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Invited review article

The molecular and cellular mechanisms of itch and the involvement of TRP channels in the peripheral sensory nervous system and skin

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Abbreviations:
AD, atopic dermatitis; TRP, transient receptor potential; TRPM, transient receptor potential melastatin; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; LOX, lipoxygenase; PL, phospholipase; DRG, dorsal root ganglion; TG, trigeminal ganglion; ET, endothelin; PAR, proteinase-activated receptor; VGLUT, vesicular glutamate transporter; DTA, diphtheria toxin A; Nppb, natriuretic polypeptide b; TLR, Toll-like receptor; PIC, a synthetic double strand RNA Poly(I:C); CQ, chloroquine; Mrgpr, Mas-related G protein-coupled receptor; BAM, bovine adrenal medulla peptide 8–22; ER, endoplasmic reticulum; AITC, allyl isothiocyanate; AEW, acetone, ether and water; TSLP, thymic stromal lymphopoietin; IL, interleukin; NFAT, nuclear factor of activated T-cells; BA, bile acid; CGRP, calcitonin gene-related peptide; SP, substance P; AC, adenylate cyclase; LT, leukotriene; LPA, lysophosphatidic acid

ABSTRACT

Itch is an unpleasant cutaneous sensation that can arise following insect bites, exposure to plant ingredients, and some diseases. Itch can also have idiopathic causes. Itch sensations are thought to protect against external insults and toxic substances. Although itch is not directly lethal, chronic and long lasting itch in certain diseases can worsen quality of life. Therefore, the mechanisms responsible for chronic itch require careful investigation. There is a significant amount of basic research concerning itch, and the effect of various itch mediators on primary sensory neurons have been studied. Interestingly, many mediators of itch involve signaling related to transient receptor potential (TRP) channels. TRP channels, especially thermosensitive TRP channels, are expressed by primary sensory neurons and skin keratinocytes, which receive multimodal stimuli, including those that cause itch sensations. Here we review the molecular and cellular mechanisms of itch and the involvement of TRP channels in mediating itch sensations.

Introduction

Itch is an unpleasant cutaneous sensation that evokes the desire to scratch.[1] Among different forms of pain that lead to avoidance of noxious stimuli, itch is primarily thought to be a means for eliminating exogenous compounds such as parasites and plant particles.

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Itch sensation and scratching behaviors are conserved across a broad range of species, from rodents and birds to humans. In humans, environmental substances such as allergens, mosquito bites, and some chemical compounds can cause itch, but chronic itch can accompany systemic diseases including atopic dermatitis (AD), kidney failure, cholestasis, and neuronal lesions.[2]

For the past two decades, significant effort has been devoted to elucidate the molecular mechanisms of itch. Several studies presented evidence showing that the peripheral nervous system in particular transduces cutaneous sensory stimuli into electrical signals and transmits them to the central nervous system. Two calcium-permeable ion channels, transient receptor potential vanilloid 1 (TRPV1) and ankyrin 1 (TRPA1), which are both well expressed in primary afferent sensory neurons, were found to play crucial roles in detecting pruritogens and nociceptive stimuli.[3–5] This review focuses on the TRP channels that detect pruritogens in the periphery and discusses the molecular and cellular mechanisms of itch that involve TRP channels.

Numerous basic experiments have been conducted to investigate the molecular mechanisms of itch sensation. Among them, the simplest and most quantitative method to evaluate itch sensation, especially in rodents, is counting scratching behaviors directed towards the sites of compound injection. The most famous method reported more than 20 years ago is counting scratching at the nape of the back to which chemicals were applied.[6] Later, the cheek injection model was developed to evaluate itch sensation by counting scratching with the ipsilateral hindpaw at the cheek to which the chemical was applied. The cheek injection model allows itch- and pain-related behaviors to be distinguished because with pain the animals wipe the cheek with the ipsilateral forepaw.[7] These models facilitated progress in itch research, and here we cite those works that focus on TRP channels and itch sensation.

TRP channels involved in itch

TRP channels are non-selective calcium-permeable cation channels that compose the TRP ion channel superfamily. TRP channels were first described in *Drosophila*, in which photoreceptors carrying *trp* gene mutations exhibited an abnormal transient responsiveness to continuous light. In mammals, TRP channels comprise six related protein families (TRPC, TRPV, TRPM, TRPA, TRPML, TRPP)[8] (Fig. 1). In general, TRP channels are ubiquitously expressed, indicating that most cells have several TRP channel proteins. Although the physiological functions of most TRP channels are unknown, their wide distribution indicates that the biological functions and activation mechanisms for these channels are diverse. As such, TRP channels are best recognized for their contributions to sensory transduction, response to temperature, nociceptive stimuli, touch, osmolarity, pheromones and other stimuli from both within and outside the cell. Several kinds of TRP channels are expressed exclusively in subsets of sensory neurons, suggesting their involvement in detecting nociceptive stimuli and itch-producing stimuli.

Among the large TRP ion channel superfamily proteins, TRPV1, TRPV2, TRPV4, TRPM (melastatin) 2, TRPM3, TRPM8, and TRPA1 channels are expressed in sensory neurons such as dorsal root ganglion (DRG) neurons and trigeminal ganglion (TG) neurons.[9–16] Meanwhile, TRPV3 and TRPV4 are expressed by skin keratinocytes.[17,18] Some of these TRP channels are reportedly involved in itch sensation.[2,19–23] Interestingly, they are all so-called thermosensitive TRP channels[10,11,13–18,24–27] and show sensitivity to multimodal stimuli that include acid,[9] alkaline,[28,29] osmolarity,[30,31] artificial compounds,[32] and phytochemicals.[9,33] We review these multimodal TRP channels with regard to their involvement in itch sensation.

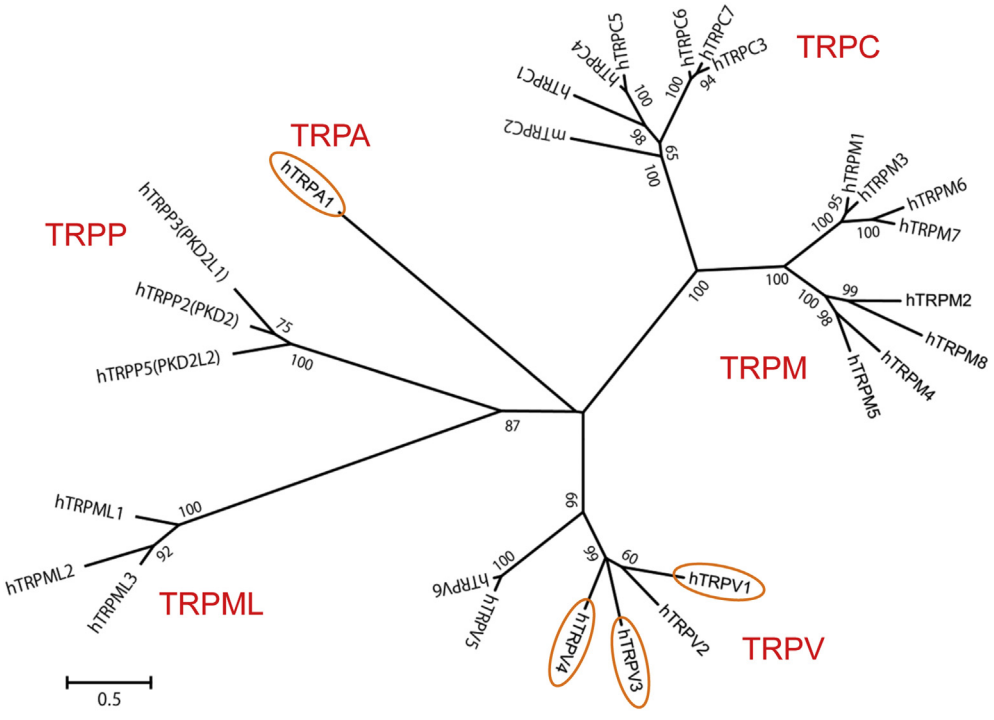

Fig. 1. A phylogenetic tree of human TRP channels. A phylogenetic tree was made with minimum evolution principle upon expecting amino acid substitutions using a JTT model. There are 27 TRP channels in 6 subfamilies (shown in red) in human. The TRP channels shown in orange circles indicate channels described in this review. Numbers at each branch indicate statistical bootstrap values. Mouse *Trpc2* gene was used because human *TRPC2* gene is a pseudogene. Scale: genetic distance (recombination rate).