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Research Summary

The Role of Transient Receptor Potential Ion Channels With Pruritus and Diseases of the Skin

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While not intended to be exhaustive, this information is designed to be informative for medical doctors and other medical practitioners involved with pruritus and other dermatological diseases. Transient Receptor Potential (TRP) channels are a group of ion channels found in cells of many animal cell types. Many of these channels mediate a variety of sensations such as: sensations of pain; warmth and hotness; cool and coldness; and itch. TRP channels represent a heterogeneous system oriented towards environment perception, and participating in sensing visual, gustatory, olfactive, auditive, mechanical, thermal, osmotic and pruritogenic stimuli. Cross-talk of TRPs and many neuropeptides is also emerging and an important area of research. While activation of various TRP ion channels causes stimulation of these nociceptors, resulting in chemical, mechanical or thermally induced pain, these same TRP ion channels can be inhibited to decrease or eliminate the sensing of pain and pruritus.

The skin is highly innervated and contains a dense network of sensory afferents. Among the unmyelinated C-afferent axons (also referred to as C-nociceptors), approximately 80% are mechano-sensitive polymodal nociceptors, which respond to mechanical, thermal (heat), and chemical stimuli; and approximately 20% do not respond to mechanical stimulation but are activated only by chemical stimuli.

Skin-localized sensory afferents are involved in the neuronal processing of multiple sensory modalities (e.g. pain, itch, touch, thermosensation). Recent research suggests that transient receptor potential (TRP) ion channels not only act as polymodal cellular sensors on sensory neurons but are also functionally expressed by many non-neuronal cell types. This is especially true in the skin.

Here we summarize and highlight very recent research directed at the mechanisms of itch with a focus on TRPA1 and TRPV1 nociceptors and their involvement with pruritus. Our NociDerm® products were designed, in part, based on this current research, as well research into natural compounds and their antinociceptive role. Pruritus in humans can be caused by various underlying diseases, including those with dermatological, neurological and systemic disorders and also from drugs with pruritic side effects. One group of the skin's sensory nerves has histamine receptors that can be blocked by antihistamines to help stop itch. However, activation of the skin's sensory nerves by known skin irritant compounds;

inflammation, from asthma and allergies; psoriasis and eczema create histamine-independent itch that is not easily treatable. Treatments for histamine-independent pruritus are ineffective when antihistamine products, such as diphenhydramine are used, other than helping with sleep. While scratching usually provides temporary itch relief, scratching is believed to prolong and be involved in itch becoming chronic by secondary mechanisms such as drying of the skin, inflammation, and infection. This phenomena is frequently referred to as the itch-scratch-itch cycle.

Pruritus has been found to be the most frequent complaint (64%) among patients suffering from psoriasis. Psoriatic pruritus does not respond to antihistaminic drugs and is a non-histaminic symptom of psoriasis. Eczema is known as the "itch that rashes" and similar to psoriasis, does not respond to antihistaminic drugs, and 87%-100% of patients with eczema have chronic itch (Lavery, et al 2016).

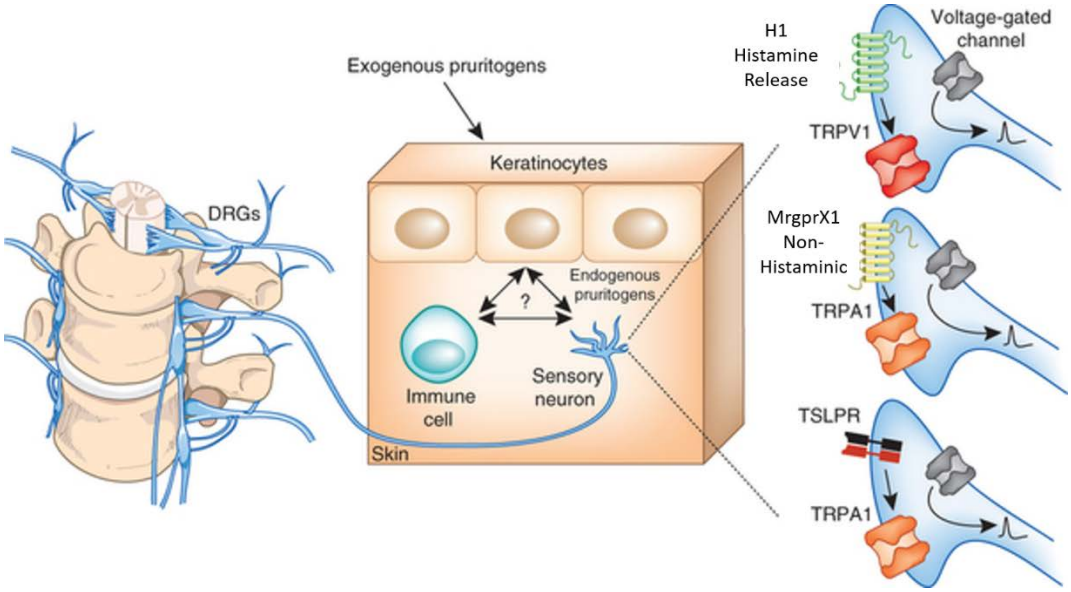
The mechanisms underlying histamine-independent itch is very much a field of emerging science.

Medical researchers involved in the field of itch have proposed a novel pruriceptive system; within which itch-inducing peripheral mediators (pruritogens), itch-selective receptors (pruriceptors), sensory afferents and spinal cord neurons, and defined, itch-processing central nervous system regions display complex, layered responses to itch (Bíró et al. (2007). Several cell types contribute to chronic itch pathologies and sensations. Tissue-resident cells in the skin, such as keratinocytes and cells that infiltrate during inflammation, such as lymphocytes, mast cells, and eosinophils, release pruritogens and activate primary afferent neurons (Mollanazar, et al. (2015).

Recent research by Wilson et al. (2011) on mice indicates that Transient Receptor Potential Ankyrin 1 (TRPA1) is essential for acute itch. TRPA1 contributes to acute endogenous histamine independent itch sensations. In addition to pain and itch, sensory nerves promote acute and delayed inflammatory responses in the skin in Allergenic Contact Dermatitis (ACD) and other pathological skin conditions. TRPA1 is a TRP channel that functions as a receptor for noxious cold temperatures and various tissue and skin irritations, for example those caused by parabens, urushiol, and burns from alkaline compounds, as well as cooling compounds, such as menthol, as well as methyl salicylate. Several TRPA1 activators are also known as triggers of migraine attack, and pruritus. Because TRPA1 is an excitatory ion channel targeted by cold nociception and inflammatory pain, TRPA1 is a promising target for use in identifying analgesic drugs that could inhibit TRPA1.

Recent research by Liu et al. (2017) on mice exhibiting antihistamine-resistant scratching behavior ACD following exposure to the two haptens; oxazolone and urushiol, showed pharmacological inhibition of scratching when exposed to a synthetic TRPA1 antagonist HC-030031. Additionally mice with genetically ablated TRPA1 showed resistance to antihistamine-resistant scratching behavior ACD following exposure to haptens; oxazolone and urushiol. Liu et al. (2017) concluded that TRPA1 is a crucial component of the inflammatory response in contact dermatitis following the cutaneous hapten oxazolone challenge. They also concluded that constant TRPA1-dependent activation of and feedback from sensory neurons is necessary to maintain chronic dermatitis and establish chronic pruritus, with Substance P (SP) playing a key role in histamine (and mast cell)-independent inflammation and pruritus. Toth et al. (2014) concluded that TRPA1 exerts a pro-inflammatory role in the skin, most probably via an orchestrated interplay between neurogenic and non-neurogenic mechanisms. TRPA1 is a downstream transduction channel onto which multiple histamine-independent itch pathways converge.

The Mas-related G protein-coupled receptor A3 (MrgprA3) has been identified by Liu et al. (2009) as a receptor for non-histaminergic itch. This work was expanded upon by Han et al (2013) who identified an itch-specific population of MrgprA3-expressing neurons in the dorsal root ganglion (DRG). These neurons exclusively supply neurons to the epidermis, respond to multiple pruritogens, and form synapses with gastrin-releasing peptide receptor-positive ($GRPR^{+}$) neurons in the dorsal horn of the spinal cord. When these neurons are ablated scratching is reduced in response to pruritogen injection.



Baustista, et al (2015) presents a current understanding of the cell types involved in the detection of itch stimuli. In the above Figure, Dorsal Root Ganglia (DRG) neurons (blue; left) innervate the skin and can be activated directly by exogenous or endogenous itch-inducing agents (pruritogens) released by keratinocytes, immune cells or neighboring neuronal afferent endings. Many endogenous compounds activate keratinocytes and different immune cells. Cross-talk between all three cell types, through the release of secreted compounds (for example, the result of neurogenic inflammation factors), further modulates cell responses and itch pathway output. Subsets of sensory neuron afferents innervate the skin and mediate itch signaling (right side of figure). The pruritogen histamine activates neurons via the histamine receptor 1 (H1) that leads to the opening of TRPV1 ion channels (red; top right). For example, pruritogens BAM8–22 and chloroquine, activate neurons via MrgprC11 and MgprA3, respectively, and lead to the opening of TRPA1 channels (red; middle right). The cytokine thymic stromal lymphopoietin (TSLP) activates neurons via TSLPR, which leads to the opening of TRPA1 channels (red; bottom right). The activation of TRPV1 or TRPA1 leads to neuronal depolarization, action potential firing and the transmission of itch signals from the periphery to the CNS.

Pruritic responses are triggered by somatosensory neurons, with several itch-inducing agents acting through a pathway involving the ion-channel TRPV1. TRPV1 was the first to be described member of the TRPV subfamily. It was identified in rat DRGs as the receptor for capsaicin, the pungent ingredient of red hot chili peppers. Agonist induced silencing of TRPV1-expressing neurons was shown to result in a

profound loss of all itch responses. The role of TRPV1 in inflammatory and neuropathic states is well established. In addition to capsaicin being TRPV1 agonist, TRPV1 is also activated by diverse stimuli including noxious temperatures (near 42^{o}C), extracellular acidic pH and bioactive lipids such as lysophosphatidic acid (LPA), herbal compounds, such as piperine, eugenol, urushiol, zingerone, resiniferatoxin, gingerol, zingerone, evodiamine, cannabidiol, polygodial,isovellera, camphor, vanillotoxin and seasonal allergens. Because TRPV1 plays a central role in the development of pruriceptive itch on both sensory neurons and non-neuronal cutaneous structures, targeting the TRPV1 to alleviate its activity, in addition to targeting TRPA1 is a promising therapeutic strategy to treat itch.

Matta, J.A. (2007) reported that Omega-3 polyunsaturated fatty acids were novel targets for TRPV1. Specifically they reported that docosahexaenoic acid exhibits the greatest efficacy as a TRPV1 agonist. However, eicosapentaenoic acid and linolenic acid were markedly more effective inhibitors. Comparatively eicosapentaenoic acid but not docosahexaenoic acid profoundly reduced capsaicin-evoked pain-related behavior in mice. Very recently Morales-Lazaro, et al (2016) reported a naturally occurring monounsaturated fatty acid, oleic acid, inhibited TRPV1 activity, and also pain and itch responses in mice by interacting with the vanilloid (capsaicin)-binding pocket and promoting the stabilization of a closed state conformation.

Hyaluronan (HA) is an anionic linear polymer that is expressed in the extracellular matrix (ECM) of mammalian tissues, where it forms loose and elastic matrices. In joints, HA is continuously secreted by the lining cells of the synovial membranes and provides a protective rheological buffer that reduces the force transmitted by joint movements to joint tissues, including nociceptive nerve endings.

Recently, Caires, R. et al. (2015) investigated the analgesic effects of HA in joints through the modulation of TRPV1 ion channel activity in nociceptive terminals. The pharmacological modulation of TRPV1 has been shown to produce anti-nociception in arthritis animal models. Caires, R. et al. (2015) observed that HA inhibits TRPV1 channel activity and reduces action potential firing in nociceptive neurons and that it shows a previously unknown molecular mechanism that explains the attenuation by HA of peripheral nociceptor activity and pain. These authors demonstrated that TRPV1 channels are molecular targets of HA and that in the presence of HA, TRPV1 opens less frequently, thereby decreasing the excitability of peripheral nociceptive neurons and reducing their responsiveness to noxious stimuli. Importantly, Caires, R. et al. (2015) observed that, HA selectively modulates TRPV1 ion channel function and that related TRP channels associated with sensory transduction of noxious and thermal stimuli such as TRPA1 and TRPM8, were not affected by HA.

Recently, Schlesinger et al. (2012) evaluated the efficacy and tolerability of hyaluronic acid sodium salt gel 0.2% in the treatment of facial seborrheic dermatitis. These authors concluded that the application of hyaluronic acid sodium salt gel 0.2% twice a day after facial cleansing improved the scale, erythema, pruritus, and PGA of subjects diagnosed with facial seborrheic dermatitis.

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