Itch in Atopic Dermatitis

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KEYWORDS

• Atopic dermatitis • Pruritus • Pruritogen • Hypersensitivity of pruritus • New therapy

KEY POINTS

- Numerous types of pruritogens produced with inflammation are involved in atopic itch.
- Hypersensitivity of pruritus occurs in the peripheral and central nervous system in atopic dermatitis.
- The appropriate conventional treatment of atopic dermatitis should generally lead to the reduction of itch sensation.
- The future development of new therapeutic drugs for itch is expected.

INTRODUCTION

Atopic dermatitis (AD) is characterized by chronic cutaneous inflammation and dry skin. Intense pruritus is the major and most burdensome symptom of AD.[1] Itch is a specialized perception of skin leading to a scratching behavior that is often recognized in terrestrial mammals. Itch-induced scratching appears to exacerbate skin lesions in clinical and experimental settings.[2] Itching and scratching cause sleep loss and severely disturb the quality of life of affected individuals.

PERIPHERAL ITCH

Transmission of Peripheral Itch

Itch is mediated by unmyelinated C-fiber afferents and thinly myelinated Aδ fiber afferents, and these cutaneous sensory nerve fibers originate from cell bodies in the dorsal root ganglion (DRG).[3–5] The free nerve endings exist in the epidermis and papillary dermis and around skin appendages and are activated by endogenous and exogenous pruritogens through relevant receptors. The electrical signals generated by sensory nerve stimulation are sent to the central nervous system. Itch-specific peripheral neurons are positive for Mas-related G-protein-coupled receptor (GPCR) A3

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(MargprA3) because genetic ablation of MargprA3 expression neurons attenuated scratch responses to chloroquine and histamine without affecting pain behaviors.[6] At least 2 types of pruriceptive neurons have been identified in the murine DRG, namely, histamine-dependent and histamine-independent afferents, with substantial overlap (Fig. 1).[7] These 2 systems, although closely related, seem to exist separately and independently from one another. The histaminergic itch pathway uses transient receptor potential channel V1 (TRPV1) as a direct downstream target. In nonhistaminergic itch, some pruritogens (eg, chloroquine) use TRPA1, whereas others are not necessary for TRPV1 or TRPA1.[8] Antipruritic effects of antihistamines are limited in the treatment of AD. This clinical observation implies that atopic itch is induced mainly by the nonhistaminergic pathway.

Hyperinnervation in Epidermis

Another intriguing finding is that epidermal hyperinnervation or elongation of sensory nerve fibers in AD may cause itchy and sensitive skin.[5] The hyperinnervation is mainly caused by an imbalance between nerve elongation factors (eg, nerve growth factor [NGF]) and nerve repulsion factors (eg, semaphorin 3A [Sema3A]) that are produced by keratinocytes. In fact, the expression of NGF is upregulated in the lesional skin of patients with AD with reciprocal downregulation of Sema3A expression. The imbalance of NGF/Sema3A in the epidermis is normalized in the improved skin lesions treated with ultraviolet radiation.

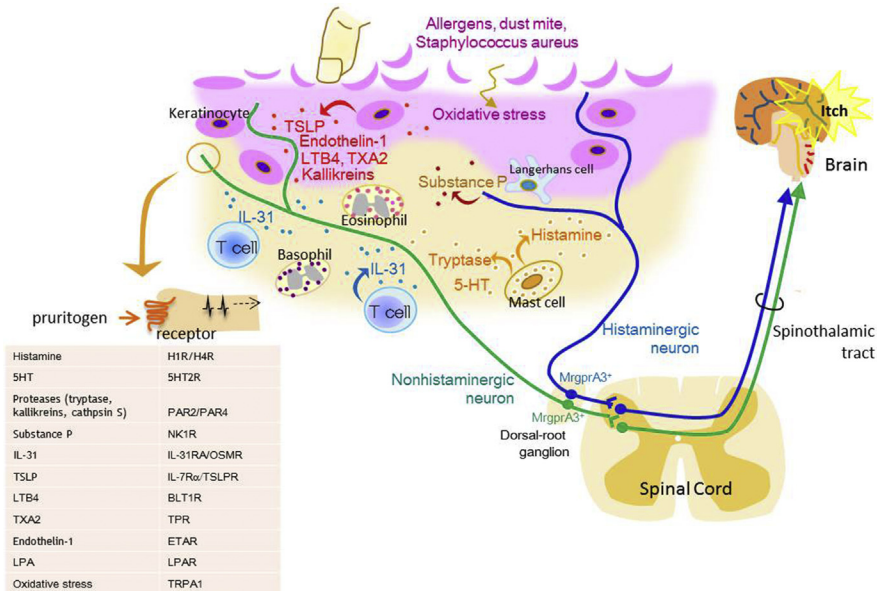

Fig. 1. Pathophysiology of pruritus in AD. 5HT, 5 hydroxytryptamine; 5HT2R, 5 hydroxytryptamine 2 receptor; BLT1R, leukotriene B4 receptor 1; ETAR, endothelin receptor type A; H1R, histamine H1 receptor; H4R, histamine H4 receptor; IL-31RA, interleukin-31 receptor A; IL-7Rα, interleukin-7 receptor alpha; LPA, lysophosphatidic acid; LPAR, lysophosphatidic acid receptor; LTB4, leukotriene B4; Mrgpr, Mas-related G-protein-coupled receptor; NK1R, neurokinin 1 receptor; OSMR, oncostatin M receptor; TPR, thromboxane prostanoid receptor; TRPA1, transient receptor potential cation channel subfamily A member 1; TSLPR, thymic stromal lymphopoietin receptor; TXA2, thromboxane A2.