

NEWS, VIEWS, & REVIEWS

Not So Vanilla: What Dermatologists Should Know About Vanilloid Receptors

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INTRODUCTION

The transient receptor potential (TRP) channel superfamily consists of several variably selective cation channels expressed throughout the human body.[1] These channels are activated through various mechanisms and primarily function as sensory receptors, mediating pain sensations, temperature, vision, pressure, osmolality, olfaction, and more.[2] The six members of the vanilloid subfamily of TRP channels (TRPV1-6) are named for the vanilloid compound capsaicin originally found to activate the first TRPV channel (vanilloid receptor 1/TRPV1). However, they are now known to be activated by many exogenous and endogenous ligands. TRPV1, TRPV3, and TRPV4 are expressed in several tissues including the skin, leading to myriad cutaneous functions.[3] Dermatologists benefit from understanding how TRPVs contribute to the neurogenic inflammation that underlies many dermatologic diseases and emerging therapeutics that leverage this connection.

Transient Receptor Potential Vanilloid subfamily

The skin is a major somatosensory organ. Afferent nerve endings throughout the epidermis and dermis detect various stimuli, transducing this information into electrical activity that the central nervous system (CNS) may interpret and respond to. TRPV in the skin are found on sensory nerve fibers as well as keratinocytes, mast cells, dendritic cells, sebaceous cells, dermal endothelial cells, hair follicles, and eccrine glands.[4] Tissue expression and cutaneous functions of TRPV1-4 are summarized in the Table.

Neurogenic Inflammation

Cutaneous neurogenic inflammation is created through the bidirectional interaction of keratinocytes and skin-residing immune cells with nerve endings and their secreted neuropeptide mediators.[5] TRPV1 and TRP ankyrin 1 (TRPA1) appear to be predominant TRP channels involved in neurogenic inflammation.[5] Activation of TRPV1 and TRPA1 located on sensory neurons leads to increased intracellular calcium and the subsequent release of the neuropeptides, namely substance P (SP) and calcitonin gene-related peptide (CGRP); these neuropeptides, in turn, promote mast cell degranulation, vasodilation, and infiltration of neutrophils and T lymphocytes.[6] Moreover, the release of neuropeptides following activation of TRPV1 and TRPA1 modulate proinflammatory gene expression and induce keratinocytes to produce interleukin (IL)-1-alpha, IL-6, and IL-8.[6] TRPV1 is a central integrator of sensation induced by pruritogenic stimuli;[7] however, although not part of the vanilloid subfamily, it has been suggested that TRPA1 is required for itch transduction and skin barrier defects found in chronic pruritus.[8] Notably, TRPV1 channels may become hypersensitive in the setting of proinflammatory or proalgesic mediators such as extracellular protons, neurotrophins, or bradykinin, thus mediating hyperalgesia.[9,10]

Neurogenic inflammation underlies many inflammatory skin diseases, including rosacea, atopic dermatitis (AD), and sensitive skin.

Table 1. Summary of TRPV1/2/3/4 Cutaneous Tissue Expression and Their Biologic Functions[1,23]

Channel	Expression	Functions	Agonists
TRPV1	Cutaneous sensory nerve fibers, mast cells, epidermal keratinocytes, dermal endothelium, hair follicles, differentiated sebaceous glands, eccrine glands	Thermosensation (noxious heat); nociception; autonomic thermoregulation	heat > 43 °C; vanilloids/capsaicin; protons, endocannabinoids; pain
TRPV2	Cutaneous sensory neurons; immune cells (macrophages, mast cells, natural killer cells, dendritic cells, lymphocytes)	Thermosensation (noxious heat); nociception; inflammatory response	heat > 52 °C; PI3 signaling; delta-9-tetrahydrocannabinol, cannabidiol
TRPV3	Keratinocytes; hair follicles	Thermosensation (moderate heat); nociception; wound healing; skin integrity; hair growth; sebaceous gland function	heat > 31 °C; farnesyl pyrophosphate; camphor
TRPV4	Keratinocytes; endothelium	Thermosensation (moderate heat); nociception; mechano-sensation; vaso-motor control; adherens junction control; modulation of cell migration	heat > 25 °C; extracellular osmolarity change; arachidonic acid metabolites; camphor

TRPV Channels and Dermatologic Disease

Rosacea

Given the various environmental triggers for rosacea, much research has been devoted to elucidating the involvement of TRP channels in rosacea pathophysiology. Across different subtypes of rosacea mast cells were found to colocalize with TRPV2 and TRPV4 and, while mRNA levels of TRPV1, TRPV2, and TRPV3 were found to be elevated in all subtypes, TRPV2, TRPV3 and TRPV4 were found to be differentially expressed.[11] Moreover, TRPV4 plays a significant role in mast cell activation in rosacea.[12]

Atopic Dermatitis

Neuroinflammation is strongly associated with AD. Histologically, AD lesions have increased SP- and CGRP-positive cutaneous sensory nerve fibers and, compared to normal controls, increased contacts between mast cells and nerve fibers are found within both lesional and non-lesional skin.[13] Altogether, these findings support the initiation and maintenance of neurogenic inflammation through mast cell activation and induction of cytokine release by keratinocytes by SP and CGRP. Furthermore, the Type 2 helper T cell (Th2) derived cytokine IL-31 directly activates TRPV1+/TRPA1+ sensory nerves in the skin of AD patients.[14]

Sensitive Skin Syndrome

Sensitive skin syndrome (SSS) is characterized by transient sensory perceptions (burning, tingling, stinging, pain, itching) invoked by otherwise innocuous stimuli. The pathogenesis is not completely understood although it is considered a neuropathic disorder.[15,16] Environmental factors such as temperature change are well-known triggers.[17] Given this information, it is suggested that SSS is a result of sensitization of TRPV1 expressed on cutaneous sensory nerves by the inflammatory neuropeptides endothelin-1 and nerve growth factor, ultimately leading to impaired barrier function and decreased thresholds for sensory nerve receptor activation.[18]

CONCLUSION & EMERGING THERAPEUTICS

Topical formulations containing Asivastrep, Pegcantratinib, and ASN008 compounds targeting TRPV1 are promising avenues for treating chronic pruritus and AD.[19] A phase IIb clinical trial demonstrated that Asivastrep cream has superior effectiveness in reducing inflammation and pruritus than placebo cream, though further evaluation of efficacy and safety in larger-scale phase III trials is necessary.[20] The findings from the PAC-14028 cream trials similarly highlighted significant improvements in AD symptoms, without notable safety concerns.[21] Additionally, applying synthetic peptides targeting TRPV1 for UV-induced skin responses holds promise for addressing inflammation and photoaging.[22] These developments offer alternative therapeutic options for patients seeking non-steroidal medications with a favorable side effect profile.

Disclosure

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