

Why does sweat lead to the development of itch in atopic dermatitis?

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Abstract

Sweating plays an important role in maintaining temperature homeostasis in humans. However, under certain circumstances, sweat can cause itching. For example, when excessive sweat accumulates on the skin surface for a long period, miliaria can develop and cause itching. Subjects with dermatoses, such as atopic dermatitis (AD), suffer from itch when exposed to heat or psychological stresses, which are also known perspiration stimuli. Recently, some mechanisms of sweat-induced itch have been revealed. For instance, attenuated sweating ability is observed in subjects with AD, causing heat retention, skin dryness, and high susceptibility to itch. Furthermore, the decreased tight junction of the sweat gland in AD leads to sweat leakage in the dermis, which could be designated as a “sweat endocrine response” and may be the cause of tingling itch during sweating. Additionally, metabolomic analysis of sweat from patients with AD revealed that glucose concentration in sweat increases according to disease severity. Sweat with elevated glucose concentration retards the recovery of the damaged skin barrier and may promote itching. This viewpoint essay outlines the relationship between sweat and itch based on recent evidence.

KEYWORDS

anhidrosis, atopic dermatitis, itch, sweat

1 | INTRODUCTION

Sweat can contribute to the development or exacerbation of itching.^[1–4] Indeed, in daily clinical practice, “itchy when sweating” is a complaint frequently heard from patients with dermatoses, especially atopic dermatitis (AD). Sweat-related itch can be divided into two categories: direct and indirect involvement of sweat. As an example of the former, it is conceivable that sweat permeates into the tissues through the epidermis or sweat gland organs and causes itching.^[2,3] Examples of the latter include itch associated with skin diseases (eg miliaria, xerosis due to anhidrosis, dyshidrotic eczema and vulvar syringoma).^[5,6] Itch can develop in similar environments as those that induce sweating (eg exercise, heat, tension or psychological stress).^[7,8] Thus, it is difficult to distinguish whether sweat is directly or indirectly associated

with itch solely from the patients' complaint. This essay outlines the current knowledge about the pathogenic role of sweat in the mechanism of itch in dermatoses, especially in relation to sweat-evoked itch in AD.

2 | FUNCTION OF SWEAT

To understand the relationship between sweat and itch, it is helpful to briefly review the basic functions of sweat. Sweat is a transparent hypotonic body fluid made in eccrine sweat glands.^[1] The pH of sweat is weakly acidic (4.0–6.8), and its main constituents include electrolytes, such as sodium chloride and potassium, sodium bicarbonate (HCO_3^-), urea, pyruvic acid and lactic acid. In addition, antimicrobial peptides, protease inhibitors, ingested drugs,

cosmetics and metals are also excreted.^[9,10] Many substances are released from the eccrine sweat gland via a transporter to the outside of the body, and sodium can be excreted through the paracellular space.^[9]

Urea and lactic acid are involved in moisture retention of the stratum corneum as natural moisturizing factors. Lactic acid is the final metabolite of glycolysis and is increased by oxidative stress, physical exertion and metabolic stress. Isolated sweat glands produce lactic acid and CO₂ in the presence of glucose in vitro.^[9] Sodium lactate derived from sweat functions as a natural moisturizing factor and is thought to be largely contained in the upper layer of stratum corneum.^[11] Thus, sweat greatly contributes to moisturizing the skin surface. Urea concentration in sweat is at the same level as in plasma, thus contributing to maintenance of the stratum corneum.^[9]

Sweat contains proteases. The presence of certain proteases, such as cathepsins, kallikreins and kininase II, has been reported. Cathepsin D is an aspartic protease, and the optimum pH for its activity is within the acidic range. Cathepsin D cleaves DCD-1L, which is generated by processing of dermcidin, and its cleaved

product has rather strong bactericidal activity.^[12] Sweat also includes tissue or glandular kallikrein (KLK).^[13,14] The sweat is particularly rich in KLK7 followed by KLK11, KLK8 and KLK5.^[14] Adhesion molecules, such as corneodesmosin in the stratum corneum and desmoglein-1 in the epidermis, are the substrates of both KLK5 and KLK7. The roles of other KLKs in sweat are not yet clear. Kininase II and cathepsin B are sweat proteases.^[15,16] Kininase II degrades kinins, such as bradykinin, which is involved in pain.^[15]

It has been confirmed that protease inhibitors are also contained in sweat. Sweat contains protease inhibitor Kazal-type 5 (SPINK5), which regulates the activity of KLK5 and KLK7.^[17] SPINK5 is believed to contribute to maintaining epidermal homeostasis.^[18] Cystine A, a cysteine protease inhibitor, is also contained in sweat. Cysteine protease inhibitory activity is strong in the early period after secretion and decreases with time.^[19] Mite antigens (eg Derf 1) and kiwifruit antigens (actinidins) are representative allergens with cysteine protease activity that cause skin barrier damage and inflammation.^[20] Sweat functions as the first line of defense against allergens with cysteine protease activity.^[2,20]

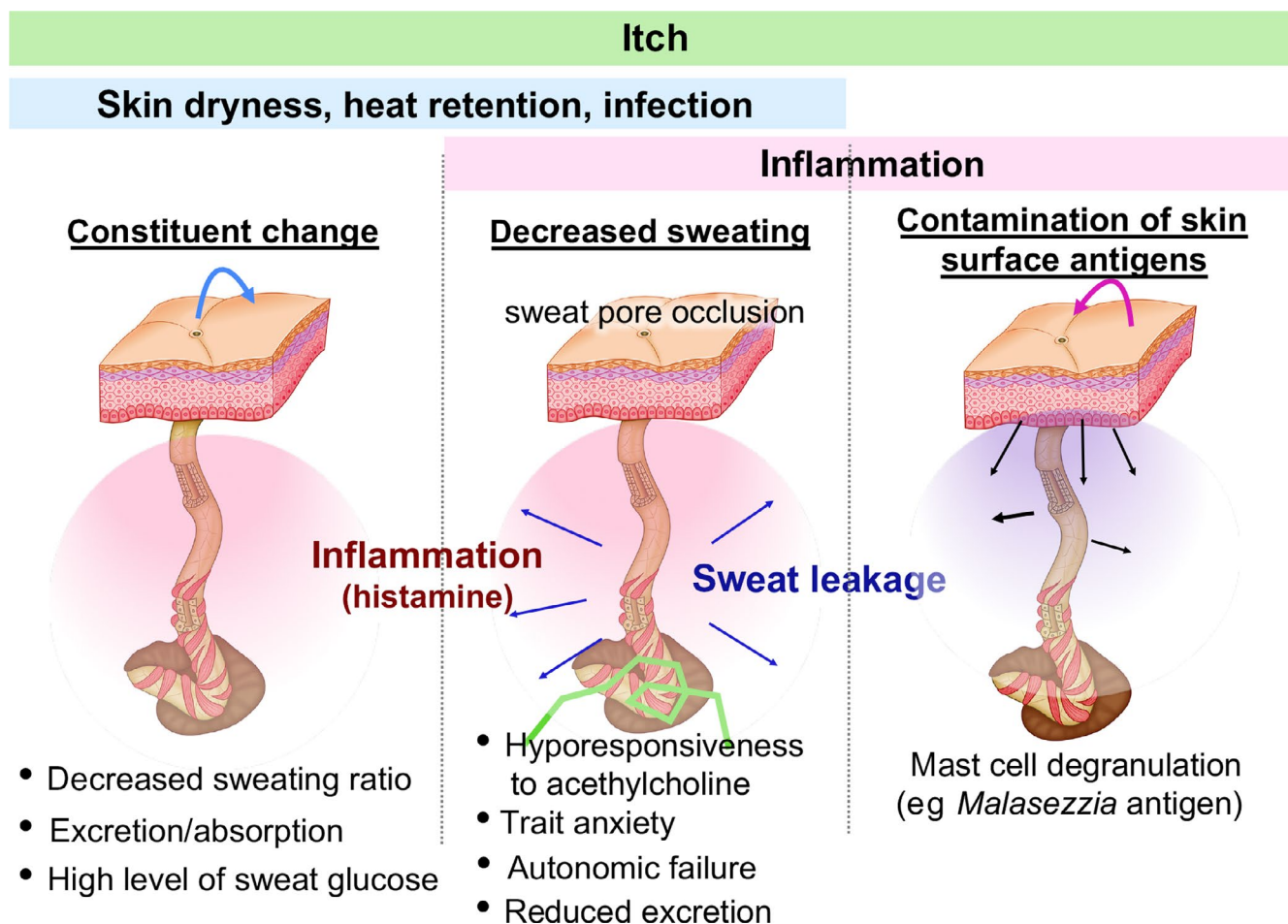


FIGURE 1 Current understanding of the mechanism of sweat-related itch in atopic dermatitis. Sweat gland damage and change in sweat components induced by inflammation make skin prone to itch. Skin surface antigens contained in sweat can penetrate damaged skin and cause itch by degranulation of mast cells

3 | ITCHY DERMATOSES WITH PATHOGENIC INVOLVEMENT OF SWEAT

3.1 | Excessive sweat and itch

When one sweats a lot, excessive sweat will remain on the skin surface. If excessive sweat is wrapped in non-porous clothes and/or is in the intertriginous area, exfoliation of the stratum corneum, occlusion of sweat pores and perturbation of skin flora will occur. Intertrigo occurs in friction-affected skin, such as axillary and inguinal regions. Continuous wetting of such sites is likely to cause skin infections, such as candidiasis, and itching of the genital area. Involvement of sweat in the pathogenesis of intertrigo is more prominent, due to the effects of the present serine proteases, which cleave corneodesmosin and induce exfoliation of stratum corneum.

Miliaria is red papules or small vesicles and is frequently accompanied by itching. Miliaria is caused by exposure to environments with high temperature and humidity after sweating. Sulzberger et al examined the pathology of miliaria caused by wrapping the skin surface over a long period of time. When the skin surface was covered with a wrap for 72 hours continuously, the wrapped area developed miliaria and anhidrosis for a few weeks.^[21,22] Histopathological observation found that keratin plugs are generated in sweat duct openings in the wrapped area.^[21] Consequently, sweat retention caused by keratin plugs caused both inflammation around the sweat gland apparatus and itch. Occlusion of sweat pores by periodic acid-Schiff stain (PAS)-positive substances, biofilms derived from *Staphylococcus epidermidis*, may be involved in the pathogenesis of miliaria.^[23] Formation of similar keratin plugs in AD has also been confirmed, as described below.^[24]

3.2 | Sweat components and itch

The components of sweat may be related to itching. As sweat is a major trigger of itch in AD, it could be speculated that a sweat component necessary to induce itch is highly concentrated in sweat derived from AD patients. Thus, the properties of sweat were compared between AD and healthy subjects who were induced to sweat in a sauna. Unexpectedly, findings revealed that the pH and salt concentration of sweat were equal or lower in AD than in healthy subjects.^[25] In sweat from subjects with AD, the concentration of LL-37, an antimicrobial peptide, varied greatly among individuals.^[25] As LL-37 is cytotoxic, it can be imagined that sweat with high sweat concentrations of LL-37 may promote inflammation and cause itching in subjects with AD (Figure 1).

3.2.1 | Effects of sweat glucose on skin

Metabolomic analysis of sweat using nuclear magnetic resonance revealed some unique characteristics of sweat in AD.^[25] Specifically, glucose concentrations were high during the acute exacerbation phase of AD and were positively correlated with disease severity.^[25] Glucose moves from blood to sweat by osmotic

pressure,^[9] but the mechanism of increased sweat glucose in AD remains obscure. Thus, it can be speculated that sweat glucose may be involved in the increased susceptibility to itch in AD via maintaining the disruption of the skin barrier or affecting the skin microbiome (Figure 1).

These results raised the possibility that sweat glucose may be involved in the skin symptoms in diabetes patients. Sweat glucose levels increase according to the blood glucose levels. Boysen et al reported that glucose levels in sweat were 0.6-1.2 mg/dL when a study using barrier disruption model mice revealed that topical glucose interferes with skin barrier recovery at concentrations similar to those in AD sweat.^[25] blood glucose increased to 200-250 mg/dL.^[26] Thus, sweat glucose may partially explain the pathogenesis of itch in subjects with diabetes mellitus.

3.2.2 | The impact of skin surface antigen contamination of sweat

IgE antibodies against the antigen derived from *Malassezia* (MGL-1304), which is a part of the normal flora on the skin, are found in sera of patients with AD and cholinergic urticaria.^[27,28] As skin surface allergens could be contained in sweat, the various skin surface allergens may penetrate the skin via sweat in individuals whose skin barrier function has deteriorated. Subsequently, allergens contained in sweat can induce itching via degranulation of mast cells. In several reports and reviews, cases in which a positive skin reaction developed by intradermally administered autologous sweat were referred to as "sweat allergy".^[29] Referring to a positive skin reaction to autologous sweat as "sweat allergy" is likely to cause misunderstanding because the term "sweat allergy" is not appropriate if it is an allergic reaction to antigens, such as *Malassezia* antigens, that are not originally included in sweat but were adhered to the skin surface and presented to the immune system via sweat. It is critical that the term "sweat allergy" be used carefully and should be used only with clear evidence of the cause.

4 | THE MECHANISM OF SWEAT-INDUCED ITCH IN AD

As mentioned above, sweat has important functions, such as temperature regulation, moisture retention and protection from infection.^[2,10] Thus, if sweat volume is too small to maintain skin homeostasis, dermatoses will develop^[2,10] (Figure 1). For example, patients with ectodermal dysplasia lacking sweat glands frequently exhibit itchy dermatitis that mimics AD.^[30] Bovell et al found that PAR2 is expressed on the sweat gland cells and may affect sweat secretion.^[31] PAR2 agonists, which are major pruritogens, potentially induce both itch and sweat secretion. Although there is no direct evidence indicating the involvement of PAR2 agonists in sweat-provoked itch, it remains a possibility.

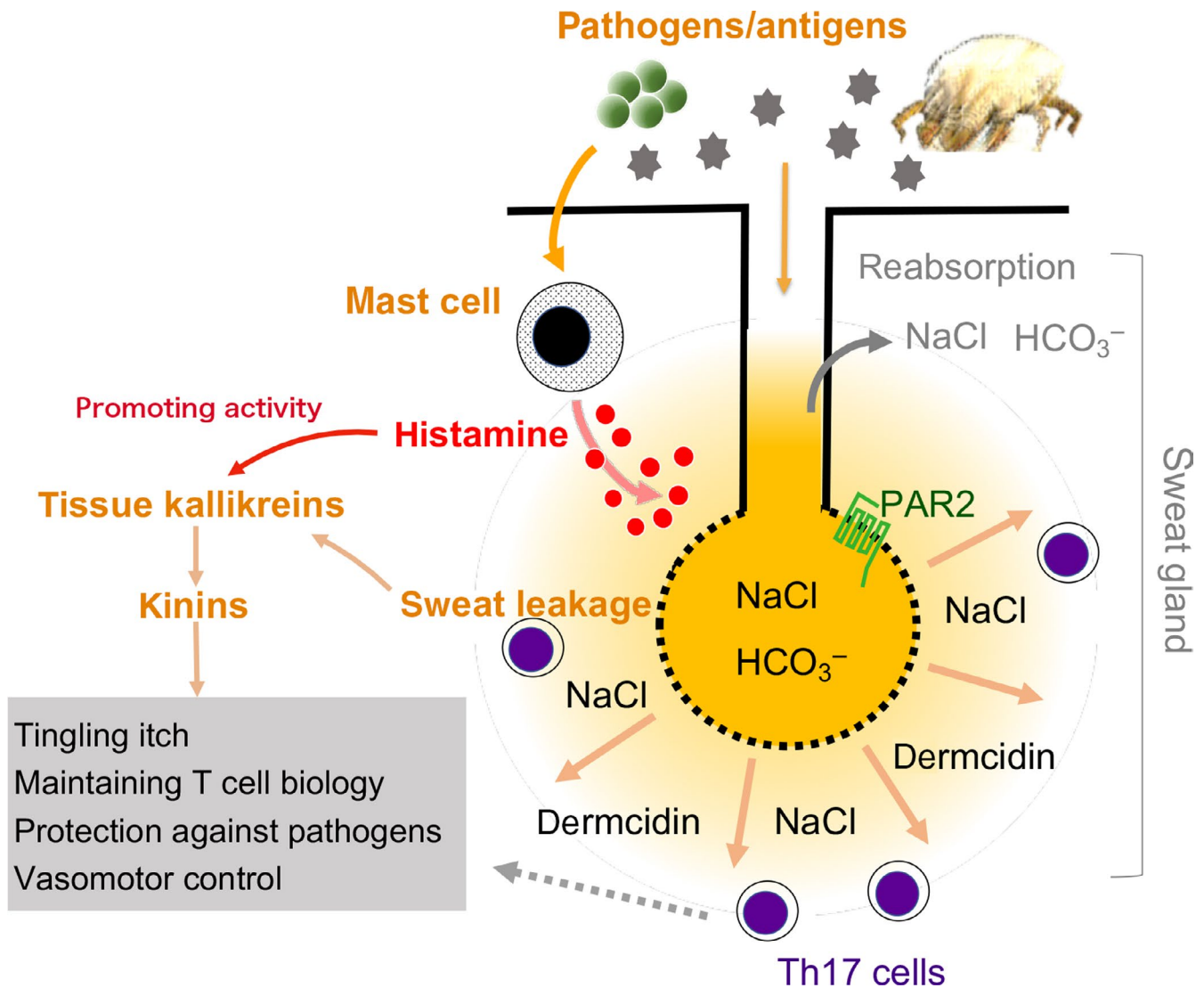


FIGURE 2 Impact of the sweat that escapes into the dermis from the sweat gland. Sweat sometimes leaks into surrounding tissue and evokes various biological responses. Constituents of sweat, such as NaCl, histamine, antimicrobial peptides and proteases (eg kallikreins, PAR2 agonists), induce tingling itch, maintain T-cell biology, protect against pathogens and affect vasomotor control

4.1 | Decreased sweating ability in AD

Sweat has been considered an aggravating factor for itch in AD.^[1] On one hand, patients with AD sweat less compared to healthy subjects.^[2,3,32–34] Interestingly, Nattkemper et al confirmed experimentally induced sweat attenuated cowhage-induced itch in both healthy and AD subjects.^[35] Subjects with AD experienced improved long-term skin symptoms by participating in activities that induced sweating.^[36] Thus, improving sweating ability should be a therapeutic goal for AD. Based on the improvement of disease severity in that study, impaired sweating ability should be improved. Therefore, patients may benefit from participating in activities that induce sweating (eg exercise, walking or bathing), but they should also rinse sweat off to not leave excessive sweat on the skin surface. Kaneko et al investigated the impact of these instructions (“incorporating activities with sweating” and “rinsing sweat off”) on patients’ global

assessment ($n = 23$).^[37] Results showed that approximately 25% of patients felt that following these instructions had a favourable impact on their symptoms. On the other hand, the remaining 75% of patients reported that “rinsing sweat off” had a positive effect but that “incorporating activities with sweating” caused worsening of itching and dermatitis.^[37] Elucidation of the mechanism leading to disease aggravation by sweat is an urgent task to achieve long-term control of AD.

The clinical features related to decreased sweating ability in AD have been reported. Kijima et al reported that the sweating response to acetylcholine stimulation was negatively correlated with the degree of patients’ anxiety.^[33] Furthermore, both anxiety and chronic stress conditions may contribute to an imbalance in the autonomic nervous system, leading to higher susceptibility to itch.^[38] Thus, autonomic nerve failure can cause itch via both increasing susceptibility to itch and decreasing sweat.

4.2 | Occlusion of sweat pores

Sweat retention due to occlusion of the sweat pores has been reported in AD. Sulzberger et al performed a histopathological examination of skin lesions in AD and confirmed that occlusion of sweat pores by horny plugs interferes with sweat excretion.^[24] This histopathological feature was confirmed by Papas and Kligman.^[39] As described above, deposits of PAS-positive materials have been confirmed along with the occlusion of sweat pores and were speculated to be due to *Staphylococcus epidermidis* biofilms.^[23] Interpretation of AD pathogenesis as a "sweat retention syndrome" is still being discussed. Skin dryness and increased skin temperature due to sweat retention may partially contribute to the aggravation of itch in AD (Figure 1).

4.3 | Impaired sweating ability due to inflammation

Quantitative sudomotor axon reflex testing (QSART) revealed dramatically decreased sweat responses in skin lesions of AD patients.^[32] Therefore, certain inflammatory mediators may decrease sweating ability. These inflammatory mediators have been explored by dynamic analysis of the sweat gland via in vivo two-photon microscopy; it was confirmed that histamine, a pruritogen, is a potent inhibitor of sweating among species.^[40,41]

4.4 | Sweat leaks into tissues outside sweat glands

The epidermis has paracellular tight junctions as a barrier to regulate the permeability of substances inside and outside the body. In epidermis, tight junctions composed of claudin-1 function as a water barrier, and a decrease in its expression causes leakage of water out of the body, causing skin dryness.^[42] Disabling the epidermal barrier allows penetration of various pathogens into the skin and causes inflammation and itching. Water barriers exist not only in the epidermis but also in skin appendages. Shiohara et al performed immunostaining for dermcidin, an antimicrobial peptide contained only in sweat, and found that dermcidin localized not only inside the sweat gland but also in tissues outside the sweat glands in AD lesions, suggesting that sweat could leak into the tissue.^[43]

Recent studies have revealed that tight junctions of water barriers in sweat glands contain claudin-3.^[2] Claudin-3 colocalizes with ZO-2 in the paracellular space of luminal cells throughout the sweat gland, indicating that claudin-3 is involved in construction of tight junctions of sweat glands. Experiments using tracer dye mimicking sweat revealed the water barrier function of tight junctions composed with claudin-3. Notably, sweat glands in claudin-3-null mice or mice with experimentally decreased claudin-3 expression exhibited leakage of sweat into the paracellular space of sweat gland cells. Therefore, the observed marked decrease in claudin-3 expression in sweat glands in AD lesions suggests that sweat leakage into the dermis can occur in AD patients.^[2] As described above, sweat contains various proteases, histamine, salt, LL-37 and contaminated skin surface antigens. If sweat leaks into the tissue, it can cause tingling pain or itch, which is frequently observed in subjects with AD (Figure 1).

4.5 | Impact of the sweat that escapes into the dermis from the sweat gland

It is possible that sweat leakage occurs frequently. Histamine, which is often released via daily physical stimuli (eg physical exercise, thermal stimuli and exposure to antigens), decreases the expression of claudin-3 and induces sweat leakage. Thus, sweat glands may frequently leak sweat into outside tissues even in non-disease states. It could be speculated that leaking sweat may play a biological role, such as biological defense and maintenance of homeostasis (Figure 2). For example, dermcidin in sweat is a unique antimicrobial peptide due to its negative charge.^[44] This characteristic of dermcidin helps to reduce tissue damage and may contribute to the host defense system. Furthermore, higher concentration of NaCl in sweat may maintain Th17 cells via activation of salt-sensing kinase, serum- and glucocorticoid-induced kinase 1 (SGK1), and may sustain inflammation via activation of Th17 cells in the tissue surrounding the sweat gland.^[45,46] Activation of Th17 cells protects against bacterial and fungal infections. Thus, sweat leakage may provide a beneficial response for biological defense and may be actively controllable. Although only a tentative theory, sweat leakage may be regarded as "sweat endocrine".

5 | FUTURE PERSPECTIVES

This essay summarizes the current findings related to sweat and itching. With respect to the detailed mechanism, there are many unresolved questions. For instance, the relationship between peripheral nerves that surround sweat glands and itch may be the subject of future investigation. Sweat can cause itching from both inside and outside of the skin and involves a diverse pathophysiology. Recent outcomes regarding impaired sweating in atopic inflammation have provided us with valuable information to inform the discussion of the possible role of sweat in itching. The involvement of sweat constituents (eg proteases, salt, antimicrobial peptides and histamines) in itching should be investigated in greater detail in the future. Accumulation of these findings will lead to formulation of novel therapeutic strategies for itch, focusing on the effects of sweat without avoiding physical activities that induce sweating.

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CONFLICT OF INTEREST

The authors have declared no conflicting interests.

AUTHOR CONTRIBUTION

HM wrote the manuscript. KY and EO performed experiments related to sweat leakage and sweat glucose, respectively. HM and NM accumulated and summarized the previous articles about sweat-related itch. HY and IK contributed to interpretation of data. HM formulated the concept of "sweat endocrine response." All co-authors gave final approval for submission.

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