New pathways for itching in patients with atopic dermatitis?

Jennifer Heimall, MD, and Jonathan M. Spergel, MD, PhD *Philadelphia, Pa*

Key words: *Atopic dermatitis, itch, substance P, gamma-aminobutyric acid*

Atopic dermatitis has been described as the itch that rashes. Indeed, the itching associated with the condition is often considered to be the most challenging feature of the disease to control. In addition, itching has been cited as the symptom most associated with effect on quality of life in patients with atopic dermatitis.[1]

The sensation of itching is mediated by complex signaling from the skin through the dorsal root ganglion to the spine and brain and is mediated by many different neurologically active molecules, including substance P. In this issue the following 2 articles address the potential for novel mechanisms underlying the vexing symptom of itching and demonstrate early proof of concept for novel treatment options. Azimi et al[2] describe the role of substance P–mediated activation of Mas-related G protein–coupled receptors (Mrgprs) in inducing itching in a mouse model, and Cevikbas et al[3] describe a synergistic role for gamma-aminobutyric acid (GABA) A and GABA-B agonists for addressing symptoms of itching in murine atopic dermatitis. Also, a recent article in press by Luo et al[4] describes how transient receptor potential vanilloid receptor 4 (TRPV4) contributes to the sensation of itching.

Substance P is known to have an association with mediating the sensation of itching in patients with atopic dermatitis, but the best known receptor family associated with substance P–signaling pathways are the neurokinin receptors (NK-1R). NK-1R antagonists have had variable results in controlling itch in human subjects.

In the article by Azimi et al,[2] it is demonstrated that substance P can activate Mrgprs, as well as neurokinin receptor. Mrgprs are known to be associated with sensory neurons of the dorsal root ganglion, leading to itch and nociception, and in human subjects are also expressed on mast cells in the form of MRGPRX2. In Mrgpr knockout mice, substance P–mediated itching was decreased. The investigators then demonstrated that a Mrgprs antagonist, Gln-D-Trp(Formyl)-Phe benzyl ester (QWF; an antagonist of NK-R1, as well as the murine receptors MrgprB2 and MrgprA1), was able to decrease substance P–induced itch, including substance P–induced degranulation from mast cells, more effectively than an isolated NK-R1 antagonist in a mouse model. A tissue-culture model was used to demonstrate that substance P was able to activate cultured dorsal root ganglia cells from NK-1R knockout mice; this effect was able to be blocked with QWF. Because mouse MrgprA1 is considered equivalent to human MRGPRX2, it is postulated that MRGPRX2 could be a target for mast cell–mediated disease and non–histamine-mediated itching. This presents an intriguing therapeutic option to address the troubling itching experienced by patients with atopic dermatitis. Although QWF was administered systemically in the reported studies, QWF is known to be rapidly hydrolyzed in plasma, and therefore this therapy might be most practical for development as a novel topical agent specifically aimed at reducing itching.

GABA inhibitory signaling is a key neurologic pathway that can inhibit sensations of pain and itching.

In their work Cevikbas et al[3] describe a synergistic role for the GABA-A and GABA-B agonists muscimol and baclofen, respectively, for addressing symptoms of itching in murine atopic dermatitis. Baclofen is a well-known therapy that is used for treating pain and spasms in human disease, such as multiple sclerosis or spinal cord disease. Because of the inhibitory nature of these therapies, the investigators first performed a titration to establish the dose above which motor coordination was impaired, sedation occurred, or both. In an experimental model to determine the effect on reducing itching, mice were injected with histamine, followed by subsedative doses of baclofen, muscimol, or both, and itch response was observed. Both drugs were found to have a very narrow therapeutic window. Baclofen was found to have onset of action of greater than 60 minutes after administration, with a beneficial effect lasting up to 6 hours, whereas muscimol had more rapid onset of action (within 30 minutes) but shorter duration of effect (<1 hour). Of note, there was an observed synergistic effect with ineffective doses of baclofen when paired with subthreshold muscimol had significant anti-itch properties.

In a second set of experiments described in this same report, sustained GABA-mediated inhibition of neuronic signaling (achieved with medial ganglionic eminence transplantation to the spinal cord in this mouse model) decreased itching and decreased the number and severity of skin lesions. The authors also found that mRNA gastrin-releasing peptide was increased in segments of spinal cord associated with affected dermatomes in the IL-31 transgenic mouse model, which led to the conclusion that peripheral IL-31 overexpression leads to increased spinal cord production of substance P and gastrin-releasing peptide and decreases expression of the GABA-B1 receptor.

At the level of the skin, in addition to histamine, other mediators contribute to initiating the sensation of itch (Fig 1). The activation of TRPV4, an osmoreceptor, was demonstrated

From the Children's Hospital of Philadelphia, and the Division of Allergy and Immunology, Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania.

J.M.S. is funded by the Stuart Starr Endowed Chair, and J.M.S. and J.H. are funded by the Children's Hospital of Philadelphia Funds for Food Allergy Research and Eosinophilic Esophagitis.

Disclosure of potential conflict of interest: J. M. Spergel serves as a consultant for DBV Technology and GlaxoSmithKline; receives grant support from DBV Technology, Aimmune Therapeutics, and Food Allergy Research & Education; receives payments for lectures from Meeting Events International and Rockpointe; receives payment for development of educational presentations from Rockpointe; holds stock options with DBV Technology; and serves on the advisory boards for the National Eczema Association, Food Allergy Research & Education, and the International Association for Food Protein Induced Enterocolitis. J. Heimall declares that she has no relevant conflicts of interest.

Received for publication April 7, 2017; revised May 31, 2017; accepted for publication June 5, 2017.

Available online June 23, 2017.

Corresponding author: Jonathan M. Spergel, MD, PhD, Children's Hospital of Philadelphia, Division of Allergy and Immunology, Wood 3552D, 3401 Civic Center Blvd, Philadelphia, PA 19104. E-mail: spergel@email.chop.edu.

J Allergy Clin Immunol 2017;140:393-4.

0091-6749/$36.00

© 2017 American Academy of Allergy, Asthma & Immunology

http://dx.doi.org/10.1016/j.jaci.2017.06.004

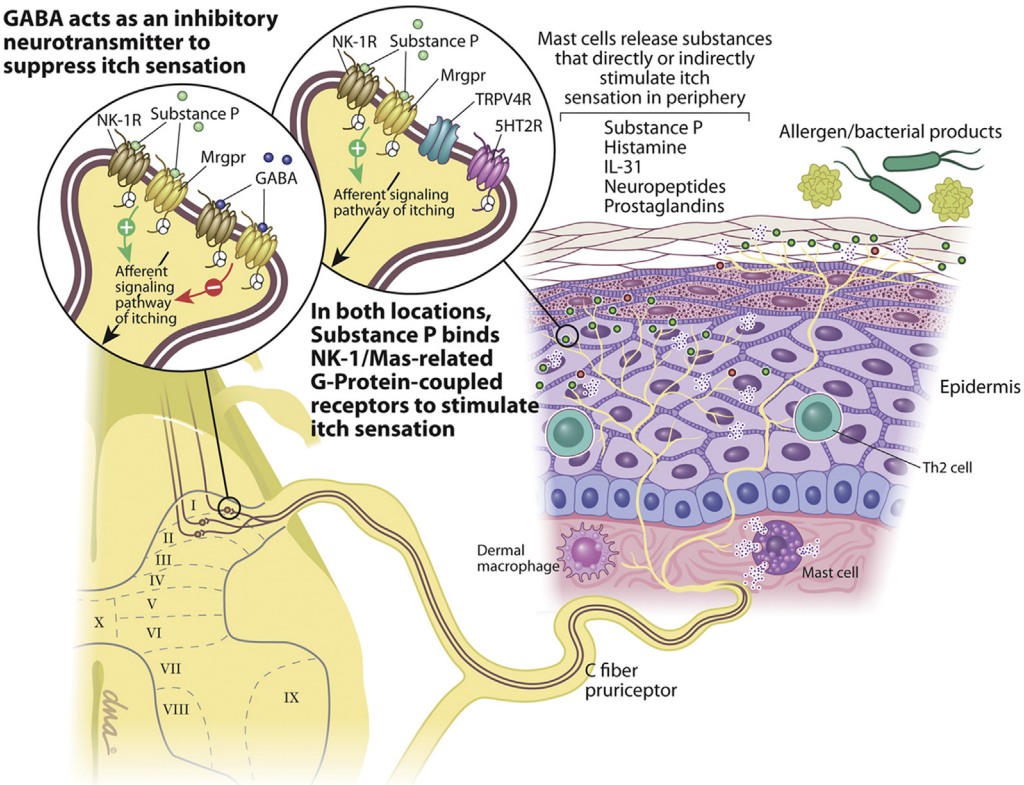

FIG 1. Pathways of itch sensation. The figure depicts 3 novel pathways of itching: (1) substance P–mediated activation of Mas-related G protein–coupled receptors (Mrgprs); (2) activation of GABA pathway; and (3) activation of TRPV4 receptor on the skin.

to promote 5-hydroxytryptophan signaling of itch in response to dry skin and allergic triggers. TRPV4 was found to be expressed at higher concentrations in the skin from patients with chronic itch. Turning to a mouse model, decreased expression of TRPV4 in keratinocytes led to decreased nonallergic itch sensation, whereas decreased expression of the same receptor in macrophages led to decreased sensation of allergic itching.

These 3 studies[2-4] present novel murine models for the treatment of central and histamine-mediated itching, which is such a vexing challenge for patients with atopic dermatitis. Historically, the management of itching in patients with atopic dermatitis has relied heavily on the use of antihistamines in conjunction with moisturizers and topical immunomodulators.[5] Despite their limited efficacy to actually manage itching associated with the disease, the side effect of sedation associated with some antihistamines gives some patients enough respite from itching to allow for sleep. Although there is potential for sedation with baclofen and muscimol, this was a side effect specifically selected against in these studies, and efficacy in a mouse model was still able to be demonstrated in terms of controlling itching. Similarly, the blockade of substance P signaling through Mrgprs is also a promising therapeutic target. Finally, association of the osmoreceptor TRPV4 with the sensation of itch also illustrates an appealing area for potential clinical application.

There is clearly a need for additional studies in human tissue for greater evidence to support proof of concept, followed by clinical trials to establish safety and efficacy and the safety of using these agents for systemic treatment of itching associated with atopic dermatitis. These proposed agents join a growing list of therapies, including systemic dupilumab[6] and topical application of phosphodiesterase 4 inhibitors,[7] which have been explored recently for a more targeted approach to treatment of both the inflammation and pruritis associated with atopic dermatitis. These and other new and emerging therapies have the potential to radically change the paradigm of atopic dermatitis as a skin-limited disease with barrier dysfunction to one with components of systemic inflammation and neurologic signaling that can be treated to achieve overall remission and alleviate the misery experienced by so many patients.

REFERENCES

1. Drucker AM, Wang AR, Li W, Sevetson E, Block J, Qureshi A. The burden of atopic dermatitis: summary of a report for the national eczema association. J Invest Dermatol 2017;137:26-30.
2. Azimi E, Reddy VB, Pereira PJ, Talbot S, Woolf CJ, Lerner EA. Substance P activates Mas-related G protein–coupled receptors to induce itch. J Allergy Clin Immunol 2017;140:447-53.
3. Cevikbas F, Braz JM, Wang X, Solorzano C, Sulk M, Buhl T, et al. Synergistic antipruritic effects of gamma aminobutyric acid A and B agonists in a mouse model of atopic dermatitis. J Allergy Clin Immunol 2017;140:454-64.
4. Luo J, Feng J, Yu G, Yang P, Mack MR, Du JH, et al. TRPV4-expressing macrophages and keratinocytes contribute differentially to allergic and nonallergic chronic itch. J Allergy Clin Immunol 2017 [In press].
5. Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, et al. Atopic dermatitis: a practice parameter update 2012. J Allergy Clin Immunol 2013;131:295-9.
6. Beck LA, Thaci D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014;371:130-9.
7. Furue M, Kitahara Y, Akama H, Hojo S, Hayashi N, Nakagawa H, et al. Safety and efficacy of topicalE6005, a phosphodiesterase 4 inhibitor, in Japanese adult patients with atopic dermatitis: results of a randomized, vehicle-controlled, multicenter clinical trial. J Dermatol 2014;41:577-85.