequently experience itch [77,78], whereas μ -opioid antagonists often suppress experimentally-induced itch [8,79]. However, not all opioids evoke itch, for example, nalbuphine (a κ -opioid agonist) has been shown to reduce μ -opioid-induced pruritus [80], and κ -opioid antagonists enhance itch, which contrasts the effects of μ -opioids [81]. Currently, it is unclear why different opioids have different effects on itch. Nevertheless, it seems evident that itch can be enhanced when pain is suppressed, and suppressed when pain is enhanced, which demonstrates the existence of an intimate physiologic interaction between underlying causes of itch and pain sensations.

Conclusion

Itch is probably viewed as trivial malady by most, but to many patients itch is a distressing condition. Although it has been revealed by many researchers that there is a histamine-independent itch, this should not detract from the fact that histamine is deeply involved in various itch sensations. Recent advances in molecular biology have helped reveal the key molecular players involved, but a considerable amount of effort will be required to determine how histamine-induced itch is mediated and can be inhibited. In our opinion, a thorough understanding of

the pruritogenic actions of *histamine* is required if we are to resolve itch symptoms at the clinical level.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

WS drafted the manuscript and UO revised the manuscript.

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