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Invited review article

Sweat allergy

Shunsuke Takahagi, Akio Tanaka, Michihiro Hide*

Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

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ABSTRACT

Sweat allergy is defined as a type I hypersensitivity against the contents of sweat, and is specifically observed in patients with atopic dermatitis (AD) and cholinergic urticaria (CholU). The allergic reaction is clinically revealed by positive reactions in the intradermal skin test and the basophil histamine release assay by sweat. A major histamine-releasing antigen in sweat, MGL_1304, has been identified. MGL_1304 is produced at a size of 29 kDa by *Malassezia (M.) globosa* and secreted into sweat after being processed and converted into the mature form of 17 kDa. It induces significant histamine release from basophils of patients with AD and/or CholU with MGL_1304-specific IgE, which is detected in their sera. Patients with AD also show cross-reactivity to MGL_1304-homologs in *Malassezia restricta* and *Malassezia sympodialis*, but MGL_1304 does not share cross antigenicity with human intrinsic proteins. *Malassezia* or its components may penetrate the damaged epidermis of AD lesions and interact with the skin immune system, resulting in the sensitization and reaction to the fungal antigen. As well as the improvement of impaired barrier functions by topical interventions, approaches such as anti-microbial treatment, the induction of tolerance and antibody/substance neutralizing the sweat antigen may be beneficial for the patients with intractable AD or CholU due to sweat allergy. The identification of antigens other than MGL_1304 in sweat should be the scope for future studies, which may lead to better understanding of sweat allergy and therapeutic innovations.

Introduction

Sweat is an indispensable means to maintain the homeostasis of the skin for the thermal regulation of the body, and the retention of moisturization on the skin surface. The anti-microbial peptides in sweat also play a role in skin defense against microbes. On the other hand, sweat is considered as the triggering or exacerbating factor for atopic dermatitis (AD) and cholinergic urticaria (CholU); the skin lesions in AD are exacerbated in association with sweating, and CholU is evoked by sweating due to an elevated body core temperature. Regarding the involvement of sweat in the pathogenesis of AD and CholU, two mechanisms are possible. One is that the irritation of damaged skin by the contamination or altered pH in sweat may result in itching in AD lesions. Another possibility is the specific hypersensitivity against sweat contents, which is suggested by positive reactions in the intradermal skin test (Fig. 1) and the basophil histamine release assay by sweat. It has been postulated that endogenously produced substances in sweat cause the observed skin reaction and histamine release. However, a major histamine-releasing antigen in sweat has been recently identified in a protein secreted by *Malassezia*, the most common fungus on the skin as part of the normal skin microbial flora, and contaminated in sweat. Moreover, there may be other intrinsic or extrinsic antigens in sweat still to be unveiled. Thus, it is controversial whether the sweat hypersensitivity is elicited exclusively by an extrinsic factor produced by the microbe and contaminated in sweat or also by an intrinsic factor secreted by the sweat gland cells. We, herein review the hypersensitivity to sweat in the context of its pathomechanism of the type I allergic reaction to sweat content.

AD and sweat

AD is a chronic, relapsing eczematous skin disease characterized by pruritus and inflammation with personal or family history of atopic diseases.[1] High levels of IgE production are observed in the sera of patients with AD, indicating that the involvement of IgE is an important factor in the pathogenesis of AD. Numerous factors such as house dust mites, foods, pollens, animals and microbes trigger the exacerbation of AD through the IgE-mediated sensitization process and the subsequent immunological responses.

* Corresponding author.
E-mail address: ed1h-w1de-road@hiroshima-u.ac.jp (M. Hide).
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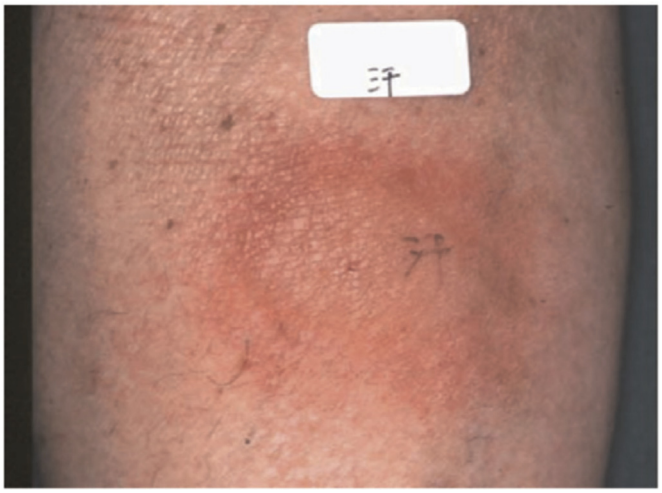

Fig. 1. A positive skin reaction in response to the intradermal injection of autologous sweat. Adapted from Hiragun M *et al.* MB Derma 2014; 220: 67–72 with permission.

Sweat is considered as one of the major exacerbation factors in AD across all age groups. Williams *et al.* reported that almost a half of children with AD viewed sweating as an aggravating factor in a large-scale study by self-completed questionnaires.[2] Moreover, atopic eczematous lesions, especially in children, distribute predominantly in sweat-susceptible parts of the body such as the cubital fossa, the popliteal fossa and the neck, implying the association of sweat in the formation of atopic skin lesions. In a clinical practice setting, the exacerbation of AD in school children is often observed at the time and/or seasons when sweating is frequent, whereas it is improved by continuous efforts to remove sweat by taking a shower or wiping with a wet towel. Kameyoshi *et al.* and other groups reported that skin symptoms of severe AD in school children improved by taking a shower at school during the summer season, indicating that dealing with sweat by showers at school is efficacious for the management of AD for children with severe disease.[3–5]

The exacerbation of AD by sweat may be associated with the primary irritation evoked by the elevation of the body temperature, the altered pH of the skin surface or the contamination of dust in sweat. Nevertheless, previous literature suggested that a certain hypersensitivity to sweat is involved in the exacerbation of AD. More than 85% of patients with AD show a positive reaction upon performance of intradermal skin tests with autologous sweat (Table 1).[6,7] The *in vitro* assay revealed that basophils from patients with AD released histamine in response to crude sweat from both healthy volunteers and patients with AD.[7] There was no difference in the histamine release activity between sweat collected from healthy volunteers and that from patients with AD.[7] Furthermore, sweat from healthy volunteers was semi-purified with reference to histamine releasing activity on basophils obtained from patients with AD.[8] The semi-purified sweat antigen induced histamine release from basophils in 77% of patients with AD (Table 1), depending on the specific IgE in the sera of patients with AD.[8] The histamine release activity in response to sweat could be transferred to basophils from healthy donors by the pre-incubation with the serum of patients with AD.[8] Levels of the specific IgE against the semi-purified sweat antigen in sera of patients with AD were detected at a higher level than that of normal controls and were related to the severity of AD.[9] These observations provide evidence that patients with AD have a specific IgE-mediated (type I) hypersensitivity to the contents in sweat.

Table 1
Positive rates of sweat allergy in patients with atopic dermatitis and cholinergic urticaria.

Authors	Methods	Atopic dermatitis	Cholinergic urticaria	Healthy control
Adachi K[6]	ASwST	96% (43/45)	–	18% (4/22)
Hide M[7]	ASwST	85% (56/66)	–	11% (3/27)
Tanaka A[8]	HRT by purified sweat antigen	77% (47/61)	–	9% (4/46)
Adachi J[12]	ASwST	–	100% (20/20)	0% (0/20)
Fukunaga A[13]	ASwST	–	65% (11/17)	0% (0/10)
	HRT by autologous sweat	–	59% (10/17)	0% (0/10)
Takahagi S[11]	HRT by purified sweat antigen	–	66% (23/35)	0% (0/14)

ASwST, autologous sweat skin test; HRT, histamine release test.

CholU and sweat

CholU is characterized by unique clinical features; pin-sized, highly pruritic wheals with surrounding erythema induced by sweating during physical exercise, taking a bath, raising the body temperature or emotional stress.[10] This disorder usually affects young adults and approximately half of the patients with CholU have atopic diathesis.[11] The precise underlying mechanism of the wheal response in CholU has not yet been clarified, but it has been proposed that the hypersensitivity to sweat may be involved in the pathogenesis. Indeed, more than 65% of patients with CholU showed positive immediate-type skin reactions when performing an intradermal skin test with autologous sweat (Table 1).[12,13] A wheal and flare reaction in patients with CholU may also be produced, in the normal-appearing skin, in response to sweating induced by the intradermal injection of acetylcholine, which stimulates the muscarinic M3 receptor and induces sweating in the local site of its injection. Moreover, 66% of patients with CholU showed histamine release against the semi-purified sweat antigen,[11] while 75% of patients with AD did (Table 1).[8] Levels of the specific IgE binding to the semi-purified sweat antigen in sera of patients with CholU were significantly higher than those of normal controls, as seen in AD.[9] Furthermore, recent reports have mentioned that omalizumab, a humanized monoclonal antibody against IgE, is effective for patients with CholU, indicating that CholU may be mediated by pathogenic IgE.[14]

These facts suggest that IgE-mediated hypersensitivity to the constituents of sweat is also involved in the pathogenesis of CholU as in AD. Nakamizo *et al.* suggested that CholU can be categorized into at least four subtypes: (i) CholU with poral occlusion; (ii) CholU with acquired generalized hypohidrosis; (iii) CholU with possible sweat allergy; and (iv) idiopathic CholU.[10]

MGL_1304 secreted by *Malassezia* as a histamine release molecule in sweat

The specific substance that induces histamine release from basophils of patients with AD and CholU had not been identified, even after more than two decades since the first report of IgE binding to crude sweat components by Adachi *et al.*[6] We semi-purified human sweat from healthy volunteers by chromatography techniques with reference to its histamine releasing activity on basophils obtained from patients with AD (Fig. 2a).[8] The semi-purified sweat antigen was further purified with two additional reverse phase chromatography steps (Fig. 2b, c). As a result, mass spectrometric analysis of a peak fraction of UV absorption, which corresponded to the peak fraction of histamine releasing activity revealed a sequence identical to a part of the hypothetical protein secreted by *Malassezia* (*M.*)