Adjunctive Management of Itch in Atopic Dermatitis

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KEYWORDS

• Itch • Atopic dermatitis • Eczema • Neuromodulator • Anti-depressant • Cannabinoid • Acupuncture • Phototherapy

KEY POINTS

- Itch is a key component of atopic dermatitis (AD) and has a negative impact on patient quality of life.
- Reducing itch symptoms is central to disease control and may require a multifaceted approach to patient care, including barrier protection, pathogen reduction, and use of neuromodulators, in addition to standard immunosuppressive strategies.
- Currently, existing evidence to support the use of topical and systemic neural-targeted therapies is limited. Thus far, the greatest benefit has been demonstrated for opioid antagonists, topical anesthetics, and systemic antidepressants.
- Alternative therapies, such as acupuncture, stress management, and behavioral therapies, may benefit atopic patients in reducing itch.

INTRODUCTION

Itch, also referred to as pruritus, is the principal symptom of AD and its presence is essential to making the diagnosis of the disease. The severity of itch in AD ranges from mild to severe based on the degree of inflammation, the extent or site of involvement, and the chronicity of disease. Pruritus can be so intense that patients scratch until they bleed or produce scarring. Chronic itch in AD often precipitates sleep disturbance, attention difficulties, and social withdrawal, all contributing to a decreased quality of life of affected individuals.[1]

Itch sensation is mediated by activation of small-diameter unmyelinated or thinly myelinated nerves, known as C fibers or Aδ fibers, respectively, whose peripheral terminals reside in the skin (**Fig. 1**). The central projections of these afferent nerve fibers send itch signals to second-order spinal neurons in the dorsal horn of the spinal cord, which in turn project to the ventrocaudal part of the nucleus medialis dorsalis in the thalamus via the contralateral spinothalamic tract and then onto higher cortical areas[2]; see **Fig. 1**). The sensation of itch is perceived after activation of the somatosensory cortex and a subsequent scratching reflex is generated in the motor cortex and associated motor cortex. The intensity and quality of itch signals may be influenced at various points along the peripheral, spinal, and/or cortical pathways by other ascending inputs from the periphery (eg, other incoming pain or tactile or temperature-evoked sensations) or descending neural circuits (eg, influence of mood and attention).[2–4] Understanding these modulatory circuits is of particular interest and relevance in atopic itch because neurophysiologic and psychomimetric testing demonstrates that patients with AD exhibit reduced thresholds for itch and alloknesis

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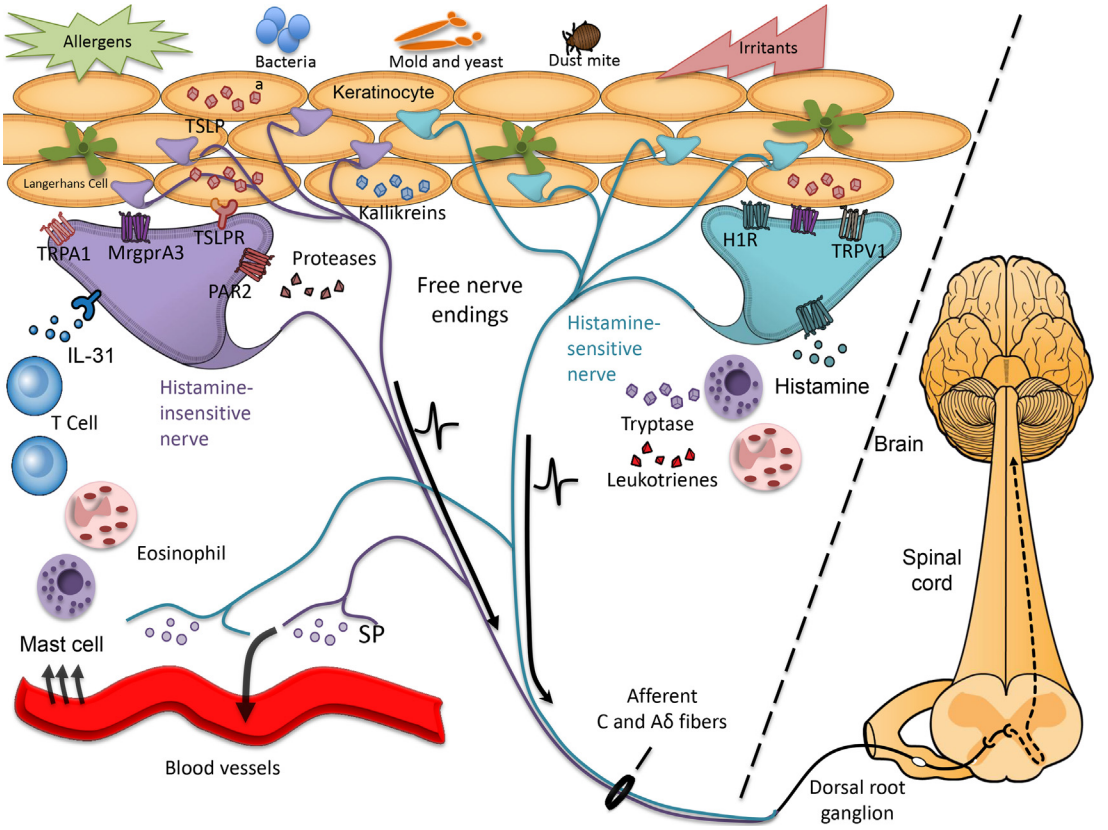

Fig. 1. Diverse pruritogens activate peripheral nerves to drive atopic itch. Sensory nerve terminals in the skin express itch sensors, known as Mas-related G protein–coupled receptors (Mrgpr); TRP channels, including TRPV1 and/or TRPA1; and protease-activated receptor (PAR) 2, all of which respond to a variety of extrinsic and intrinsic pruritogens. Exogenous stimuli (eg, irritants, house dust mite allergen, bacteria, and yeast) may directly activate the peripheral terminals of cutaneous itch-sensing nerve fibers. In atopic skin, barrier defects, such as those caused by filaggrin deficiency, result in increased release of keratinocyte-derived cytokines (eg, TSLP and proteases [eg, kallikreins]) or activation of immune mediators (eg, IL-31, tryptase, histamine, and leukotrienes) that bind directly to receptors on peripheral sensory nerves and evoke itch. Although a subset of pruriceptors also respond to histamine, histamine-evoked itch plays a minor role in atopic itch overall. Once activated, itch signals are transmitted from the periphery to the central nervous system by unmyelinated C fibers or thinly myelinated Aδ fibers, whose cell bodies reside in the dorsal root ganglia and whose central projections synapse onto neurons in the dorsal horn of the spinal cord. These spinal neurons project to second-order and then third-order spinal neurons, which ascend via the contralateral spinothalamic tract to the thalamus and onto the somatosensory cortex. Activation of peripheral pruriceptors may also elicit a peripheral feedback mechanism in which nerve endings release neuropeptides, including SP, to provoke increased vascular permability and immune cell infiltration, accounting for the erythema and inflammation observed in acute eczematous lesions.

(the ability of a nonpruritic stimulus to evoke itch) in involved and uninvolved skin.[5]

The skin-nerve interface is altered in atopic skin, with several studies demonstrating increased innervation density and expression of inflammatory neuropeptides (eg, substance P [SP], calcitonin gene–related peptide [CGRP], and vasoactive intestinal peptide in lesional atopic skin[6,7]; reviewed by Mollanazar and colleagues[8]; see **Fig. 1**). Numerous exogenous stimuli (eg, irritants and house dust mite allergens) and endogenous factors, including histamine, leukotrienes, cytokines, proteases, neuropeptides, and many other inflammatory molecules, activate cutaneous pruriceptors (itch-sensing fibers).[9–12] The repertoire of pruritogens is expanded in AD such that nonpruritogenic and/or painful stimuli, including acetylcholine[13] and bradykinin,[14] evoke itch rather than pain.[5] Inflammatory cytokines interleukin (IL)-31 and thymic stromal lymphopoeitin (TSLP), both elevated in atopic skin, are capable of directly activating peripheral nerves to induce itch signaling in animal models.[15] Pathogenic bacteria and yeast, often colonizing atopic skin, may also