The Transient Receptor Potential (TRP) Channels and Itch

Subjects: Dermatology

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Itch (pruritus) is a sensation in the skin that provokes the desire to scratch. The sensation of itch is mediated through a subclass of primary afferent sensory neurons, termed pruriceptors, which express molecular receptors that are activated by itch-evoking ligands. Also expressed in pruriceptors are several types of Transient Receptor Potential (TRP) channels. TRP channels are a diverse class of cation channels that are responsive to various somatosensory stimuli like touch, pain, itch, and temperature. In pruriceptors, TRP channels can be activated through intracellular signaling cascades initiated by pruritogen receptors and underly neuronal activation.

Keywords: acute itch ; atopic dermatitis ; chronic itch

1. Introduction

Itch (or pruritus) is defined as an unpleasant sensation that provokes the desire to scratch and is associated with an innate reaction to scratch away insects or plant spicules from the skin surface or to dig out invasive parasites. While everyday acute itch reflects an adaptive mechanism to maintain the integrity of the skin, chronic itch can adversely affect the quality of life to the point of suicidal ideation [1]. It is estimated that itchy skin conditions such as atopic dermatitis (AD) or psoriasis affect upwards of 10% or more of the general population, with associated annual health care and economic costs in the billions of dollars [2][3][4][5][6][7]. Chronic itch is thus a major health issue that demands more scientific attention. While major strides have been made in our understanding of itch mechanisms over the past few decades, the treatment of chronic itch remains challenging and requires the development of therapeutic approaches and pharmaceuticals targeting the currently known itch transducers and signaling pathways.

Itch is generally classified as acute (<6 weeks) or chronic, lasting longer than six weeks. Chronic itch is a common symptom of multiple skin diseases, namely allergic contact dermatitis (ACD), AD, psoriasis, chronic urticaria, xerosis cutis, and other skin diseases such as prurigo nodularis, epidermolysis bullosa, lichen planus, actinic prurigo, Morgellons disease, and aquagenic pruritus [8][9][10][11]. Chronic itch is divided into four categories: dermatological, systemic, neurological, and psychogenic [12]. The dermatological itch comes from skin conditions such as AD, psoriasis, and urticaria. Systemic itch can be caused by the pathology of other organs; for example, liver cholestasis and kidney dialysis. Neurological itch is induced by direct damage to the peripheral or central nervous system. Finally, psychogenic itch is associated with mental disorders [12][13].

2. The Transient Receptor Potential (TRP) Channels and Itch

TRP channels involve diverse sensory functions (smell, taste, touch, pain, temperature), including histamine-dependent and -independent itch. TRP superfamily ion channels, especially the TRP cation channel, subfamily A, member 1 (TRPA1), TRP cation channel, subfamily C (Canonical), Members 3 and 4 (TRPC3/4), TRP Cation Channel Subfamily M (Melastatin) Member 8 (TRPM8), TRP cation channel, subfamily V (Vanilloid), member 1 (TRPV1), TRP cation channel, subfamily V (Vanilloid), member 3 (TRPV3), and TRP cation channel, subfamily V (Vanilloid), member 4 (TRPV4), are key elements for signal transduction downstream of the G-protein-coupled receptors (GPCRs) and protease-activated receptors (PARs) (**Figure 1**). The opening of TRP channels allows calcium and sodium influx, leading to the depolarization of neuronal membranes and the opening of voltage-gated sodium channels to generate action potentials, thereby transmitting pruriceptive signals in primary afferents into the spinal cord to access ascending pathways to the brain to elicit itch sensations.

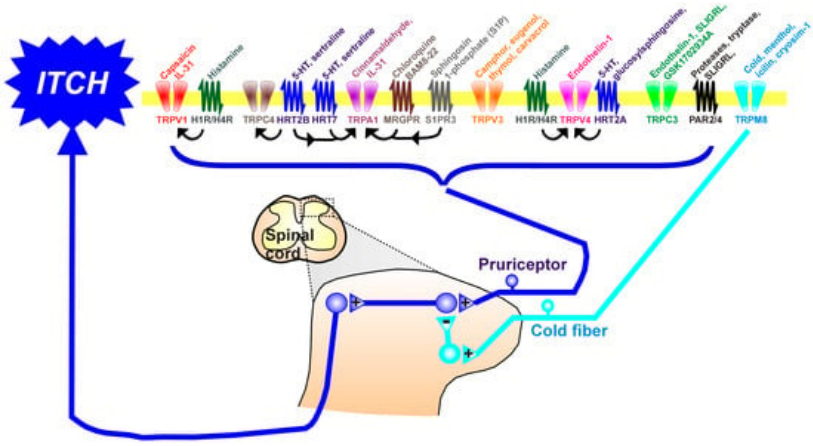

Figure 1. The upper part of the figure shows the variety of TRP channels and G-protein-coupled receptors (GPCRs), nearly all of which are expressed in the membranes of pruriceptive nerve endings in the skin. Many TRP channels and GPCRs are also expressed in skin keratinocytes. Above each TRP channel and GPCR are shown known ligands. Arrows indicate known interactions between GPCRs and TRP channels. The lower part of the figure shows afferent fibers of pruriceptors (blue) that enter the spinal cord via the dorsal roots, where they contact second-order neurons involved in processing itch. Itch signals project into ascending tracts (spinothalamic and spinoparabrachial) to reach higher centers involved in itch sensation. TRPM8-expressing cold fibers also enter the spinal cord to contact inhibitory interneurons (turquoise) that inhibit itch-transmitting spinal neurons. +: excitatory synapse; −: inhibitory synapse. Abbreviations: 5-HT: serotonin (5-hydroxytryptamine); HRT2A, 2B, 7: serotonin (5-hydroxytryptamine) receptor subtypes 2A, 2B, 7; IL-31: interleukin 31; Mrgpr: mas-related protein-coupled receptor; PAR: protease-activated receptor; S1PR3: sphingosine-1-phosphate receptor 3; TRP: transient receptor potential; TRPA1: TRP cation channel, subfamily A, member 1, TRPC3/4: cation channel, subfamily C (Canonical), Members 3 and 4, TRPM8: TRP Cation Channel Subfamily M (Melastatin) Member 8, TRPV1: TRP cation channel, subfamily V (Vanilloid), member 1; TRPV3: TRP cation channel, subfamily V (Vanilloid), member 3; TRPV4: TRP cation channel, subfamily V (Vanilloid), member 4.

Roles for TRP channels have been elucidated in complex diseases of the nervous, intestinal, renal, urogenital, respiratory, and cardiovascular systems in diverse functions including pain and itch, headache, pulmonary function, oncology, neurology, visceral organs, and genetic diseases [14]. Some TRP channels are involved in thermosensation and are stimulated by thermal stimuli across a specific temperature range [14][15].

2.1. TRP Cation Channel, Subfamily A, Member 1 (TRPA1) in Acute Itch

TRPA1 is a non-selective cation channel for calcium ion influx and is widely expressed in the skin, sensory neurons, and many other tissues. TRPA1 is involved in sensory physiology and numerous systemic diseases. It is activated by a range of endogenous and exogenous stimuli, including natural molecules such as allyl isothiocyanate (AITC, the main compound of mustard oil), eugenol, and cinnamaldehyde (CA). TRPA1 plays a significant role in mediating and regulating acute and chronic itching, and many itch-related GPCRs positively modulate TRPA1 [16]. Knockout mice (KO) lacking TRPA1 exhibited significantly reduced acute scratching elicited by chloroquine (CQ) and bovine adrenal medullary (BAM8-22) peptide [17] and sphingosine 1-phosphate (S1P) [18], as well as scratching in a model of chronic dry skin itch [19], indicating a role for TRPA1 in acute non-histaminergic as well as chronic itch. It was recently reported that TRPA1 inhibition reduced scratching behavior and calcium influx into dorsal root ganglion (DRG) cells elicited by a histamine H4 but not H1 receptor agonist, whereas TRPV1 inhibition reduced scratching and DRG neuronal calcium responses to both, suggesting that both TRPV1 and TRPA1 are involved in the transmission of histamine-induced itch [20][21]. In animal models, the study of DRG neurons has led to significant steps in our understanding of itch (and somatosensory) transduction. DRG neurons are a diverse population of primary afferent neurons that express different receptor mosaics allowing differentials in the responses to various modalities of stimulation (i.e., mechanical, warm, hot, cold, itch, etc.). The field has characterized several populations of itch-sensitive primary afferent neurons, allowing for a greater understanding of the neuronal circuitry as well as a deeper understanding of the intracellular signaling pathways relevant to itch transmission. While the DRG neurons have been well characterized in mice, human DRG neurons are less understood given the lack of available human DRGs for experimental usage. RNA expression studies have shown a significant correlation between the itch-relevant mouse and human DRGs, making the mouse a viable model organism [22].

In conclusion, TRPA1 is critical for acute non-histaminergic itch as well as chronic itch in dry skin and is partially involved in acute histaminergic itch. TRPA1 represents a promising target for the development of antipruritics.

TRPA1 in Chronic Itch

AD is an inflammatory skin condition associated with intense itch, which generally develops in early childhood [23]. In AD, the occurrence of itch can precede the development of skin lesions and it is suggested to be neurogenic in origin [24][25]. In AD, thymic stromal lymphopoietin (TSLP) is released from epithelial cells and is critical to the atopic march triggering skin inflammation [26]. In the mouse, a genetic overexpression of TSLP in keratinocytes triggers itch and the development of AD-like skin. The injection of TSLP-induced scratching behaviors, and KO of TRPA1 attenuated TSLP-evoked scratching, suggesting that TRPA1 is involved in TSLP-mediated itch in AD [27][28]. Topical application of the vitamin D analog calcipotriol (MC-903) produces AD-like pathology including increased itch and skin hyperplasia, and increased TSLP expression [29]. In TRPA1 KO mice treated with MC-903, there was a significantly reduced lesion area and fewer scratching bouts when compared to treated wild-type mice [30]. In AD, there is an increased expression of interleukin-13 (IL-13) which promotes inflammation and is associated with increased nerve-ending innervation of lesioned skin [31]. In transgenic mice with an overexpression of IL-13, AD symptoms develop including increased itch, which is attenuated following the injection of the TRPA1 antagonist, HC-030031 [31]. In the DNCB (2,4-dinitro-chlorobenzene) model of AD, TRPA1 antagonism or KO resulted in a lower dermatitis score and fewer scratch bouts [32]. Glucosylsphingosine (GS) is an endogenous sphingolipid which is upregulated in the skin of AD patients. GS evokes the itch sensation and can activate neurons through a serotonin 2A receptor/TRPV4 interaction [33]. New evidence suggests that GS can activate neurons through a serotonin 2 receptor/TRPA1 but not TRPV1 interaction [34]. These results provide strong preclinical evidence for the importance of TRPA1 in the regulation of itch and skin inflammation in AD.

In the oxazolone and SADBE (squaric acid dibutyl ester) models of allergic contact dermatitis (ACD), the KO of TRPA1 reduced skin inflammation, skin edema, keratinocyte hyperplasia, and scratching behaviors [35][36]. Itch elicited by the application of the plant chemical urushiol, as commonly found in poison ivy, was reduced in TRPA1 but not TRPV1 knockout mice [35].

Psoriasis is an inflammatory skin disease that evokes an itch sensation in 60–90% of patients [37]. Psoriasis is mediated through the release of IL-17 from T helper-17 (Th17) cells, which induces feed-forward inflammation [37][38]. In the mouse, a commonly used model for psoriasis is the topical application of imiquimod (IMQ), which induces many of the hallmarks of psoriasis [39]. Using the IMQ model in wildtype and TRPA1 KO mice, there was a significant reduction in the immune cells, inflammatory cytokines, skin inflammation, and skin barrier defects in the TRPA1 KO mice [40]. Interestingly, when scratching behaviors were measured in the IMQ model, both male and female mice exhibited increased alloknesis (light touch-evoked scratching), but only male mice showed significantly increased spontaneous scratch bouts. In KO mice lacking TRPA1, spontaneous scratching behavior was not significantly affected while alloknesis scores were partially reduced in male mice [41]. Combined, these data imply that TRPA1 is necessary for the inflammation and disruption to the skin barrier in psoriasis and the development of alloknesis in males, but not for the underlying spontaneous scratching behaviors. Perhaps the inflammation of the skin in the IMQ model is mediated by TRPA1 expression via non-neuronal cells. At the same time, itch is regulated by endogenous itch mediators acting through several parallel pathways.

2.2. TRP Cation Channel, Subfamily V (Vanilloid), Member 1 (TRPV1) in Acute Itch

Twenty-five years after its cloning [42], TRPV1 has become the first subfamily member linked to thermal pain and itch. Histamine activates primary sensory neurons via the histamine type 1 receptor (H1R) linked to TRPV1 [43] and histamine-evoked scratching is attenuated in knockout mice lacking TRPV1 [44].

It has recently found that an intraplantar injection of histamine in mice resulted in significant thermal hyperalgesia and mechanical allodynia ipsilaterally that persisted for 1 h. Pretreatment with the TRPV1 antagonist AMG-517, but not the TRPA1 antagonist HC-030031, significantly attenuated the magnitude and time course of thermal hyperalgesia and mechanical allodynia elicited by histamine, indicating that these effects are mediated by TRPV1 [10][45].

In addition, non-histaminergic pruritus such as that in cholestasis has also been related to TRPV1 sensitization by pruritogens [46]. TRPV1 also plays a role in non-histaminergic itch indirectly via PAR2 and PAR4, which are involved in chronic neurogenic inflammation. The latter sensitizes TRPV1 channels and induces itch [47].

TRPV1 in Chronic Itch

Understanding the influence of temperature fluctuations on skin diseases is critical to the development of measures for the prevention and treatment of allergic disorders. Nowadays, a number of studies have concluded that both cold and hot temperatures affect skin homeostasis and barrier function, and promote the development of AD. The temperature-driven activation of TRPV subfamily cation channels is involved in the induction of pruritus, flares, skin barrier dysfunction, the development of AD, and asthma attacks. The blocking of TRPV channels may attenuate temperature-mediated itch, skin barrier dysfunction, and the exacerbation of AD [48].

In the mice house dust mite (HDM) model of ACD, it was discovered that the administration of the TRPV1 antagonist, PAC-14028, reduced scratching and improved skin barrier function and recovery [49][50]. Similarly, in the SADBE model of ACD, the ablation of TRPV1-positive nerve fibers with the capsaicin analog, resiniferatoxin, or knockout of TRPV1 reduced scratching behaviors. SADBE directly activated HEK cells expressing TRPV1 (or TRPA1), inducing calcium transients. Interestingly, the antagonism or knockout of TRPV1 increased edema in the SADBE treatment [36]. These results suggest that TRPV1 promotes itch but negatively regulates inflammation in the SADBE model.

Capsaicin, an agonist of TRPV1, has been used to treat the chronic itch of notalgia paresthetica [51][52], although the topical application of high-dose capsaicin induces discomfort and pain [53]. The topical application of TRPV1 antagonists, PAC-14028 and Asivatrep, resulted in a significant reduction in pruritus-related visual analog scale (VAS) scores in patients with AD [54][55][56]. Asivatrep (PAC-14028) was one of the first of a new class of non-vanilloid potent and selective TRPV1 antagonists. In a mouse AD model, oral treatment with asivatrep significantly reduced scratching behavior and suppressed the release of substance P (SP) through the inhibition of TRPV1 activation [49][50]. Asivatrep cream was well-tolerated and was not associated with clinically significant skin reactions and had an acceptable safety profile [57]. SB-705498 is another potent and selective TRPV1 antagonist [58], but had little effect on histamine- or cowhage-evoked itch in humans [59]. These results highlight the dissociation between itch and inflammation. While they often accompany each other in dermatological maladies, itch can occur without the presence of lesions, and lesions can occur without itch. Nevertheless, TRPV1 remains a promising target for the development of antipruritic pharmaceuticals.

2.3. TRP Cation Channel, Subfamily V (Vanilloid), Member 2 (TRPV2)

TRPV2 is a nonspecific cation channel expressed in a subset of medium- to large-diameter DRG neurons. However, little information is available concerning its contribution to itch sensation and there is no concrete evidence yet whether TRPV2 is involved in various itch conditions [15]. Only one study reported that the *trpv2* gene was upregulated in the skin of patients with AD [60]. In a second study, the activation of TRPV2 in the human mast cell line (HMC-1) resulted in degranulation, a process through which endogenous pruritogens such as histamine are released [61].

2.4. TRP Cation Channel, Subfamily V (Vanilloid), Member 3 (TRPV3)

In the last few years, the TRPV3 channel has received much interest for its similarity to TRPV1. TRPV3 is a non-selective mainly calcium-permeable cation channel that is expressed in skin keratinocytes and is involved in multiple physiological and pathological functions of the skin, such as AD and Olmsted syndrome (OS). The human TRPV3 gene shows different degrees of sequence similar to TRPV1 and TRPV4. TRPV3 is expressed in diverse human tissues, among them the skin, DRG, spinal cord, brain, and testes [62].

Similar to TRPV1, the TRPV3 channel is a calcium-permeable, nonselective cation channel involved in itch and activated by temperature (>33 °C). Plant-derived camphor activates TRPV3 and sensitizes responses of the channel to warmth. Warm temperature stimulates TRPV3 in keratinocytes, releasing various inflammatory factors which activate pruriceptors in sensory neurons to transmit itch signals [15].

TRPV3 can also be activated by chemicals such as eugenol, thymol, and carvacrol—major components of oregano, savory, clove, and thyme. In mice, TRPV3 was not detected in DRG neurons, but it was detected in keratinocytes and is essential in causing allergic and pruritic dermatitis in rodents. In contrast, in primates, TRPV3 expression is also observed in DRG, TG sensory neurons, the hypothalamus, and several nonneuronal tissues [63].

Overall, recent studies in rodents evaluated the relation of TRPV3 to itch in AD and psoriasis. However, less is known concerning the clinical relevance of TRPV3 in human studies. Further research is needed to reveal the roles of TRPV3 in human skin abnormalities in detail.

2.5. TRP Cation Channel, Subfamily V (Vanilloid), Member 4 (TRPV4)

TRPV4 was originally described as an osmo- and mechanosensor [64]. An unexpected role for TRPV4 in itch came with the discovery that scratching behavior elicited by histamine [65][66] and serotonin [67] was reduced in KO mice lacking TRPV4, and that serotonin-evoked scratching and the activation of DRG neurons was reduced by a TRPV4 antagonist in wildtype mice [67] (for a review, see [68]).

Scratching elicited by the intradermal injection of endothelin-1 was also attenuated in TRPV4 KO mice [65]. Scratching elicited by glucosyl sphingosine [33] and CA [69] was also reduced in TRPV4 KO mice.

2.6. TRP Cation Channel, Subfamily C (Canonical), Members 3,4 (TRPC3 and TRPC4)

TRPC3 is strongly expressed in DRG cells, and mice lacking TRPC3 exhibited significantly reduced scratching elicited by intradermal injections of endothelin-1, the PAR-2 agonist SLIGRL, and the TRPC3 agonist GSK1702934A [70], supporting a role for TRPC3 in non-histaminergic itch. The intradermal injection of the serotonergic antidepressant sertraline at a dose of 1 mmol was reported to elicit scratching behavior in mice via the 5HT-2B receptor and TRPC4 channel [71].

2.7. TRP Cation Channel, Subfamily M (Melastatin), Member 8 (TRPM8)

TRPM8 was originally described as a receptor for cold and menthol [72][73][74], conveying thermosensitivity in cold fibers. While skin cooling has been used for centuries to relieve itch, it was only recently shown that skin cooling and menthol can alleviate both histaminergic and nonhistaminergic itch-related behavior in mice in a TRPM8-dependent manner [75]. Cold fibers are thought to activate inhibitory spinal interneurons that suppress spinal itch transmission (**Figure 1**). Indeed, mice lacking a particular class of itch-inhibitory spinal interneuron (B5-I) exhibited a reduction in the antipruritic effect of menthol [76]. Recent clinical studies suggest that the cooling agent cryosim-1 may be antipruritic in various types of chronic itch, including scalp itch [77][78].

3. Conclusions

Emerging evidence clearly implicates TRP channels, Mrgprs, and PARs in a variety of itch-inducing mechanisms relevant to diseases that produce chronic itch. Since these channels and receptors are peripherally expressed and can mediate both inflammation and itch, they represent promising targets for the development of antipruritic pharmaceuticals. Several TRPV1 antagonists are in development for the treatment of pruritus, but with mixed results. Despite the strong preclinical evidence for TRPA1, there is a current lack of reports regarding pharmaceutical development for this promising target. More studies, including clinical trials of promising pharmaceutical agents that act at TRP channels, Mrgprs, and PARs, are sorely needed since most types of chronic itch are poorly treated by current therapeutics. Moreover, as we learn more about the central itch circuitry, it is hoped that pharmaceutical development will target other receptors, such as Gastrin Releasing Peptide (GRP)-expressing spinal neurons known to be involved in the central transmission of itch signals to relieve itch.

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